Viscoelastic Properties of Pharmaceutical Semisolids III: Nondestructive Oscillatory Testing

STANLEY S. DAVIS

Abstract ☐ Semisolid ointments and creams were examined by nondestructive oscillatory methods, using the Weissenberg rheogoniometer and a digital transfer function analyser. Fundamental rheological parameters (η', G', and G'') were measured over the frequency range from 2.5×10^{-4} to 25 Hz. The variation with frequency of the loss tangent (a ratio of viscous to elastic contributions) provides a useful "consistency spectrum" for characterization of pharmaceutical products. The shapes of spectra and the magnitudes of the loss tangent are discussed with relation to seven ointments and four creams. A comparison of oscillatory and transient (creep) methods is also made.

Keyphrases ☐ Ointments, creams, semisolid—viscoelastic properties ☐ Creams, ointments, semisolid—viscoelastic properties ☐ Viscoelasticity, nondestructive oscillatory testing—semisolid formulations ☐ Rheological parameters, oscillatory method—semisolid systems ☐ Oscillatory testing, nondestructive—semisolid rheological parameters

Figure 1—*Generalized Maxwell model representing behavior of a viscoelastic material.*

It is becoming increasingly important to be able to characterize the "consistency" of semisolid gels, ointments, and creams in a meaningful fashion. Rheological parameters are now required in various pharmaceutical areas, including: (a) quality control of semisolid products; (b) storage stability of semisolid products; (c) correlation of physical parameters with sensory assessment and consumer evaluation; (d) effects of consistency on the percutaneous absorption of drugs; (e) effects of formulation on consistency (e.g., action of self-bodying agents); (f) prediction of flow behavior under the shear conditions met in manufacture (e.g., pumping, milling, and packaging); (g) effects of mucolytic agents on properties of mucoid body fluids; and (h) effects of radiation sterilization on the physical properties of topical products.

Moreover, in a recent review, Boylan (1) considered that rheological characterization is a must when developing semisolid dosage formulations.

The important question that one must answer is: "What are suitable rheological parameters?"

For many years, the usual approach to the rheological testing of pharmaceutical semisolids has been some form of continuous shear viscometry or penetrometry. Unfortunately, such methods have a number of basic disadvantages and limitations (2, 3), and derived consistency values have been of limited application. In parts I and II (4, 5), it was shown that creep testing, along with the subsequent derivation of fundamental viscoelastic parameters, provides a suitable method for the rheological evaluation of semisolids. However, to obtain complete information about viscoelastic behavior and the molecular properties it reflects, it is often necessary to make measurements over a wide range of the time scale (6). Transient methods, such as creep, are limited at short times by inertial effects and by t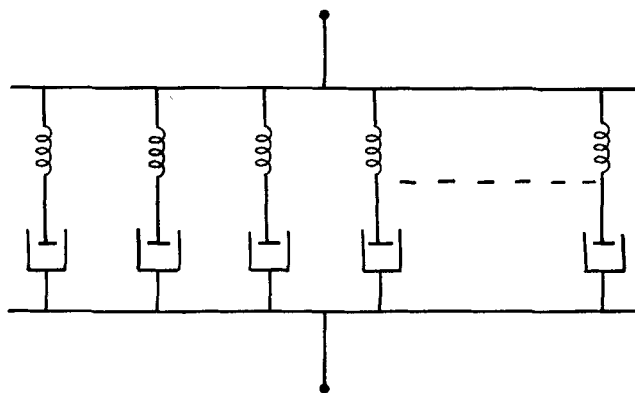he impossibility of having an instantaneous application of stress at the beginning of the experiment. Creep tests can be supplemented by oscillatory (dynamic) tests to provide information at short times, since a periodic experiment of frequency ω (rad. sec.$^{-1}$) ($\omega = 2\pi n, n$ = frequency in hertz) is qualitatively equivalent to a creep experiment of time $t = 1/\omega$ (6). Therefore, the semisolid systems of parts I and II (4, 5) were studied using oscillatory methods and the theory of linear viscoelasticity.

It is possible in many cases to derive full dynamic data from creep experiments by using suitable formulas (4, 7). Therefore, the methods of interconversion and their limitations for pharmaceutical systems were examined.

