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Viscoelastic Properties of Pharmaceutical Semisolids IV: Destructive Oscillatory Testing

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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

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

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.

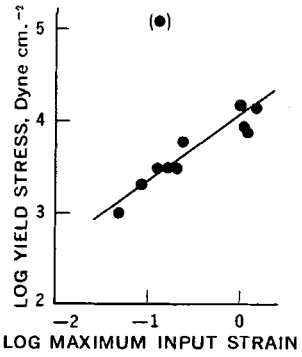

Figure 1—*Correlation between yield strain in oscillation and yield stress in continuous shear (cone and plate) studies.*

form of circular parallel plates (available with the Weissenberg rheogoniometer), and the gap between them can be altered at will to cover a range of usage conditions.

By reexamining the Henderson *et al.* (4) model in these terms, maximum shear rates can be calculated. Four strokes per second is equivalent to an oscillatory frequency of 2 Hz., and a 6-cm. stroke gives an amplitude of 3 cm. Six centimeters can be taken as the suitable plate diameter. The shear rate ($\dot{\gamma}$) alters throughout the cycle of deformation, but for small gaps its maximum value is given by (3):

$$\dot{\gamma} = n\theta_I Ka/h \qquad \text{(Eq. 1)}$$

where n is the frequency of oscillation (in Hz.), θ_I is the input amplitude, K an apparatus constant, a the plate radius, and h the gap width. Using the values quoted, the approximate relation is:

$$\dot{\gamma} \sim 4/h \qquad \text{(Eq. 2)}$$

so that for the Henderson *et al.* (4) values of h = 0.1–0.3 cm., $\dot{\gamma}$ has maximum values of 40 and 13 sec.$^{-1}$, respectively. Likewise, for the smallest thickness quoted by Setnikar *et al.* (5) of 0.02 cm., $\dot{\gamma}$ = 200 sec.$^{-1}$.

EXPERIMENTAL

The Weissenberg rheogoniometer in parallel plate geometry (plate diameter = 7.5 cm.) provides an extremely useful means of studying the behavior of semisolids under dermatological usage conditions. Equation 1 shows that the maximum shear rate depends on the frequency of oscillation, the gap width between the plates, and the strain amplitude. Experiments were performed to investigate each of these factors in turn, as well as the effect of formulation. As already discussed, fundamental rheological parameters such as elasticities and viscosities are difficult, if not impossible, to obtain in nonlinear testing. However, one is able to study the rate of breakdown of viscoelastic structure under various imposed shear conditions. At high frequencies, this breakdown was followed using a digital transfer function analyzer (DTFA) (1); at low frequency, an *X-Y* plotter was used.

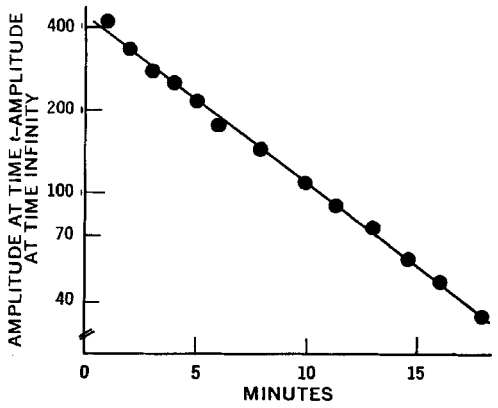

Figure 3—*First-order representation of data in Fig. 2.*

RESULTS AND DISCUSSION

Nonlinear Strain—The onset of nonlinearity at a given frequency is shown by a sudden change in a previously constant amplitude ratio and phase angle (1). The maximum input strain can be calculated by integrating Eq. 1, and some representative values are listed in Table I. The range of strain is quite extensive, with values from 0.05 to 1.5. This range is related to the shear sensitivities of the various semisolids which, in turn, depend on their molecular makeup. Microcrystalline materials, such as white soft paraffin, wool alcohols ointment, and simple ointment, are very susceptible to breakdown under shear and, therefore, have a small linear region. On the other hand, materials made from long viscoelastic threads (*e.g.*, wool fat and lanolin) or large bundles of long acicular crystals (*e.g.*, lard) have much larger linear regions.

