

Phenomenological Viscoelasticity of a Heterogeneous Pharmaceutical Semisolid

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Abstract □ This study presents the results of an investigation of the viscoelastic properties of anhydrous lanolin USP, as determined by dynamic mechanical testing. The elastic shear modulus (G'), viscous shear modulus (G''), and loss tangent ($\tan \delta$) were determined as a function of shear frequency, ν , (0.01–10.0 Hz) and temperature, T , (0–30°). These viscoelastic parameters were found to be temperature and shear frequency dependent. Up to 100-fold changes in shear moduli and $\tan \delta$ values were observed with appropriate changes in T and ν . Many of the observed properties are also characteristic of high molecular weight polymers and can be attributed to a high degree of molecular structure. It was found that dynamic mechanical testing was a sensitive tool for measuring structural changes, and was especially useful in detecting a major structural transition well below the accepted melting temperature of anhydrous lanolin.

Keyphrases □ Viscoelasticity—properties of anhydrous lanolin, determination by dynamic mechanical testing □ Lanolin, anhydrous—viscoelastic properties as determined by dynamic mechanical testing □ Dynamic mechanical testing—determination of viscoelastic properties of anhydrous lanolin

The rheology of pharmaceutical semisolids can not be understood adequately without including a discussion of viscoelastic properties. The viscoelastic properties of pharmaceutical semisolids have not been adequately investigated because pharmaceutical scientists generally lack the appropriate testing equipment. Much of the existing literature on the measurement of viscoelasticity of pharmaceutical systems, including the use of dynamic mechanical testing, has been reviewed (1). It was apparent that dynamic mechanical testing could yield unique information that could not be obtained by other available methods, and that it was important that the application of dynamic mechanical testing to measure the viscoelastic properties of pharmaceutical systems be investigated and demonstrated. For this reason this study was undertaken using anhydrous lanolin.

Dynamic mechanical testing has been used primarily by materials scientists to characterize the viscoelastic properties of polymeric systems (2, 3). For example, polymers are routinely characterized for moduli, crystallinity, plasticizer effectiveness, filler effects, creep, and stress relaxation. A knowledge of these viscoelastic properties is necessary to determine proper manufacturing techniques and end-use properties of polymeric systems.

Many rheological testing procedures used by pharmaceutical scientists are insensitive to the microcrystalline or amorphous three-dimensional networks which determine basic rheological properties. Generally, these methods use a simple shear viscometer and determine a non-Newtonian viscosity (4–6). Simple shear methods destroy the structure that one is attempting to measure and introduce the additional parameter of structural variation with time. As a result, simple shear viscometers are unable to measure fundamental viscoelastic parameters such as elastic and viscous moduli (7, 8).

This report describes the nondestructive technique, dynamic mechanical testing, and the results obtained when it was used to measure the viscoelastic properties of anhydrous lanolin. Test samples were deformed sinusoidally with respect to time and temperature, and measurements of the strain amplitude, stress amplitude, and phase angle between them were made in terms of the complex dynamic modulus. The complex dynamic modulus was then resolved into a real component (elastic or storage modulus) and an imaginary component (viscous or loss modulus.) The elastic modulus is associated with the energy stored in elastic deformation, while the viscous modulus is associated with energy dissipation effects. These moduli were used to interpret the viscoelastic behavior of anhydrous lanolin in terms of the inter- and intramolecular interactions within the semisolid.

BACKGROUND

Phenomenological Viscoelasticity—The deformation of semisolids can be divided arbitrarily into two general types: spontaneously reversible deformation (called elasticity) and irreversible deformation (called flow). Most pharmaceutical semisolids exhibit both of these phenomena and are rheologically classified as viscoelastic. Phenomenological viscoelasticity can be categorized as either linear or nonlinear, but only the former can be described theoretically with uncomplicated mathematics. The fundamental viscoelastic parameters of a linear viscoelastic system do not depend on the magnitude of the stress (or strain) and the time during which it acts; the parameters for a nonlinear viscoelastic system are dependent on stress and/or strain magnitude. Complex constitutive equations are necessary to describe nonlinear viscoelasticity (9–11).

When the input strain on a test sample is small, the strain (γ) is proportional to the stress (σ) and the sample exhibits linear viscoelasticity. Though stress and strain are proportional, they are not in phase; in addition to moduli, a phase angle or damping term is determined. The elastic modulus (G'), viscous modulus (G''), complex modulus (G^*), and phase angle (δ) are a function of shear frequency (ν) and temperature (T). For shear experiments, frequency can also be expressed in terms of radians per second (ω) where ω equals $2\pi\nu$.

Linear viscoelasticity also means that the rheology must obey the Boltzmann superposition principle (2, 12). This principle states that mechanical behavior is a function of the entire stress history of a sample. It also assumes that the effect of each deformation is independent of the others, and that the behavior of the sample can be calculated by a simple addition of the effects that would occur if the deformations took place singly.

Most theoretical treatments of dynamic mechanical testing and linear viscoelasticity use stress as the forcing function, though either stress or strain may be used. Both methods are mathematically equivalent. A theoretical treatment of the mathematics of linear viscoelasticity is given in *Appendix I*. Two important relationships are derived therein which relate G^* , G' , G'' , and $\tan \delta$:

$$G^* = G' + iG'' \quad (\text{Eq. A11})$$

and

$$\tan \delta = G''/G' \quad (\text{Eq. A15})$$

where $\tan \delta$ is equal to the ratio of the energy dissipated–maximum energy stored per cycle of deformation.

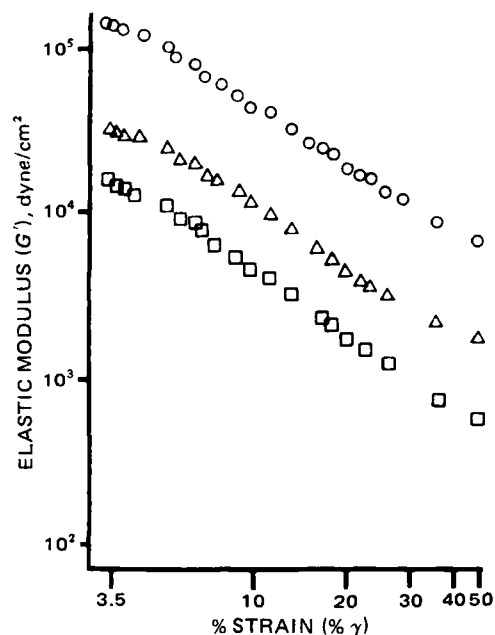


Figure 1—Effect of shear strain on the elastic modulus of anhydrous lanolin USP, at 20°. Key: (O) 10.0 Hz, (Δ) 1.0 Hz and (\square) 0.10 Hz.