THEORY

The behavior of a semisolid material under oscillation can best be considered in terms of a mechanical model made up from a combination of springs (elastic elements) and dashpots (viscous elements) (Fig. 1). At high frequency, the springs can elongate and contract under imposed shear but the dashpots have very little time in which to move. The system, therefore, behaves essentially as an elastic solid of modulus G. At low frequency, the springs also can extend, but in this case the dashpots have ample time to move and their extension greatly exceeds that for the springs. The system, therefore, behaves essentially as a viscous fluid of viscosity η. The interrelationship between G and η is the relaxation time, τ ($= \eta/G$). If $1/\omega \gg \tau$, the dashpots can keep up with the oscillation, and energy stored in each cycle is almost completely dissipated. But if $1/\omega \ll \tau$, almost no energy is dissipated and solid behavior dominates. When $1/\omega \cong \tau$, both G and η have definite contributions; one is then dealing with the so-called viscoelastic region.

Any experimental system can be considered to be made up from an infinite number of such springs and dashpots. Nonetheless, the manner in which G and η change with frequency is often highly characteristic and can be correlated with definite structures or molecular entities (6, 8).

The equation of state, for a linear viscoelastic material undergoing harmonic oscillation, can be written in the form (9):

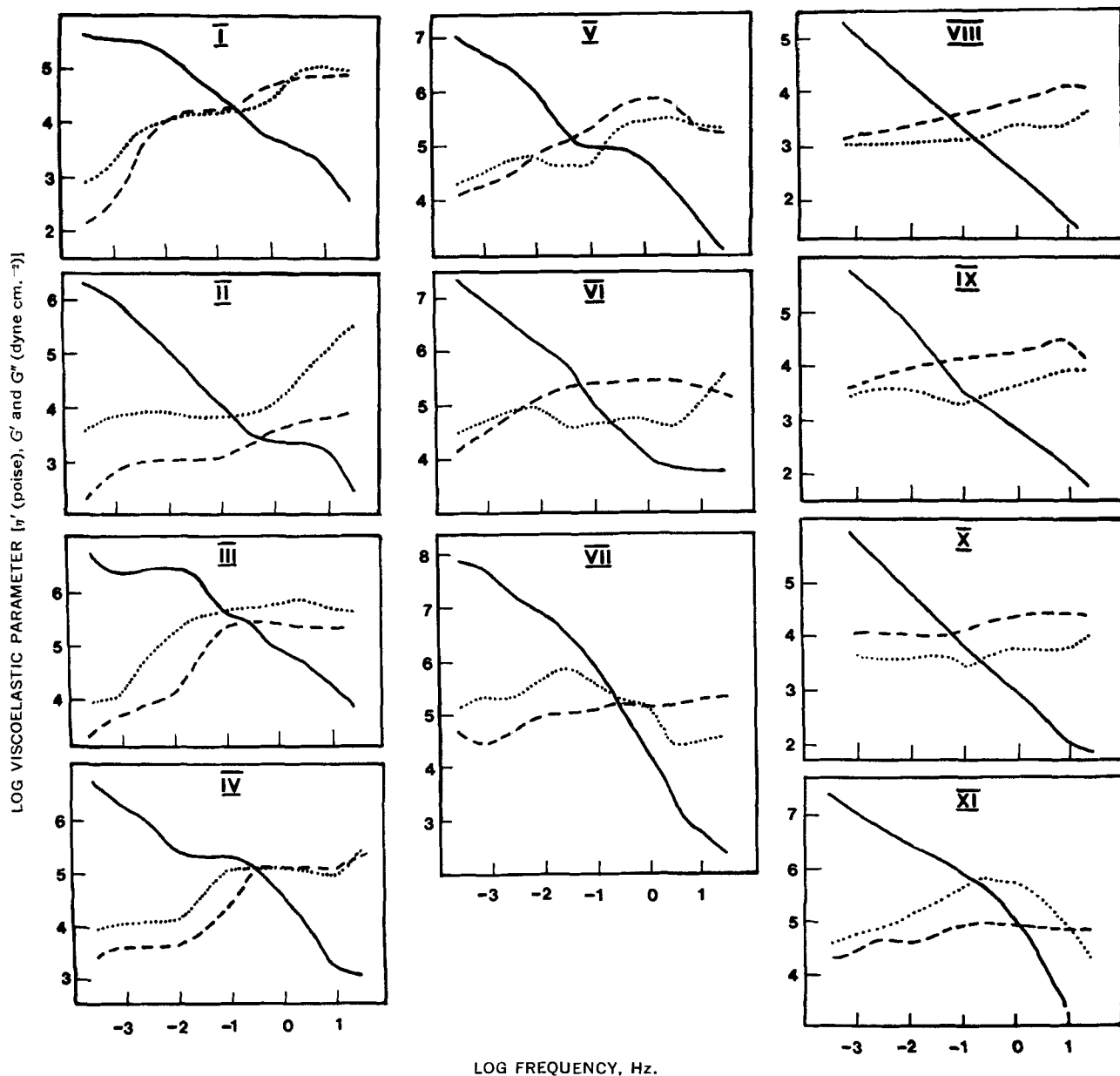$$\sigma = 2\,\eta^*\dot{\gamma} \qquad \text{(Eq. 1)}$$

