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

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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:

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

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:

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

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:

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

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.
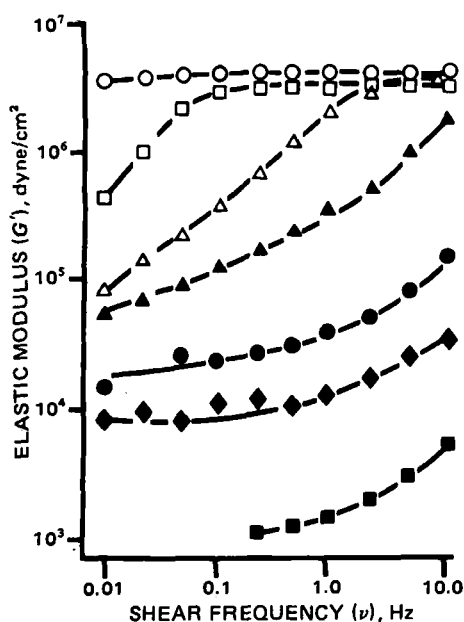
Figure 1—*Effect of shear frequency on the elastic modulus of anhydrous lanolin USP, at 3.54% strain. Key: (O) 0°, (□) 5°, (△) 10°, (▲) 15 °, (●) 20°, (◆) 25°, and (■) 30°.*

Ferry was among the first to use this technique, so the procedure is often referred to as a Ferry reduction scheme (1, 9, 11). Superposition, which is also referred to as the method of reduced variables, can reduce experimental work and extend the effective frequency range of results obtained with an instrument of limited frequency capabilities. When the temperature of testing is varied through an appropriate temperature range, a reduced frequency range of many more decades usually can be covered.

If it is theorized that the temperature dependence of the shift factors takes on the Arrhenius form, then:

$$a_T = A \exp(E_a/RT) \tag{Eq. 4}$$

where A is the preexponential term, R is the gas constant, T is temperature, and E_a is the energy of activation (1, 12, 13). By taking the logarithm and then differentiating both sides of Eq. 4, it can be rearranged to obtain:

$$E_a = 2.303R \frac{d(\log a_T)}{d(1/T)} \tag{Eq. 5}$$

Therefore, the shift factors of superposition can be plotted as $\log a_T$
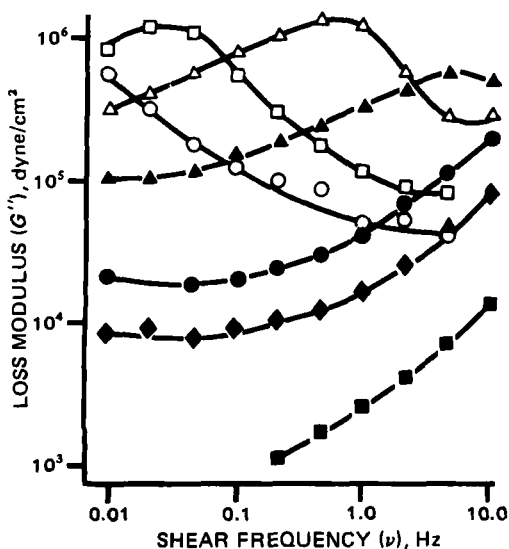

Figure 2—*Effect of shear frequency on the viscous modulus of anhydrous lanolin USP, at 3.54% strain. Key: (O) 0°, (□) 5°, (△) 10°, (▲) 15 °, (●) 20°, (◆) 25°, and (■) 30°.*
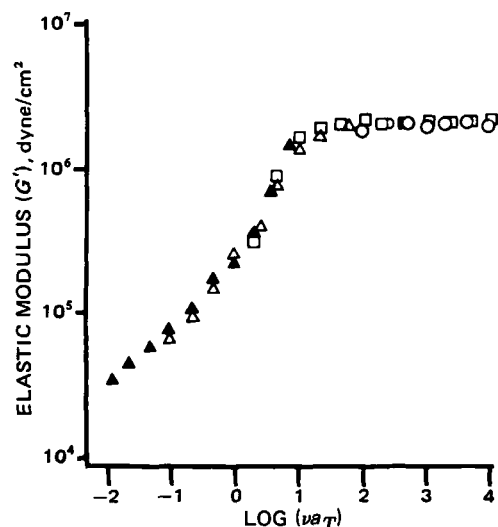

Figure 3—*Reduced frequency master curve of elastic modulus for anhydrous lanolin USP. Key: (O) 0°, (□) 5°, (△) 10°, and (▲) 15°.*

versus $(1/T)$ and the E_a for a given transition can be calculated from the slope of the plot.