The more shear sensitive a material, the less work is needed to cause it to undergo structural breakdown. Thus, in continuous shear, one would expect that the yield stress (minimum shear stress to cause observable flow) would be lower for a shear-sensitive material than for less shear-sensitive material. Yield values from Ferranti–Shirley cone and plate viscometer studies are listed in Table I (8, 9); there appears to be a reasonable rank-order correlation between strain and yield value (Fig. 1), except for the case of simple ointment.

Rate of Breakdown of Viscoelastic Structure—The rate of breakdown of viscoelastic structure was followed by measuring the change in the rheogoniometer output amplitude (stress) with time under an imposed sinusoidal strain. At high frequencies, the output signal voltage from the DTFA was plotted directly against time from the onset of the shearing procedure (Fig. 2). The samples were sheared until a constant stress was obtained, and the data were then plotted in the form of a conventional first-order representation (Fig. 3). In general, the semisolid systems all gave reasonable first-order plots from which rate constants for breakdown could be calculated. This type of first-order change in shear stress was presented in earlier studies on thixotorpic materials, where a constant shear rate

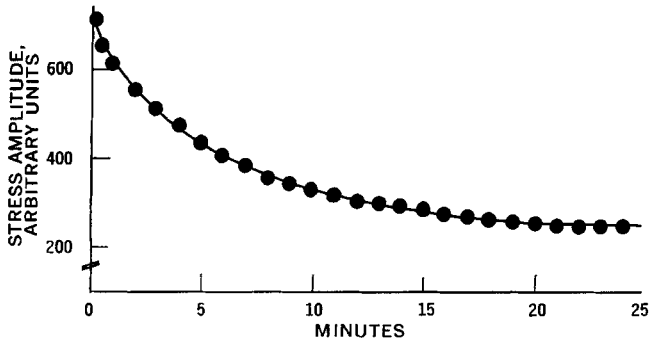

Figure 2—*Breakdown of viscoelastic structure in oily cream by oscillation (nonlinear region),* n = 2.5 × 10^{-1} *Hz. Strain amplitude* = 2.0 × 10^{-2} *rad. Gap* = 6.4 × 10^{-2} *cm.*

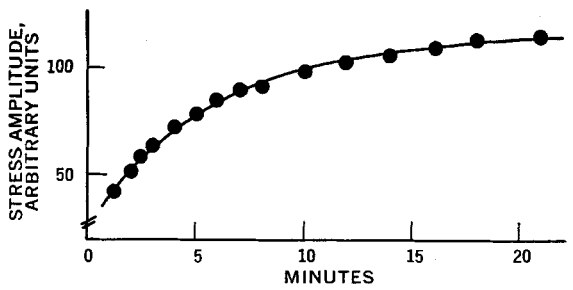

Figure 4—*Reformation of viscoelastic structure in oily cream. Testing in linear viscoelastic region,* n = 2.5 × 10^{-1} *Hz. Strain amplitude* = 2.0 × 10^{-3} *rad. Gap* = 6.4 × 10^{-2} *cm.*

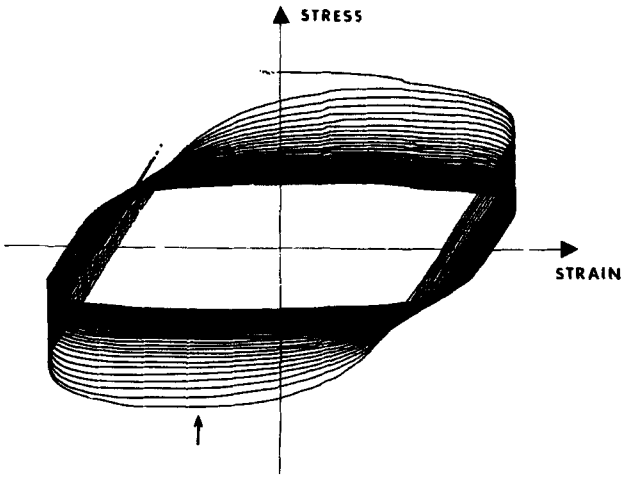

Figure 5—*Stress/strain hysteresis loop for oily cream undergoing structural breakdown,* n = 7.9×10^{-3} *Hz. Strain amplitude* = 8.1×10^{-3} *rad. Gap* = 6.4×10^{-2} *cm.*

was suddenly imposed and the fall in shear stress with time was followed (10).

In some cases, after stress reached a constant value, the input strain could be reduced to a value in the linear viscoelastic region (nondestructive testing), and the slow build-up of structure was followed by measuring the increase in output stress (Fig. 4). Structural build-up is discussed later in this report.