Figure 2—*Dynamic viscoelastic data for ointments and creams. Key:* ——, η'; - - -, G'; ......, G''; *I, wool fat; II, lanolin; III, paraffin ointment; IV, wool alcohols ointment; V, white soft paraffin; VI, simple ointment; VII, emulsifying ointment; VIII, chlorhexidine cream; IX, aqueous cream; X, cetrimide cream; and XI, oily cream.*

where σ is the shear stress, $\dot{\gamma}$ is the shear rate, and η^* is the complex dynamic viscosity; η^* is usually expressed as real and imaginary parts:

$$\eta^* = \eta' - iG'/\omega \qquad \text{(Eq. 2)}$$

where η' is the dynamic viscosity, and i is the square root of -1. For a purely viscous liquid, η' is constant with change in frequency and G' is zero. G' is also known as the storage modulus and is a measure of the energy stored and recovered per cycle. The loss modulus:

$$G'' = \eta'\omega \qquad \text{(Eq. 3)}$$

is a measure of the energy dissipated or lost as heat per cycle (6).

Experimentally, the material under test is subjected to a small sinusoidal shear strain, and the subsequent shear stress is measured. If the behavior is linear viscoelastic, the stress also is sinusoidal but is out of phase with the input strain. This response can be resolved vectorially into two components, one in phase with the input (real) and one 90° out of phase (imaginary).

EXPERIMENTAL

The sample under test is contained in a suitable geometry; by measuring the amplitudes of stress and strain and their phase difference, G' and η' can be obtained at selected frequencies. Different geometries have been reported in the literature, but parallel plates are the most convenient on theoretical grounds (10). This system also has the advantages that the gap between the plates can be altered without difficulty and a series of experiments can be performed on the same sample.

A Weissenberg rheogoniometer (R 16) was used for all experiments[1]. Data collection was greatly simplified by the use of a digital transfer function analyzer (DTFA) (11–13).

Seven ointments and four creams were examined in their linear viscoelastic region (11), over the frequency range from 2.5×10^{-4} to 25 Hz. Their formulations were presented previously (4, 5).