In cases of amorphous polymers where the data are taken near the glass transition, the shift factors may obey an empirical equation developed by Williams, Landel, and Ferry (14). This relationship, known as the W-L-F equation, is written as:

$$\log a_T = -C_1(T - T_g)/(C_2 + T - T_g) \tag{Eq. 6}$$

where C_1 and C_2 are constants and T_g is the glass transition temperature. The glass transition temperature is that temperature below which the configurational rearrangements of polymer chain backbones essentially cease. The empirical constants, C_1 and C_2, were originally thought to be universal but have hence shown slight variation from polymer to polymer (6). The apparent energy of activation for a transition can also be calculated for data that fit the W-L-F relationship. By taking the derivative of Eq. 6 with respect to T, one obtains:

$$d(\log a_t)/dt = -C_1C_2/(C_2 + T - T_g)^2 \tag{Eq. 7}$$

Equation 7 can then be combined with Eq. 5 to obtain:

$$E_a = 2.303RC_1C_2T^2/(C_2 + T - T_g)^2 \tag{Eq. 8}$$

The magnitude of the energy of activation is an indication of the magnitude of the transition. Primary transitions usually have an energy of activation >40 kcal. Their damping peaks will shift ~7–10° for every decade change in frequency. Minor or secondary transitions with much lower energies of activation are more sensitive to frequency and show greater movement on the temperature scale with changes in frequency.
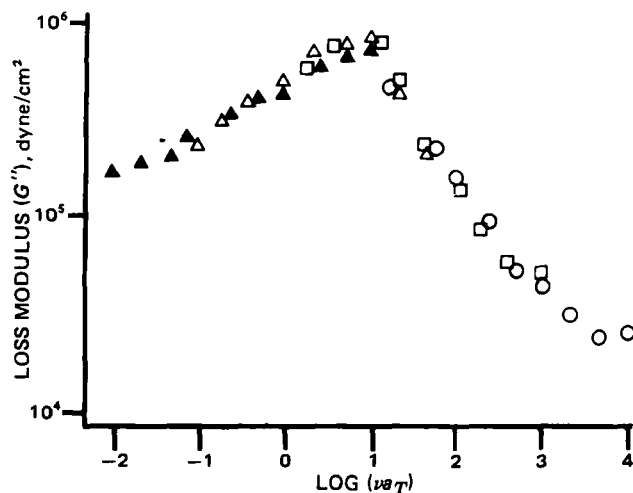

Figure 4—*Reduced frequency master curve of viscous modulus for anhydrous lanolin USP. Key: (O) 0°, (□) 5°, (△) 10°, and (▲) 15°.*

Table I—Shift Factors Determined by Superposition of Elastic Modulus *versus* Frequency Curves

$T°$	$T - T_R$	$G'(T_R°,\nu \text{ Hz}) = G'(T°,\nu \text{ Hz}/a_T)$	a_T	$\log a_T$
0	−15	$G'(15,0.01) = G'(0,46.3/a_T)$	4637	3.67
5	−10	$G'(15,0.01) = G'(5,2.15/a_T)$	215	2.33
10	− 5	$G'(15,0.01) = G'(10,0.10/a_T)$	10	1.00
15	0	$G'(15,0.01) = G'(15,0.01/a_T)$	1	0

Table II—Shift Factors Determined by Superposition of Viscous Modulus *versus* Frequency Curves

$T°$	$T - T_R$	$G''(T_R°,\nu \text{ Hz}) = G''(T°,\nu \text{ Hz}/a_T)$	a_T	$\log a_T$
0	−15	$G''(15,0.01) = G''(0,46.3/a_T)$	4637	3.67
5	−10	$G''(15,0.01) = G''(5,2.15/a_T)$	215	2.33
10	− 5	$G''(15,0.01) = G''(10,0.10/a_T)$	10	1.00
15	0	$G''(15,0.01) = G''(15,0.01/a_T)$	1	0

EXPERIMENTAL

The viscoelastic properties of anhydrous lanolin USP were determined with a mechanical spectrometer[1]. Complete descriptions of the materials, apparatus, method of sample preparation, and experimental procedures were given in the preceding paper (5). The procedures for calculating the elastic modulus (G') and the viscous modulus (G'') as a function of shear frequency (ν) and temperature (T) were also discussed.

RESULTS AND DISCUSSION

As previously reported, the dynamic mechanical properties of anhydrous lanolin are dependent on ν and T (5). Examination of the elastic modulus and loss modulus *versus* shear frequency curves obtained at that time (reproduced in Figs. 1 and 2, respectively) indicates that these curves lend themselves to temperature–frequency superposition. By using the superposition methods of Ferry (1) and Tobolsky (8), it was found that empirical shifts of these curves could produce the log modulus *versus* log νa_T master curves shown in Figs. 3 and 4.

