

19 Rheology

Chapter Objectives

At the conclusion of this chapter the student should be able to:

1. Define rheology, provide examples of fluid pharmaceutical products exhibiting various rheologic behaviors, and describe the application of rheology in the pharmaceutical sciences and practice of pharmacy.
2. Understand and define the following concepts: shear rate, shear stress, viscosity, kinematic viscosity, fluidity, plasticity, yield point, pseudoplasticity, shear thinning, dilatancy, shear thickening, thixotropy, hysteresis, antithixotropy, rheopexy, plug flow, and viscoelasticity.
3. Define and understand Newton's law of flow and its application.
4. Differentiate flow properties and corresponding rheograms between Newtonian and non-Newtonian materials.
5. Understand and calculate the effects of temperature on viscosity and recognize similarities between viscous flow and diffusion relative to temperature.
6. Recognize and identify specific rheologic behaviors with their corresponding rheograms.
7. Appreciate the fundamentals of the practical determination of rheologic properties and describe four types of viscometers and their utility and limitations in determining rheologic properties of various systems.
8. Appreciate the differences between continuous or steady shear rheometry and oscillatory and creep measurements in determining the consistency of viscoelastic materials.

The term "rheology," from the Greek *rheo* ("to flow") and *logos* ("science"), was suggested by Bingham and Crawford (as reported by Fischer¹) to describe the flow of liquids and the deformation of solids. *Viscosity* is an expression of the resistance of a fluid to flow; the higher the viscosity, the greater is the resistance. As will be seen later, simple liquids can be described in terms of absolute viscosity. Rheologic properties of heterogeneous dispersions are more complex, however, and cannot be expressed by a single value.

Fundamental principles of rheology are used to study paints, inks, doughs, road-building materials, cosmetics, dairy products, and other materials. An understanding of the viscosity of liquids, solutions, and dilute and concentrated colloidal systems has both practical and theoretical value. Scott-Blair² recognized the importance of rheology in pharmacy and suggested its application in the formulation and analysis of such pharmaceutical products as emulsions, pastes, suppositories, and tablet coatings. Manufacturers of medicinal and cosmetic creams, pastes, and lotions must be capable of producing products with acceptable consistency and smoothness and reproducing these qualities each time a new batch is prepared. In many industries, a trained person with extensive experience handles in-process material periodically during manufacture to determine its "feel" and "body" and judge proper consistency. The variability of such subjective tests at different times under varying environmental conditions is, however, well recognized. A more serious objection, from a scientific standpoint, is the failure of subjective tests to distinguish various properties that make up the total consistency of the product. If these individual physical characteristics are delineated and studied objectively according to the analytic methods of rheology, valuable information can be obtained for use in formulating better pharmaceutical products.

Rheology is involved in the mixing and flow of materials, their packaging into containers, and their removal prior to use, whether this is achieved by pouring from a bottle, extrusion from a tube, or passage through a syringe needle. The rheology of a particular product, which can range in consistency from fluid to semisolid to solid, can affect its patient acceptability, physical stability, and even biologic

availability. For example, viscosity has been shown to affect absorption rates of drugs from the gastrointestinal tract.

Rheologic properties of a pharmaceutical system can influence the selection of processing equipment used in its manufacture. Inappropriate equipment from this perspective may result in an undesirable product, at least in terms of its flow characteristics. These and other aspects of rheology that apply to pharmacy are discussed by Martin et al.³

When classifying materials according to types of flow and deformation, it is customary to place them in one of two categories: Newtonian or non-Newtonian systems. The choice depends on whether or not their flow properties are in accord with Newton's law of flow.

Newtonian Systems

Newton's Law of Flow

Consider a "block" of liquid consisting of parallel plates of molecules, similar to a deck of cards, as shown in Figure 19-1. If the bottom layer is fixed in place and the top plane of liquid is moved at a constant velocity, each lower layer will move with a velocity directly proportional to its distance

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from the stationary bottom layer. The difference of velocity, dv , between two planes of liquid separated by an infinitesimal distance, dr , is the *velocity gradient* or *rate of shear*, dv/dr . The force per unit area, F/A , required to bring about flow is called the *shearing stress* and is given the symbol F' . Newton was the first to study flow properties of liquids in a quantitative way. He recognized that the higher the viscosity of a liquid, the greater is the force per unit area (*shearing stress*) required to produce a certain rate of shear. Rate of shear is given the symbol G . Hence, rate of shear should be directly proportional to shearing stress, or

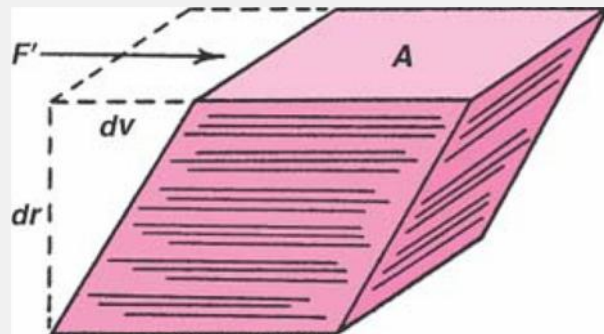


Fig. 19-1. Representation of the shearing force required to produce a definite velocity gradient between the parallel planes of a block of material.

$$\frac{F'}{A} = \eta \frac{dv}{dr} \quad (19-1)$$

where η is the *coefficient of viscosity*, usually referred to simply as *viscosity*.

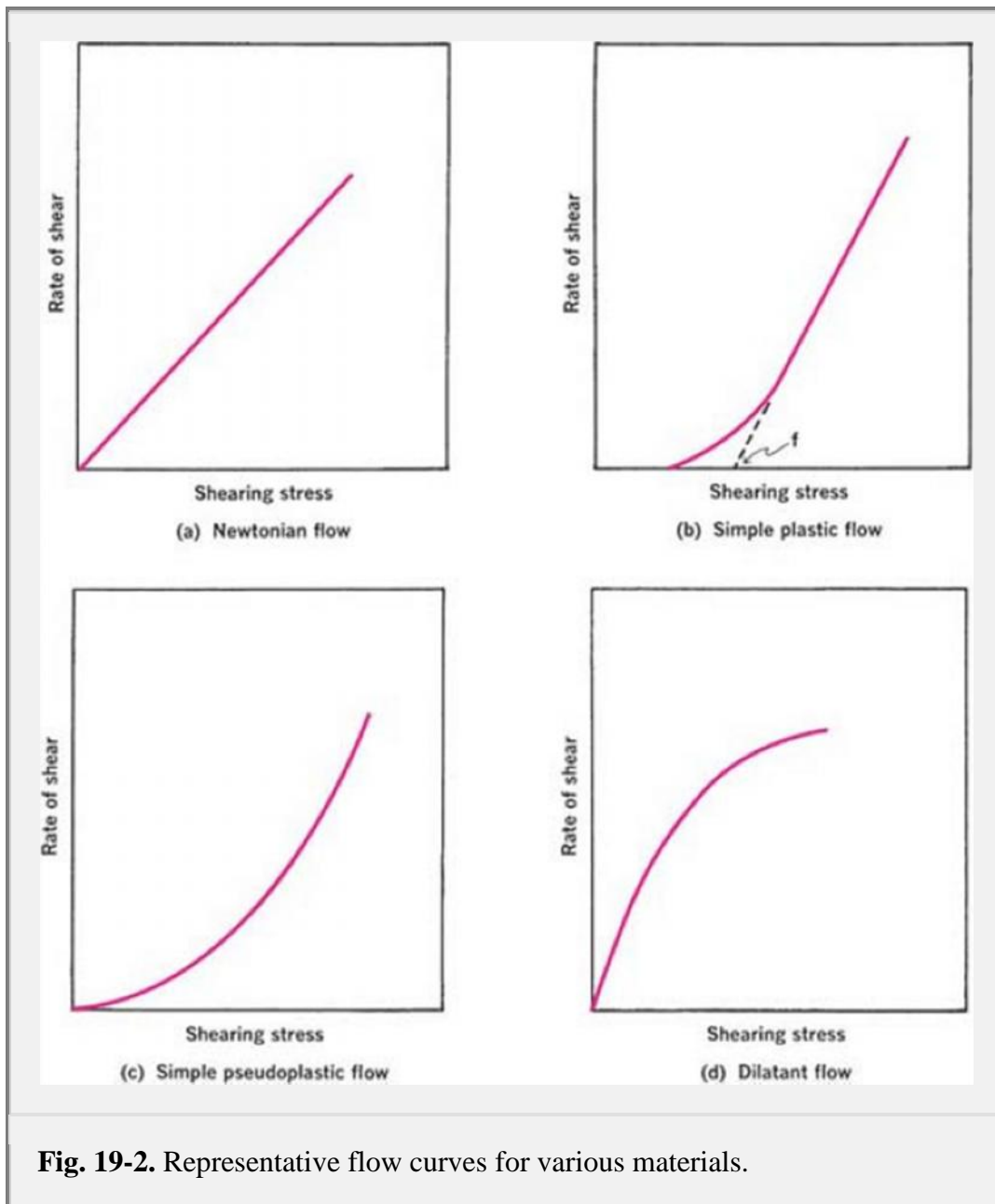


Fig. 19-2. Representative flow curves for various materials.

Equation (19-1) is frequently written as

$$\eta = \frac{F}{G} \quad (19-2)$$

where $F = F/A$ and $G = dv/dr$. A representative flow curve, or *rheogram*, obtained by plotting F versus G for a Newtonian system is shown in Figure 19-2a. As implied by equation (19-2), a straight line passing through the origin is obtained.

The unit of viscosity is the *poise*, defined with reference to Figure 19-1 as the shearing force required to produce a velocity of 1 cm/sec between two parallel planes of liquid each 1 cm² in area and separated by a distance of 1 cm. The cgs units for poise are dyne sec cm⁻² (i.e., dyne sec/cm²) or g cm⁻¹ sec⁻¹ (i.e., g/cm sec). These units are readily obtained by a dimensional analysis of the viscosity coefficient.

Rearranging equation (19-1) to

$$\eta = \frac{F' dr}{A dv} = \frac{\text{dynes} \times \text{cm}}{\text{cm}^2 \times \text{cm/sec}} = \frac{\text{dyne sec}}{\text{cm}^2}$$

gives the result

$$\frac{\text{dyne sec}}{\text{cm}^2} = \frac{\text{g} \times \text{cm/sec}^2 \times \text{sec}}{\text{cm}^2} = \frac{\text{g}}{\text{cm sec}}$$

A more convenient unit for most work is the *centipoise* (cp, plural cps), 1 cp being equal to 0.01 poise. *Fluidity*, ϕ , a term sometimes used, is defined as the reciprocal of viscosity:

$$\phi = \frac{1}{\eta} \quad (19-3)$$

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Table 19-1 Absolute Viscosity of Some Newtonian Liquids at 20°C

Liquid	Viscosity (cp)
Castor oil	1000
Chloroform	0.563
Ethyl alcohol	1.19
Glycerin, 93%	400
Olive oil	100
Water	1.0019

Kinematic Viscosity

Kinematic viscosity is the absolute viscosity [as defined in equation(19-1)] divided by the density of the liquid at a specific temperature:

$$\text{Kinematic viscosity} = \frac{\eta}{\rho} \quad (19-4)$$

The units of kinematic viscosity are the *stoke* (s) and the *centistoke*(cs). Arbitrary scales (e.g., Saybolt, Redwood, Engler, and others) for measurement of viscosity are used in various industries; these are sometimes converted by use of tables or formulas to absolute viscosities and vice versa.

Viscosities of some liquids commonly used in pharmacy are given in Table 19-1 at 20°C. A number of viscosity-increasing agents are described in the *United States Pharmacopeia*.

Example 19-1

Measuring Viscosity

- An Ostwald viscometer (see Fig. 19-11) was used to measure acetone, which was found to have a viscosity of 0.313 cp at 25°C. Its density at 25°C is 0.788 g/cm³. What is the kinematic viscosity of acetone at 25°C?
- Water is ordinarily used as a standard for viscosity of liquids. Its viscosity at 25°C is 0.8904 cp. What is the viscosity of acetone relative to that of water (relative viscosity, ν_{rel}) at 25°C?

Solutions:

- Kinematic viscosity = 0.313 cp ÷ 0.788 g/cm³ = 0.397 poise/(g/cm³), or 0.397 cs.

b. $\text{rel(acetone)} = 0.313 \text{ cp}/0.8904 \text{ cp} = 0.352$ (dimensionless).

Table 19-2 Viscosity of Glycerin at Several Temperatures*

Temperature (°C)	-42	-20	0	6	15	20	25	30
Temperature (K)	231	253	273	279	288	293	298	303
1/T (K ⁻¹)	0.00432	0.00395	0.00366	0.00358	0.00347	0.00341	0.00336	0.00333
(cp)	6.71 × 10 ⁶	1.34 × 10 ⁵	1210	6260	2330	1490	954	629
ln	15.719	11.806	9.402	8.742	7.754	7.307	6.861	6.444

*Data from *CRC Handbook of Chemistry and Physics*, 63rd Ed., CRC Press, Boca Raton, Fla., 1982, p. F-44.

Temperature Dependence and the Theory of Viscosity

Whereas the viscosity of a gas increases with temperature, that of a liquid decreases as temperature is raised, and the fluidity of a liquid (the reciprocal of viscosity) increases with temperature. The dependence of the viscosity of a liquid on temperature is expressed approximately for many substances by an equation analogous to the Arrhenius equation of chemical kinetics:

$$\eta = Ae^{E_v/RT} \quad (19-5)$$

where A is a constant depending on the molecular weight and molar volume of the liquid and E_v is an "activation energy" required to initiate flow between molecules.

The energy of vaporization of a liquid is the energy required to remove a molecule from the liquid, leaving a "hole" behind equal in size to that of the molecule that has departed. A hole must also be made available in a liquid if one molecule is to flow past another. The activation energy for flow has been found to be about one-third that of the energy of vaporization, and it can be concluded that the free space needed for flow is about one-third the volume of a molecule. This is presumably because a molecule in flow can back, turn, and maneuver in a space smaller than its actual size, like a car in a crowded parking lot. More energy is required to break bonds and permit flow in liquids composed of molecules that are associated through hydrogen bonds. These bonds are broken at higher temperatures by thermal movement, however, and E_v decreases markedly. Diffusional phenomena (Chapter 12) exhibit a similar dependence on temperature; like fluidity (the reciprocal of viscosity), rates of diffusion increase exponentially with temperature.

Example 19-2

Temperature Dependence of Viscosity

The modified Arrhenius equation (19-5) is used to obtain the dependence of viscosity of liquids on temperature. Use equation (19-5) and the viscosity versus temperature data for glycerin (Table 19-2) to obtain the constant A and E_v (activation energy to initiate flow). What is the value of r^2 , the square of the correlation coefficient?

Equation (19-5) is written in logarithmic form

$$\ln \eta = \ln A + \frac{E_v}{R} \frac{1}{T} \quad (19-6)$$

According to equation (19-6), a regression of $\ln \eta$ against $1/T$ gives E_v from the slope and $\ln A$ from the intercept. Using the values given in Table 19-2, we obtain

$$\ln \eta = -23.4706 + 9012 \frac{1}{T}$$

Slope = 9012 = E_v/R ; $E_v = 9012 \times 1.9872 = 17,909$ cal/mole
Intercept = -23.4706 = $\ln A$; $A = 6.40985 \times 10^{-11}$; $r^2 = 0.997$

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Non-Newtonian Systems

The majority of fluid pharmaceutical products are not simple liquids and do not follow Newton's law of flow. These systems are referred to as *non-Newtonian*. Non-Newtonian behavior is generally exhibited by liquid and solid heterogeneous dispersions such as colloidal solutions, emulsions, liquid suspensions, and ointments. When non-Newtonian materials are analyzed in a rotational viscometer and results are plotted, various consistency curves, representing three classes of flow, are recognized: *plastic*, *pseudoplastic*, and *dilatant*.

Plastic Flow

In Figure 19-2b, the curve represents a body that exhibits plastic flow; such materials are known as *Bingham bodies* in honor of the pioneer of modern rheology and the first investigator to study plastic substances in a systematic manner.

Plastic flow curves do not pass through the origin but rather intersect the shearing stress axis (or will if the straight part of the curve is extrapolated to the axis) at a particular point referred to as the *yield value*. A Bingham body does not begin to flow until a shearing stress corresponding to the yield value is exceeded. At stresses below the yield value, the substance acts as an elastic material. The rheologist classifies Bingham bodies, that is, those substances that exhibit a yield value, as solids, whereas substances that begin to flow at the smallest shearing stress and show no yield value are defined as liquids. Yield value is an important property of certain dispersions.

The slope of the rheogram in Figure 19-2b is termed the *mobility*, analogous to fluidity in Newtonian systems, and its reciprocal is known as the *plastic viscosity*, U . The equation describing plastic flow is

$$U = \frac{F - f}{G} \quad (19-7)$$

where f is the yield value, or intercept, on the shear stress axis in dynes/cm², and F and G are as previously defined.

Plastic flow is associated with the presence of flocculated particles in concentrated suspensions. As a result, a continuous structure is set up throughout the system. A yield value exists because of the contacts between adjacent particles (brought about by van der Waals forces), which must be broken down before flow can occur. Consequently, the yield value is an indication of force of flocculation: The more flocculated the suspension, the higher will be the yield value. Frictional forces between moving particles can also contribute to yield value. As shown in the following example, once the yield value has been exceeded, any further increase in shearing stress (i.e., $F - f$) brings about a directly proportional increase in G , rate of shear. In effect, a plastic system resembles a Newtonian system at shear stresses above the yield value.

Example 19-3

Calculating Plastic Viscosity

A plastic material was found to have a yield value of 5200 dynes/cm². At shearing stresses above the yield value, F was found to increase linearly with G . If the rate of shear was 150 sec⁻¹ when F was 8000 dynes/cm², calculate U , the plastic viscosity of the sample.

Substituting into equation (19-7), we find

$$\begin{aligned}U &= (8000 - 5200)/150 \\ &= 2800/150 \\ &= 18.67 \text{ poise}\end{aligned}$$

Pseudoplastic Flow

Many pharmaceutical products, including liquid dispersions of natural and synthetic gums (e.g., tragacanth, sodium alginate, methylcellulose, and sodium carboxymethyl cellulose) exhibit *pseudoplastic flow*. Pseudoplastic flow is typically exhibited by polymers in solution, in contrast to plastic systems, which are composed of flocculated particles in suspension. As seen in Figure 19-2c, the consistency curve for a pseudoplastic material begins at the origin (or at least approaches it at low rates of shear). Therefore, there is no yield value as there is in a plastic system. Furthermore, because no part of the curve is linear, the viscosity of a pseudoplastic material cannot be expressed by any single value. The viscosity of a pseudoplastic substance decreases with increasing rate of shear. An apparent viscosity can be obtained at any rate of shear from the slope of the tangent to the curve at the specified point. The most satisfactory representation for a pseudoplastic material, however, is probably a graphic plot of the entire consistency curve.