The relationship of $\tan \delta$ and G'' to energy dissipation is fundamental to proper interpretation of dynamic mechanical data. A system with high values of $\tan \delta$ exhibits high energy dissipation and is termed high damping or lossy. The significance of various transitions of a system depend on the location and intensity of the damping peaks, where $\tan \delta$ or G'' is a maximum. The associated maximum in energy dissipation is interpreted in terms of an accountable increase in internal freedom, such as molecular segmental and side group motion or chain rotation. These changes can identify chemical or mechanical transitions.

Chemical Nature of Anhydrous Lanolin USP—Anhydrous lanolin, or wool fat, is designated by the USP to contain not more than 0.25% water (13). It is prepared by the purification of fatty matter (suint) obtained from the wool of sheep. The chemical composition of anhydrous lanolin is complex and can vary with the type of sheep (14). Conrad (15) and Barnett (16) have elaborated extensively on lanolin chemistry.

Anhydrous lanolin is chemically a wax and not a fat. It melts between 36 and 42°. In general, it contains trace amounts of hydrocarbons and free fatty acids, 3–4% free alcohols (mostly cholesterol), and 96% wax esters. Saponification of the wax esters gives a free lanolin alcohol fraction and a free fatty acid fraction. The free alcohol fraction is composed of aliphatic, sterol, triterpene, and unclassified alcohols in approximately equal proportions. The free fatty acid fraction is composed of ~10% normal acids ($n = 4$ –12), 4% hydroxy acids ($n = 6, 7$), 29% iso acids ($n = 3$ –11), 38% anteiso acids ($n = 2$ –13), and 19% unclassified acids.

From this information, anhydrous lanolin can be typified as a mixture of wax esters with a chemical structure much like a cholesterol molecule linked to a long-chain alcohol molecule. It can be postulated that 99% of the molecules in anhydrous lanolin have a molecular weight in the range of 400–950, with an average of ~700.

EXPERIMENTAL

Materials and Apparatus—The anhydrous lanolin USP used for all experiments was from the same production lot¹. The viscoelastic properties of anhydrous lanolin were determined with a mechanical spectrometer². This rotational rheometer puts into a test sample a known deformation at a specified rate and temperature (17).

Samples of anhydrous lanolin were mounted between 50-mm diameter, hollow stainless steel cone and plate test fixtures. The cone fixture was oscillated sinusoidally at determined shear strains (γ) and frequencies (ν) by the output from a digital function generator and phase analyzer³ (FGPA). Stresses from the sample were transmitted through the fixed plate to a multiple-stress detecting transducer. Deflections in the transducer were converted to electrical signals and relayed back to the

function generator and analyzer, where they were resolved into the storage and loss components of the complex modulus. The digital outputs of the FGPA were used to calculate the dynamic moduli in terms of dyne/cm² (Appendix II).

Temperature control was maintained by enclosing the sample and test fixtures in an environmental chamber⁴. The chamber used high-velocity recirculated air and nichrome heating coils. A platinum resistance bulb temperature sensor, located close to the test sample, maintained temperature to $\pm 0.5^\circ$. Temperatures below the ambient were achieved by placing solid carbon dioxide into the chamber, in the path of circulating air on the side of the sample away from the direction of flow. Excess temperature reduction was prevented by the heating coils. Chamber temperature was monitored by placing an iron–constantan thermocouple with digital readout in the path of circulating air, immediately upstream of the sample. The chamber was equipped also with a light and window for sample observation.

Differential thermal analysis⁵ was used to look for structural transitions in anhydrous lanolin. This thermoanalytical technique is often useful in detecting crystallization and crystalline and glass transitions.

Sample Preparation—Anhydrous lanolin was placed in a beaker and lowered into a hot water bath at 50°. After melting, the molten lanolin was placed into a desiccator which was evacuated by a filter pump to remove entrapped air from the samples. Deaerated samples were poured onto the flat test fixture, in a manner preventing air pocket formation. After 30 min at room temperature, the plate was mounted and the cone lowered to the preset gap. Extruded lanolin was removed and the sample was allowed to equilibrate at the test temperature for 15 min.

Description of Experiments—Samples were equilibrated at 0, 5, 10, 15, 20, 25, and 30°. At each temperature, a sample was oscillated over three decades of ν , 0.01–10.0 Hz, at γ equal to 3.54%⁶. Readouts of the FGPA were used to calculate G' , G'' , and $\tan \delta$ as a function of ν and T .

For differential thermal analysis, a sample in an aluminum pan and an empty identical reference pan were heated. A liquid nitrogen chamber was used to lower the initial temperature to -40° . The difference in T between the sample and the reference pan was recorded as function of T_r , the temperature of the reference cell.

RESULTS AND DISCUSSION

The dynamic mechanical properties of anhydrous lanolin were determined as a function of shear strain, frequency, and temperature.

Effects of Strain—The relationship between G' and γ , at 25°, is shown in Fig. 1. There is no apparent range of linear viscoelastic behavior over the entire range of γ studied (3.54–50.0%). Linear behavior would be identified as a region of constant G' with changing γ . Since linear viscoelastic behavior could not be achieved, the lowest obtainable γ (3.54%) was used in all experiments to ensure the least possible effect on molecular structure.

Because of observed nonlinear behavior, it may be said that the test samples in this study were not in their absolute rheological ground state. It has been reported that at least 24 hr were necessary for stresses produced in anhydrous lanolin by sample loading to relax prior to creep testing (18). In this study, it was not feasible to permit each sample to relax 24 hr before testing.

Even though the mechanical spectrometer was not able to reach a low enough γ to achieve linear behavior, it must be noted that the decline of G' with increasing γ is apparently a continuously smooth relationship, devoid of breaks or irregularities in the curve. Hence at any given γ , it can be assumed that there exists a small region around the corresponding point on the $\log G'$ versus $\log \gamma$ curve where linear viscoelastic behavior can be approximated. This is particularly true at low γ where the slope has significantly decreased. Therefore, an infinitesimal increase or decrease in deformation gives a negligible change in the value of $\log G'$. This justification for the use of linear viscoelastic theory to calculate dynamic moduli is reasonable and is commonly used in the literature.

Data Reproducibility—Since it was believed that the samples of anhydrous lanolin were not in a rheological ground state, and since reproducible data can only be obtained from reproducible structural states, it was necessary to examine data reproducibility. It was found that defined differences in sample mixing, setting time, and temperature equilibration time were found to produce differences in FGPA “a” and

¹ Ruger Chemical Co. Inc., Irvington-on-Hudson, N.Y.

² Model RMS-7200, Rheometrics, Inc., Union, NJ 07083.

³ Model SA-2200, Rheometrics, Inc., Union, NJ 07083.

⁴ Model EC-1000, Rheometrics, Inc., Union, NJ 07083.

⁵ Dupont Model 990.

⁶ Percentage shear strain is defined as $100 \times$ amplitude of oscillation/cone angle.