___

[1] One of the few commercial instruments with facilities for oscillatory testing (11).
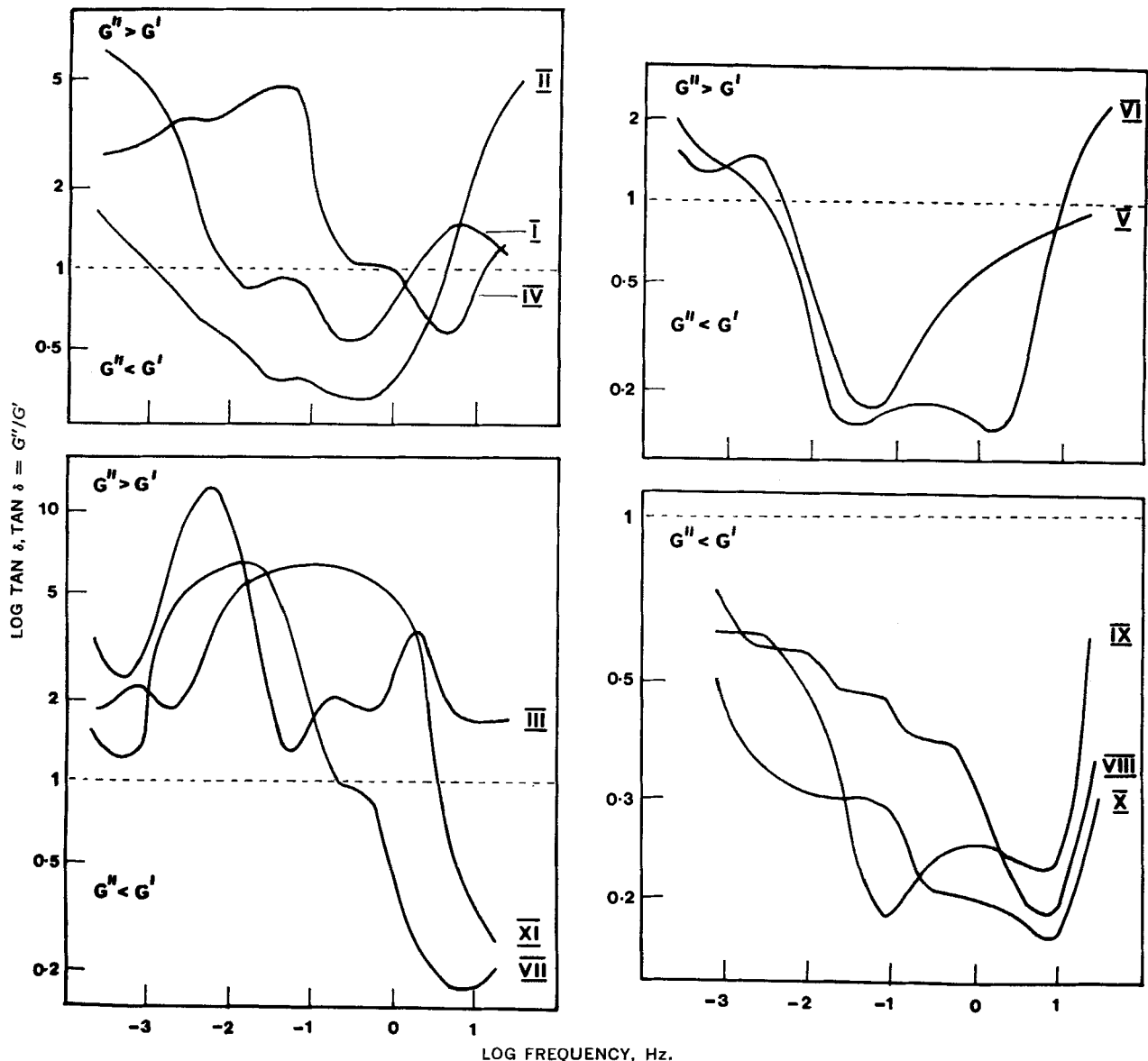
Figure 3—*Variation of loss tangent with frequency. Numerals refer to the systems listed in Fig. 2.*

RESULTS AND DISCUSSION

Calculated Viscoelastic Parameters—Values for dynamic viscosity (η'), storage modulus (G'), and loss modulus (G'') were calculated from the raw data, using the equations of Walters and Kemp (10), and are presented in Fig. 2. A useful dimensionless parameter, tan δ, the loss tangent, was also calculated. It is a measure of the ratio of energy lost to energy stored in a cyclic deformation (G''/G'); it has considerable practical interest because it provides a comparative parameter that combines both the elastic and viscous contributions (Fig. 3).

The parameters η', G', and G'' change characteristically with frequency. At low frequency, η' is high but it falls more or less monotonically as the frequency is increased. At very low frequencies, η' approaches η_0, the steady-state viscosity obtained in the creep studies described previously (4, 5).

It is clear from Eq. 3 that when η' is inversely proportional to frequency (e.g., Systems VIII, IX, and X), the G'' versus n relation is almost flat. Alternatively, when η' flattens out, G'' rises steeply.

The storage modulus G' increases gradually as the frequency is increased. As already discussed, G' should approach zero at low frequency (the terminal zone), but this condition was not reached for any of the systems. It requires that the difference in phase angle approaches 90° and that the energy stored per cycle of deformation becomes negligible compared with that dissipated as heat (6). Wool

fat (I) is the only system that comes close to this condition. At high frequencies, G' approaches a limiting value for all systems. In regions where G' changes slowly with frequency, the behavior can be considered as being nearly perfectly elastic (6). Therefore, G'' tends to be considerably less than G' (Systems VIII, IX, and X). At high frequency, as the movement of the dashpots in Fig. 1 becomes negligible to that for the springs, G'' should approach zero.

The more or less flat relation between G' and n is often called the plateau region of viscoelastic behavior and can exist for up to 10 decades of frequency. Here, viscoelastic properties are dominated by the presence of a network arrangement such as cross-linkages or the entanglement of polymeric fibers. The smaller the ratio of G''/G' ($= \tan \delta$), the more rubbery or elastomeric is the behavior (6). Plots of tan δ versus frequency (Fig. 3) are reminiscent of spectra from UV spectrophotometry. Each system has a characteristic curve containing maxima and minima. I suggest that this ratio of viscous to elastic contribution provides an extremely useful rheological parameter and will subsequently refer to the change of tan δ with frequency as a consistency spectrum.