The curved rheogram for pseudoplastic materials results from a shearing action on long-chain molecules of materials such as linear polymers. As shearing stress is increased, normally disarranged molecules begin to align their long axes in the direction of flow. This orientation reduces internal resistance of the material and allows a greater rate of shear at each successive shearing stress. In addition, some of the solvent associated with the molecules may be released, resulting in an effective lowering of both the concentration and the size of the dispersed molecules. This, too, will decrease apparent viscosity.

Objective comparisons between different pseudoplastic systems are more difficult than with either Newtonian or plastic systems. For example, Newtonian systems are completely described by viscosity, η , and plastic systems are adequately described by yield value, f , and plastic viscosity, U . However, several approaches have been used to obtain meaningful parameters that will allow different pseudoplastic materials

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to be compared. Of those discussed by Martin et al.,³ the exponential formula

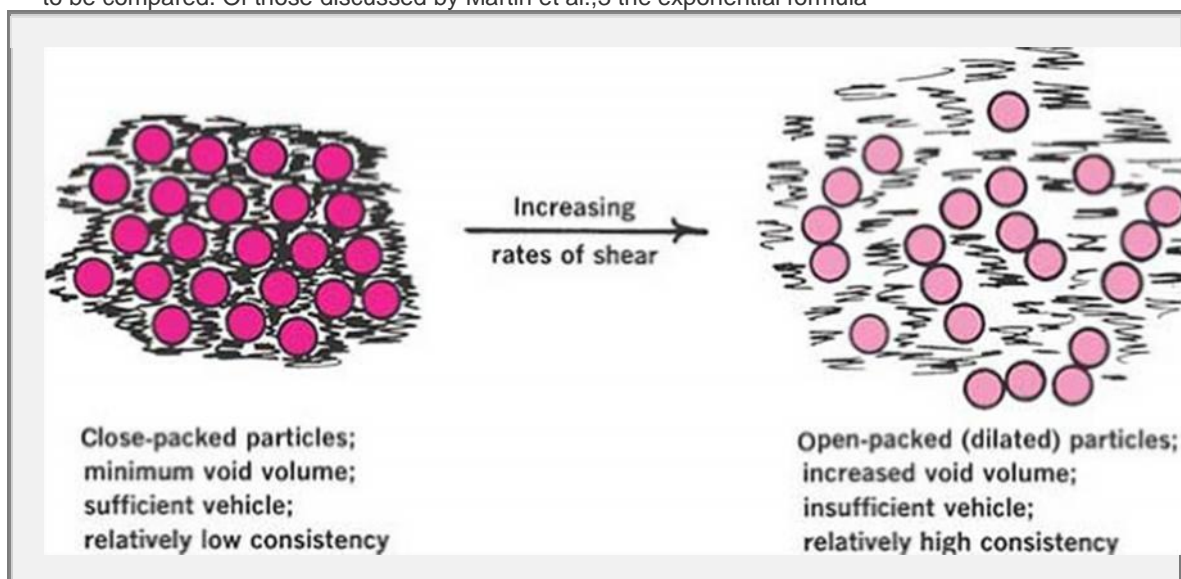


Fig. 19-3. Explanation of dilatant flow behavior.

$$F^N = \eta' G \quad (19-8)$$

has been used most frequently for pseudoplastics. The exponent N rises as flow becomes increasingly non-Newtonian. When $N = 1$, equation (19-8) reduces to equation (19-2) and flow is Newtonian. The term η' is a viscosity coefficient. Following rearrangement, we can write equation (19-8) in the logarithmic form

$$\log G = N \log F - \log \eta' \quad (19-9)$$

This is an equation for a straight line. Many pseudoplastic systems fit this equation when $\log G$ is plotted as a function of $\log F$.⁴ Several of the more important pseudoplastic suspending agents used in pharmacy, however, do not conform to equation (19-9).⁵ Modified equations were suggested by Shangraw et al. and Casson and Patton.⁶ Pseudoplastic systems have been characterized on the basis of the assumption that the typical rheogram of a pseudoplastic substance is composed of a first-order segment and a zero-order segment.⁷

Dilatant Flow

Certain suspensions with a high percentage of dispersed solids exhibit an increase in resistance to flow with increasing rates of shear. Such systems actually increase in volume when sheared and are hence termed *dilatant*; Figure 19-2d illustrates their flow properties. This type of flow is the inverse of that possessed by pseudoplastic systems. Whereas pseudoplastic materials are frequently referred to as "shear-thinning systems," dilatant materials are often termed "shear-thickening systems." When stress is removed, a dilatant system returns to its original state of fluidity.

Equation (19-8) can be used to describe dilatancy in quantitative terms. In this case, N is always less than 1 and decreases as degree of dilatancy increases. As N approaches 1, the system becomes increasingly Newtonian in behavior.

Substances possessing dilatant flow properties are invariably suspensions containing a high concentration (about 50% or greater) of small, deflocculated particles. As discussed previously, particulate systems of this type that are flocculated would be expected to possess plastic, rather than dilatant, flow characteristics. Dilatant behavior can be explained as follows. At rest, particles are closely packed with minimal interparticle volume (voids). The amount of vehicle in the suspension is sufficient, however, to fill voids and permits particles to move relative to one another at low rates of shear. Thus, a dilatant suspension can be poured from a bottle because under these conditions it is reasonably fluid. As shear stress is increased, the bulk of the system expands or dilates; hence the term *dilatant*. The particles, in an attempt to move quickly past each other, take on an open form of packing, as depicted in Figure 19-3. Such an arrangement leads to a significant increase in interparticle void volume. The amount of vehicle remains constant and, at some point, becomes insufficient to fill the increased voids between particles. Accordingly, resistance to flow increases because particles are no longer completely wetted, or lubricated, by the vehicle. Eventually, the suspension will set up as a firm paste.

Behavior of this type suggests that appropriate precaution be used during processing of dilatant materials. Conventionally, processing of dispersions containing solid particles is facilitated by the use of high-speed mixers, blenders, or mills. Although this is advantageous with all other rheologic systems, dilatant materials may solidify under these conditions of high shear, thereby overloading and damaging processing equipment.

Thixotropy

As described in the previous sections, several types of behavior are observed when rate of shear is progressively increased and plotted against resulting shear stress. It may have been assumed that if the rate of shear were reduced once the desired maximum had been reached, the downcurve would be identical with, and superimposable on, the upcurve. Although this is true for Newtonian systems, the downcurve for non-Newtonian systems can be displaced relative to the upcurve. With shear-thinning systems (i.e., pseudoplastic), the downcurve is frequently displaced to the left of the upcurve

(as in Fig. 19-4), showing that the material has a lower consistency at any one rate of shear on the downcurve than it had on the upcurve. This indicates a breakdown of structure (and hence shear thinning) that does not reform immediately when stress is removed or reduced. This phenomenon, known as *thixotropy*, can be defined as “an isothermal and comparatively slow recovery, on standing of a material, of a consistency lost through shearing.” As so defined, thixotropy can be applied only to shear-thinning systems. Typical rheograms for plastic and pseudoplastic systems exhibiting this behavior are shown in Figure 19-4.

Key Concept

Rheograms

A *rheogram* is a plot of *shear rate*, G , as a function of *shear stress*, F . Rheograms are also known as consistency curves or flow curves. The rheologic properties of a given material are most completely described by its unique rheogram.

The simplest form of a rheogram is produced by Newtonian systems, which follow the equation for a straight line passing through the origin:

$$G = fF$$

The slope, f , is known as *fluidity* and is the reciprocal of *viscosity*, η :

$$f = 1/\eta$$

Therefore, the greater the slope of the line, the greater is the fluidity or, conversely, the lower is the viscosity. The rheogram of Newtonian systems can easily be obtained with a single-point determination.

Plasticity is the simplest type of non-Newtonian behavior in which the curve is linear only at values of F , beyond its yield value. If the curve is nonlinear throughout the entire range of F values tested, then the system is non-Newtonian and either *pseudoplastic* (shear thinning; slope increases with F) or *dilatant* (shear thickening; slope decreases with F) or a combination of the two. If the curve shows a hysteresis loop, that is, the curve obtained on increasing shear stress is not superimposable with that obtained on decreasing shear stress, then the system is *thixotropic*.

A non-Newtonian system can only be fully characterized by generating its complete rheogram, which requires use of a multipoint rheometer.

Thixotropic systems usually contain asymmetric particles that, through numerous points of contact, set up a loose three-dimensional network throughout the sample. At rest, this structure confers some degree of rigidity on the system, and it resembles a gel. As shear is applied and flow starts, this structure begins to break down as points of contact are disrupted and particles become aligned. The material undergoes a gel-to-sol transformation and exhibits shear thinning. On removal of stress, the structure starts to reform. This process is not instantaneous; rather, it is a progressive restoration of consistency as asymmetric particles come into contact with one another by undergoing random Brownian movement. Rheograms obtained with thixotropic materials are therefore highly dependent on the rate at which shear is increased or decreased and the length of time a sample is subjected to any one rate of shear. In other words, the previous history of the sample has a significant effect on the rheologic properties of a thixotropic system. For example, suppose that in Figure 19-5 the shear rate of a thixotropic material is increased in a constant manner from point a to point b and is then decreased at the same rate back to e . Typically, this would result in the so-called *hysteresis loop* abe . If, however, the sample was taken to point b and the shear rate held constant for a certain period of time (say, t_1 seconds), shearing stress, and hence consistency, would decrease to an extent depending on time of shear, rate of shear, and degree of structure in the sample. Decreasing the shear rate would then result in the *hysteresis loop* $abcde$. If the sample had been held at the same rate of shear for t_2 seconds, the loop $abcde$ would

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have been observed. Therefore, the rheogram of a thixotropic material is not unique but will depend on

rheologic history of the sample and approach used in obtaining the rheogram. This is an important point to bear in mind when attempting to obtain a quantitative measure of thixotropy. This will become apparent in the next section.

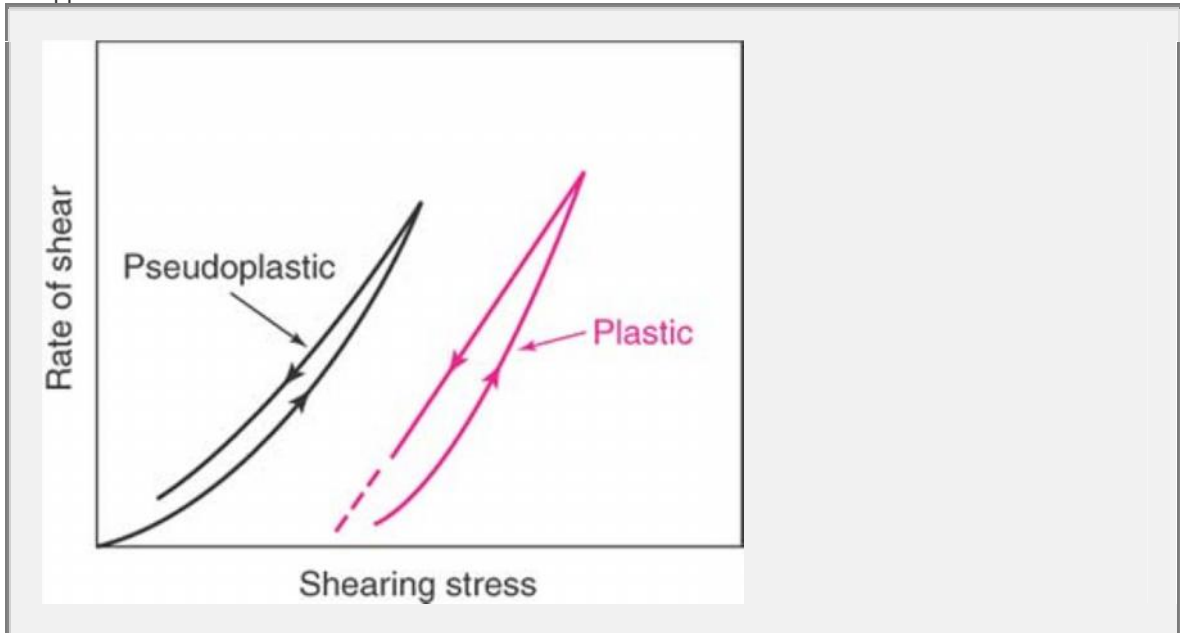


Fig. 19-4. Thixotropy in plastic and pseudoplastic flow systems.

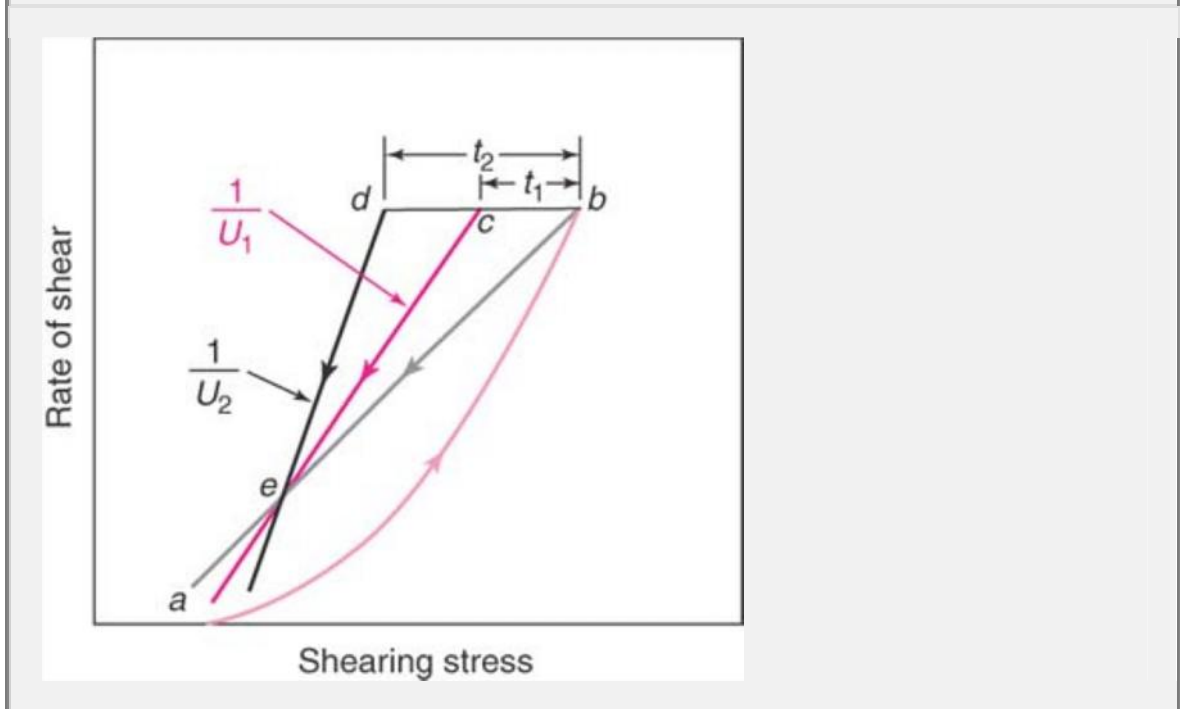


Fig. 19-5. Structural breakdown with time of a plastic system possessing thixotropy when subjected to a constant rate of shear for t_1 and t_2 seconds. See text for discussion.

Measurement of Thixotropy

A quantitative measurement of thixotropy can be attempted in several ways. The most apparent characteristic of a thixotropic system is the hysteresis loop formed by the upcurves and downcurves of

the rheogram. This *area of hysteresis* has been proposed as a measure of thixotropic breakdown; it can be obtained readily by means of a planimeter or other suitable technique.

With plastic (Bingham) bodies, two approaches are frequently used to estimate degree of thixotropy.

The first is to determine structural breakdown with time at a *constant* rate of shear. The type of rheogram needed for this estimation is shown in Figure 19-5; the steps necessary to obtain it have already been described. Based on such a rheogram, a thixotropic coefficient, B , the rate of breakdown with time at constant shear rate, is calculated as follows:

$$B = \frac{U_1 - U_2}{\ln \frac{t_2}{t_1}} \quad (19-10)$$

where U_1 and U_2 are the plastic viscosities of the two downcurves, calculated from equation (19-7), after shearing at a constant rate for t_1 and t_2 seconds, respectively. The choice of shear rate is arbitrary. A more meaningful, though time-consuming, method for characterizing thixotropic behavior is to measure fall in stress with time at several rates of shear.

The second approach is to determine the structural breakdown due to *increasing* shear rate. The principle involved in this approach is shown in Figure 19-6, in which two hysteresis loops are obtained having different maximum rates of shear, v_1 and v_2 . In this case, a thixotropic coefficient, M , the loss in shearing stress per unit increase in shear rate, is obtained from

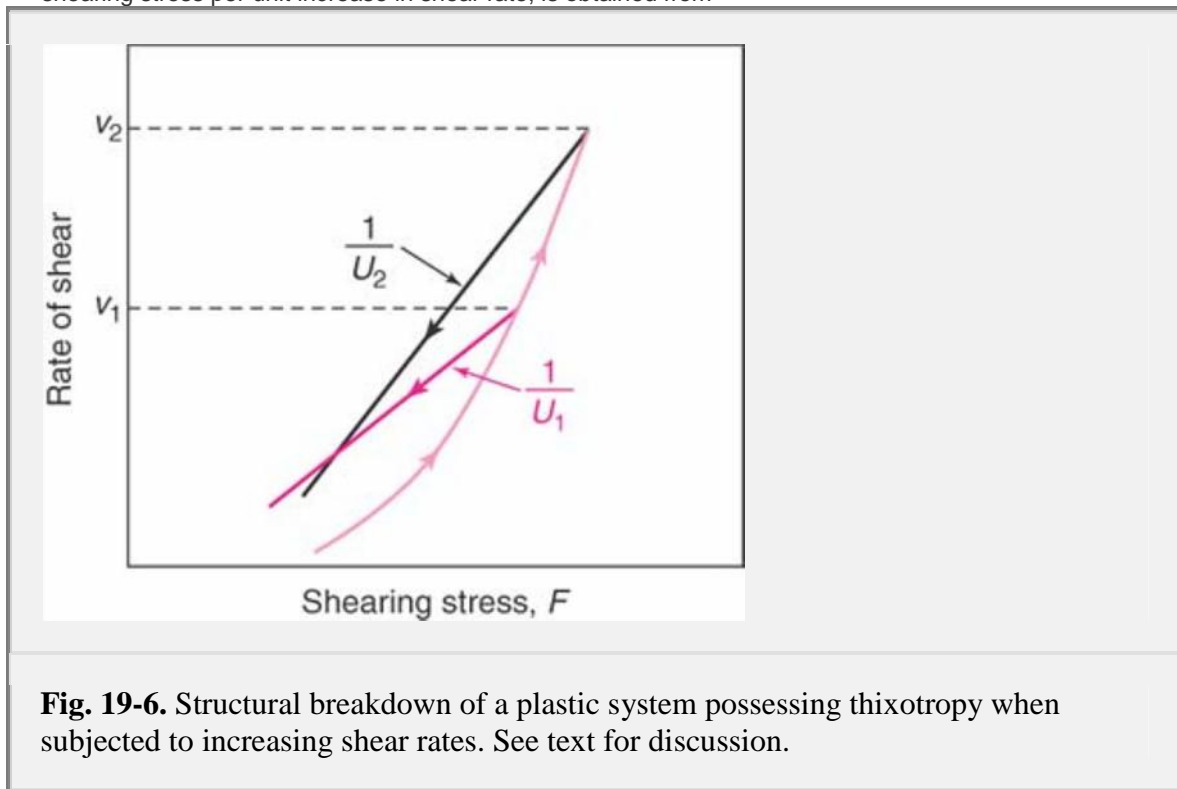


Fig. 19-6. Structural breakdown of a plastic system possessing thixotropy when subjected to increasing shear rates. See text for discussion.

$$M = \frac{U_1 - U_2}{\ln(v_2/v_1)} \quad (19-11)$$

where M is in dynes sec/cm² and U_1 and U_2 are the plastic viscosities for two separate downcurves having maximum shearing rates of v_1 and v_2 , respectively. A criticism of this technique is that the two rates of shear, v_1 and v_2 , are chosen arbitrarily; the value of M will depend on the rate of shear chosen because these shear rates will affect the downcurves and hence the values of U that are calculated.