The DTFA requires three input cycles to perform its data analysis and integration. Therefore, at periods longer than 15 sec., much of the structure was broken down before the instrument could give its first result. An alternative method of data collection was therefore used. If, in an oscillatory experiment, one arranges that the stress and strain signals are placed at right angles to each other, using an *X-Y* plotter or oscilloscope, then for a phase-angle difference of 0°, a straight line at 45° to the axis results. But for a 90° phase difference, an ellipse or circle is produced (stress/strain hysteresis loop). A viscoelastic material, undergoing structural breakdown, gives a series of ellipses of changing shapes; a typical result, obtained with an *X-Y* plotter for oily cream, is shown in Fig. 5. The strain amplitude (*X*-axis) is constant, but the stress amplitude (*Y*-axis) gradually decreases as structure is broken down. By taking a suitable point in the cycle (arrow), the change in amplitude per period can be calculated and compared to the final infinity value to give a first-order representation (Fig. 6). In effect, the *X-Y* plotter provides an automatic method of following structure loss, which would be useful in quality control processes. (The DTFA also has provision for automatic data collection, but the DTFA is many times more expensive than an *X-Y* plotter.)

Formulation—The change of the rate constant for breakdown with formulation was investigated at a constant frequency of 7.9×10^{-3} Hz. The use of a constant input amplitude (strain) would naturally give different results, because each sample had different linearity characteristics. To compare the samples under the same conditions, they were examined at an input strain four times that in Table I for the onset of nonlinearity. The results (Table II) for those systems that could be examined by the rheogoniometer under such conditions show that the ointments (and oily cream) have similar rate constants (in the region of 8×10^{-4} sec.$^{-1}$) while the creams have higher values (around 2.5×10^{-3} sec.$^{-1}$). The creams are more susceptible to breakdown, under shear at the given frequency, than are the ointments.

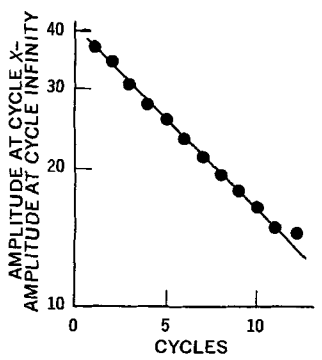

Figure 6—*First-order representation of data in Fig. 5.*

Table II—Effect of Formulation on Rate Constant for Breakdown of Viscoelastic Structure[a]

System	Input Strain (Maximum)	Rate Constant, sec.$^{-1}$
White soft paraffin	0.32	7.8×10^{-4}
Oily cream	0.92	7.8×10^{-4}
Simple ointment	0.52	7.2×10^{-4}
Wool alcohols ointment	0.52	9.0×10^{-4}
Aqueous cream	0.64	2.0×10^{-3}
Cetrimide cream	0.80	2.5×10^{-3}
Chlorhexidine cream	0.20	3.4×10^{-3}

[a] $n = 7.9 \times 10^{-3}$ Hz. Strain amplitude = four times maximum strain values in Table I. Gap = 6.4×10^{-2} cm.

Each system could, of course, be examined over a wide range of frequency (including the usage frequency of about 2 Hz.) and a "spectrum" for each presented.

Amplitude—The effect of strain amplitude was studied, using oily cream as a representative material (Table III). The change in rate constant is not excessive for a four-times change in input strain and indicates that the predominant breakdown processes involve structures and mechanisms that change little with the input strain at constant frequency.

Gap—Decreasing the gap thickness increases the rate of breakdown quite markedly (Table IV). The maximum shear rate per cycle increases with a decrease in the gap thickness, as predicted by Eq. 1. The smaller the gap, the smaller is the shear wave between the plates and, thus, more energy is available for destructive breakdown. When the gap is very small, the rate of breakdown becomes high; in any usage test or model, the sample thickness is the most important variable. Any rheological method of simulating product usage must, therefore, have provision for altering sample thickness.