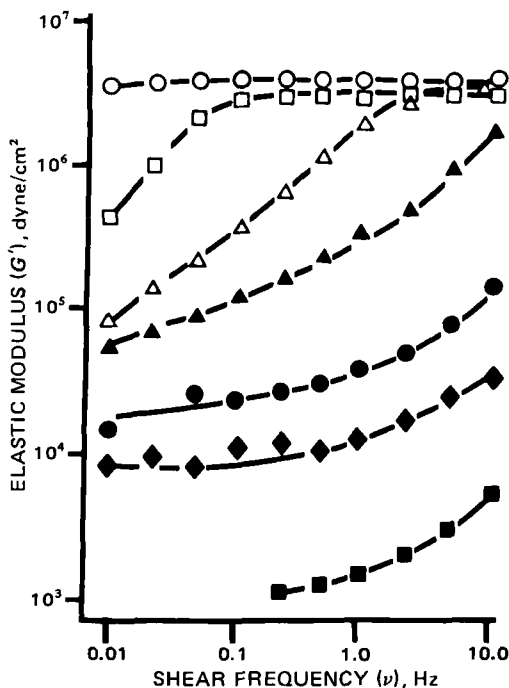


Figure 2.—Effect of shear frequency on the elastic modulus of anhydrous lanolin USP, at 3.54% strain. Key: (O) 0°, (□) 5°, (Δ) 10°, (▲) 15°, (●) 20°, (◆) 25°, and (■) 30°.

“b” outputs. Differences in observed moduli of up to 50% could be produced by exacerbated variations in sample preparation, loading, and equilibration. For that reason, care and practice were necessary to master the aforementioned sample preparation techniques before reproducible data could be obtained with confidence. It should be noted that variations of as much as $\pm 10\%$ in G' were tolerable as this would be small when compared with changes in G' due to temperature and shear frequency.

Effects of Temperature and Shear Frequency.—From the $\log G'$ and $\log G''$ versus $\log \nu$ plots (Figs. 2 and 3) it is evident that ν and T are profound determinants of the viscoelastic behavior of anhydrous lanolin. In general, an increase in T causes a decrease in G' , while an increase in ν causes an increase in G' . The effect of T and ν on G'' are not as simple to describe, as a maximum appears in some of the curves. If one assumes that a maximum exists in all of the curves, it can be stated that the maximum ν is increased with an increase in T . The patterns of change of G' and G'' with T and ν are characteristic and will be discussed in terms of proposed molecular changes. Figure 2 shows that an increase in ν increases G' over the temperature range of 30–25°. At 25°, this trend is modified by the formation of a plateau at the high end of the frequency spectrum. The extent of this plateau expands with decreasing T until it extends over the entire frequency spectrum at 0°.

In this plateau region, G' asymptotes to a limiting modulus, G_E . When this limiting value is attained, it can be concluded that the molecular chains are not able to rearrange themselves at all during the time of stressing. The molecules appear frozen and the only deformation is by distortion of primary and secondary bonds and bond angles. Such a limiting modulus is also observed for polymers in the glassy state (*i.e.*, at low temperatures).

Barlow and Lamb (19) gathered data of G_E for a number of organic compounds. These included glycerol, polytetrafluorethylene, 1,2,6-hexanetriol, 1,3-butanediol, and vulcanized and unvulcanized rubber. All of the G_E values for these substances were within a factor of two of 2×10^{10} dyne/cm², even though these compounds represent a molecular weight distribution from 90 to $>10^6$. These values can be compared with crystalline solids which generally have rigidity moduli between 10^{11} and 10^{12} dyne/cm². The values of G_E for the organic compounds studied by Barlow and Lamb are probably lower because they are not subject to the constraints of a crystal lattice. It was noted that the introduction of strong polar groups, hydrogen bonding, or polymerization generally caused increases in G_E , but these increases were small when compared with the magnitude of G_E . Hence it was suggested that the straining of van der Waals bonds and the flexing of main chain bonds are the origin of G_E as these phenomena are relatively independent of structure for polymers.

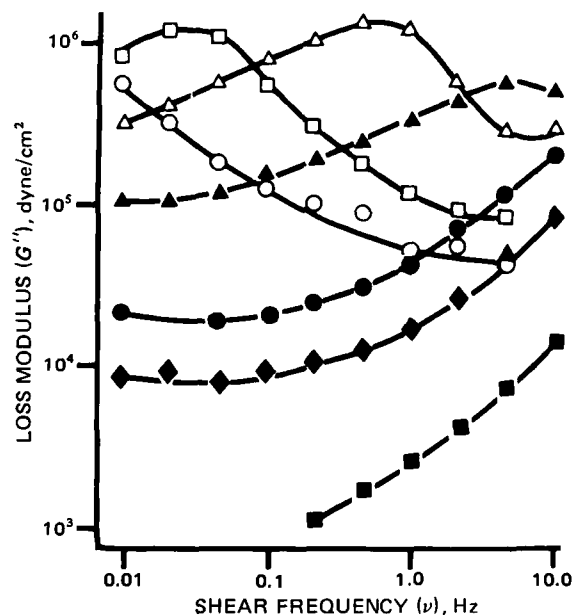


Figure 3.—Effect of shear frequency on the viscous modulus of anhydrous lanolin USP, at 3.54% strain. Key: (O) 0°, (□) 5°, (Δ) 10°, (▲) 15°, (●) 20°, (◆) 25°, and (■) 30°.

The value of G_E for anhydrous lanolin is $\sim 5 \times 10^6$ dyne/cm², a factor of 4×10^3 less than the values observed by Barlow and Lamb. This difference indicates that it may not be appropriate to refer to anhydrous lanolin as being in the glassy state. It must be noted that G_E was not reached for the listed organic compounds until T approached the vicinity of -80° . Hence, the plateau attained from 0 to 5° for anhydrous lanolin may not represent G_E , but instead a plateau in the rubbery region. Further testing at $T < 0^\circ$ may show a rise in G' until another plateau is attained at lower T . This assumption is reasonable when one considers the fact that anhydrous lanolin is an organic mixture with an average molecular weight of ~ 700 , which is within the range of molecular weights listed by Barlow and Lamb.

The appearance of the nonglassy state plateau between 0 and 5° can be explained on the basis that anhydrous lanolin is a complex mixture with each constituent having its own melting point. So at a given temperature, some fractions may be solid and others liquid. The solid fractions then act as a rigid matrix to give structure with the liquid fractions dispersed in its rigid matrix. Consequently, one could speculate that, from 0 to 5°, the solid matrix is sufficiently rigid to enable its elastic characteristic to mask any temperature-dependent contribution of the liquid fraction. Since the glassy state observed in the Barlow and Lamb work exhibited a considerably greater G_E at lower temperatures, it would be expected on the basis of this model that the contribution of the liquid fraction to G' would become evident as the temperature is lowered below 0° giving rise to an increase in G' until reaching the glassy state plateau.

Figure 3 shows that G'' behaves similarly to G' from 30 to 20°. At 15° however, a rounded peak appears between 2.15 and 10.0 Hz. With each successive drop in T , the location of the peak shifts horizontally to lower ν until, at 0°, the peak has apparently shifted to a ν below the range of frequency testing. The variation of G'' as opposed to G' is difficult to visualize in terms of molecular processes because it is basically a feature of a dynamic rather than a static response.