Bulges and Spurs

Dispersions employed in pharmacy may yield complex hysteresis loops when sheared in a viscometer in which shear rate (rather than shear stress) is increased to a point, then decreased, and the shear stress is read at each shear rate value to yield appropriate rheograms. Two such complex structures are shown in Figures 19-7 and 19-8. A concentrated aqueous bentonite gel, 10% to 15% by weight,

produces a hysteresis loop with a characteristic *bulge* in the upcurve. It is presumed that the crystalline plates of bentonite form a “house-of-cards structure” that causes the swelling of bentonite magmas. This three-dimensional structure results in a bulged hysteresis loop as observed in Figure 19-7. In still more highly structured systems, such as a procaine penicillin gel formulated by Ober et al.9 for intramuscular injection, the bulged curve may actually develop into a spurlike protrusion (Fig. 19-8). The structure demonstrates a high yield or *spur value*, that traces out a bowed upcurve when the three-dimensional structure breaks in the viscometer, as observed in Figure 19-8. The spur value represents a sharp point of structural breakdown at low shear rate. It is difficult to produce the spur, and it may not be observed unless a sample of the gel is allowed to age undisturbed in the cup-and-bob assembly for some time before the rheologic run is made. The

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spur value is obtained by using an instrument in which the rate of shear can be slowly and uniformly increased, preferably automatically, and the shear stress read out or plotted on an X-Y recorder as a function of shear rate. Ober et al.9 found that penicillin gels having definite values were very thixotropic, forming intramuscular depots upon injection that afforded prolonged blood levels of the drug.

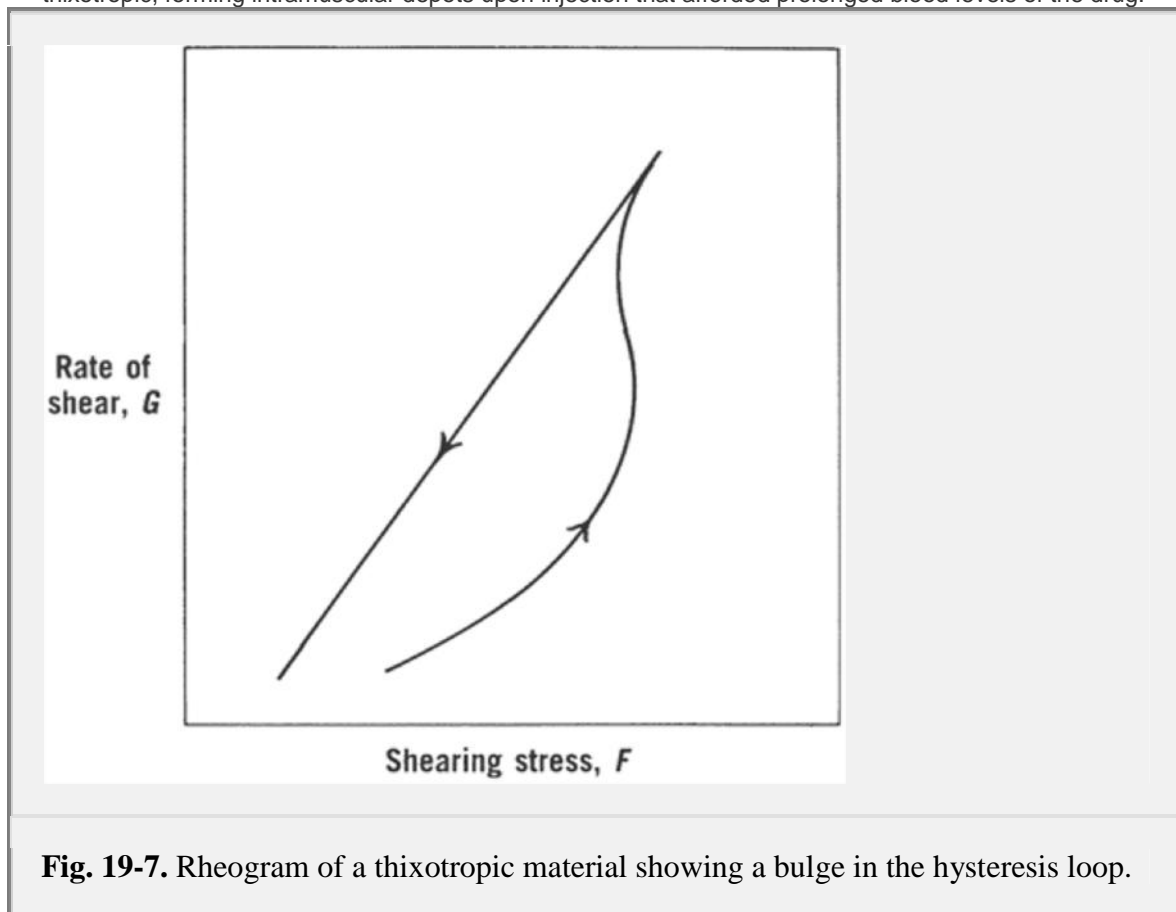


Fig. 19-7. Rheogram of a thixotropic material showing a bulge in the hysteresis loop.

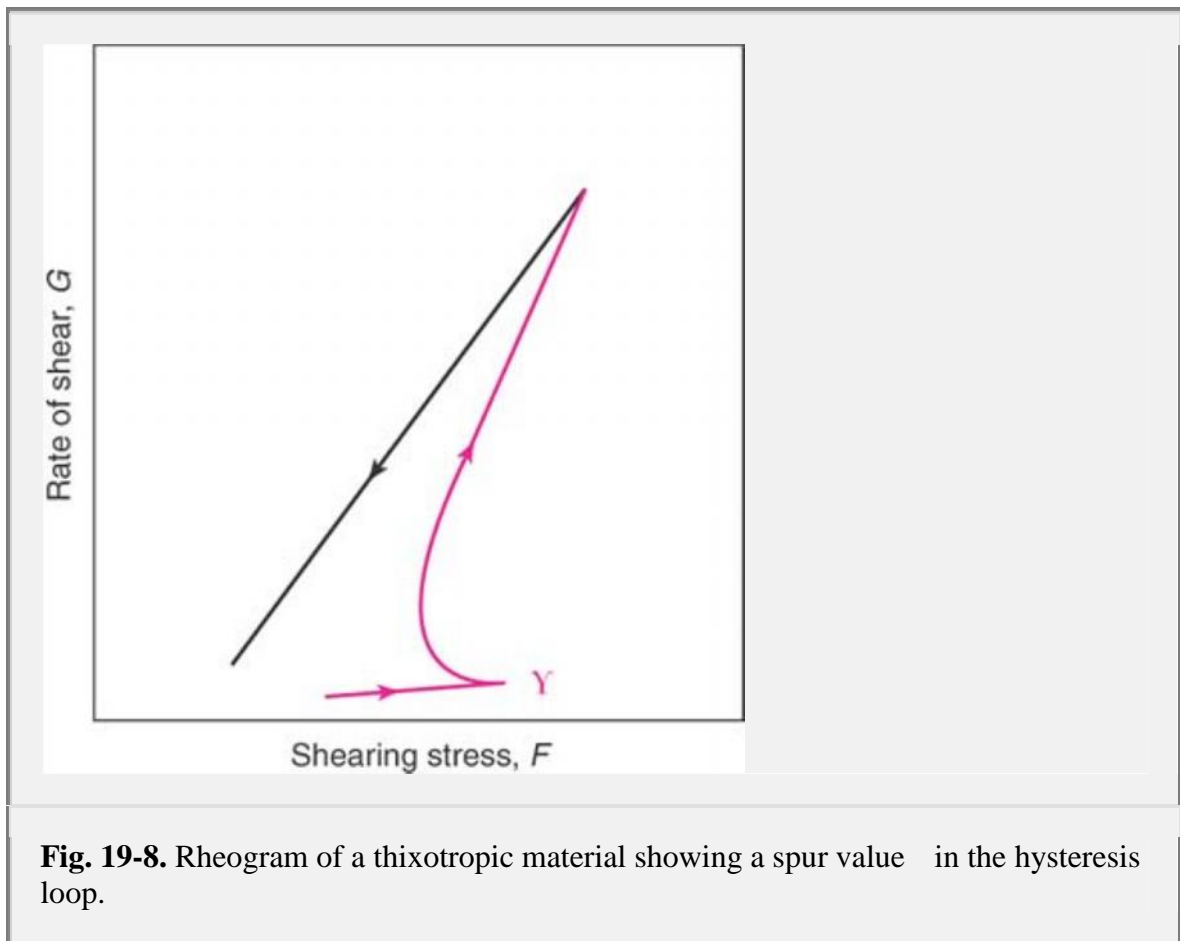


Fig. 19-8. Rheogram of a thixotropic material showing a spur value in the hysteresis loop.

Negative Thixotropy

From time to time in the measurement of supposedly thixotropic materials, one observes a phenomenon called *negative thixotropy* or *antithixotropy*, which represents an increase rather than a decrease in consistency on the downcurve. This increase in thickness or resistance to flow with increased time of shear was observed by Chong et al.¹⁰ in the rheologic analysis of magnesia magma. It was detected at shear rates of greater than 30 sec^{-1} ; below 30 sec^{-1} the magma showed normal thixotropy, the downcurve appearing to the left of the upcurve. As pointed out by Chong et al., antithixotropy had been reported by other investigators but not in pharmaceutical systems.

It was observed that when magnesia magma was alternately sheared at increasing and then at decreasing rates of shear, the magma continuously thickened (an increase in shearing stress per unit shear rate) but at a decreasing rate, and it finally reached an equilibrium state in which further cycles of increasing–decreasing shear rates no longer increased the consistency of the material. The antithixotropic character of magnesia magma is demonstrated in Figure 19-9. The equilibrium system was found to be gel-like and to provide great suspendability, yet it was readily pourable. When allowed to stand, however, the material returned to its sol-like properties.

Antithixotropy or negative thixotropy should not be confused with dilatancy or rheopexy. Dilatant systems are deflocculated and ordinarily contain greater than 50% by volume of solid dispersed phase, whereas antithixotropic systems have low solids content (1%–10%) and are flocculated, according to Samyn and Jung.¹¹ *Rheopexy* is a phenomenon in which a solid forms a gel more readily when gently shaken or otherwise sheared than when allowed to form the gel while the material is kept at rest.¹² In a rheopexic system, the gel is the equilibrium form, whereas in antithixotropy, the equilibrium state is the sol. Samyn and Jung noted that magnesia magma and clay suspensions may show a negative rheopexy, analogous to negative thixotropy. It is believed that antithixotropy results from an increased collision frequency of dispersed particles or polymer molecules in suspension, resulting in increased interparticle bonding with time. This changes an original state consisting of a large number of individual

particles and small floccules to an eventual equilibrium state consisting of a small number of relatively large floccules. At rest, the large floccules break up and gradually return to the original state of small floccules and individual particles.

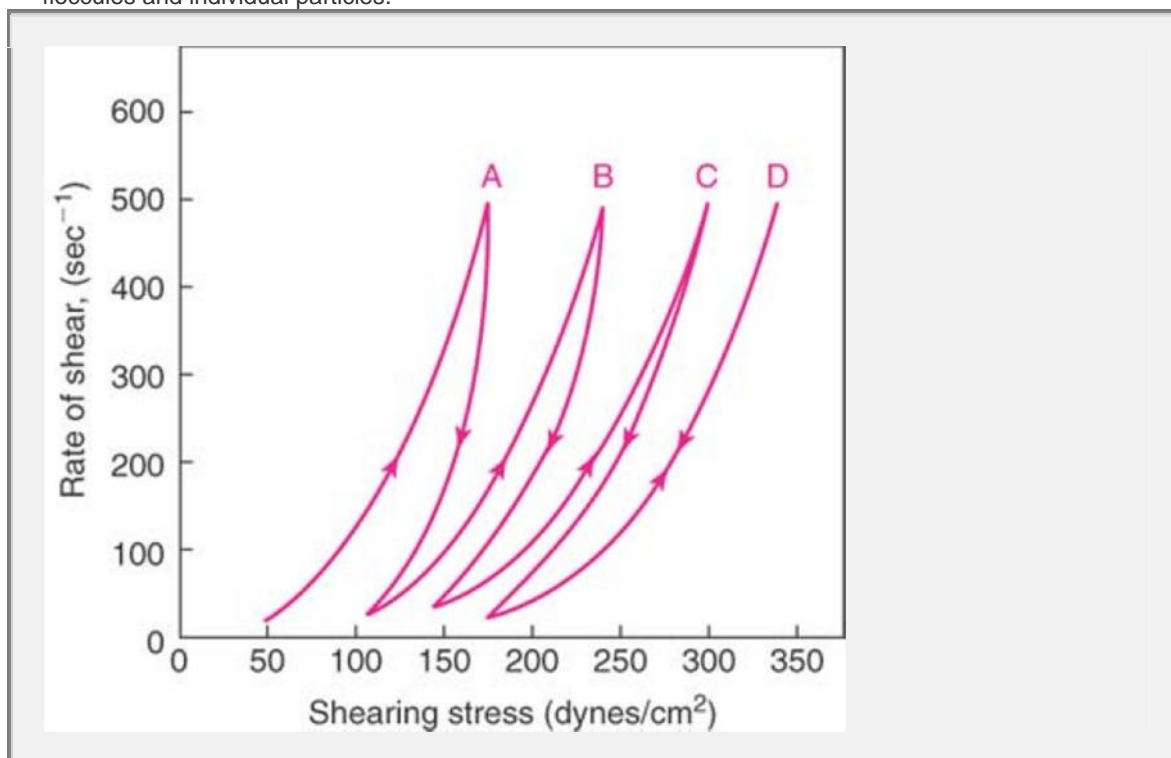


Fig. 19-9. Rheogram of magnesia magma showing antithixotropic behavior. The material is sheared at repeated increasing and then decreasing rates of shear. At stage *D*, further cycling no longer increased the consistency, and the upcurves and downcurves coincided. (From C. W. Chong, S. P. Eriksen, and J. W. Swintosky, *J. Am. Pharm. Assoc. Sci. Ed.* **49**, 547, 1960. With permission.)

As more rheologic studies are done with pharmaceuticals, negative thixotropy no doubt will be observed in other materials.

Thixotropy in Formulation

Thixotropy is a desirable property in liquid pharmaceutical systems that ideally should have a high consistency in the container, yet pour or spread easily. For example, a well-formulated thixotropic suspension will not settle out readily in the container, will become fluid on shaking, and will remain long enough for a dose to be dispensed. Finally, it will regain consistency rapidly enough so as to maintain the particles in a suspended state. A similar pattern of behavior is desirable with emulsions, lotions, creams, ointments, and parenteral suspensions to be used for intramuscular depot therapy.

With regard to suspension stability, there is a relationship between degree of thixotropy and rate of sedimentation;

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the greater the thixotropy, the lower the rate of settling. Concentrated parenteral suspensions containing from 40% to 70% w/v of procaine penicillin G in water were found to have a high inherent thixotropy and were shear thinning.⁹ Consequently, breakdown of the structure occurred when the suspension was caused to pass through the hypodermic needle. Consistency was then recovered as rheologic structure reformed. This led to formation of a depot of drug at the site of intramuscular injection where drug was slowly removed and made available to the body. The degree of thixotropy was related to the specific surface of the penicillin used.

Degree of thixotropy may change over time and result in an inadequate formulation. Thixotropic systems are complex, and it is unrealistic to expect that rheologic changes can be meaningfully followed by the use of one parameter. Thus, in a study concerned with the aging effects of thixotropic clay, Levy¹³ found it necessary to follow changes in plastic viscosity, area of hysteresis, yield value, and spur value.

Determination of Rheologic Properties

Choice of Viscometer

Successful determination and evaluation of rheologic properties of any particular system depend, in large part, on choosing the correct instrumental method. Because shear rate in a Newtonian system is directly proportional to shearing stress, instruments that operate at a single shear rate can be used. These "single-point" instruments provide a single point on the rheogram; extrapolation of a line through this point to the origin will result in a complete rheogram. Implicit in the use of a single-point instrument is prior knowledge that the flow characteristics of the material are Newtonian. Unfortunately, this is not always the case, and, if the system is non-Newtonian, a single-point determination is virtually useless in characterizing its flow properties. It is therefore essential that, with non-Newtonian systems, the instrument can operate at a variety of shear rates. Such multipoint instruments are capable of producing a complete rheogram for non-Newtonian systems. For example, multipoint evaluation of pseudoplastic materials would allow assessment of viscosity of a suspending agent at rest (negligible shear rate), while being agitated, poured from a bottle, or applied to the skin (moderately high shear rate). Single-point instruments are unable to describe these changes. As illustrated in Figure 19-10, single-point instruments can lead to erroneous results if used to evaluate non-Newtonian systems because flow properties could vary significantly despite identical measured viscosities. Even multipoint instruments, unless properly designed, will not give satisfactory results.