By examining the results presented in Figs. 2 and 3 in some detail, characteristic behavior for the different semisolid systems can be distinguished. Wool fat (I) and lanolin (II), although of similar formulation, have quite distinct behavior. For wool fat, $G' \simeq G''$ (tan δ = 1), except at the lowest frequency. However, the addition of 30% water to produce lanolin increases the elastic contribution and re-
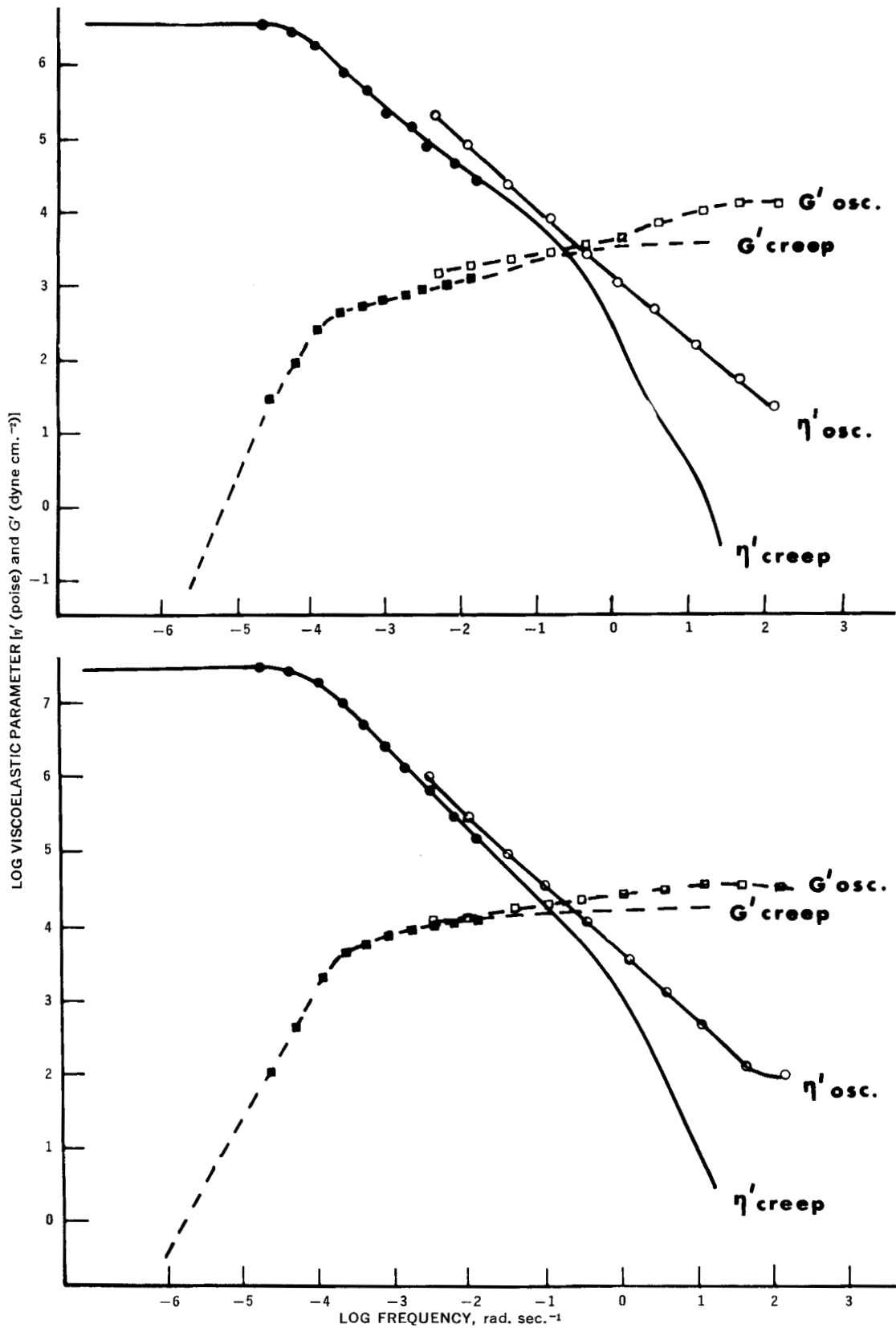
Figure 4—*Comparison of creep and oscillatory techniques using data for chlorhexidine cream (top) and cetrimide cream (bottom). Key: - - -, dynamic viscosity and shear modulus derived from the creep model using Ferry's equations (6) and the data in* Reference 5; ●, ■, *dynamic viscosity and storage modulus values calculated from raw creep data using Schwarzl's equations (7); and* O, □, *dynamic viscosity and storage modulus values obtained from oscillatory experiments (Fig. 2).*