Frequency—The rate constant for breakdown is directly related to the frequency of oscillation. At high frequency, more material is broken down in unit time than at low frequency. However, this can be allowed for if the rate constant for breakdown is normalized in terms of each cycle. If the same destructive processes occur at different frequencies, the amount of breakdown per cycle should be constant. The results in Fig. 7 show that the rate constant *per cycle* falls as frequency increases. That is, less structure is broken down per cycle at high frequency than at low; the mechanisms of breakdown are not frequency independent. At high frequency, there is less time in each cycle for breakdown to occur than at low frequency. The Maxwell model and linear behavior were discussed previously (1). At high frequency, a viscoelastic material is essentially elastic in nature and viscous effects have insufficient time to manifest themselves. At low frequency, the viscous contribution has more than enough time to respond to the imposed strain; as a result, the material appears to be essentially viscous. When dealing with nonlinear behavior, one must not use model interpretations too widely. But, in a similar manner, one can postulate that at low frequency both elastic and viscous contributions are affected by the imposed nonlinear strain, while at high frequency the elastic contribution protects the system from rapid loss of structure.

Table III—Effect of Input Strain Amplitude on Rate Constant for Breakdown of Viscoelastic Structure in Oily Cream[a]

Input Strain (Maximum)	Shear Rate (Maximum), sec.$^{-1}$	Rate Constant, sec.$^{-1}$
0.35	1.7×10^{-2}	8.1×10^{-3}
0.70	3.4×10^{-2}	1.6×10^{-2}
1.05	5.1×10^{-2}	2.3×10^{-2}
1.38	6.8×10^{-2}	3.1×10^{-2}

[a] $n = 7.9 \times 10^{-3}$ Hz. Gap = 6.4×10^{-2} cm.

Table IV—Effect of Gap Thickness on Rate Constant for Breakdown of Viscoelastic Structure in Oily Cream[a]

Gap, cm.	Input Strain (Maximum)	Shear Rate (Maximum), sec.$^{-1}$	Rate Constant, sec.$^{-1}$
0.25	0.22	1.1×10^{-2}	6.6×10^{-4}
0.15	0.35	1.8×10^{-2}	1.0×10^{-3}
0.10	0.53	2.7×10^{-2}	1.4×10^{-3}
0.06	0.86	4.3×10^{-2}	1.5×10^{-3}
0.04	1.40	7.1×10^{-2}	1.7×10^{-3}
0.025	2.14	1.1×10^{-1}	2.0×10^{-3}

[a] $n = 7.9 \times 10^{-3}$ Hz. Strain amplitude = 2.0×10^{-2} rad.

For white soft paraffin, a plot of the rate constant against log frequency (Fig. 7) gives a reasonably straight line and suggests that quality control experiments could be performed at more convenient low frequencies and an extrapolation then made to the frequency of usage. The total fall in amplitude (percent) follows a more curved relation, but it indicates that less structure is destroyed at high frequency than at low, even at infinite time. Hence, different mechanisms of breakdown are occurring at different frequencies.

Recovery (Thixotropy)—Besides following the rate of breakdown of viscoelastic structure, one can also examine the rate of structure recovery. The increase in stress for an oily cream sample is presented in Fig. 4. The reformation of structure with time is a demonstration of the phenomenon of thixotropy, which is usually defined as the time-dependent reversible breakdown of structure upon shear. Attempts to measure thixotropy using continuous shear methods, such as the Ferranti–Shirley viscometer, have been limited in their success (11). Highly viscoelastic materials exhibit shear fracture when subjected to high shear rates, with the result that material is expelled from the measuring surfaces of the viscometer. This, of course, gives an apparent irreversible loss of structure.

With nonaqueous systems, the recovery of the structure broken down under oscillatory shear can be studied by allowing the material to rest in the rheogoniometer for periods of up to 1 week before retesting it in the linear or nonlinear regions. However, in some cases, such as with white soft paraffin (Fig. 8), there is little evidence of any reformation after the initial breakdown process (except for a stress peak in the first test cycle). In addition, highly viscoelastic materials may show little structural breakdown in oscillation, even under the severest oscillatory conditions available with the rheogoniometer. However, the continuous shear facility of the instrument provides an alternative method.

A sample of wool fat was examined for thixotropy in this manner by first shearing it at a constant shear rate until the shear stress reached an equilibrium value. It was then allowed to recover and was tested at intervals, in oscillation, in its linear viscoelastic region. Immediately after shearing (Fig. 9), the stress/strain hysteresis loop was of small amplitude and large phase angle. However, as the structure rebuilt, the phase angle decreased and the stress amplitude increased. After 2 days of storage, the material was gradually returning to its unsheared condition (phase angle 5° at 2.5×10^{-2} Hz.).