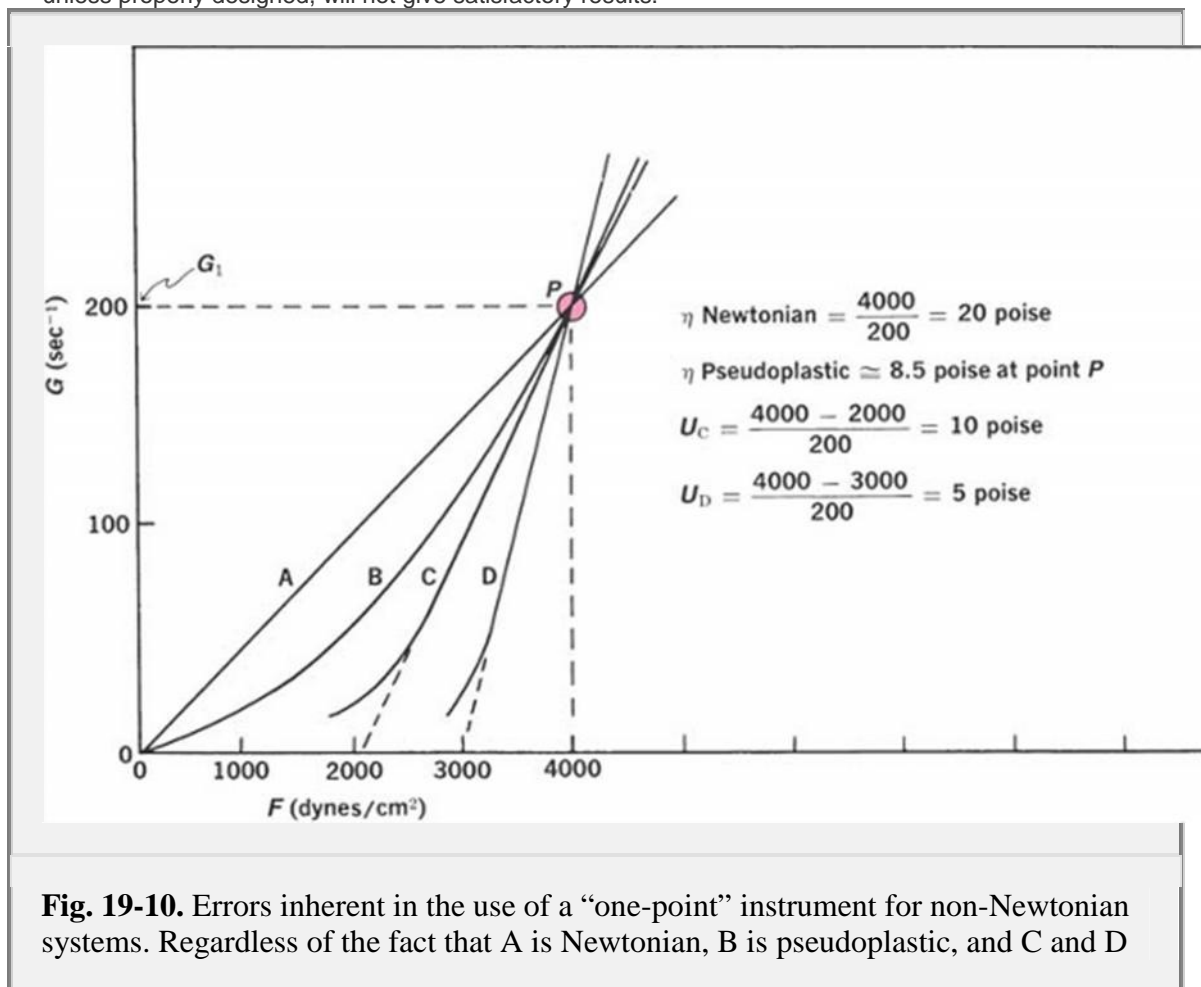


Fig. 19-10. Errors inherent in the use of a "one-point" instrument for non-Newtonian systems. Regardless of the fact that A is Newtonian, B is pseudoplastic, and C and D

are two different plastic systems, a “one-point” instrument could indicate a common viscosity of 20 poise ($F = 4000 \text{ dynes/cm}^2$ and $G = 200 \text{ sec}^{-1}$). Use of a “one-point” instrument is proper only in the case of the Newtonian systems. (From A. Martin, G. S. Banker, and A. H. C. Chun, in H. S. Bean, A. H. Beckett, and J. E. Carless (Eds.), *Advances in Pharmaceutical Sciences*, Academic Press, London, 1964, Chapter 1. With permission.)

The important conclusion, therefore, is that although all viscometers can be used to determine viscosity of Newtonian

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systems, only those with variable–shear-rate controls can be used for non-Newtonian materials. Many types of viscometers have been discussed in detail.^{3·14·15·16} This discussion will be limited to four instruments: capillary, falling-sphere, cup-and-bob, and cone-and-plate viscometers. The first two are single–shear-rate instruments suitable for use only with Newtonian materials, whereas the latter two (multipoint, rotational instruments) can be used with both Newtonian and non-Newtonian systems. Other rheologic properties such as tackiness or stickiness, “body,” “slip,” and “spreadability” are difficult to measure by means of conventional apparatus and, in fact, do not have precise meanings. However, the individual factors—viscosity, yield value, thixotropy, and the other properties that contribute to the total consistency of non-Newtonian pharmaceuticals—can be analyzed to some degree of satisfaction in reliable apparatus. An attempt must be made to express these properties in meaningful terms if rheology is to aid in the development, production, and control of pharmaceutical preparations.

Capillary Viscometer

The viscosity of a Newtonian liquid can be determined by measuring the time required for the liquid to pass between two marks as it flows by gravity through a vertical capillary tube known as an *Ostwald viscometer*. A modern adaptation of the original Ostwald viscometer is shown in Figure 19-11. The time of flow of the liquid under test is compared with the time required for a liquid of known viscosity (usually water) to pass between the two marks. If η_1 and η_2 are the viscosities of the unknown and the standard liquids, respectively, ρ_1 and ρ_2 are the respective densities of the liquids, and t_1 and t_2 are the respective flow times in seconds, the absolute viscosity of the unknown liquid, η_1 , is determined by substituting the experimental values in the equation

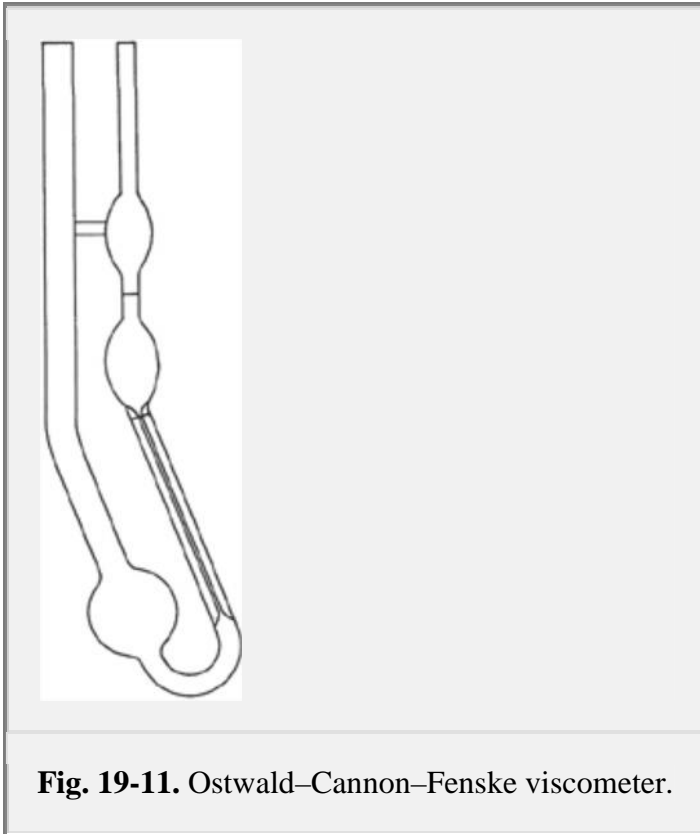


Fig. 19-11. Ostwald–Cannon–Fenske viscometer.

$$\frac{\eta_1}{\eta_2} = \frac{\rho_1 t_1}{\rho_2 t_2} \quad (19-12)$$

The value $t_1/t_2 = \eta_1/\eta_2$ is known as the *relative viscosity* of the liquid under test.

Example 19-4

Viscosity of Acetone

Consider the viscosity measurement of acetone discussed in Example 19-1. Assume that the time required for acetone to flow between the two marks on the capillary viscometer was 45 sec and for water the time was 100 sec, at 25°C. The density of acetone is 0.786 g/cm³ and that of water is 0.997 g/cm³ at 25°C. The viscosity of water is 0.8904 cp at this temperature. The viscosity of acetone at 25°C can be calculated using equation (19-12):

$$\frac{\eta_1}{0.8904} = \frac{0.786 \times 45.0}{0.997 \times 100}$$

$$\eta_1 = 0.316 \text{ cp}$$

Equation (19-12) is based on *Poiseuille's law* for a liquid flowing through a capillary tube,

$$\eta = \frac{\pi r^4 t \Delta P}{8lV} \quad (19-13)$$

where r is the radius of the inside of the capillary, t is the time of flow, P is the pressure head in dyne/cm² under which the liquid flows, l is the length of the capillary, and V is the volume of liquid flowing. Equation (19-12) is obtained from Poiseuille's law, equation (19-13), as follows. The radius, length, and volume of a given capillary viscometer are invariants and can be combined into a constant, K . Equation (19-13) can then be written as

$$\eta = Kt \Delta P \quad (19-14)$$

The pressure head P depends on density of the liquid being measured, the acceleration of gravity, and the difference in heights of liquid levels in the two arms of the viscometer. Acceleration of gravity is a constant, however, and if the levels in the capillary are kept constant for all liquids, these terms can be incorporated in the constant and the viscosities of the unknown and the standard liquids can be written as

$$\eta_1 = K' t_1 \rho_1 \quad (19-15)$$

$$\eta_2 = K' t_2 \rho_2 \quad (19-16)$$

Therefore, when flow periods for two liquids are compared in the same capillary viscometer, the division of (19-15) by (19-16) gives equation (19-12). The *United States Pharmacopeia* suggests a capillary apparatus for determining the viscosity of high-viscosity types of methylcellulose solutions.

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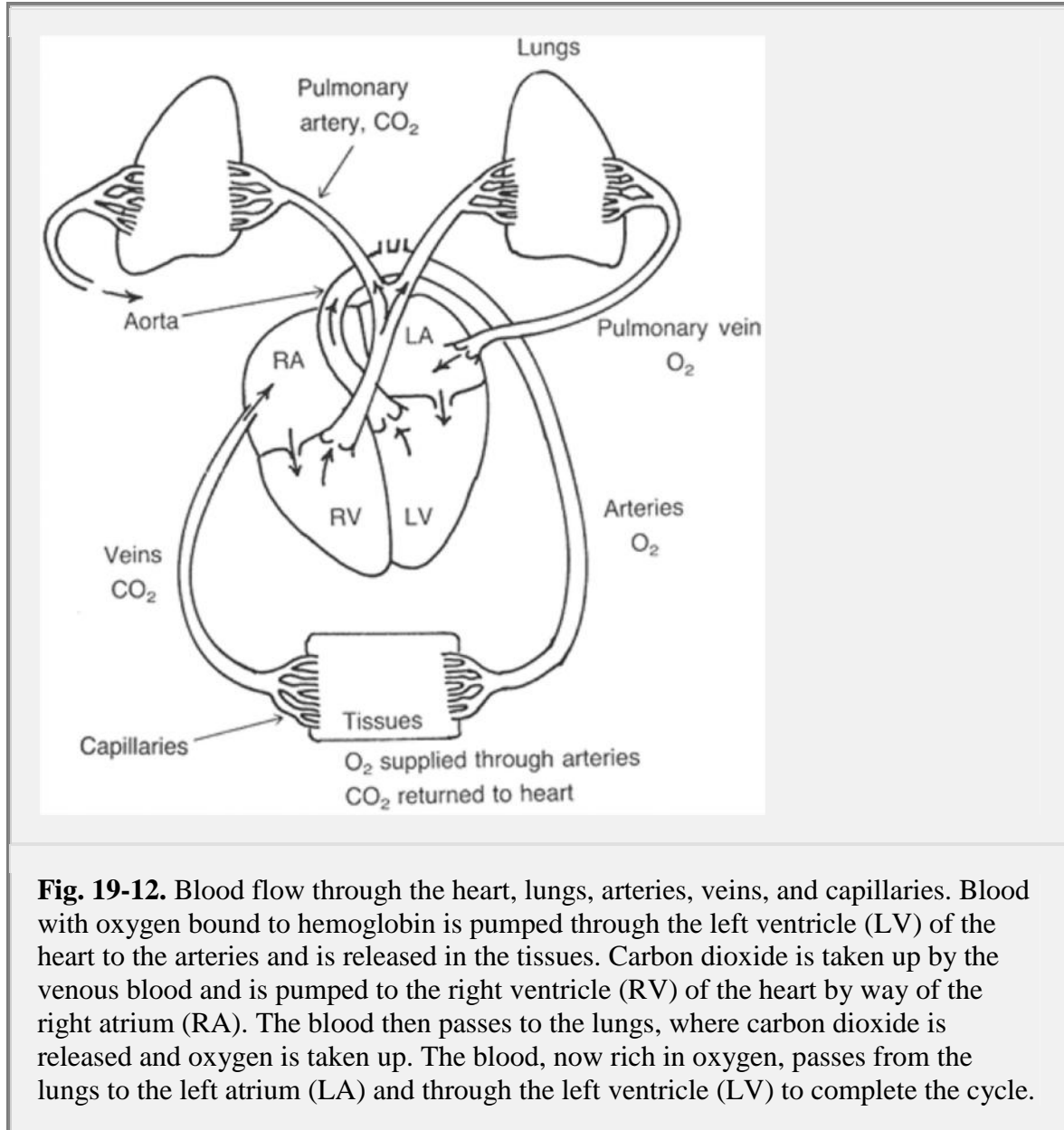


Fig. 19-12. Blood flow through the heart, lungs, arteries, veins, and capillaries. Blood with oxygen bound to hemoglobin is pumped through the left ventricle (LV) of the heart to the arteries and is released in the tissues. Carbon dioxide is taken up by the venous blood and is pumped to the right ventricle (RV) of the heart by way of the right atrium (RA). The blood then passes to the lungs, where carbon dioxide is released and oxygen is taken up. The blood, now rich in oxygen, passes from the lungs to the left atrium (LA) and through the left ventricle (LV) to complete the cycle.

Clinical Correlate: Poiseuille's Law

Poiseuille's law can be used to calculate the pressure difference in the arteries and capillaries: Figure 19-12 depicts blood circulation in the body.¹⁷ The systolic pressure is normally about 120 mm Hg and the diastolic pressure about 80 mm Hg. Therefore, at rest the average blood pressure is about 100 mm Hg.

The Poiseuille equation (19-13) can be written as

$$r = \left(\frac{8\eta l(V/t)}{\pi \Delta P} \right)^{1/4}$$

where the viscosity, η , of the blood at normal body temperature is 4 cp or 0.04 poise = 0.04 dyne sec/cm², and l is the distance, say 1 cm, along an artery. The average rate of blood flow, V/t , at rest is 80 cm³/sec, and the pressure drop, P , over a distance of 1 cm along the artery is 3.8 mm Hg (1 dyne/cm² = 7.5 × 10⁻⁴ mm Hg). The radius, r (cm), of the artery can be calculated as follows:

$$r(\text{cm}) = \left(\frac{8(0.04 \text{ dyne sec/cm}^2)(1 \text{ cm})(80 \text{ cm}^3/\text{sec})}{\pi(3.8 \text{ mm Hg}) \times (1 \text{ dyne cm}^{-2}/7.50 \times 10^{-4} \text{ mm Hg})} \right)^{1/4}$$

The radius is $(0.001608)^{1/4} = 0.200$ cm.

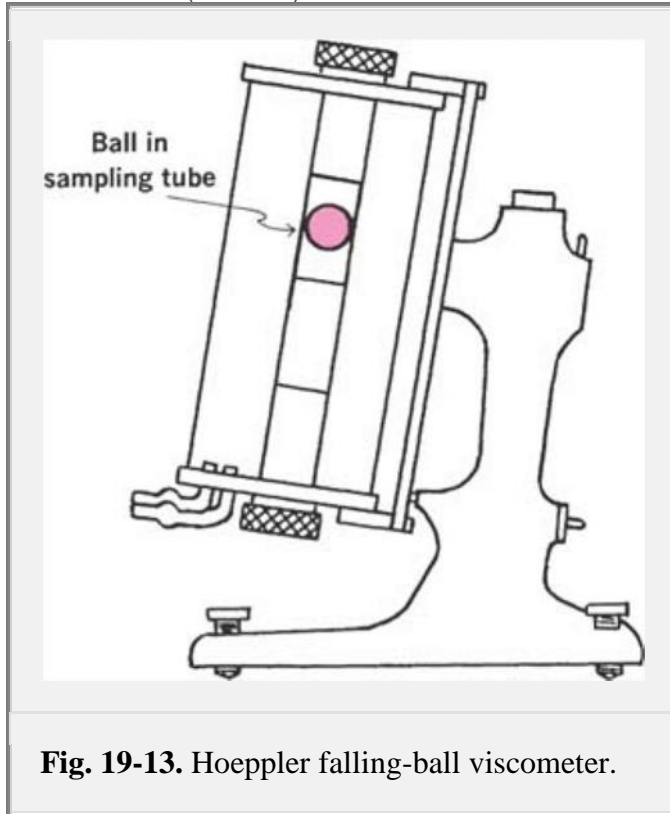


Fig. 19-13. Hoeppler falling-ball viscometer.

Falling-Sphere Viscometer

In this type of viscometer, a glass or steel ball rolls down an almost vertical glass tube containing the test liquid at a known constant temperature. The rate at which a ball of a particular density and diameter falls is an inverse function of the viscosity of the sample. The Hoeppler viscometer, shown in Figure 19-13, is a commercial instrument based on this principle. The sample and ball are placed in the inner glass tube and allowed to reach temperature equilibrium with the water in the surrounding constant-temperature jacket. The tube and jacket are then inverted, which effectively places the ball at the top of the inner glass tube. The time for the ball to fall between two marks is accurately measured and repeated several times. The viscosity of a Newtonian liquid is then calculated from

$$\eta = t(S_b - S_f)B \quad (19-17)$$

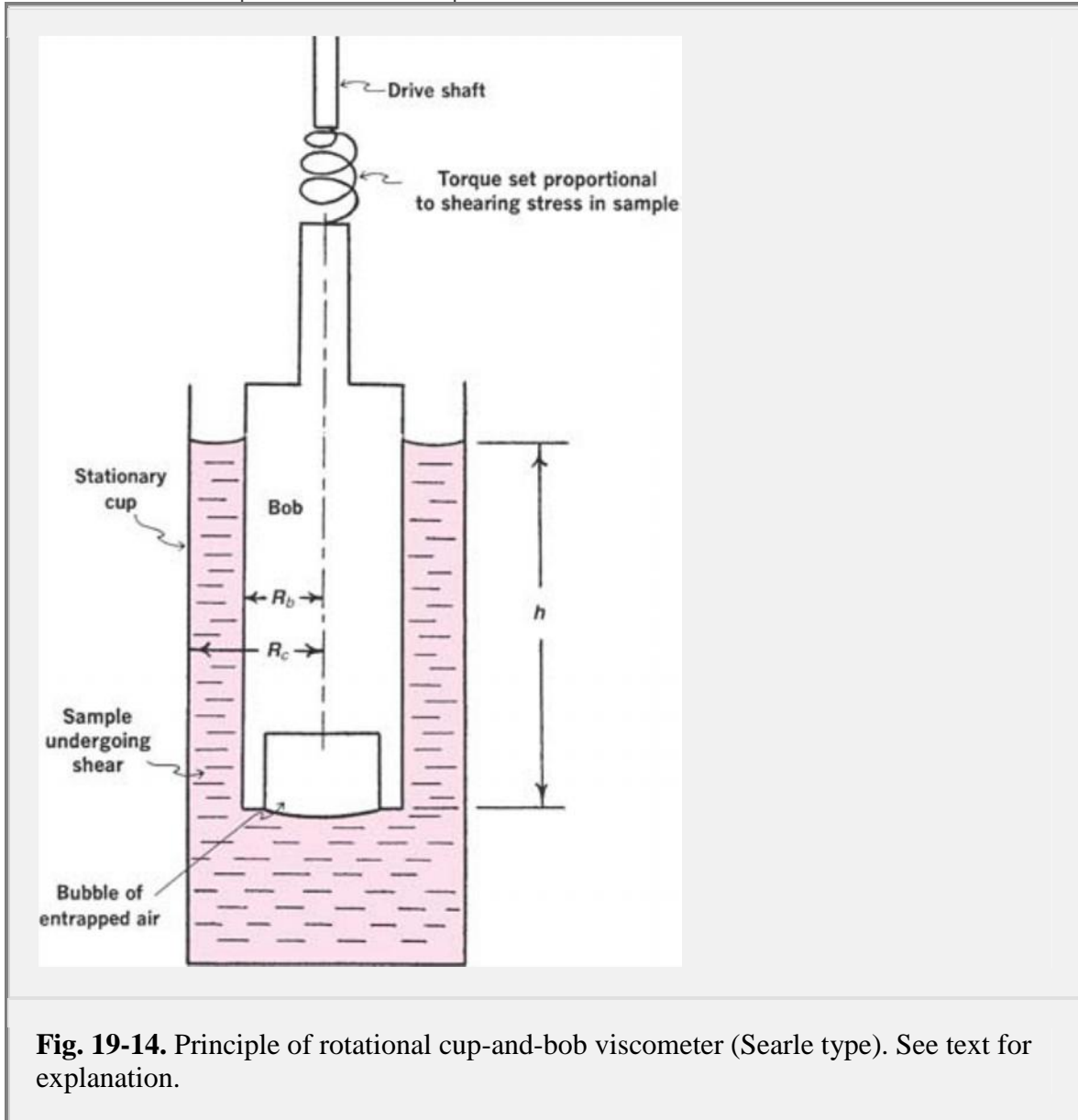
where t is the time interval in seconds for the ball to fall between the two points and S_b and S_f are the specific gravities of the ball and fluid, respectively, at the temperature being used. B is a constant for a particular ball and is supplied by the manufacturer. Because a variety of glass and steel balls of different diameters are available, this instrument can be used over the range 0.5 to 200,000 poise. For best results, a ball should be used such that t is not less than 30 sec.