When ν is low, the molecules can rearrange themselves completely within the time scale of stressing. At maximum γ , energy is stored in the system by virtue of entropy effects. During the portion of the cycle in which σ decreases to zero, the stored strain energy is recovered elastically because the molecules rearrange faster than σ changes. Since the strain energy is almost completely elastically recoverable at low ν , the energy loss is small. Consequently G'' is small. On the other hand, G'' is small at high ν because the molecules are frozen in place and only pure elastic deformation occurs. G'' increases at intermediate ν because the molecules have time for only partial configurational rearrangement during a cycle of stressing.

At this point, it is necessary to consider the energetics responsible for the variation of dynamic moduli as a function of shear frequency and temperature. Aspects of this discussion have their foundation in the idea

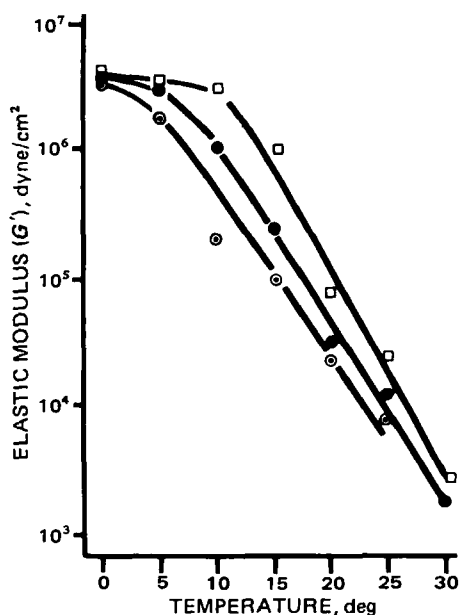


Figure 4.—Effect of temperature on the elastic modulus of anhydrous lanolin USP, at 3.54% strain. Key: (○) 0.0464 Hz, (●) 0.464 Hz, and (□) 4.64 Hz.

of a theory for rubber-like elasticity (2, 20). The idea of a network accounts for the main features of equilibrium value of rubber-like elasticity. The following account is a brief outline of the principles involved.

Consider a single molecule which possesses free rotation about all of the main chain bonds. Each C—C bond may rotate mutually provided a bond angle of $\sim 110^\circ$ is maintained. The most probable distance from the final carbon to the first carbon atom can be determined by assuming that each successive bond can fully rotate and using a probability distribution function. The most probable distance can be shown to be slightly greater than $(nl^2)^{1/2}$ where n is the total number of bonds, each of length l . For an amorphous rubber-like system, there are a large number of intertwining molecules each rapidly changing in configuration but on the average sufficiently coiled to have an end distance of approximately $(nl^2)^{1/2}$.

The state of maximum entropy (S) and minimum free energy (F)⁷ occurs when the molecules are in the most probable configurational distribution. Therefore, any change in entropy is due to a change in the distribution. When the system is strained it causes the configurational distribution to change to a less probable state and the distance between the first and final atoms of a molecular chain becomes greater than the average or most probable value. While the molecule is extended, the number of different molecular configurations, w_σ , which the molecule can attain is considerably less than the maximum number, w_m , obtainable in the most probable state. The subscript σ designates the extended state, while the subscript m designates the most probable state.

Straining a system in its most probable configurational state changes the configurational distribution to a less probable state, which results in a decrease in entropy. This decrease in entropy can be described according to Boltzmann's entropy relation:

$$\Delta S_\sigma = -k \ln(w_\sigma/w_m) \quad (\text{Eq. 1})$$

where ΔS_σ is the decrease in entropy on the stretching of an average molecule and k is the Boltzmann constant. The greater the extension of the molecule, the greater the decrease in entropy due to the smaller number of configurations (w_σ) it can attain.

The decrease in ΔS_σ causes an increase in ΔF_σ , change in the Helmholtz free energy of the system. By definition:

$$\Delta F_\sigma = \Delta E_\sigma - T\Delta S_\sigma \quad (\text{Eq. 2})$$

⁷ A good deal of confusion exists over which letter should be used to symbolize the free energy. The letter A is generally used as the Helmholtz free energy and G is used as the Gibbs free energy. A represents that part of the internal energy which is isothermally available, while G represents that portion of heat content which is isothermally available. It should be noted that $G = A + pV$, and hence $\Delta G = \Delta A + p\Delta V$. Since volume change has been assumed negligible in the anhydrous lanolin, $\Delta G \approx \Delta A$. The letter F will be used to represent free energy in this report because G is recognized in the rheological community as the shear modulus.

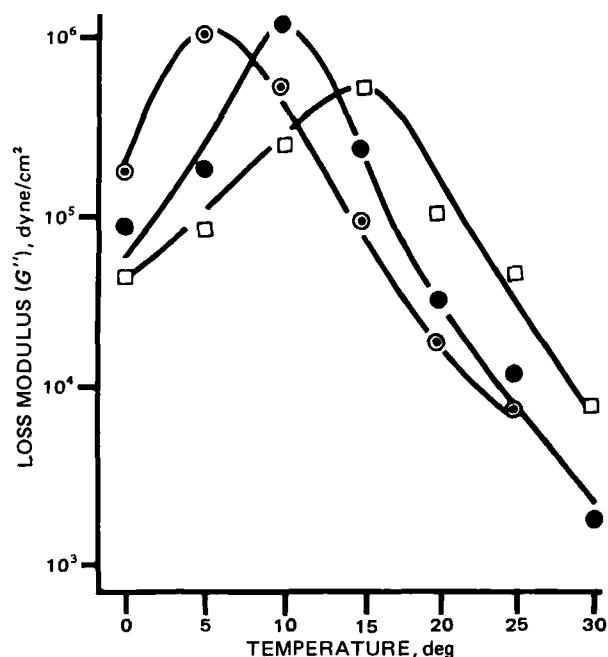


Figure 5.—Effect of temperature on the viscous modulus of anhydrous lanolin USP, at 3.54% strain. Key: (○) 0.0464 Hz, (●) 0.464 Hz, and (□) 4.64 Hz.

where ΔE_σ is the change in the internal energy of the system. The symbol ΔS_σ can be replaced with $-\Delta \bar{S}_\sigma$, the average entropy decrease per molecule, from the Boltzmann relation. This value is negative because the entropy change is decreasing. It can be assumed that the internal energy is constant, *i.e.*, $\Delta E_\sigma = 0$, because the average environment of each atom in the stretched and unstretched states are identical. Consequently:

$$\Delta F_\sigma = -(-\Delta \bar{S}_\sigma)T \quad (\text{Eq. 3})$$

which indicates that ΔF_σ is increasingly positive as $-\Delta \bar{S}_\sigma$ becomes more negative on molecular stretching. Since every system seeks to attain the state of least free energy (unstretched state), it can be deduced that elastic behavior is due to spontaneous changes which attempt to revert the system to the state of least free energy. Rubber-like elasticity is thus explained in terms of an entropic rather than an internal energetic effect.