The shifting procedure matched portions of adjacent curves by horizontal shifting (and minor vertical shifting as necessary) such that only one smooth composite curve resulted. The horizontal shift from the curve at the reference temperature was quantitated in terms of a_T. The reference temperature used was 15°, the highest temperature at which both the elastic modulus and viscous modulus curves fit the reduction scheme. The shift factors obtained by constructing Figs. 3 and 4 are tabulated in Tables I and II.

The shift factor calculations were made on the assumption that the density (and hence the test sample volume) was constant over the entire range of superposition (0–15°). In actuality, the density is a function of temperature and changes in sample volume may have accounted for minor vertical shifts of the modulus curves. Vertical adjustments were not uniform and were essential to produce smooth master curves.

The master curves of log modulus *versus* log νa_T can be used to represent the viscoelastic behavior of anhydrous lanolin at shear frequencies up to 10^5 Hz (628,000 radians/sec) at 15°. This exceeds the maximum shear frequency used in these tests by four decades of frequency. Consequently, the two master curves can be used to predict the dynamic moduli of anhydrous lanolin at shear frequencies which are probably unobtainable with any commercially available mechanical property tester. Knowledge of the mechanical properties of a pharmaceutical
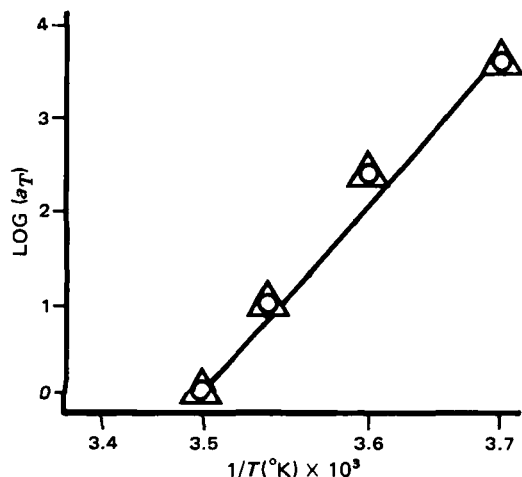
semisolid at high shear frequencies is of more than academic interest. The rates of shear of many pharmaceutical processes such as mixing, milling, filling, extrusion, and application approach the magnitude of 10^4 Hz (15).

For polymeric materials, T_R is usually taken to be the glass transition temperature T_g. The glass transition temperature is the temperature at which the polymer undergoes transition from a rubbery to a glassy state. At temperatures above T_g, the polymer is generally soft and flexible and is either an elastomer or a very viscous fluid. The glass transition temperature is important because mechanical properties change profoundly in the region of the glass transition. It is in this region of transition where a temperature–frequency reduction scheme is most applicable (11).

For anhydrous lanolin, the modulus curves are horizontally superposable only over the temperature range of 0–15°. Hence, it is reasonable to say that anhydrous lanolin undergoes a major mechanical transition in this temperature range, from a rubber-like to a nonrubber-like state. The reduction scheme does not hold at temperatures >15° due to the loss of the rubber-like structure.

Previously it was reported that the damping curves (log tan δ *versus* T) for anhydrous lanolin were at a maximum at ~15° (5). The damping maxima were suggested as being a point of significant structure change. These curves support the hypothesis that anhydrous lanolin may be in transition from a nonrubber-like to a rubber-like state.

In Fig. 5 it appears that the shift factors follow the Arrhenius relationship. The apparent energy of activation (E_a) for the molecular processes involved was calculated from the plot of log a_T *versus* $1/T$ using a least-squares fit and Eq. 5. The E_a was found to be ~90 kcal. A plot of this type can be curvilinear for polymeric materials. In such cases, E_a is temperature dependent and is approximated from the slope of the tangent line at any given point on the curve.

The significance of the value of E_a for anhydrous lanolin becomes more evident when the E_a is compared with values for polymeric systems. For main glass transitions where T_R is taken as T_g, the E_a is of the order of 10^5 cal/mole (2). Secondary transitions at cryogenic temperatures are of the order of 10^3–10^4 cal/mole. Comparison of the E_a for anhydrous lanolin with experimentally obtained E_a values for polymers would indicate that the structural transitions that occur in anhydrous lanolin at ~15° rival those of a glass transition. But this is not what would be expected by inspection of Fig. 1. The limiting value of the elastic modulus is not as large as would be expected for substances in a glassy state.
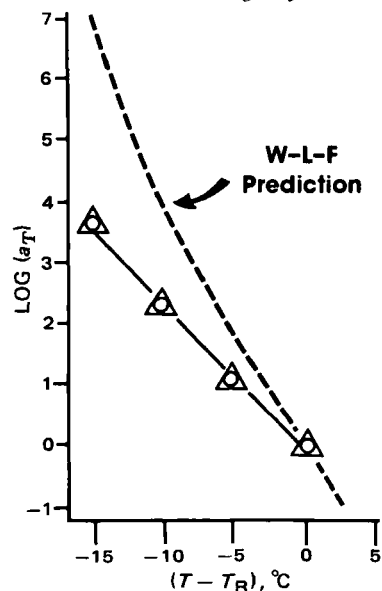

Figure 5—*Semilog plot of shift factor* versus *reciprocal temperature for anhydrous lanolin USP. Key: (○) from* G' *superposition and (△) from* G" *superposition.*

[1] Model RMS-7200, Rheometrics, Inc., Union, NJ 07083.