Cup-and-Bob Viscometer

In cup-and-bob viscometers, the sample is sheared in the space between the outer wall of a bob and the inner wall of a cup into which the bob fits. The principle is illustrated in Figure 19-14. The various instruments available differ mainly in whether the torque results from rotation of the cup or of the bob. In the *Couette* type of viscometer, the cup is rotated. The viscous drag on the bob due to the sample causes it to turn. The resultant torque is proportional to the viscosity of the sample. The MacMichael

viscometer is an example of such an instrument. The *Searle* type of viscometer uses a stationary cup and a rotating bob. The torque resulting from
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the viscous drag of the system under examination is generally measured by a spring or sensor in the drive to the bob. The Rotovisco viscometer, shown in Figure 19-15, is an example of this type; it can also be modified to operate as a cone and plate instrument.



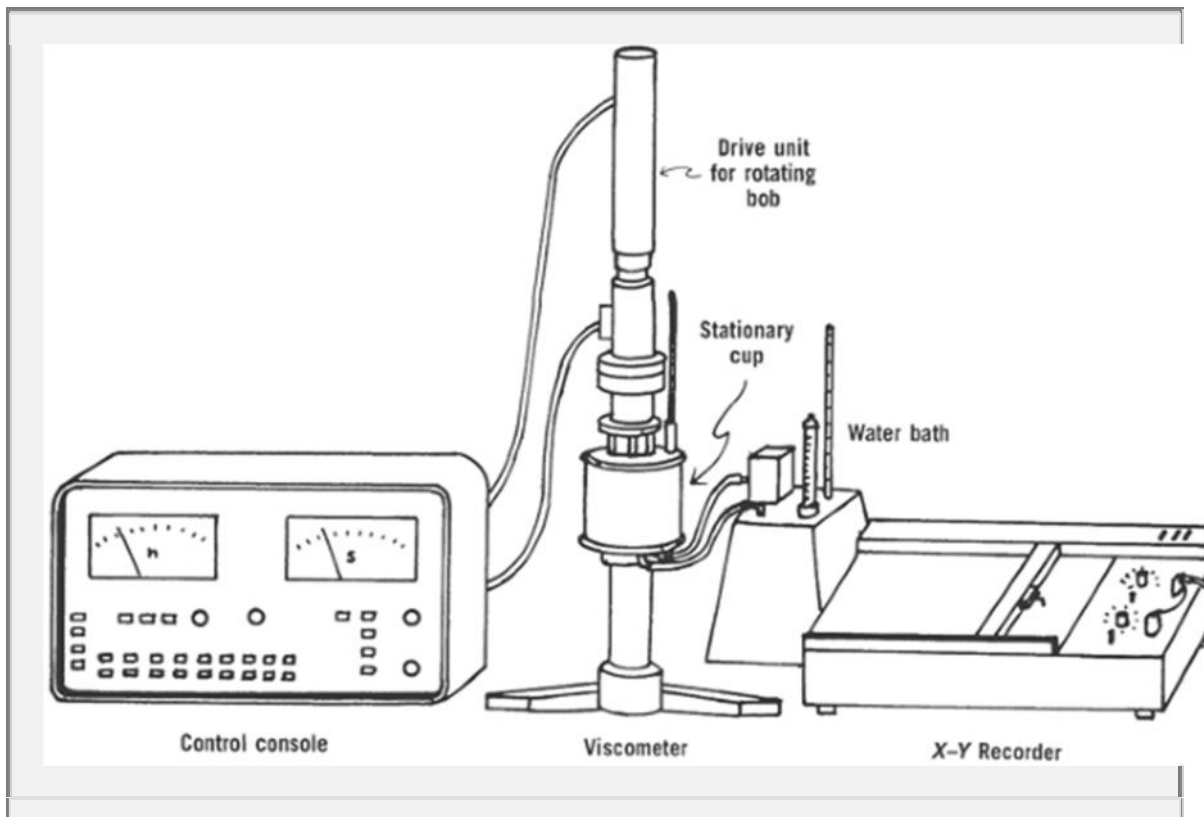


Fig. 19-15. Haake Rotovisco viscometer. The rate of shear, G , is selected manually or programmed for automatic plotting of upcurves and downcurves. Its value in sec^{-1} is proportional to the speed of the bob shaft, dialed in and read as n on the console. The shear stress is read on the scale S or obtained from the rheogram, plotted on the X-Y recorder.

Example 19-5

Shear Stress and Rate of Shear

The Haake Rotovisco apparatus uses interchangeable measuring heads, MK-50 and MK-500. The shear stress, F , in dyne/cm^2 is obtained from a dial reading S and is calculated using the formula

$$F \text{ (dynes/cm}^2\text{)} = K_F \cdot S \quad (19-18)$$

where K_F is a shear stress factor.

The shear rate, G , in sec^{-1} , is proportional to the adjustable speed, n , in revolutions per minute of the rotating cylinder in the cup containing the sample. The formula for shear rate is

$$G \text{ (sec}^{-1}\text{)} = K_G \cdot n \quad (19-19)$$

where K_G is a shear rate factor that varies with the particular rotating cylinder used. Three cups and cylinders (sensor systems) are supplied with the instrument, MVI, MVII, and MVIII. For the measuring head MK-50 and the sensor system MVI, the values for the constants K_F and K_G are 2.95 dyne/cm^2 and $= 2.35 \text{ min/sec}$, respectively.

In the analysis of a solution of a new glucose derivative that is found to be Newtonian, the following data were obtained in a typical experimental run at 25°C using the Haake viscometer with the MK-50 head and the MVI sensor system. With the cylinder rotating at 180 rpm, the dial reading S was obtained as 65.5 scale divisions.¹⁸ Calculate the Newtonian viscosity of the new glucose derivative. What are the values of shear stress, F , and the rate of shear, G ?

Using equations (19-18) and (19-19), we obtain

$$F = 2.95 \times 65.5 = 193.2 \text{ dynes/cm}^2$$

$$G = 2.35 \times 180 = 423.0 \text{ sec}^{-1}$$

Now, the Newtonian viscosity is readily obtained as

$$\eta = \frac{F}{G} = \frac{193.2}{423.0} = 0.457 \text{ poise, or } 45.7 \text{ cp}$$

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A popular viscometer based on the Searle principle is the Stormer instrument. This viscometer, a modification of that described by Fischer,¹⁹ is shown in Figure 19-16. In operation, the test system is placed in the space between the cup and the bob and allowed to reach temperature equilibrium. A weight is placed on the hanger, and the time required for the bob to make 100 revolutions is recorded. These data are then converted to revolutions per minute (rpm). The weight is increased and the whole procedure repeated. In this way, a rheogram can be constructed by plotting rpm versus weight added. By the use of appropriate constants, the rpm values can be converted to actual shear rates in sec^{-1} . Similarly, the weights added can be transposed into the units of shear stress, namely, dyne/cm^2 . According to Araujo,²⁰ the Stormer instrument should not be used with systems having a viscosity below 20 cp.

It can be shown that, for a rotational viscometer, equation (19-1) becomes

$$\Omega = \frac{1}{\eta} \frac{T}{4\pi h} \left(\frac{1}{R_b^2} - \frac{1}{R_c^2} \right) \quad (19-20)$$

where Ω is the angular velocity in radians/sec produced by T , the torque in dynes cm. The depth to which the bob is immersed in the liquids is h , and R_b and R_c are the radii of the bob and cup, respectively (see Fig. 19-14). The viscous drag of the sample on the base of the bob is not taken into account by equation (19-20). Either an "end correction" must be applied or, more usually, the base of the bob is recessed, as shown in Figure 19-14. In this case, a pocket of air is entrapped between the sample and the base of the bob, rendering the contribution from the base of the bob negligible. It is frequently more convenient to combine all the constants in equation (19-20), with the result that

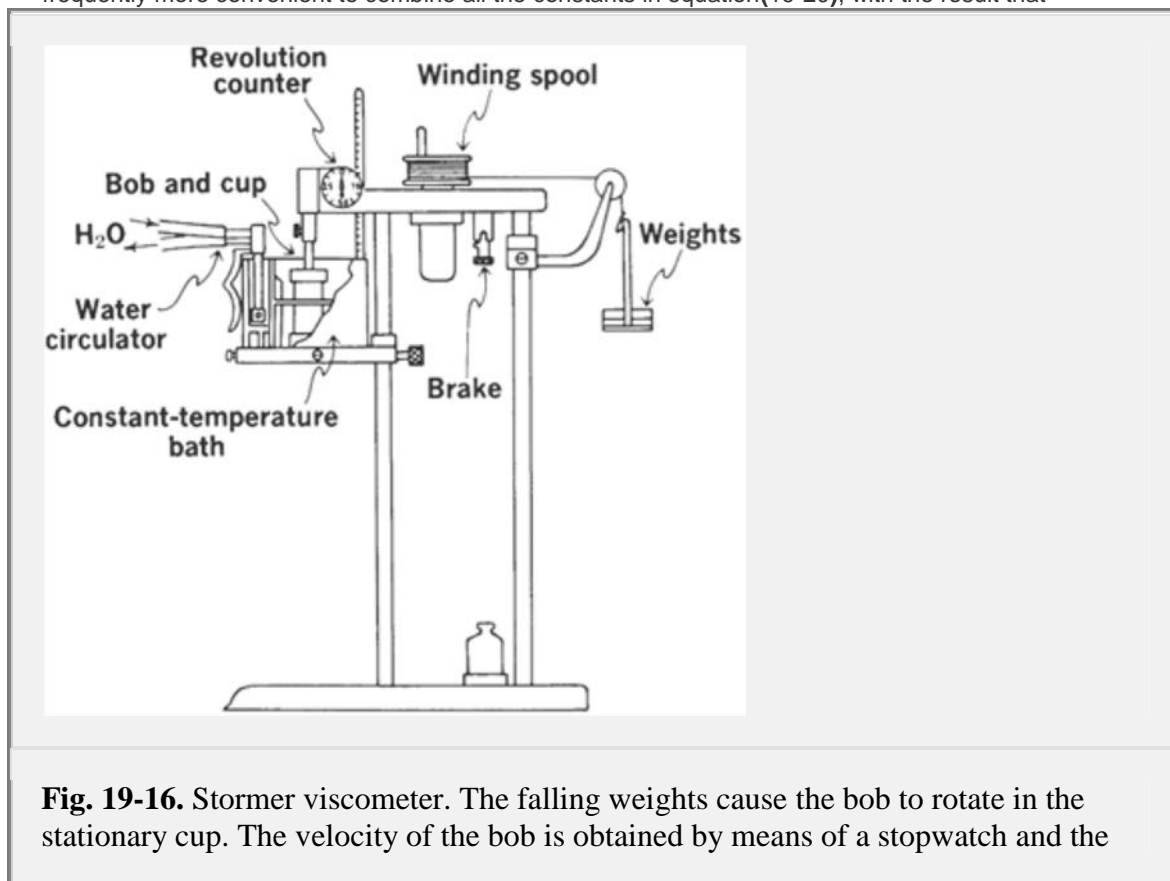


Fig. 19-16. Stormer viscometer. The falling weights cause the bob to rotate in the stationary cup. The velocity of the bob is obtained by means of a stopwatch and the

revolution counter.

$$\eta = K_v \frac{T}{\Omega} \quad (19-21)$$

where K_v is a constant for the instrument. With the modified Stormer viscometer, η is a function of v , the rpm generated by the weight, w , in grams, which is proportional to T . Equation (19-21) can then be written as

$$\eta = K_v \frac{w}{v} \quad (19-22)$$

The constant K_v can be determined by analyzing an oil of known viscosity in the instrument; reference oils for this purpose are obtained from the National Bureau of Standards.

The equation for plastic viscosity when employing the Stormer viscometer is

$$U = K_v \frac{w - w_f}{v} \quad (19-23)$$

where U is the plastic viscosity in poises, w_f is the yield value intercept in grams, and the other symbols have the meaning given in equation (19-22).

The yield value of a plastic system is obtained by use of the expression

$$f = K_f \times w_f \quad (19-24)$$

where K_f is equal to

$$K_v \times \frac{2\pi}{60} \times \frac{1}{2.303 \log(R_c/R_b)}$$

where R_c is the radius of the cup and R_b is the radius of the bob.

Example 19-6

Plastic Viscosity of a Gel

A sample of a gel was analyzed in a modified Stormer viscometer (see Fig. 19-16). A driving weight, w , of 450 g produced a bob velocity, v , of 350 rpm. A series of velocities was obtained using other driving weights, and the data were plotted as shown in Figure 19-2b. The yield value intercept, w_f , was obtained by extrapolating the curve to the shearing stress axis where $v = 0$, and the value of w_f was found to be 225 g. The instrumental constant, K_v , is 52.0, and K_f is 20.0. What is the plastic viscosity and the yield value of the sample?

We have

$$U = 52.0 \times \frac{450 - 225}{350} = 33.4 \text{ poise}$$

$$f = 20 \times 225 = 4500 \text{ dynes/cm}^2$$

The Brookfield viscometer is a rotational viscometer of the Searle type that is popular in the quality-control laboratories of pharmaceutical manufacturers. A number of spindles (bobs) of various geometries, including cylinders, t-bars, and a cone-plate configuration, are available to provide scientific rheologic data for Newtonian and non-Newtonian liquids and for empirical viscosity measurements on pastes and other

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semisolid materials. Various models of the Brookfield viscometer are available for high-, medium-, and low-viscosity applications. Figure 19-17 depicts a cone-and-plate type of Brookfield viscometer.

Key Concept

Plug Flow

One potential disadvantage of cup-and-bob viscometers is variable shear stress across the sample between the bob and the cup. In contrast to Newtonian systems, the apparent viscosity of non-Newtonian systems varies with shear stress. With plastic materials, the apparent viscosity below the yield value can be regarded as infinite. Above the yield value, the system possesses a finite viscosity U , the plastic viscosity. In a viscometer of the Searle type, the shear stress close to the rotating bob at relatively low rates of shear may be

sufficiently high so as to exceed the yield value. The shear stress at the inner wall of the cup could (and frequently does), however, lie below the yield value. Material in this zone would therefore remain as a solid plug and the measured viscosity would be in error. A major factor determining whether or not *plug flow* occurs is the gap between the cup and the bob. The operator should always use the largest bob possible with a cup of a definite circumference so as to reduce the gap and minimize the chances of plug flow. In a system exhibiting plug flow in the viscometer, more and more of the sample is sheared at a stress above the yield value as the speed of rotation of the bob is increased. It is only when the shear stress at the wall of the cup exceeds the yield value, however, that the system as a whole undergoes laminar, rather than plug, flow and the correct plastic viscosity is obtained.

The phenomenon of plug flow is important in the flow of pastes and concentrated suspensions through an orifice (e.g., the extrusion of toothpaste from a tube). High-shear conditions along the inner circumference of the tube aperture cause a drop in consistency. This facilitates extrusion of the material in the core as a plug. This phenomenon is, however, undesirable when attempting to obtain the rheogram of a plastic system with a cup-and-bob viscometer. Cone-and-plate viscometers do not suffer from this drawback.

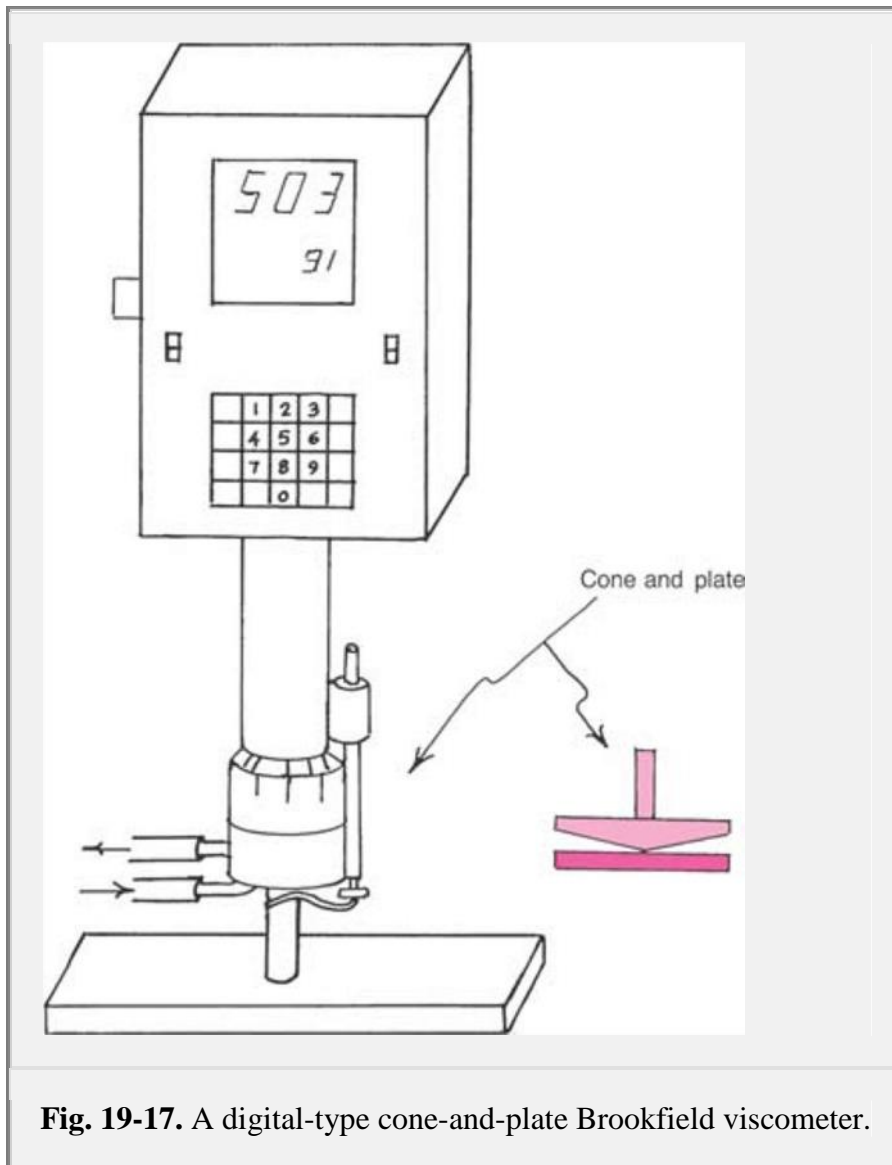


Fig. 19-17. A digital-type cone-and-plate Brookfield viscometer.