duces the viscous contribution, with $G' \gg G''$. The presence of water modifies the shape of the consistency spectrum slightly, but the minimum occurs at the same frequency for both systems. The water droplets increase the elastic nature of wool fat by forming an interlinked network of emulsion droplets. In general, the ointment systems are characterized by $G'' \geqslant G'$ (as is also the case with oily cream). The change of η' with n is far from linear, and some plateau regions are evident. The sizes of the plateaus in the log G' versus log n plots are related to a distribution of relaxation times; in polymeric systems, they can be used to estimate the molecular weight between entanglement points (6). Systems III, IV, VII, and XI all show pronounced maxima in tan δ at intermediate frequencies. This condition can be associated with an amorphous structure containing some primary linkages (cross-linkages). On the other hand, Systems V and VI have pronounced minima in their consistency spectra at intermediate frequencies. These can be tentatively associated with a lack of primary linkages.

It is somewhat surprising to find that System V, white soft paraffin, has viscoelastic properties, since it was purely elastic in previous creep investigations. However, the samples of paraffin used in the present work were different from those studied in creep, although they were both of BP specification. Different paraffin samples can have differing viscoelastic properties (14, 15), depending upon the method of manufacture and the microcrystalline makeup.

System III, paraffin ointment, contains 90% white soft paraffin and only 3% hard paraffin, 2% beeswax, and 5% cetostearyl alcohol. Nevertheless, these small quantities of additional materials can profoundly alter the viscoelastic properties of the paraffin base. Figure 3 shows that white soft paraffin (V) has a pronounced minimum in its spectrum and $G'' \ll G'$, whereas paraffin ointment has a large maximum in its spectrum and $G'' > G'$.

Those systems containing long-chain wool alcohols (I, II, IV, and VI) all have pronounced minima in their spectra. This may be characteristic for these materials.

System VII shows a complete reversal in G' and G'' at around 1 Hz. The fall in η' with frequency is very steep, and the relative change in η', over the five decades of frequency, is 200 times greater than for any other system. This is clearly due to the presence of a highly shear-sensitive viscous contribution.

The oil-in-water creams (VIII, IX, and X) have $G' \gg G''$ in all cases, indicating that the elastic properties greatly exceed the viscous. All three systems have formulations based on surfactant-long-chain alcohol complexes, which give a self-bodying action (15-19). It is known that a viscoelastic gel network links the emulsion droplets and entraps continuous phase, thereby giving the high elastic component. The differences in consistency between the three systems can be rationalized on the basis of differing oil contents and the natures of the emulsifying agents (5). The consistency spectra are of similar shapes, all with minima at around 10 Hz. The products tested (aqueous cream, cetrimide cream, and chlorhexidine cream) are all popular pharmaceuticals in the United Kingdom. In future work, it is the author's hope to correlate viscoelastic parameters with sensory assessment and consumer evaluation. At that time, it may become apparent that a "satisfactory" cream has $G' \gg G''$ and a consistency spectrum similar to those in Fig. 3.

Oily cream (XI) is a water-in-oil emulsion. The continuous phase consists of liquid and soft and hard paraffins; it is, therefore, not surprising that this material is unlike the oil-in-water creams and behaves rheologically in a similar fashion to the ointments.

Calculation of Dynamic Data from Creep Experiments—Although creep experiments give viscoelastic data at long time periods, it is possible to convert these to dynamic data. These data can be used either to supplement oscillatory experiments and to cover as many decades of frequency as possible or to provide a single source of dynamic data.

Previously in creep (4, 5), the systems were examined over a wide range of temperature; few, if any were examined specifically at 25°. Quite small changes in temperature were shown to lead to large changes in viscoelastic parameters. The comparison of creep and oscillatory results is, therefore, somewhat limited, except for the oil-in-water creams, which are only slightly affected by temperature changes (5). Little error will be introduced if data for chlorhexidine and cetrimide creams (VIII and X) are used for comparison.