Figure 6—*Semilog plot of shift factor* versus reduced temperature for anhydrous lanolin USP. Key: (○) from G' superposition and (△) from G" superposition.*

With these thoughts in mind, the shift factors were also plotted according to the W-L-F relationship (Eq. 6) in Fig. 6. The ideal W-L-F curve generated with the "universal" constants of $C_1 = 17.4$ and $C_2 = 51.6$ is also presented in Fig. 6 for comparison. The "universal" constants do not hold for many polymers, and it is apparent that the experimentally obtained plot of $\log a_T$ versus $(T - T_R)$ for anhydrous lanolin does not lie where the W-L-F relationship (with "universal" constants) predicts. The lack of fit of the experimental data with the W-L-F prediction also suggests that the transition is probably not a glass transition as most polymers that undergo a glass transition obey the W-L-F prediction.

CONCLUSION

It has been demonstrated that the energy of activation for the structural changes occurring in the transition of anhydrous lanolin between 10 and 15° can be calculated by a temperature–shear frequency reduction scheme and an Arrhenius-type relationship. The E_a, which is ~90 kcal, compares favorably with the magnitude of the E_a of a high molecular weight polymer undergoing a glass transition. This comparison is significant when one considers the generally low molecular weight composition of anhydrous lanolin. The magnitude of the E_a for anhydrous lanolin suggests that the intra- and intermolecular forces are as great as those in high molecular weight polymers. Hence, the nature of the functional groups and the chain length of the molecules determine the strength of the structure of the system.

Overall, the experimental data suggest that anhydrous lanolin undergoes a major mechanical transition between 10 and 15°. Both the ability to superpose modulus versus shear frequency data and an E_a of 90 kcal for the transition are characteristic of a glass transition, but other observations are not. As described in the preceding paper (5), these observations are: a lower limiting value of the elastic modulus than would be expected for a glass transition, a slower rate of change of tan δ with temperature about the transition than would be expected for a glass transition, and a lack of fit of experimental data to the W-L-F relationship. Rather than a sharp transition from a rubbery to an ordered glassy state, it appears that anhydrous lanolin undergoes a mechanical transition from a rubber-like state to a structural state which is less ordered than a glassy state.

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Reverse Permeation of Salicylate Ion Through Cellulose Membrane

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Abstract □ The reverse permeation of salicylate ion and the effect of bovine serum albumin on the permeation were studied in a sodium salicylate–sodium oxalate–water system. In passive transport the permeation flux of an ion is expressed by the linear combination of the two terms which represent the concentration and electric potential gradients. Because the mobility of the sodium ion is greater than the oxalate ion, salicylate ion moves against the concentration gradient, and follows the electric potential gradient in the initial stage of permeation. The reverse permeation of salicylate ion through a cellulose membrane was accelerated with a high concentration ratio of oxalate to salicylate ions and reached a maximum value after 10 hr in the absence of bovine serum albumin. After reaching a maximum value, the salicylate ion permeated along the concentration gradient. The maximum concentration efficiency was 11.2%. In the presence of bovine serum albumin, the reverse permeation of salicylate ion reached a maximum value after 3 hr.

Keyphrases □ Reverse permeation—of salicylate ion with oxalate ion, through a cellulose membrane, protein effect on permeation flux □ Salicylate ion—permeation through a cellulose membrane, concentration by oxalate ion, protein effect on permeation flux □ Oxalate ion—permeation through a cellulose membrane with salicylate ion, protein effect on permeation flux

Most organic drugs dissociate in aqueous solutions and exist in ionic forms under biological conditions. Salicylate ion, one of the most commonly used drugs for analgesia, displaces other drugs such as the sulfonylureas (1) and sulfonamides (2), from the binding sites of the serum proteins. It has been reported that the absorption of salicylic acid is 61% in 0.1 N hydrochloric acid, 13% in sodium bicarbonate (pH 8) from the rat stomach (3), and 60% in physiological solution from the rat intestine (4). Effect of buffer constituents on salicylate absorption was studied with everted rat intestine and the inhibitory effect of potassium ions was reported (5–8). Since a variety of sub-