Cone-and-Plate Viscometer

The Ferranti–Shirley viscometer is an example of a rotational cone-and-plate viscometer. The measuring unit of the apparatus is shown in Figure 19-18; the indicator unit and speed control amplifier are not shown. In operation, the sample is placed at the center of the plate, which is then raised into position under the cone, as shown in Figure 19-19. A variable-speed motor drives the cone, and the sample is sheared in

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the narrow gap between the stationary plate and the rotating cone. The rate of shear in revolutions per minute is increased and decreased by a selector dial and the viscous traction or torque (shearing stress) produced on the cone is read on the indicator scale. A plot of rpm or rate of shear versus scale reading or shearing stress can thus be constructed in the ordinary manner.

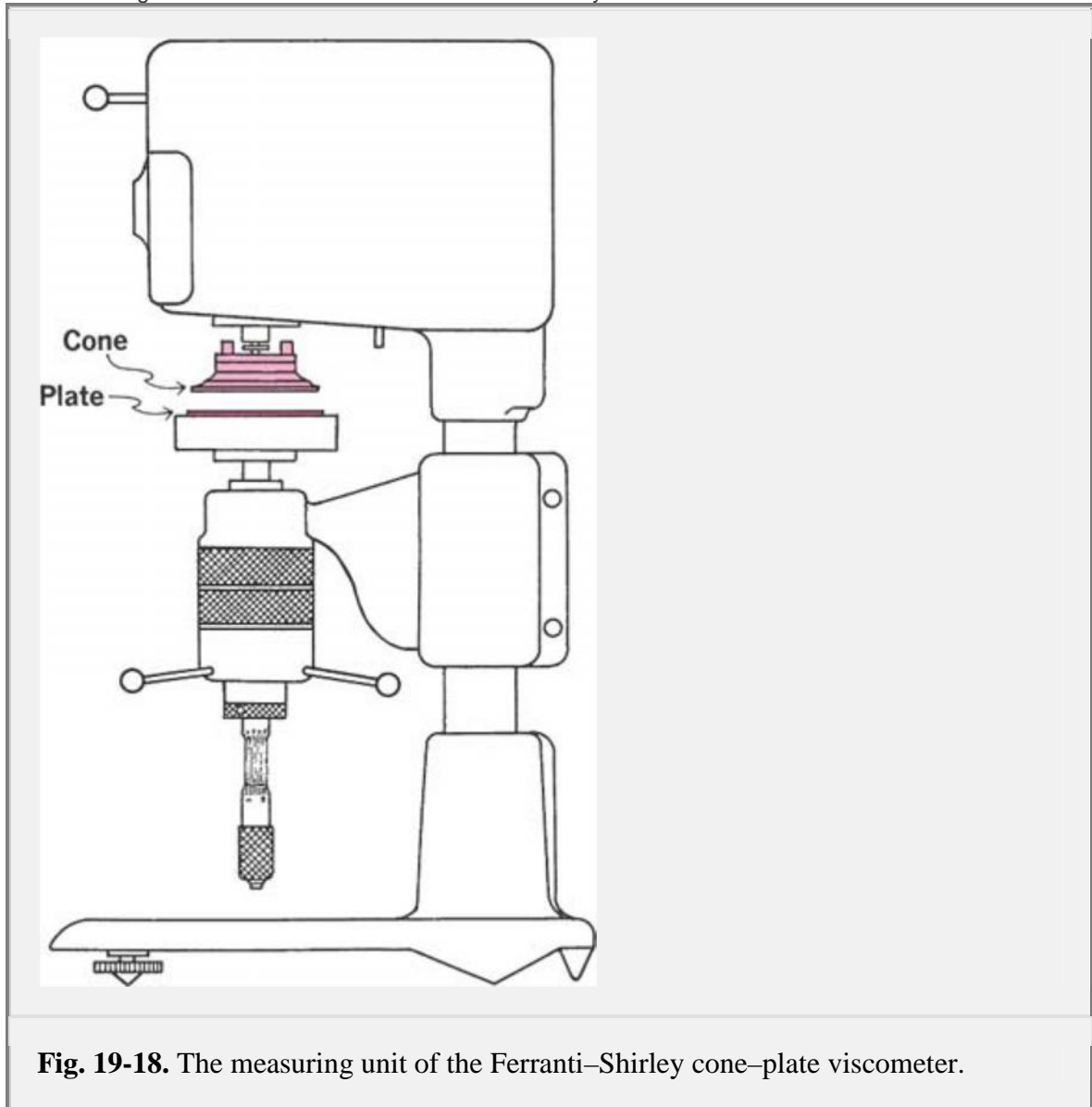


Fig. 19-18. The measuring unit of the Ferranti–Shirley cone–plate viscometer.

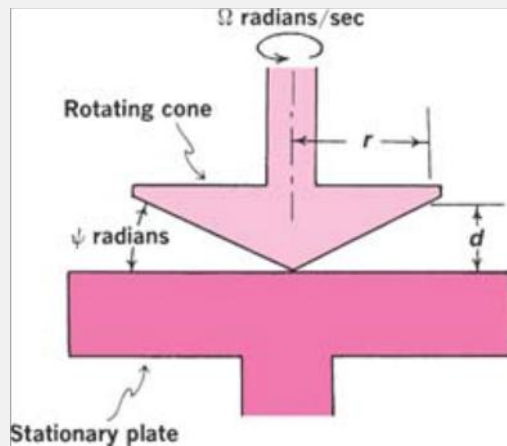


Fig. 19-19. Constant-shear-rate conditions in the cone and plate viscometer. The cone-to-plate angle, ψ , is greatly exaggerated here; it is ordinarily less than 1° (<0.02 rad).

The viscosity in poise of a Newtonian liquid measured in the cone-plate viscometer is calculated by use of the equation

$$\eta = C \frac{T}{v} \quad (19-25)$$

where C is an instrumental constant, T is the torque reading, and v is the speed of the cone in revolutions per minute. For a material showing plastic flow, the plastic viscosity is given by the equation

$$U = C \frac{T - T_f}{v} \quad (19-26)$$

and the yield value is given by

$$f = C_f \times T_f \quad (19-27)$$

where T_f is the torque at the shearing stress axis (extrapolated from the linear portion of the curve) and C_f is an instrumental constant.

Example 19-7

Plastic Viscosity of an Ointment Base

A new ointment base was designed and subjected to rheologic analysis at 20°C in a cone-plate viscometer with an instrumental constant, C , of 6.277 cm^{-3} . At a cone velocity of $v = 125$ rpm the torque reading, T , was 1287.0 dyne cm. The torque, T_f , at the shearing stress axis was found to be 63.5 dyne cm.

The plastic viscosity of the ointment base at 20°C was thus calculated using equation (19-26) to be

$$U = \frac{1287 - 63.5}{125} \times 6.277 = 61.44 \text{ poise}$$

The yield value, f , is obtained using equation (19-27), where $C_f = 113.6 \text{ cm}^{-3}$ for a medium-size cone (radius of 2.007 cm):

$$f = 113.6 \times 63.5 = 7214 \text{ dynes/cm}^2$$

A cone-and-plate viscometer possesses several significant advantages over the cup-and-bob type of instrument. Most important is the fact that the rate of shear is constant throughout the entire sample being sheared. As a result, any chance of plug flow is avoided. The principle is illustrated in Figure 19-19, from which it can be seen that G , the rate of shear at any diameter, is the ratio of the linear velocity, v , to the gap width, d . Thus,

$$G = \frac{\Omega r}{d} \frac{\text{cm/sec}}{\text{cm}} \quad (19-28)$$

The ratio r/d is a constant and is proportional to ψ , the angle between the cone and the plate in radians. Thus,

$$G = \frac{\Omega}{\psi} \text{sec}^{-1} \quad (19-29)$$

and is independent of the radius of the cone. The cone angle generally ranges from 0.3° to 4° , with the smaller angles being preferred. Other advantages of a cone-and-plate viscometer are the time saved in cleaning and filling and the temperature stabilization of the sample during a run. Whereas a cup-and-bob viscometer may require 20 to 50 mL of a sample for a determination, the cone-and-plate viscometer requires a sample volume of only 0.1 to 0.2 mL. By means of a suitable attachment, it is also possible to increase and then decrease the rate of shear in a predetermined, reproducible manner. At the same time, the shear stress is plotted as a function of the rate of shear on an X-Y recorder. This is a valuable aid when determining the area of hysteresis or thixotropic coefficients because it allows comparative studies to be run in a consistent manner. The use of this instrument in the rheologic evaluation of some pharmaceutical semisolids has been described by Hamlow,²¹ Gerding,²² and Boylan.²³

Viscoelasticity

A number of methods have been used to measure the consistency of pharmaceutical and cosmetic semisolid products. The discussion in this chapter has centered on the fundamentals of continuous or steady shear rheometry of non-Newtonian materials. Oscillatory and creep measurements are also of considerable importance for investigating the properties of semisolid drug products, foods, and cosmetics that are classified as viscoelastic materials.

Continuous shear mainly employs the rotational viscometer and is plotted as flow curves (see Fig. 19-2), which provide useful information by which to characterize and control products in industry. Continuous shear does not keep the material being tested in its rheologic "ground state" but resorts to gross deformation and alteration of the material during measurement. Analysis of viscoelastic materials is designed instead not to destroy the structure, so that measurements can provide information on the intermolecular and interparticle forces in the material.

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Viscoelastic measurements are based on the mechanical properties of materials that exhibit both viscous properties of liquids and elastic properties of solids. Many of the systems studied in pharmacy belong to this class, examples being creams, lotions, ointments, suppositories, suspensions, and the colloidal dispersing, emulsifying, and suspending agents. Biologic materials such as blood, sputum, and cervical fluid also show viscoelastic properties. Whereas steady shear in rotational viscometers and similar flow instruments yields large deformations and may produce false results, oscillatory and creep methods allow the examination of rheologic materials under nearly quiescent equilibrium conditions. Davis²⁴ described creep and oscillatory methods for evaluating the viscoelastic properties of pharmaceutical materials, and Barry²⁵ reviewed these methods for pharmaceutical and cosmetic semisolids.

A semisolid is considered to demonstrate both solid and liquid characteristics. The flow of a Newtonian fluid is expressed by using equation (19-2),

$$\eta = F/G$$

relating shear stress, F , and shear rate, G . A solid material, on the other hand, is not characterized by flow but rather by elasticity, and its behavior is expressed by the equation for a spring (derived from Hooke's law):

$$E = F/\gamma \quad (19-30)$$

where E is the elastic modulus (dyne/cm^2), F is the stress (dyne/cm^2), and γ is the strain (dimensionless). Using a mechanical model, we can represent a viscous fluid as movement of a piston in a cylinder (or *dashpot*, as it is called) filled with a liquid, as seen in Figure 19-20a. An example of a

dashpot is an automobile shock absorber. An elastic solid is modeled by the movement of a Hooke spring (Fig. 19-20b). The behavior of a semisolid as a viscoelastic body can therefore be described by the combination of the dashpot and spring, as observed in Figure 19-20c. The combination of spring and shock absorber in a car, which provides a relatively smooth ride over rough roads, is analogous to the spring and dashpot of Figure 19-20c.

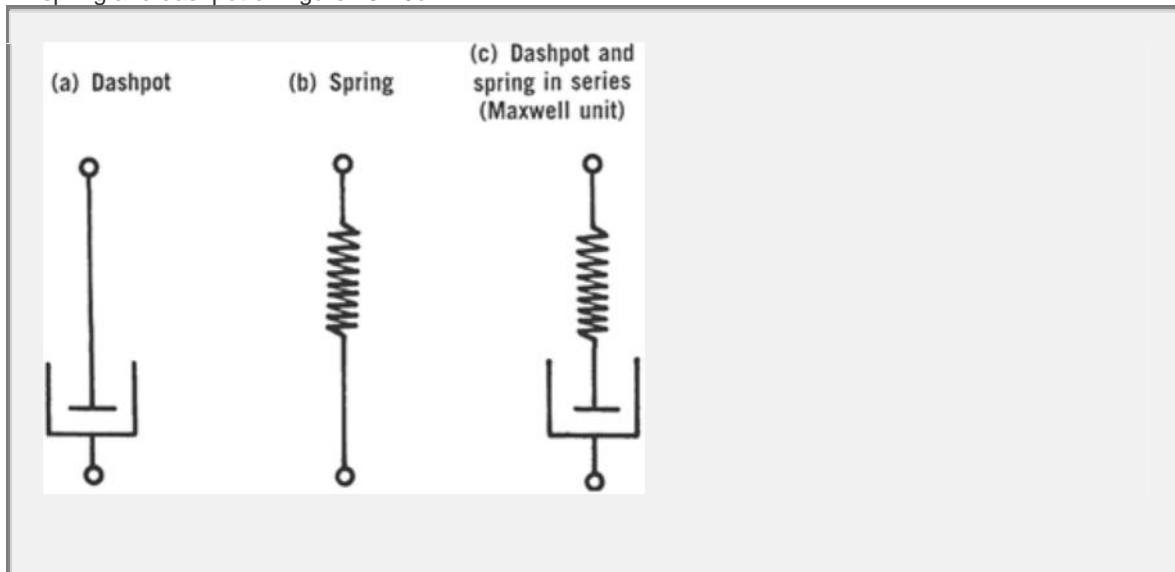


Fig. 19-20. Mechanical representation of a viscoelastic material using a dashpot and spring. The dashpot and spring in series is called a *Maxwell element* or *unit*.

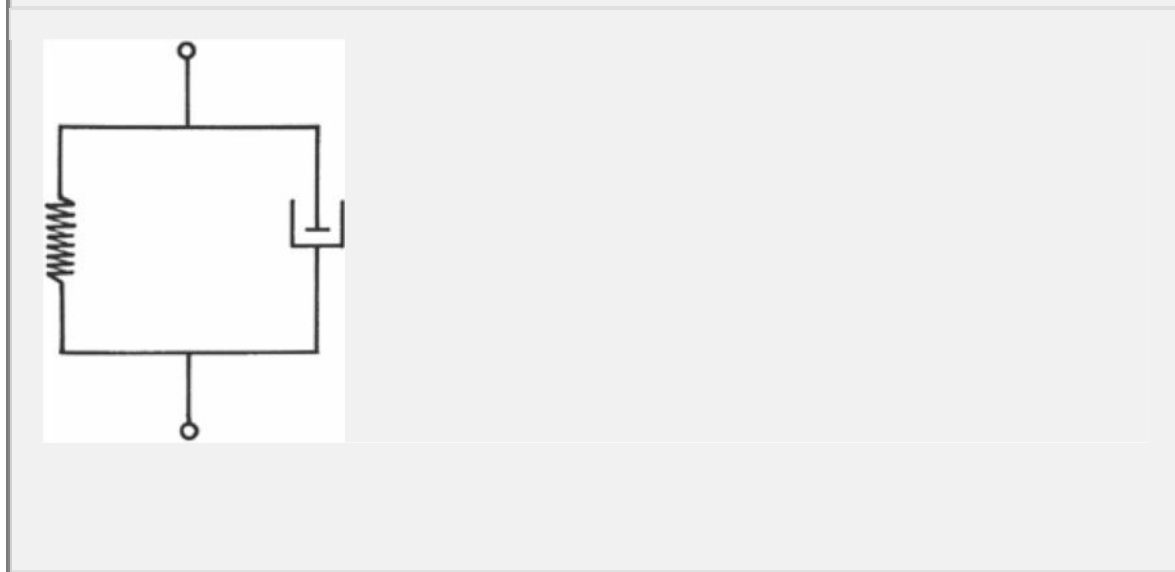


Fig. 19-21. Spring and dashpot combined in parallel as a mechanical model of a viscoelastic material, known as a *Voigt element*.

This mechanical model of a viscoelastic material, a non-Newtonian material showing both viscosity of the liquid state and elasticity of the solid state, and combined in *series* is called a *Maxwell element*. The spring and dashpot can also be combined in a *parallel* arrangement as seen in Figure 19-21. This second model for viscoelasticity is known as a *Voigt element*.

As a constant stress is applied to the Maxwell unit, there is a strain on the material that can be thought of as a displacement of the spring. The applied stress can be thought of as also producing a movement of the piston in the dashpot due to viscous flow. Removal of the stress leads to complete recovery of the

spring, but the viscous flow shows no recovery, that is, no tendency to return to its original state. In the Voigt model, in which the spring and the dashpot are attached in parallel rather than in series, the drag of the viscous fluid in the dashpot simultaneously influences the extension and compression of the spring that characterizes the solid nature of the material, and the strain will vary in an exponential manner with time. Strain is expressed as a deformation or *compliance*, J , of the test material, in which J is strain per unit stress. The compliance of a viscoelastic material following the Voigt model is given as a function of time, t , by the expression

$$J = J_{\infty}(1 - e^{-t/\tau}) \quad (19-31)$$

where J is the compliance or strain per unit stress at infinite time and τ is viscosity per unit modulus, $\tau = \eta/E$ (dyne sec cm⁻²/dyne cm⁻²), which is called *retardation time* and has the unit of seconds.

The Maxwell and Voigt mechanical models representing viscoelastic behavior in two different ways can be combined into a generalized model to incorporate all possibilities of flow and deformation of non-Newtonian materials. One of

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several Voigt units can be combined with Maxwell elements to represent the changes that a pharmaceutical solid, such as an ointment or a cream, undergoes as it is stressed. As observed in Figure 19-22, two Voigt elements are combined with a Maxwell element to reproduce the behavior of a sample of wool fat²⁴ at 30°C. The compliance, J , as a function of time is measured with an instrument known as a *creep viscometer* (Fig. 19-23) and is plotted in Figure 19-22 to obtain a *creep curve*. The creep curve is observed to be constructed of three parts, first a sharply rising portion AB corresponding to the elastic movement of the uppermost spring; second, a curved portion BC , a viscoelastic region representing the action of the two Voigt units; and third, a linear portion CD corresponding to movement of the piston in the dashpot at the bottom of the Maxwell–Voigt model representing viscous flow.