The almost complete absence of viscous flow must also be accounted for by entanglements or crosslinks. These interaction or junction points give rise to a structured network, which is a function of ν and T . An increase in side-chain branching increases the probability of entanglements, while functional groups generally cause greater intermolecular attraction. Each of these phenomena results in an increase in structure and a loss in degrees of freedom. Consequently, when a system is strained, the entanglements and crosslinks decrease entropy further and increase the driving force to return the system to the state of least free energy.

Figures 4 and 5 give additional insight into the effects of T and ν upon the dynamic mechanical properties of anhydrous lanolin. As evident in Fig. 4, T and ν are inversely related. An increase in T decreases G' , while an increase in ν shifts the $\log G'$ versus T curves to higher temperatures. Similar shifting can be seen with $\log G''$ versus T curves as a function of ν (Fig. 5). Such behavior commonly is observed for amorphous polymers (3).

Tan δ or damping is a dimensionless parameter, which is defined as the ratio of $G''-G'$. More significantly, tan δ is also proportional to the ratio of the energy lost—energy stored in a cycle of deformation. The role of tan δ is not well known. It is often the most sensitive indicator of various molecular motions within a material. All mechanical properties, and especially tan δ , are extremely sensitive to crystalline or structural transitions, relaxation processes, and the morphology of multiphase systems such as crystalline and filled polymers.

Log tan δ versus T curves for anhydrous lanolin are illustrated in Fig. 6. At lower ν , a maximum is evident around 10° . With an increase in ν , the height and sharpness of each successive peak decreases until it has disappeared at the highest ν . With an increase in T , the damping curves converge (possibly at one point) in the neighborhood of 17° . To the right of the convergence region, the relationship between ν and tan δ is inverse of the relationship to the left of the convergence.

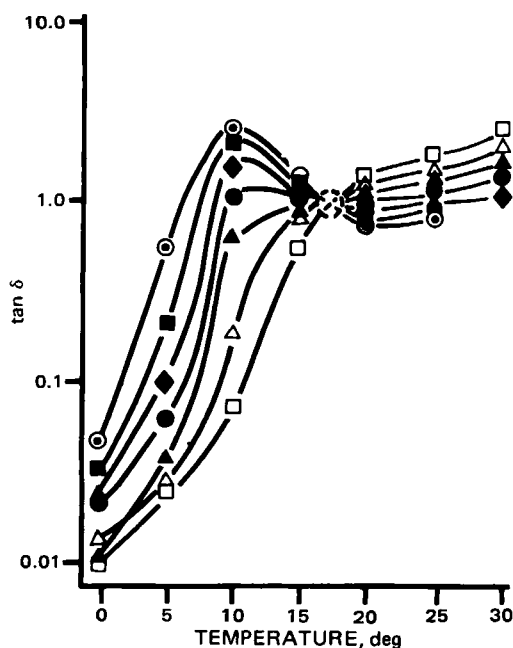


Figure 6.—Effect of temperature on the loss tangent of anhydrous lanolin USP, at 3.54% strain. Key: (○) 0.0464 Hz, (■) 0.10 Hz, (◆) 0.215 Hz, (●) 0.464 Hz, (▲) 1.0 Hz, (△) 2.15 Hz, and (□) 4.64 Hz.

At the convergence point, the damping properties of anhydrous lanolin are independent of ν , and the damping properties reverse with respect to ν at the convergence temperature. This is a very interesting phenomenon. The fact that there is a convergence point, where the material is independent of ν , suggests that this is only possible when constituent phases are in certain ratios, such that the effects of one phase cancel out the effects of another.

Evidence for a temperature-dependent transition can be found in a differential thermal analysis thermogram of anhydrous lanolin (Fig. 7). From -40 to 25° , there is a linear relationship between ΔT and T_r . A short shoulder develops at $\sim 20^\circ$. This peak falls slightly and is followed by another linear increase until a peak is attained at 30° . This peak then rolls off and descends to 40° , where another peak rises to peak at 45° . It is evident that changes in the structure of anhydrous lanolin are occurring over the entire temperature range. But since the test temperature range for dynamic mechanical testing was 0 – 30° , attention will be focused on the shoulder peak that occurs around 20° .

At least two factors are operating which could move the apparent peak to a lower T . One could be the consequence of a smaller peak, at $\sim 17^\circ$, adding onto a larger peak which occurs at $\sim 30^\circ$. By addition, the larger peak may have pulled the smaller peak toward the larger peak by several degrees. Consequently, the smaller peak may in reality lie several degrees below 20° . The shoulder, at 20° , is probably related to the mechanical transition which was evidenced by a peak in the $\log \tan \delta$ versus T plots at 10° , from 0.0464 to 0.464 Hz. Differences are often found between the thermally indicated and the mechanically determined temperature of transition.

The second factor that can account for a thermogram shift to higher T is the thermal lag of the sample and furnace environment, which is a function of the sample heating rate and the thermal conductivity of the sample. A large difference exists between the thermal conductivities of the aluminum sample pans and anhydrous lanolin. The difference, which is of the magnitude of 10^5 in favor of aluminum, can cause the entire thermogram to shift to higher temperatures⁸. For anhydrous lanolin, it can be approximated that the thermogram shift could be as high as 5 – 10° . Consequently, correction for peak addition and sample thermoconductivity could place a thermogram peak in the sample temperature region where the damping maxima occur in Fig. 6.

It should be noted that this type of thermogram generally should be expected for materials composed of a large range of molecular weights and

functional groups, e.g., butter, lard, and cocoa butter (22). Essentially, these materials have a wide (50 – 100°) apparent melting range.

A better way to describe the behavior of fats, waxes, and oils is to use the concept of degrees of freedom gained as a function of T . Therefore, the thermogram for anhydrous lanolin shows that the sample is in the process of gaining degrees of freedom throughout the temperature range studied. Degrees of freedom could be gained by a decrease in the inter- and intramolecular forces. For example, a new degree of rotational freedom can allow a greater number of molecular configurations.

Heijboer (23) has presented a $\log \tan \delta$ versus T plot similar in appearance to Fig. 6. He showed that $\tan \delta$ can be used to identify the composition of a composite polymer blend. The dynamic mechanical properties of a series of copolymers of cyclohexyl methacrylate and methyl methacrylate were examined as a function of weight, percentage composition, and T at constant ν . At any given T on the $\log \tan \delta$ versus T plot, $\tan \delta$ maxima heights vary with percentage composition rather than ν as exhibited with anhydrous lanolin.