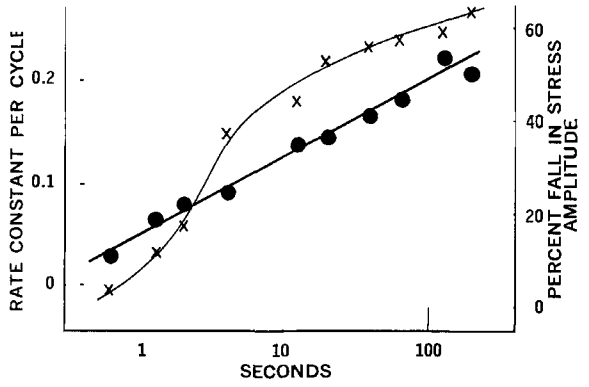

Figure 7—*Change of rate constant for breakdown and total breakdown with frequency for white soft paraffin. Rate constant per cycle,* ●, *and percent fall in stress amplitude,* ×. *Strain amplitude = 2.0 × 10^{-2} rad. Gap = 6.4 × 10^{-2} cm.*

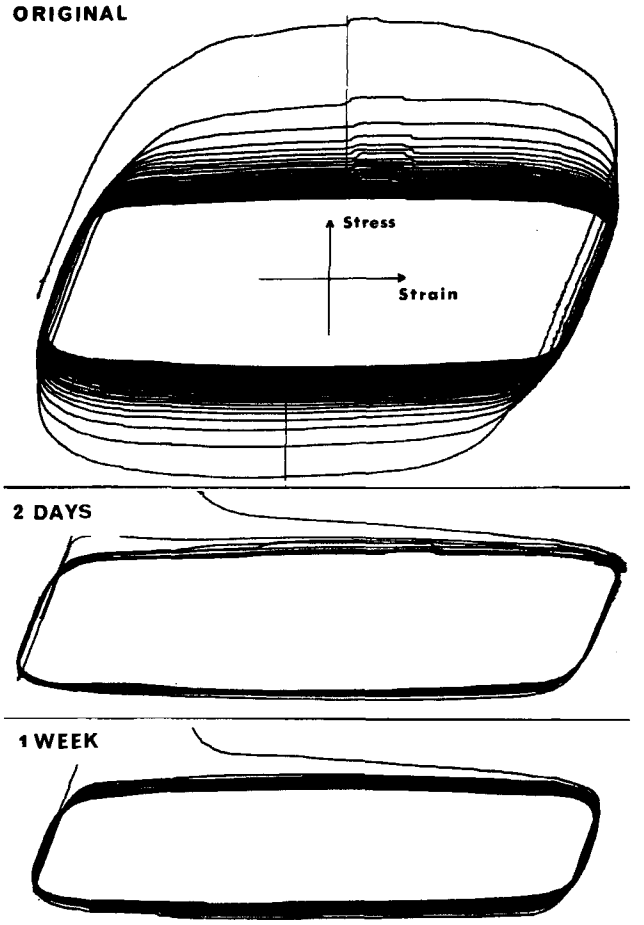

Figure 8—*Effect of storage on stress/strain hysteresis loop for white soft paraffin, nonlinear testing,* n = *5 × 10^{-3} Hz. Strain amplitude = 2.0 × 10^{-2} rad. Gap = 6.4 × 10^{-2} cm.*

CONCLUSIONS

Although destructive oscillatory testing does not provide fundamental rheological parameters, it does provide extremely useful information for quality control and for the correlation of physical properties with product assessment and consumer evaluation. The rate of breakdown of viscoelastic structure is approximately first order, and rate constants can be determined using the rheogoniometer in parallel plate geometry. Variables, such as amplitude and frequency of oscillation and the sample thickness, can be altered to determine the characteristic behavior of a given formulation. In

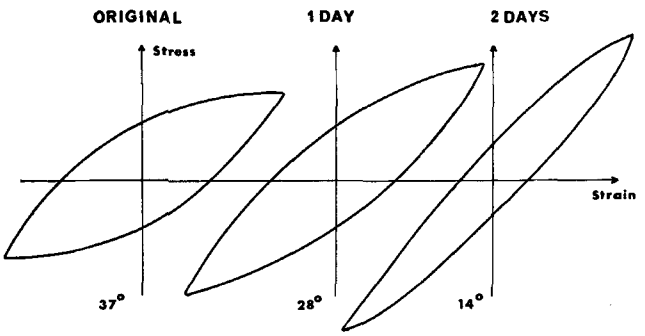

Figure 9—*Effect of storage on stress/strain hysteresis loop for wool fat, linear testing,* n = *2.5 × 10^{-2} Hz. Strain amplitude = 2.3 × 10^{-2} rad. Gap = 6.4 × 10^{-2} cm. Phase angle calculated from graphical method of Lammiman and Roberts (12).*

general, materials that have high elastic contributions (1) (*e.g.*, o/w creams) break down more rapidly than ointments and w/o creams, which are more viscous (1).