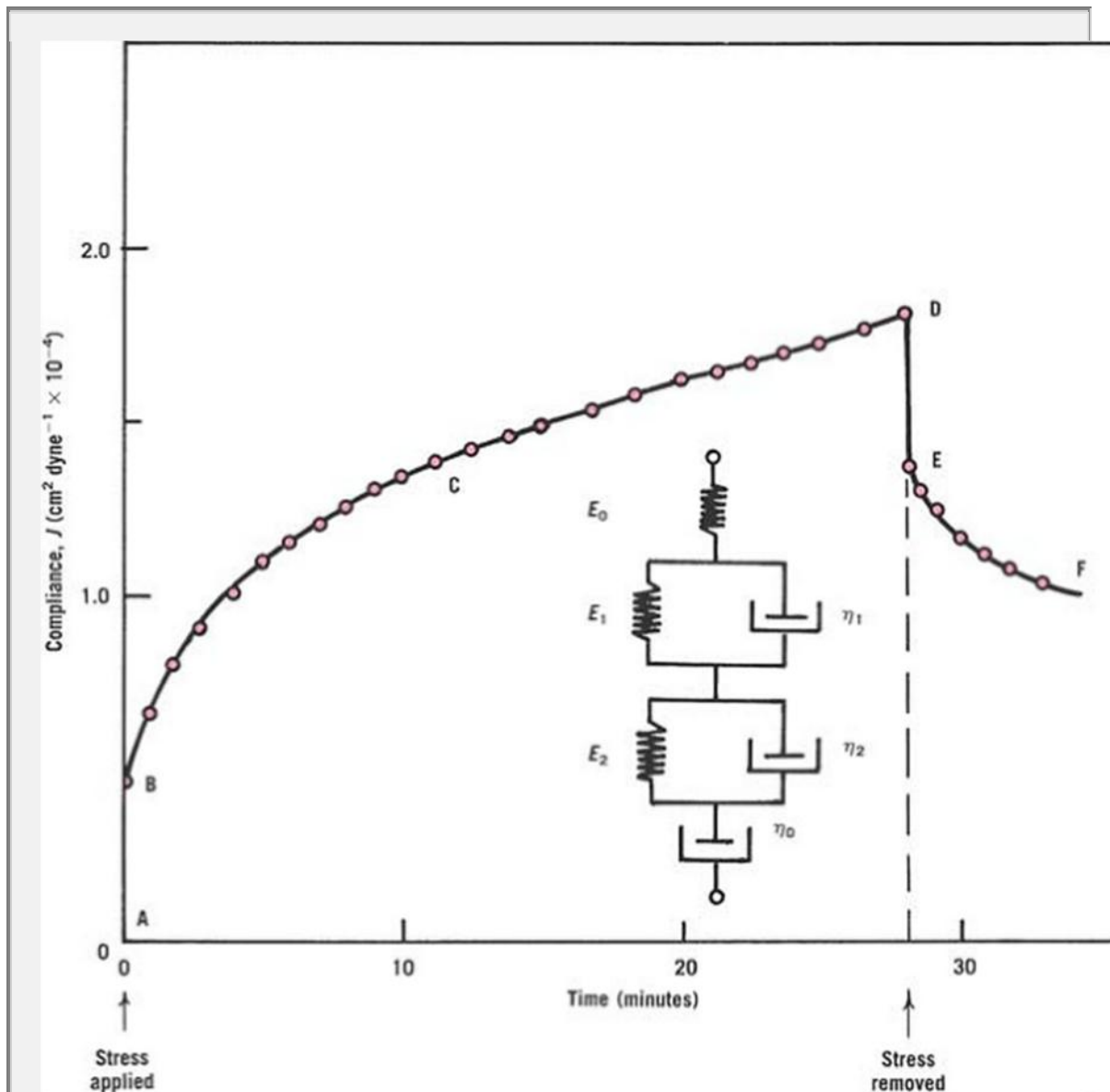


Fig. 19-22. A creep curve obtained by analyzing a sample of wool fat in a creep viscometer (Fig. 19-23) at 30°C. The creep curve results from a plot of compliance, J , equation (19-31), against the time in minutes during which a stress is applied to the sample. The inset shows the combination of Maxwell and Voigt elements required to represent the viscoelasticity of the wool fat sample. E_0 , E_1 , and E_2 , the spring moduli, can be calculated from the plot and by use of equation (19-32) and the three viscosities η_1 , η_2 , and η_0 . (From S. S. Davis, *Pharm. Acta Helv.* **49**, 161, 1974. With permission.)

The compliance equation corresponding to the observed behavior of wool fat (Fig. 19-22), as simulated by the Maxwell–Voigt model (inset in Fig. 19-22), is

$$J = \frac{\gamma_0}{F} + J_m(1 - e^{-t/\tau_m}) + J_n(1 - e^{-t/\tau_n}) + \frac{\gamma}{F} \quad (19-32)$$

where γ_0 is the instantaneous strain and F is the constant applied shear stress.^{24,25} The quantity γ_0/F is readily obtained from the experimental curve (region AB) in Figure 19-22. The viscoelastic region of the curve (BC) is represented by the intermediate term of equation (19-32), where J_m and J_n are the mean compliance of bonds in the material and τ_m and τ_n are the mean retardation times for the two Voigt units

of Figure 19-22. It is sometimes found that three or more Voigt units are needed in the model to reflect the
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observed behavior of the material. The final term of equation (19-32) corresponds to the linear portion, *CD*, of the creep curve. This section represents a condition of Newtonian compliance in which the rupture of bonds leads to the flow of the material, where *F* is the constant applied stress and γ is the shear strain in this region of the curve.

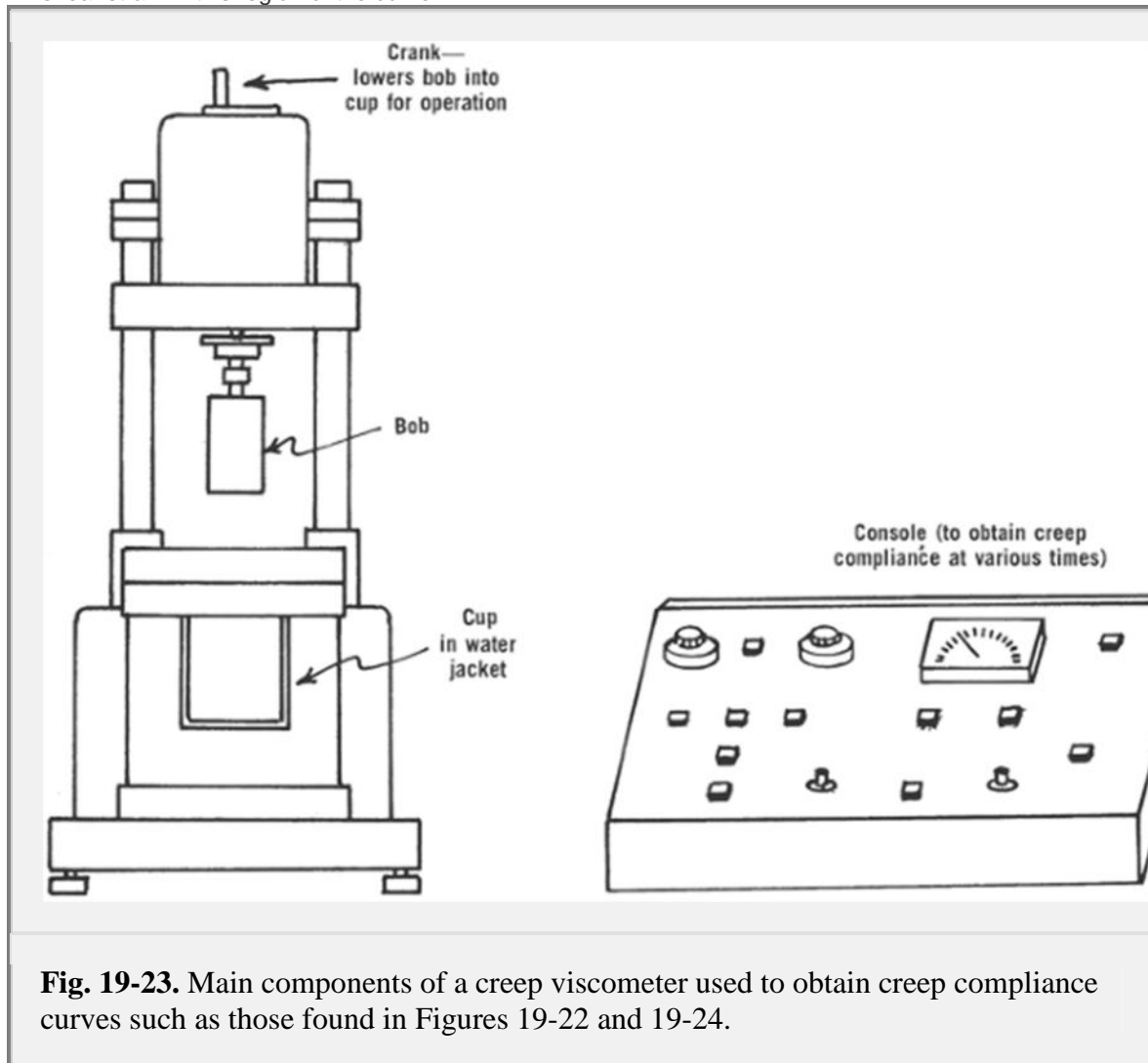


Fig. 19-23. Main components of a creep viscometer used to obtain creep compliance curves such as those found in Figures 19-22 and 19-24.

When stress is removed by the operator of the creep rheometer (Fig. 19-23), a recovery (*DEF*) of the sample is obtained. It is composed of an instantaneous elastic recovery, *DE*, equivalent to *AB*, followed by an elastic recovery region, *EF*, equivalent to *BC*. In the creep compliance curve of Figure 19-22, flow occurs in region *CD*, irreversibly destroying the structure, and in the recovery curve this portion is not reproduced. By such an analysis, Davis²⁴ obtained the elastic moduli (inset of Fig. 19-22) $E_0 = 2.7 \times 10^4$ dynes/cm, $E_1 = 5.4 \times 10^4$ dynes/cm, and $E_2 = 1.4 \times 10^4$ dynes/cm, and the three viscosities $\eta_1 = 7.2 \times 10^5$ poise, $\eta_2 = 4.5 \times 10^6$ poise, and $\eta_0 = 3.1 \times 10^7$ poise for wool fat.

The creep curve used to measure the viscoelasticity of non-Newtonian pharmaceutical, dermatologic, and cosmetic materials can shed some light on the molecular structure of the materials and therefore provide information for modification and improvement of these vehicles. Creep compliance curves were used by Barry²⁵ to study the changes with temperature in samples of white petrolatum (White Soft Paraffin, British *Pharmacopoeia*) as observed in Figure 19-24.

The behavior was complex, requiring five Voigt units and one Maxwell element to describe the observed creep compliance curves at 5°C and 25°C and three Voigt units at 45°C, where some of the structure had been destroyed by melting. Three curves are characteristic of the crystalline bonding and the interaction of crystalline and amorphous material that constitute petrolatum. The curves were automatically plotted on an X-Y recorder as the material was stressed in the creep viscometer. The circles plotted along the lines of Figure 19-24 were obtained by use of an equation similar to equation (19-32), showing the accuracy with which the creep curves can be reproduced by a theoretical model of Voigt and Maxwell units.

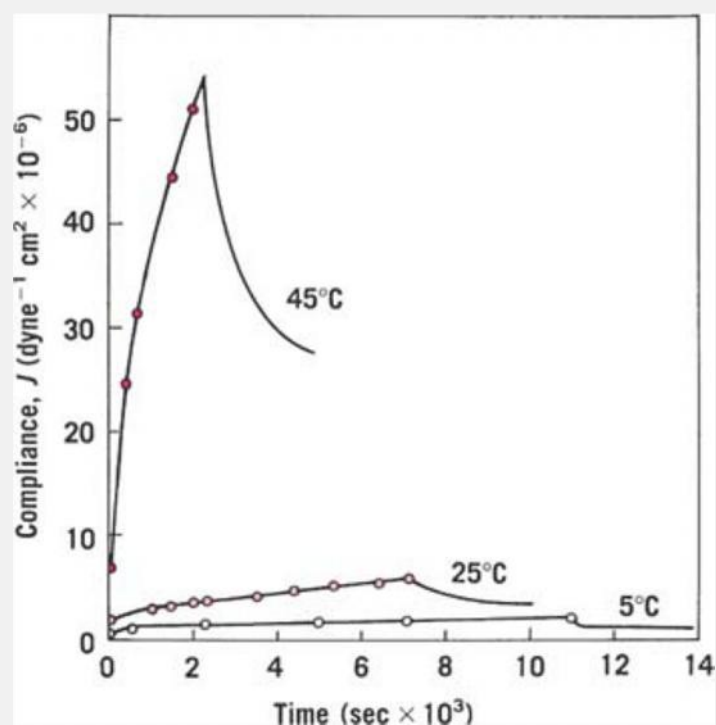


Fig. 19-24. Creep compliance curves of Soft White Paraffin (British Pharmacopoeia) at three temperatures. (From B. W. Barry, in H. S. Bean, A. H. Beckett, and J. E. Carless (Eds.), *Advances in Pharmaceutical Sciences*, Vol. 4, Academic Press, New York, 1974, p. 36. With permission.)

Another dynamic rheologic method that does not disturb the structure of a material is that of oscillatory testing.^{24,25,26,27} A thin layer of material is subjected to an oscillatory driving force in an apparatus known as a rheogoniometer, such as that shown in Figure 19-25. The shearing stress produced by the oscillating force in the membrane of the apparatus results in a shear rate proportional to the surface velocity of the material. The viscoelastic behavior of materials obtained by oscillatory shear measurements can be analyzed by an extension of the Maxwell spring-and-dashpot model. Steady shear methods involving rotational viscometers tend to break down materials under analysis, and although they yield useful data on thixotropy and yield stress, for example, they do not provide information about the original structure and bonding in pharmaceutical and cosmetic semisolids. Viscoelastic analysis performed by creep or oscillatory methods is particularly useful for studying the structure of liquid and semisolid emulsions and gels.²⁶ Viscoelastic measurements can also be used to measure the rheologic changes occurring in a cream after it is broken down in various stages by milling, incorporation of drugs, or spreading on the skin.

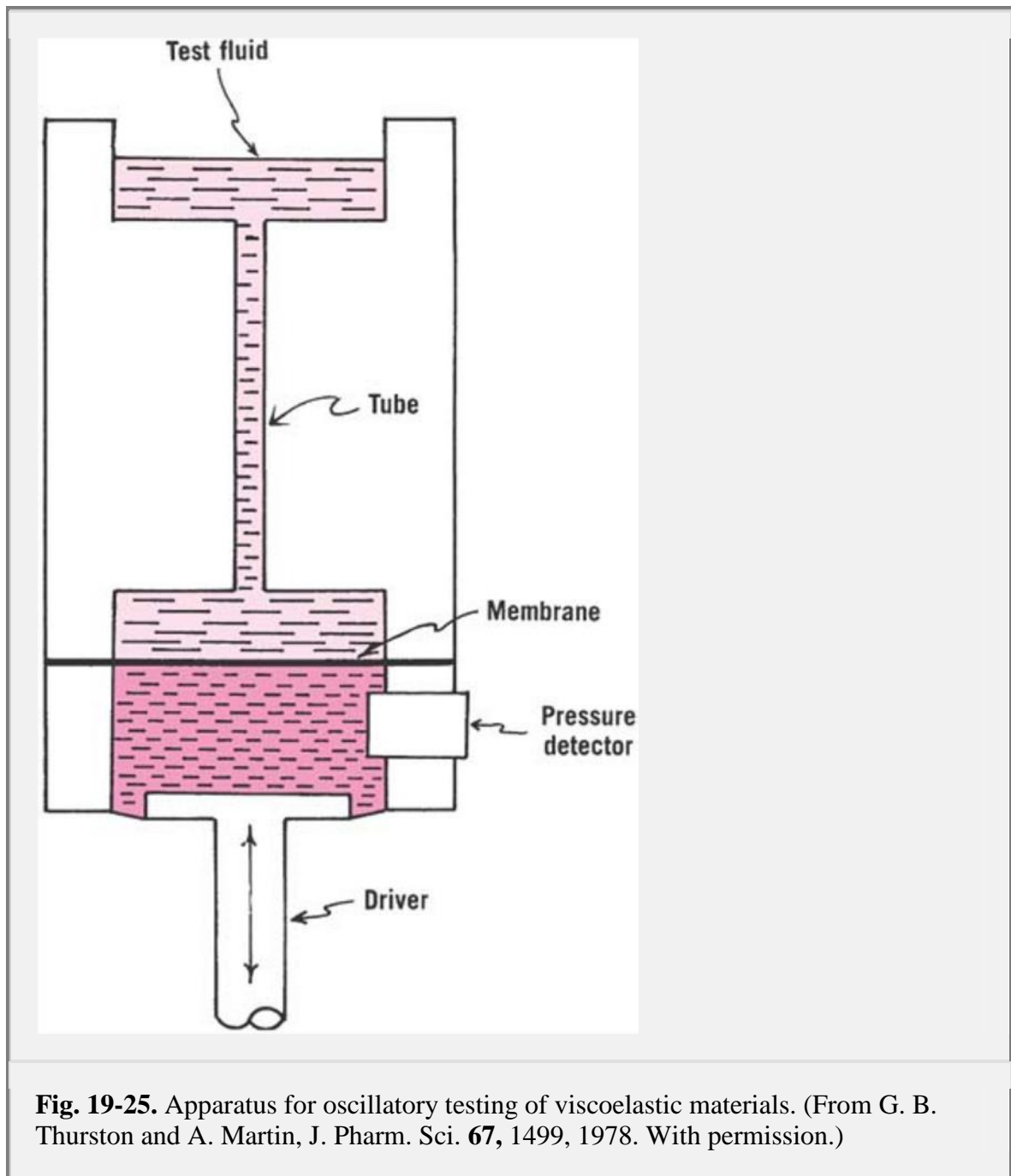


Fig. 19-25. Apparatus for oscillatory testing of viscoelastic materials. (From G. B. Thurston and A. Martin, *J. Pharm. Sci.* **67**, 1499, 1978. With permission.)

Radebaugh and Simonelli²⁸ studied the viscoelastic properties of anhydrous lanolin, which were found to be a function of strain, shear frequency, shear history, and temperature. The energy of activation, E_v , was calculated for the structural changes of the lanolin sample, which was found to undergo a major mechanical transition between 10°C and 15°C. The E_v for the transition was about 90 kcal that expected for glass transition. Rather than a sharp change from a rubbery to a glasslike state, however, anhydrous lanolin appeared to change to a state less ordered than glass. The glass-rubber transition and the glass transition temperature are discussed in Chapter 20. The viscoelastic properties were determined using a Rheometrics mechanical spectrometer (RMS 7200; Rheometrics, Inc., Union, N.J.). The rheometer introduces a definite deformation into the sample at a specified rate and at a chosen temperature. For the design of mucolytic agents in the treatment of bronchitis, asthma, and cystic fibrosis, viscoelastic methods are also of value in the analysis of sputum. Other biologic fluids such as blood, vaginal material, and synovial fluids may be analyzed by viscoelastic test methods. The unsteady shear to which synovial fluids are subjected in the body during the movement of leg and arm joints requires the

elastic properties of these fluids, in addition to viscous properties that are observed only in steady shear. Thurston and Greiling²⁹ used oscillatory shear to analyze cases of noninflammatory and inflammatory joint disease associated with arthritis. The macromolecule hyaluronic acid is primarily responsible for the high viscosity and non-Newtonian character of synovial fluid and gives it simple Newtonian rather than the desired non-Newtonian properties. Changes in viscoelasticity of synovial fluids, measured in the oscillatory instrument shown in Figure 19-25, can therefore serve as sensitive indicators of joint disease.