The composition of anhydrous lanolin as defined previously is a heterogeneous mixture of esters, alcohols, and fatty acids; therefore, a correlation between composition and ν must be considered. One could speculate that certain frequencies have orienting effects on specific fractions (entire molecules or portions thereof) of anhydrous lanolin, creating new molecular environments and consequently new molecular interactions. Shear frequency, like T , influences the degrees of freedom possessed by molecules in anhydrous lanolin. The degrees of freedom gained or lost vary for each molecular component. The effect of ν on the viscoelastic properties of anhydrous lanolin is similar to effect of composition upon Heijboer's methacrylate systems (23). It should be noted that Heijboer does not venture to describe or speculate on the nature of the convergence point.

CONCLUSIONS

Anhydrous lanolin is a thermorheologically complex material whose viscoelastic properties can be characterized with dynamic mechanical testing. Its viscoelastic properties are a function of strain, temperature, shear frequency, and shear history. Even though anhydrous lanolin is a relatively low molecular weight mixture, it has certain viscoelastic properties which are characteristic of higher molecular weight polymers. These properties include the presence of a previously undescribed structural transition and the existence of a limiting value of the elastic modulus.

The extent of data generated in this study does not permit definite conclusions to be drawn about the nature of individual inter- and intramolecular interactions of the various molecular fractions. More insight on interactions may result from studies on purified fractions of known proportion. Ultimately, these studies may enhance the ability to predict *a priori* the optimum blending of semisolid components for desired end-use properties.

APPENDIX I: MATHEMATICAL TREATMENT OF THE THEORY OF LINEAR VISCOELASTICITY

In a dynamic experiment, the stress and strain are sine or cosine functions and they can be treated as rotating vectors. The magnitudes of the vectors are equivalent to the amplitudes of the maximum stress and maximum peak strain. One revolution of the vector is equal to a full cycle of oscillation (Fig. 8).

The stress, strain, and rate of stress are complex variables which can be defined by the following equations:

$$\sigma^* = \sigma_0 \exp[i(\omega t + \delta)] \quad (\text{Eq. A1})$$

$$\gamma^* = \gamma_0 \exp(i\omega t) \quad (\text{Eq. A2})$$

where σ^* is the complex stress, γ^* is the complex strain, σ_0 is the maximum magnitude of the stress, γ_0 is the maximum magnitude of the strain, δ is the phase angle between strain and stress, t is time, ω is the angular frequency, and i equals $(-1)^{1/2}$. Differentiation of Eq. A2 is equivalent to a 90° counterclockwise rotation of the vector so that:

$$d\gamma^*/dt = i\omega\gamma_0 \exp(i\omega t) = \omega\gamma_0 \exp[i(\omega t + \pi/2)] \quad (\text{Eq. A3})$$

where $\omega\gamma_0$ is the magnitude of the rate of strain vector.

The complex shear modulus, G^* , is defined as the ratio of σ^* to γ^* :

$$G^* = \sigma^*/\gamma^* \quad (\text{Eq. A4})$$

⁸ The thermal conductivity of pure aluminum, between 0 and 30° , is ~ 34 cal/sec cm deg. In contrast, the thermal conductivities of organic compounds similar to those found in anhydrous lanolin are of the order of 2 – 4×10^{-4} cal/sec cm deg (21). For a heating rate of $10^\circ/\text{min}$ and a sample thickness of 0.25 mm, a lag of $\sim 5^\circ$ could occur. A sample thickness of 0.5 mm would mean a lag of 10° .

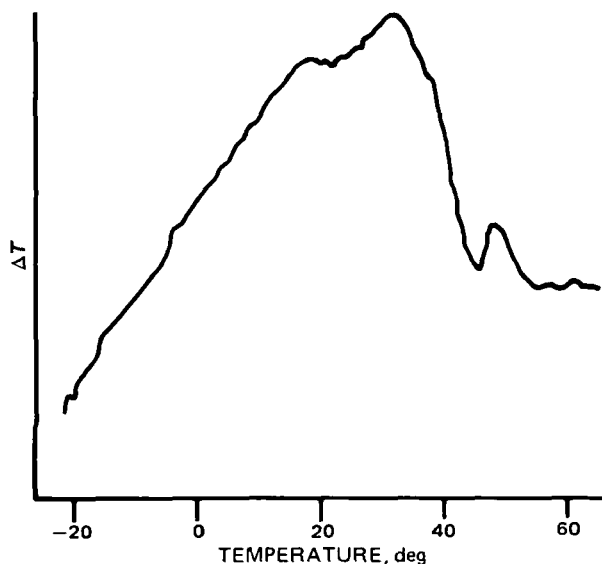


Figure 7.—Differential thermal analysis thermogram for anhydrous lanolin USP; 10°/min, normal atmosphere.

By substituting Eqs. A1 and A2 into Eq. A3 we obtain:

$$G^* = (\sigma_0/\gamma_0) \exp[i(\omega t + \delta)] \exp(-i\omega t) \quad (\text{Eq. A5})$$

or

$$G^* = (\sigma_0/\gamma_0) \exp(i\delta) \quad (\text{Eq. A6})$$

From Euler's formula, one knows that:

$$\exp(i\delta) = \cos\delta + i(\sin\delta) \quad (\text{Eq. A7})$$

Some special values of the complex exponential are $\exp(i\pi/2) = i$ and $\exp(i\pi) = -1$. Equation A7 can then be substituted into Eq. A6 to obtain:

$$G^* = (\sigma_0/\gamma_0) \cos\delta + i(\sigma_0/\gamma_0) \sin\delta. \quad (\text{Eq. A8})$$

But:

$$G' = (\sigma_0/\gamma_0) \cos\delta \quad (\text{Eq. A9})$$

and

$$G'' = (\sigma_0/\gamma_0) \sin\delta \quad (\text{Eq. A10})$$

Consequently:

$$G^* = G' + iG'' \quad (\text{Eq. A11})$$

where G' is known as the elastic modulus, storage modulus, or the real modulus. The viscous or loss modulus, G'' , is also known as the imaginary modulus.

The relationship between G' , G'' , and G^* can also be examined by referring to Fig. 8. One can see that the stress vector can be considered as the sum of two perpendicular components, one of which, σ' ($= \sigma_0 \cos\delta$), is in phase with the strain and the other, σ'' ($= \sigma_0 \sin\delta$), is out of phase. Two corresponding moduli can be defined as:

$$G' = (\sigma'/\gamma_0) = (\sigma_0/\gamma_0) \cos\delta = G^* \cos\delta \quad (\text{Eq. A12})$$

and

$$G'' = (\sigma''/\gamma_0) = G^* \sin\delta \quad (\text{Eq. A13})$$

Hence, G' is also referred to as the in-phase modulus, while G'' is given the out-of-phase designation. By taking the square root of the sum of the squares of Eqs. A12 and A13, one obtains:

$$G^* = [(G')^2 + (G'')^2]^{1/2} \quad (\text{Eq. A14})$$

This relationship between G' , G'' , and G^* may be illustrated vectorially as in Fig. 9. The angle between G^* and G' , δ , is known as the phase angle, and it is the lag between the forcing stress function and the resultant function, strain. It can also be seen from Fig. 9 that:

$$\tan\delta = G''/G' \quad (\text{Eq. A15})$$

The physical significance of $\tan\delta$ becomes clearer when one considers

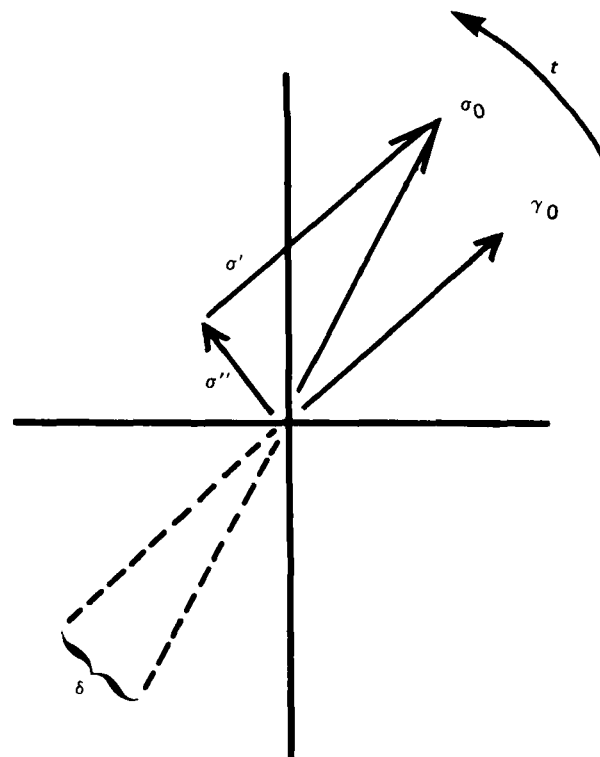


Figure 8—Rotating vector treatment of sinusoidal deformation.

the energy dissipated and stored per cycle of deformation for linearly viscoelastic materials. The energy dissipated per cycle is:

$$W = \oint \sigma d\gamma = \oint \sigma (d\gamma/dt) dt \quad (\text{Eq. A16})$$

So if it is assumed that the stress is the forcing function according to:

$$\sigma(t) = \sigma_0 \sin(\omega t) \quad (\text{Eq. A17})$$

and the resultant strain can be represented by:

$$\gamma(t) = \gamma_0 \sin(\omega t - \delta) \quad (\text{Eq. A18})$$

then Eqs. A17 and A18, with the proper trigonometric identity can be used to expand Eq. A16 to:

$$\Delta W = \sigma_0 \gamma_0 \omega \oint \sin(\omega t) [\cos(\omega t) \cos\delta + \sin(\omega t) \cos\delta] dt \quad (\text{Eq. A19})$$

The first term inside of the closed integral is an odd function and becomes zero upon integration. The value of the integral of the second term is $(\pi/\omega) \sin\delta$, so that the energy dissipated per cycle of deformation is given as:

$$\Delta W_{\text{cycle}} = \pi \sigma_0 \gamma_0 \sin\delta \quad (\text{Eq. A20})$$

The maximum energy stored per cycle, analogous to the potential energy of a spring at the maximum displacement, is:

$$W = (1/2) G' \gamma_0^2 \quad (\text{Eq. A21})$$

where G' is the elastic modulus of the material, equivalent to the spring constant. Since $G' = G^* \cos\delta$ and $G^* \gamma_0 = \sigma_0$, then:

$$W = (1/2) \sigma_0 \gamma_0 \cos\delta \quad (\text{Eq. A22})$$

Eqs. A20 and A22 can be combined to give the ratio of energy dissipated—maximum energy stored per cycle as:

$$\Delta W/W = 2\pi \tan\delta = 2\pi(G''/G') \quad (\text{Eq. A23})$$

APPENDIX II: CALCULATION OF DYNAMIC MODULI

During testing, digital readouts of "a" and "b" are given at each test frequency by the function generator and phase analyzer. The readout "a" is directly proportional to G' and "b" is directly proportional to G'' . By neglecting inertial forces and utilizing infinitesimally small deformations, these stress-strain ratios can be related to angular displace-

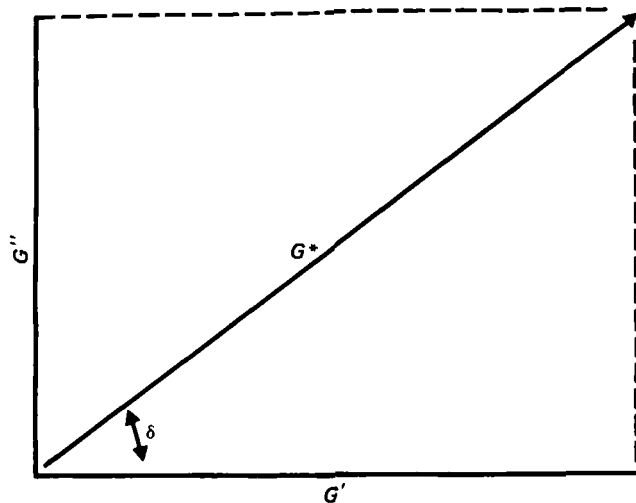


Figure 9—Vectorial resolution of components of the complex modulus in sinusoidal deformation.

ment-torque ratios by form factors that depend on apparatus geometry. For the viscoelastic semisolid in these experiments, the deformation corresponds to simple shear torsion between cone and plate.

The cone and plate geometry produces a strain that is nearly homogeneous throughout the sample and can provide information for the shear strain-stress ratio in small deformations. The geometrical factors for torsion between cone and plate (2) are:

$$\gamma_0/\sigma_0 = k\alpha/M_0 \quad (\text{Eq. A24})$$

and

$$k = 2\pi r^3/3\beta \quad (\text{Eq. A25})$$

where k is the form factor, γ_0 is the maximum shear strain, σ_0 is the maximum shear stress, r is the radius of sample (cm), α is the angular displacement (radians), M_0 is the torque, and β is the angle between cone and plate. If inertial and edge effects are assumed negligible, the maximum stress is expressed as:

$$\sigma_0 = 3M_0/2\pi r^3 \quad (\text{Eq. A26})$$

while the maximum strain is:

$$\gamma_0 = \alpha/\beta \quad (\text{Eq. A27})$$

The "a" and "b" outputs of the function generator and phase analyzer are equivalent to the following expressions:

$$a = \frac{M_0(\cos\delta)}{\alpha(980 \text{ dyne/g})(10^4 \text{ g cm})} \quad (\text{Eq. A28})$$

and

$$b = \frac{M_0(\sin\delta)}{\alpha(980 \text{ dyne/g})(10^4 \text{ g cm})} \quad (\text{Eq. A29})$$

The values of 980 dyne/g and 10^4 g cm are instrument constants dependent on the transducers and torque control setting used in the experiments. By substituting Eqs. A26 and A27 into Eqs. A28 and A29, respectively, one obtains:

$$a = \frac{\sigma_0 2\pi r^3 (\cos\delta)}{3\beta \gamma_0 (980 \text{ dyne/g})(10^4 \text{ g cm})} \quad (\text{Eq. A30})$$

and

$$b = \frac{\sigma_0 2\pi r^3 (\sin\delta)}{3\beta \gamma_0 (980 \text{ dyne/g})(10^4 \text{ g cm})} \quad (\text{Eq. A31})$$

Eqs. A9 and A10 are then combined with Eqs. A30 and A31, respectively, to obtain:

$$G' = \frac{3\beta(980 \text{ dyne/g})(10^4 \text{ g cm})(a)}{2\pi r^3} \quad (\text{Eq. A32})$$

and

$$G'' = \frac{3\beta(980 \text{ dyne/g})(10^4 \text{ g cm})(b)}{2\pi r^3} \quad (\text{Eq. A33})$$

APPENDIX III: GLOSSARY

Where applicable, the symbols in this report conform to those proposed as a uniform standard by the Society of Rheology⁹ (24).