The creep data were analyzed using a line spectrum Voigt model representation for viscoelastic parameters (4, 5), and dynamic data can be calculated using the equations of Ferry (6).

If only the raw creep compliance values are available, the ap-

proximate equations of Schwarzl (7) can be employed. Data derived, using both the methods, are shown in Fig. 4.

In general, the results show that the agreement between creep and oscillation at intermediate frequency is very good, if one bears in mind that the values refer to slightly different temperatures and that the samples were examined on widely differing occasions. As expected, at low frequency, η' levels off and approaches the steady-state η_0 value and G' falls rapidly and eventually becomes less than G''.

It is clear from Fig. 4 that derived data from creep will be unreliable at times shorter than about 5 sec. due to inertial effects, the response time of the recording system, and the impossibility of applying a truely instantaneous stress. Thus, the extrapolation of creep results to frequencies greater than those covered by creep itself is liable to considerable error. As a result, three different frequency regions can be defined for the testing of semisolid ointments and creams: (a) $\omega > 10^{-1}$, oscillatory testing only; (b) $4 \times 10^{-3} < \omega < 10^{-1}$, creep or oscillatory methods; and (c) $\omega < 4 \times 10^{-3}$, creep testing only [$\omega$ — rad. sec.$^{-1}$ ($= 2\pi n$)].

The judicious combination of creep and oscillatory methods will provide dynamic data over at least nine decades of frequency. This should be ample to characterize any pharmaceutical semisolid formulation in detail.

CONCLUSIONS

The testing of pharmaceutical semisolids by an oscillatory method provides a wealth of fundamental rheological information. It has the advantage over transient (creep) methods of covering a far wider time scale; therefore, it will allow one to postulate, with more confidence, processes occurring at a molecular level. There are various ways of presenting the data, but a "consistency spectrum" in the form of log tan δ versus log frequency is the most suitable for pharmaceutical systems. It provides a measure of the ratio of viscous to elastic contributions. Maxima and minima in the spectra are characteristic for given systems, and they can be changed markedly by changes in formulation. The author strongly recommends the use of such spectra when correlating experimental data on semisolids with rheological parameters. For example, if one returns to the list in the introduction, it is apparent that the consistency spectrum approach can be applied directly to follow rheological changes in formulation, quality control, storage stability, the action of mucolytic agents, and radiation sterilization. Its direct use in percutaneous absorption, product assessment, and shear behavior is not as yet clear, but it will certainly provide a convenient starting point for further investigations. In part IV, the author examines destructive oscillatory testing and its importance in product assessment (20).

REFERENCES

(1) J. C. Boylan, Abstracts, APhA Academy of Pharmaceutical Sciences, Washington, D. C. meeting, Apr. 1970, p. 6.
(2) S. S. Davis, Amer. Perfum. Cosmet., 85, 45(1970).
(3) S. S. Davis, E. Shotton, and B. Warburton, J. Pharm. Pharmacol., 20, 157S(1968).
(4) S. S. Davis, J. Pharm. Sci., 58, 412(1969).
(5) Ibid., 58, 418(1969).
(6) J. D. Ferry, "Viscoelastic Properties of Polymers," Wiley, New York, N. Y., 1961.
(7) F. R. Schwarzl, Rheol. Acta, 8, 6(1969).
(8) T. Alfrey and E. F. Gurney, in "Rheology. Theory and Application," vol. 1., F. R. Eirich, Ed., Academic, New York, N. Y., 1956, p. 387.
(9) K. Walters, "Basic Concepts and Formulae for the Rheogoniometer," Sangamo Controls, Bognor, England, 1968.
(10) K. Walters and R. A. Kemp, Rheol. Acta, 7, 1(1968).
(11) B. Warburton and S. S. Davis, ibid., 8, 205(1969).
(12) J. D. Watson, ibid., 8, 201(1969).
(13) J. Harris and W. L. Wilkinson, Bull. Brit. Soc. Rheol., 1, 1(1969).
(14) B. W. Barry and A. J. Grace, paper presented to British Society of Rheology Conference, London, England, Apr. 1970, to be published.
(15) B. W. Barry and A. J. Grace, J. Pharm. Pharmacol., 22, 147S (1970).

(16) B. W. Barry, *J. Colloid Interface Sci.*, **28**, 82(1968).
(17) B. W. Barry, paper presented to British Society of Rheology Conference, London, England, Apr. 1970, to be published.
(18) B. W. Barry, *J. Colloid Interface Sci.*, **32**, 551(1970).
(19) B. W. Barry, *J. Pharm. Pharmacol.*, **21**, 533(1969).
(20) S. S. Davis, *J. Pharm. Sci.*, **60**, 1356(1971).