Psychorheology

In addition to desirable pharmaceutical and pharmacologic properties, topical preparations must meet criteria of feel, spreadability, color, odor, and other psychological and sensory characteristics. Workers in the food industry have long tested products such as butter, chocolate, mayonnaise, and bread dough for proper consistency during manufacture, packaging, and end use. Sensations in the mouth, between the fingers, and on the skin are important considerations for manufacturers of foods, cosmetics, and dermatologic products. Scott-Blair³⁰ discussed *psychorheology* (as this subject is called)

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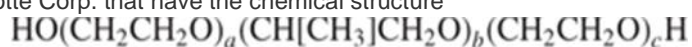
in the food industry. Kostenbauder and Martin³¹ assessed the spreadability of ointments in relation to their rheologic properties. In consultation with dermatologists, they divided the products into three classes. Class I products were soft, mainly for ophthalmic use; class II products included common medicated ointments of intermediate consistency; and class III products involved stiff protective products for use in moist ulcerative conditions. The yield values and plastic viscosity for each class of product were reported.

Boylan²³ showed that the thixotropy, consistency, and yield value of bacitracin ointment, USP, decreased markedly as the temperature was raised from 20°C to 35°C. Thus, although a product may be sufficiently thixotropic in its container, this property can be lost following application to the skin.

Barry et al.³² carried out sensory testing on topical preparations. They used a panel to differentiate textural parameters and established rheologic methods for use in industry as control procedures for maintaining uniform skin feel and spreadability of dermatologic products. Cussler et al.³³ studied the texture of non-Newtonian liquids of widely different rheologic properties applied to the skin. They found that a panel of untrained subjects could accurately assess the consistency of a material by the use of only three attributes: smoothness, thinness, and warmth. Smoothness was related to a coefficient of friction and thinness to non-Newtonian viscous parameters that could be measured with appropriate instruments. The characteristic of warmth was found to be sufficiently complex to require further study.

Applications to Pharmacy

The rheologic behavior of poloxamer vehicles was studied as a function of concentration over a temperature range of 5°C to 35°C using a cone-plate viscometer.³⁴ Poloxamers are block polymers from BASF Wyandotte Corp. that have the chemical structure



Poloxamers with a wide range of molecular weights are available as Pluronics. Some of the poloxamers are used in dermatologic bases or topical ophthalmic preparations because of their low toxicity and their ability to form clear water-based gels.

The aqueous solubility of the poloxamers decreases with an increase in temperature, the hydration of the polymer being reduced by the breaking of hydrogen bonds at higher temperatures. The desolvation that results, together with the entanglement of the polymer chains, probably accounts for the gel formation of the poloxamers.

A linear relationship was found between shear rate and shear stress (Newtonian behavior) for the poloxamer vehicles in the sol state, which exists at low concentrations and low temperatures. As the concentration and temperature were increased, some of the poloxamers exhibited a sol-gel transformation and became non-Newtonian in their rheologic character. The addition of sodium chloride, glycerin, or propylene glycol resulted in increased apparent viscosities of the vehicles.

Polymer solutions can be used in ophthalmic preparations, as wetting solutions for contact lenses, and as tear replacement solutions for the condition known as *dry eye syndrome*. Both natural (e.g., dextran)

and synthetic (e.g., polyvinyl alcohol) polymers are used with the addition of various preservatives. A high-molecular-weight preparation of sodium hyaluronate at concentrations of 0.1% to 0.2% has been introduced to overcome the dry eye condition.

For high-polymer solutions, the viscosity levels off to a *zero-shear viscosity* (a high viscosity) at low shear rates. The viscosity decreases as the shear rate is increased because the normally twisted and matted polymer molecules align in the streamlined flow pattern and exhibit pseudoplasticity or shear thinning.

Bothner et al.³⁵ suggested that a suitable tear substitute should have shear-thinning properties as do natural tears to conform to the low shear rate during nonblinking and the very high shear rate during blinking. The low viscosity at high shear rates produces lubrication during blinking, and the high viscosity at zero shear rate prevents the fluid from flowing away from the cornea when the lids are not blinking. Using a computer-controlled Couette viscometer, they studied the rheologic properties of eight commercial tear substitutes, together with 0.1% and 0.2% solutions of sodium hyaluronate. For five of the commercial products, the viscosity was independent of shear rate; thus, these products behaved as Newtonian liquids. Two products showed slight shear thinning at high shear rates. Only the commercial product Neo-Tears and the two noncommercial sodium hyaluronate solutions showed the desired pseudoplastic behavior. For Neo-Tears the viscosity at high shear rate, 1000 sec^{-1} , was 3-fold that at zero shear. For 0.1% sodium hyaluronate the value was 5-fold and for 0.2% sodium hyaluronate it was 30-fold. Therefore, sodium hyaluronate appears to be an excellent candidate as a tear replacement solution.

The rheologic properties of suppositories at rectal temperatures can influence the release and bioabsorption of drugs from suppositories, particularly those having a fatty base. Grant and Liversidge³⁶ studied the characteristics of triglyceride suppository bases at various temperatures, using a rotational rheometer. Depending on the molten (melted) character of the base, it behaved either as Newtonian material or as a plastic with thixotropy.

Fong-Spaven and Hollenbeck³⁷ studied the rheologic properties as a function of the temperature of mineral oil–water emulsions stabilized with triethanolamine stearate (TEAS). The stress required to maintain a constant rate of shear was monitored as temperature increased from 25°C to 75°C. Unexpected, but reproducible discontinuities in the plots of temperature versus apparent viscosity were obtained using a Brookfield digital viscometer and were attributed

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possibly to shifts in the liquid crystalline structures. As seen in Figure 19-26, where apparent viscosity is plotted versus temperature for a 5% TEAS mineral oil–water emulsion, viscosity decreases as temperature is raised to about 48°C. The viscosity reverses and increases to a small peak at 54°C and then decreases again with increasing temperature. This unusual behavior is considered to result from gel formation, which stabilizes the internal phase. Liquid-crystalline structures of TEAS exist, and at higher temperatures the structures disintegrate or “melt” to form a large number of TEAS molecules in a gel-like arrangement that exhibits increased resistance to flow. As the temperature rises above 54°C the gel structure is gradually destroyed and viscosity again decreases, as shown in Figure 19-26.

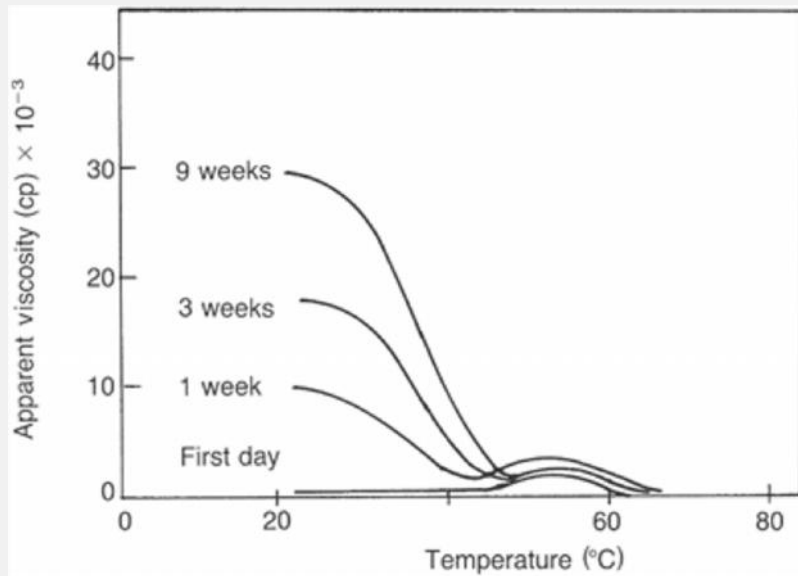


Fig. 19-26. Viscosity versus temperature plots of an oil–water emulsion over a period of 9 weeks. (From F. Fong-Spaven and R. G. Hollenbeck, *Drug Dev. Ind. Pharm.* **12**,289, 1986. With permission.)

Patterned after the manufacture and use of cosmetic sticks, solidified sodium stearate–based sticks were prepared and tested for topical application using a Ferranti–Shirley cone–plate viscometer. The sticks contained propylene glycol, polyethylene glycol 400, and polyethylene glycol 600 as humectants and the topically active drugs panthenol, chlorphenesin, and lignocaine. Thixotropic breakdown was much lower in these medicated sticks than in comparable bases. The addition of the three topical drugs to the stearate-based sticks caused changes in yield values, thixotropy, and plastic viscosity; possible reasons for the changes were advanced.³⁸

Rowe and Sadeghnejad³⁹ studied the rheologic properties of microcrystalline cellulose, an ingredient incorporated into wet powder masses to facilitate granulation in the manufacture of tablets and granules. The authors designed a *mixer torque rheometer* to measure the torque changes as water was added to the powder mixture (*torque* is the force acting to produce rotation of a body). As the mixture became wetter, torque increased until the mass was saturated, then decreased with further addition of water as a slurry (suspension) was formed. A plot of torque in Newton meters (1 N m = 1 joule) against increasing water content produced a bell-shaped curve, as shown in Figure 19-27. This behavior was explained, according to the authors, by the three states of liquid saturation of a powder mass, as described by Newitt and Conway-Jones.⁴⁰

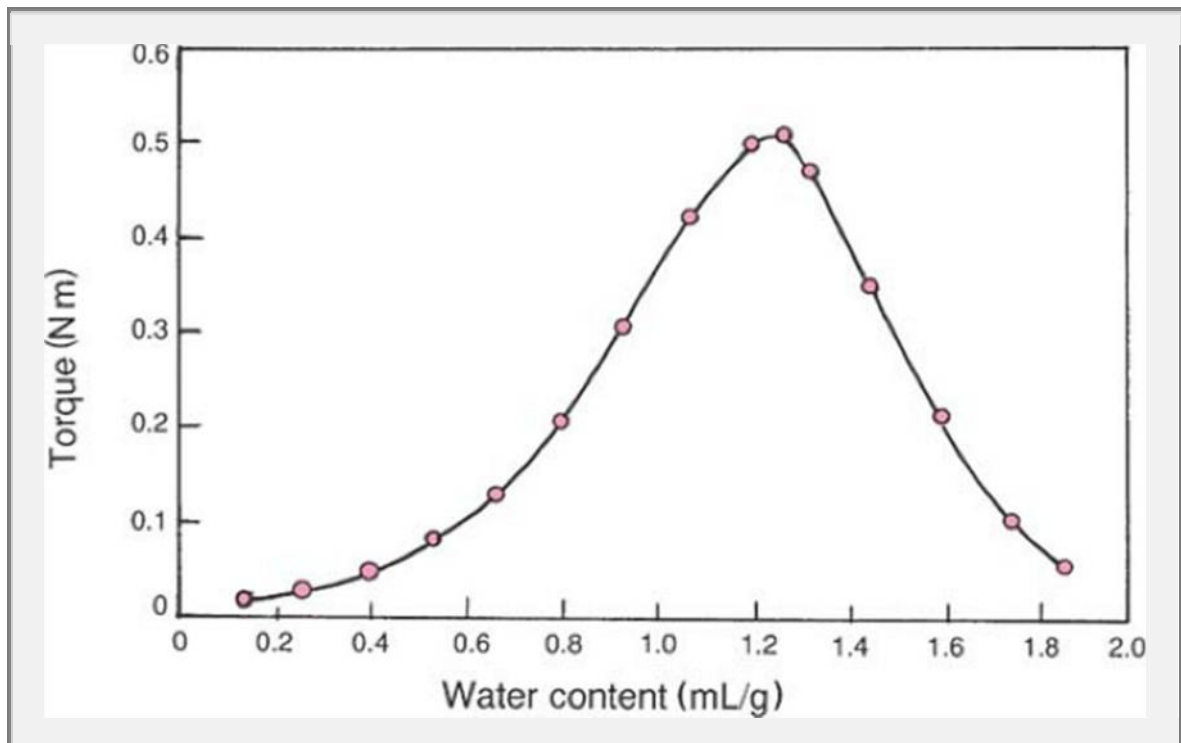


Fig. 19-27. Changes of torque in a mixer torque rheometer as water is added to a mixture of powders. (From R. C. Rowe and G. R. Sadeghnejad, *Int. J. Pharm.***38**, 227, 1987. With permission.)

With the early addition of liquid, a *pendular state* exists (see Fig. 19-28) with lenses of liquid at the contact points of the particles. The liquid forces out some of the air originally filling the spaces between particles. As more liquid is added, a mixture of liquid and air exists between the particles to produce the *funicular state*. The torque on the mixer increases for these two conditions until the end of the funicular state. The pores are then filled with liquid to yield the *capillary state*, and with the addition of more liquid the torque decreases as a slurry (suspension) is produced (*liquid-droplet state*). These stages of saturation are depicted schematically in Figure 19-28.

The three microcrystalline celluloses from different sources³⁹ exhibited essentially the same plot of torque versus water added (see Fig. 19-27). Yet the curves, only one of three shown here, rose to slightly different heights and the maxima occurred at different amounts of water added.

An account of the rheology of suspensions, emulsions, and semisolids is presented in Chapter 19, and the flow properties of powders are dealt with in Chapter 20. Consideration is given in Chapter 18 to the rheology of colloid materials,

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which find wide application in pharmacy as suspending agents. Boylan²³ considered some of the rheologic aspects of parenteral suspensions and emulsions.

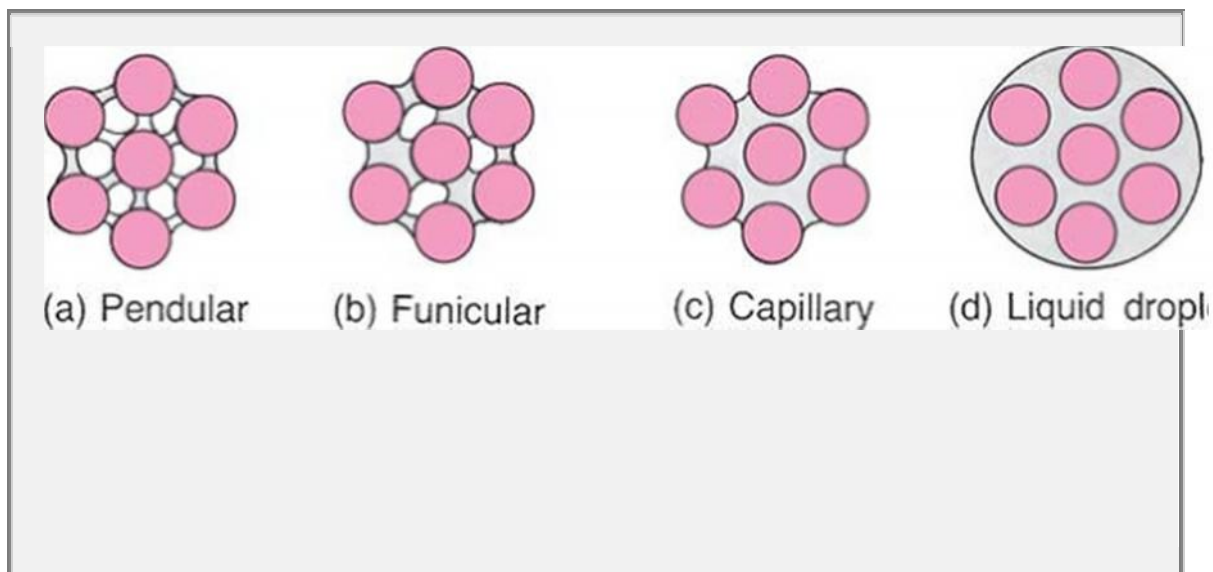


Fig. 19-28. The states of liquid saturation of a powder. (a) *Pendular* state with lenses of liquid at the contact points of the particles. (b) A mixture of liquid and air between the particles, producing the *funicular* state. (c) Pores filled with liquid to yield the capillary state. (d) Liquid droplets completely enveloping particles (the *liquid-droplet* state). (Modified from D. M. Newitt and J. M. Conway-Jones, *Trans. Inst. Chem. Eng.* **36**, 422, 1958.)

Table 19-3 Pharmaceutical Areas in which Rheology is Significant*

1. Fluids
 - a. Mixing
 - b. Particle-size reduction of disperse systems with shear
 - c. Passage through orifices, including pouring, packaging in bottles, and passage through hypodermic needles
 - d. Fluid transfer, including pumping and flow through pipes
 - e. Physical stability of disperse systems
2. Quasisolids
 - a. Spreading and adherence on the skin
 - b. Removal from jars or extrusion from tubes
 - c. Capacity of solids to mix with miscible liquids
 - d. Release of the drug from the base
3. Solids
 - a. Flow of powders from hoppers and into die cavities in tableting or into capsules during encapsulation
 - b. Packagability of powdered or granular solids
4. Processing
 - a. Production capacity of the equipment
 - b. Processing efficiency

*From A. Martin, G. S. Banker, and A. H. C. Chun, in H. S. Bean, A. H. Beckett, and J. E. Carless (Eds.), *Advances in Pharmaceutical Sciences*, Academic Press, London, 1964, Chapter 1. With permission.

A summary of the major areas of product design and processing in which rheology is significant is given in Table 19-3. Although the effects of processing can affect the flow properties of pharmaceutical systems, a detailed discussion of this area is outside the scope of this text. For an account of this topic as well as a comprehensive presentation of the theoretical and instrumental aspects of rheology, refer to the review by Martin et al.³ The theory and application of viscoelasticity were briefly reviewed in the previous section. Detailed discussions of this approach are given in the references cited.

Chapter Summary

In this chapter the basics of rheology were presented. An understanding of the viscosity of liquids, solutions, and dilute and concentrated colloidal systems has both practical and theoretical values in the pharmaceutical sciences. Rheology is involved in the mixing and flow of materials, their packaging into containers, and their removal prior to use, whether this is achieved by pouring from a bottle, extrusion from a tube, or passage through a syringe needle. The rheology of a particular product, which can range in consistency from fluid to semisolid to solid, can affect its patient acceptability, physical stability, and even biologic availability. Materials are classified according to types of flow and deformation. Finally, the theory and methods for determining the rheologic properties of pharmaceutical materials as well as the application to the pharmaceutical sciences were discussed.

Practice problems for this chapter can be found at thePoint.lww.com/Sinko6e.

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Chapter Legacy

Fifth Edition: published as Chapter 20 (Rheology). Updated by Patrick Sinko.

Sixth Edition: published as Chapter 19 (Rheology). Updated by Patrick Sinko.