E	= internal energy of a system
F	= free energy of a system
G'	= elastic, real, or storage modulus
G''	= viscous, imaginary, or loss modulus
G^*	= complex modulus
G_E	= limiting value of G'
M_0	= torque
R	= gas constant
S	= entropy
T	= temperature
ΔT	= temperature difference between sample and reference pan
T_r	= temperature of reference pan
W	= energy stored per cycle of deformation
ΔW	= energy dissipated per cycle of deformation
a	= readout of FGPA directly proportional to G'
b	= readout of FGPA directly proportional to G''
i	= $(-1)^{1/2}$
k	= Boltzmann's constant
l	= bond length between atoms
r_σ	= distance between first and final atoms of a molecular chain
t	= time
w_σ	= number of obtainable molecular configurations in extended state
w_m	= maximum number of molecular configurations obtainable in the most probable state
α	= angle of oscillation
β	= cone angle
δ	= phase angle between stress and strain vectors
γ	= strain
$\dot{\gamma}$	= rate of strain
γ_0	= maximum strain amplitude
γ^*	= complex strain
σ	= stress
σ'	= real component of complex stress
σ''	= imaginary component of complex stress
σ^*	= complex stress
σ_0	= maximum stress amplitude
ν	= shear frequency (Hz)
ω	= angular shear frequency (rad/sec)

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Temperature-Frequency Equivalence of the Viscoelastic Properties of Anhydrous Lanolin USP

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Received April 5 1982, from the College of Pharmacy and Institute of Materials Science, University of Connecticut, Storrs, CT 06268. Accepted for publication July 15, 1982. * Present address: Department of Pharmaceutics, Smith Kline and French Laboratories, Philadelphia, PA 19101.

Abstract □ Methods of data analysis novel to pharmaceutical semisolids have been applied to the dynamic mechanical data obtained for anhydrous lanolin USP. It was found that the viscoelastic parameters determined over a wide range of temperatures and shear frequencies could be superposed. Elastic moduli (G') and viscous moduli (G'') obtained at low temperatures (T) and frequencies (ν), were equivalent to moduli obtained at high T and ν . Empirical shifts of modulus versus shear frequency data obtained at different temperatures were used to produce G' and G'' versus ν master curves (complete log modulus versus log frequency behavior at a constant temperature). A method of reduced variables, in conjunction with an Arrhenius-type relation, proved useful in calculating the energy of activation for the structural processes involved in a major mechanical transition.

Keyphrases □ Viscoelasticity—properties of anhydrous lanolin determined by dynamic mechanical testing, temperature-frequency equivalence, superposition of parameters □ Anhydrous lanolin—viscoelastic parameter determination, temperature-frequency equivalence □ Dynamic mechanical testing—viscoelastic parameter determination for anhydrous lanolin, energy of activation for mechanical transitions

Most research which has examined the effect of temperature on viscoelastic properties has focused on rubber and nonpharmaceutical synthetic polymers (1, 2). Though the effect of temperature on viscosity has been well documented for pharmaceutical systems, little information is available on the effect of temperature on their viscoelastic properties (3, 4).

In the preceding paper, data showed that the viscoelastic properties of anhydrous lanolin USP are significantly dependent on temperature as well as shear frequency (5). Small changes in temperature caused dramatic shifts in modulus versus shear frequency plots. This report examines those shifts and presents a method of reduced variables, which is novel to pharmaceutical systems, to analyze the data.

THEORETICAL

The viscoelastic properties of polymeric systems have been shown to be dependent on temperature and shear frequency. According to the theory of rubber-like elasticity, the elastic moduli of ideal elastomers are proportional to absolute temperature (6). Since the deformation of a rubber-like material is an activated process in which molecular segments

can only move by overcoming potential barriers, a direct relationship exists between the temperature and time dependence of viscoelastic properties.

Dynamic mechanical data taken over a range of shear frequencies (which is equivalent to reciprocal time) can be superposed in the same manner that time-temperature superposition is applied to creep and stress relaxation data (7-10). This phenomenon is extremely useful because the limitations of instrumentation or time often do not allow the measurement of a complete modulus versus shear frequency spectrum. In spite of this limitation, a curve-shifting procedure can be used to construct a master curve (complete log modulus versus log frequency spectrum at a given temperature). A change in temperature shifts the distribution of modulus curves without changing the shape of the function. The shift of a modulus curve is quantitated in terms of a_T , the shift factor.

Mathematically, the concept of temperature-shear frequency superposition can be expressed as:

$$G(T_R, \nu) = G(T, \nu/a_T) \quad (\text{Eq. 1})$$

where G is either the elastic or viscous modulus, ν is the shear frequency, T_R is the reference temperature of superposition, T is the test temperature, and a_T is the shift factor. The effect of a change in temperature is the same as applying a multiplicative factor to the shear frequency scale (i.e., an additive factor to the log shear frequency scale). Ideally, there is often an inherent change in modulus brought about by changes in temperature. There is also a need to correct for the change in sample mass per unit volume as a function of temperature. Each of these changes are compensated for by vertical shifts during the construction of the log modulus versus log frequency master curve.

Consequently, these considerations lead to:

$$\frac{G(T_R, \nu)}{T_R \rho(T_R)} = \frac{G(T, \nu/a_T)}{T \rho(T)} \quad (\text{Eq. 2})$$

where $\rho(T_R)$ and $\rho(T)$ are the densities of the test sample at the reference temperature and test temperature, respectively (8). Division by the test temperature corrects for changes in modulus due to the inherent dependence of modulus on temperature, while division by the density corrects for volume changes. To construct a master curve, a reference temperature is arbitrarily chosen and moduli are measured at various shear frequencies and temperatures.

By rearranging Eq. 2, the modulus at any shear frequency with respect to the reference temperature can be expressed as:

$$G(T_R, \nu) = \frac{T_R \rho(T_R)}{T \rho(T)} G(T, \nu/a_T) \quad (\text{Eq. 3})$$

The shift factors are a function of temperature and are determined relative to the reference temperature. The values of the shift factors must be found empirically by matching the results of adjacent temperatures.