Viscoelastic Properties of Pharmaceutical Semisolids IV: Destructive Oscillatory Testing

STANLEY S. DAVIS

Abstract ☐ Rheogoniometer oscillatory tests of large amplitude were used to simulate the conditions of dermatological usage of semisolid ointments and creams. The onset of nonlinear viscoelastic behavior can be correlated with the yield stress found from continuous shear experiments. The rate of breakdown of viscoelastic structure follows a first-order process and is dependent on the oscillatory frequency and amplitude, product formulation, and, above all, sample thickness. Reformation of structure (thixotropy) was also studied for representative materials. The importance of these tests in product assessment and consumer evaluation is discussed.

Keyphrases ☐ Ointments, creams, semisolid—viscoelastic properties ☐ Creams, ointments, semisolid—viscoelastic properties ☐ Viscoelasticity, destructive oscillatory testing—semisolid formulations ☐ Oscillatory shear—semisolid breakdown parameters ☐ Thixotropy—semisolids ☐ Topical formulations—viscoelastic properties

Table I—Correlation between Maximum Input Strain for Linearity and Yield Stress from Continuous Shear Experiments[a]

System	Input Strain (Maximum)	Yield Stress, Dynes cm.$^{-2}$
Chlorhexidine cream	0.05	1.0×10^3
Aqueous cream	0.16	3.0×10^3
Cetrimide cream	0.20	3.0×10^3
Oily cream	0.23	6.1×10^3
White soft paraffin	0.08	2.0×10^3
Lanolin	0.9	—
Wool fat	0.9	—
Paraffin ointment	1.0	1.5×10^4
Wool alcohols ointment	0.13	3.0×10^3
Emulsifying ointment	1.2	7.6×10^3
Simple ointment	0.13	1.2×10^5
Shortening (7)	1.1	7.0×10^3
Lard (7)	1.5	1.4×10^4

[a] $n = 7.9 \times 10^{-2}$ Hz. Gap $= 6.4 \times 10^{-2}$ cm.

In part III (1), the viscoelastic properties of pharmaceutical semisolids were examined using nondestructive oscillatory techniques. The imposed shear strains were such that the ointments and creams were measured in their linear viscoelastic region. The calculated parameters (dynamic viscosity, storage modulus, and loss tangent) and their change with frequency were suitable for fundamental rheological characterization. However, it is realized that in actual product usage, such as the rubbing of an ointment onto the skin, the imposed shear strains and stresses are large and the materials are nonlinear in their response. The essential difference between linear and nonlinear behavior is that the former is nondestructive while the latter is destructive, and viscoelastic structures are broken down either reversibly or irreversibly.

The mathematical interpretation of nonlinear viscoelasticity is extremely complex (2, 3); as yet, no formalized treatment exists that can be usefully applied to pharmaceutical semisolids. Even so, it is rewarding to enlarge deliberately the shear strain in an oscillatory experiment, and to penetrate the nonlinear region, to reveal new sets of shear properties which govern the effects of second and higher degrees (3).

The rubbing of a semisolid onto the skin was considered by Henderson *et al.* (4), who obtained a rough approximation of the possible shear rates involved. Their model consisted of two parallel plates, with a gap of 1–3 mm., with a stroke length of 6 cm. and four strokes performed per second. All these variables were highly arbitrary but reasonably described the rubbing process within an order of magnitude. By considering constant shearing conditions, they arrived at a shear rate value of 120 sec.$^{-1}$. Setnikar *et al.* (5) also reported values ranging from 3 to 250 sec.$^{-1}$ for dermatological lotions of 0.2–3-mm. thickness rubbed in at a velocity of 1–5 cm./sec. And, in extreme cases, values as high as 10,000 sec.$^{-1}$ were reported (6).

A more detailed examination of the Henderson *et al.* (4) model should be made. If the reasonable assumption is made that most rubbing processes are periodic in nature (*i.e.*, so many strokes per second), then an oscillatory motion rather than continuous shear should be considered. The shear rate, therefore, varies during the stroke and is not constant as usually assumed. It is zero at each end of the stroke and has a maximum value in the middle. Therefore, to test a semisolid material rheologically under conditions similar to those in usage, oscillatory testing is far more realistic than continuous shear. The skin and hand surfaces can be idealized in the