The rate constant for breakdown under oscillatory shear is an important parameter when assessing consumer utilization of topical products. In future studies, both nondestructive and destructive oscillatory tests and consumer panels will be used to arrive at a detailed viscoelastic specification for a range of semisolid products.

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Kinetics of Drug Absorption in Goldfish

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Abstract □ A two-compartment reversible model describing the occurrence of pharmacologic effect in goldfish as a function of drug concentration in the bathing solution was examined. The derived expressions were applied to 4-aminoantipyrine-induced overturn. The rate constants of absorption and exsorption for this drug were 4.0×10^{-4} hr.$^{-1}$ and 7.8×10^{-3} hr.$^{-1}$, respectively. The theoretical drug concentration in the fish body necessary for overturn was 19.5 mg. %, which agrees with the experimental results. The mathematical relationships and experimental data demonstrate that a critical concentration is necessary in the fish body before a pharmacologic response will occur. At low drug concentration in the bathing solution, the reciprocal time–drug concentration plots will be hyperbolic rather than linear. The results of this study suggest that 4-aminoantipyrine-induced overturn in the goldfish is absorption rate limited.

Keyphrases □ Goldfish, overturn—4-aminoantipyrine absorption–exsorption kinetics □ Pharmacokinetics, 4-aminoantipyrine absorption–exsorption—goldfish □ 4-Aminoantipyrine, absorption–exsorption kinetics—goldfish

The kinetics of drug absorption in goldfish were recently studied by several workers (1–5). One model, describing the uptake of drugs and toxic chemicals by fish, was developed by Levy and Gucinski (1). As noted by these authors, this theoretical treatment possesses certain limitations due to the simplifying assumptions. The model predicts that a plot of reciprocal time of occurrence of pharmacological effect (time of death or overturn time) *versus* drug concentration in the solution in which the fish are immersed will be linear and pass through the origin. Although the model successfully described the time course of pharmacologic effect of several drugs in the goldfish, some exceptions to the model also were reported. For example, Powers (6) found a number of positive concentration intercept values in plots of reciprocal time of death *versus* concentration of a variety of drug and toxic substances. Powers proposed that there is a concentration of every toxic substance below which no pharmacologic response is observed, regardless of the exposure time. This concentration was designated as a threshold of toxicity. Hall and Hayton (5) subsequently arrived at a similar conclusion by placing goldfish in dilute ethanol solutions for over 24 hr. without observing overturn. In their experiments, it was found that in ethanol-induced overturn and death of goldfish, a plot of reciprocal time of occurrence of the pharmacological end-point *versus* ethanol concentration resulted in a 1% (v/v) intercept. This finding was verified by Gibaldi and Nightingale (2), using the overturn end-point at low ethanol concentrations.

The purpose of the present study was to extend the Levy–Gucinski kinetic model of pharmacologic effect in the goldfish to situations where an apparent threshold concentration does exist.

THEORETICAL

The model of Levy and Gucinski (1) describes the relationship between the drug concentration in the fluids bathing the fish, the absorption rate, and the time of occurrence of pharmacologic effect in the goldfish. The basis of this model is Fick's first law of diffusion:

$$\frac{dA_B}{dt} = \frac{DA}{l}(C_o - C_i) \qquad \text{(Eq. 1)}$$

where A_B is the amount of drug absorbed by the goldfish, (dA_B/dt) is the rate of drug absorption, D is the diffusion coefficient, A is the surface area of biologic membrane, l is the thickness of the biologic membrane, C_o is the drug concentration outside the membrane (the solution bathing the fish), and C_i is the drug concentration on the inside of the membrane.

If one assumes that $C_o \gg C_i$ and integrates Eq. 1 between the limits of zero time and the time necessary to produce a pharmaco-