Method for Studying Rheology of Gelatin Melts

By HAROLD L. SMITH* and JERE E. GOYAN†

Procedures and instrumentation for measuring the stress relaxation modulus of melts employed as soft gelatin encapsulating formulations are reported. Changes in this parameter during thermal aging of the melts are reported for various formula modifications. These data are presented as constants obtained by fitting the stress relaxation curves to an appropriate equation on the analog computer and as log-log plots of these curves.

IT HAS BEEN reported (1) that the parameters classically employed in evaluating gelatin are not suitable for characterizing formulations used in preparing soft gelatin capsules. Therefore, a study was undertaken to determine whether a viscoelastic parameter would be suitable for evaluating these systems. The shear-stress relaxation modulus was chosen primarily because of the simplicity of instrumentation. This measurement has the additional advantage of being obtained directly from the melts as they are used in the capsule manufacturing procedure and avoids the principle disadvantage of similar measurements on films (*i.e.*, controlling moisture content).

Stress relaxation curves for viscoelastic systems are obtained by imposing an instantaneous strain on the sample of interest and following the resulting stress with time. An appropriate combination of Hooke's and Newton's laws has been employed by Reiner (2) and others (3) to derive the equation which describes the variation of stress with time after deformation

$$\sigma(t) = \sigma_0 e^{-[G/\eta]t} \qquad \text{(Eq. 1)}$$

where

$\sigma(t)$ = stress at time t
σ_0 = stress at $t = 0$
G = modulus of rigidity
η = coefficient of viscosity

Viscoelastic behavior has been depicted by various mechanical models, of which the Maxwell element (a Hookean spring in series with a dash pot containing a Newtonian oil) has been employed extensively. Further, Wiechert (2) suggested that the complex response of a polymeric system could be described by a series of Maxwell elements connected in parallel. These models are represented by the following equations:

Maxwell Model

$$\sigma(t) = \sigma_0 e^{-[t/\tau} \qquad \text{(Eq. 2)}$$

where

τ = the Maxwell relaxation time (the time required for the stress to equal $1/e$ times its initial value)

$$\tau = \eta/G \qquad \text{(Eq. 3)}$$

η = coefficient of viscosity of dash pot oil
G = spring constant

Wiechert's Model

$$\sigma(t) = \sum_{i=1}^{\eta} \sigma_i e^{-[t/\tau_i]} \qquad \text{(Eq. 4)}$$

where

σ_i = partial stress contributed by the ith element
τ_i = Maxwell relaxation time of the ith element

$$\tau_i = \eta_i/G_i \qquad \text{(Eq. 5)}$$

A more complete discussion of models for describing viscoelastic systems may be found elsewhere (4, 5).

Viscoelastic theory specifies that force as a function of time for the shear type of deformation is related to the stress relaxation modulus $[G(t)]$ according to the equation

$$G(t) = f(t)/bx \qquad \text{(Eq. 6)}$$

where

$G(t)$ = shear-stress relaxation modulus
$f(t)$ = force at time t
x = linear displacement of the bob
b = a form factor

The form factor for the Pochettino-type geometry (rising cylinder) is

$$b = 2\pi L/\ln(R_2/R_1)$$

where

L = length of shearing surface
R_1 = radius of the bob
R_2 = radius of the cup

The shear-stress relaxation curves were fitted on an Applied Dynamics Analog Computer according to the method previously reported for gelatin films (1). All curves were found to fit the equation

Received June 1, 1964, from the College of Pharmacy, University of Michigan, Ann Arbor.
Accepted for publication November 24, 1964.
This research was supported by funds provided by Lederle Laboratories, Division of American Cyanamid Co., Pearl River, N. Y.
* Present address: Lederle Laboratories, Division of American Cyanamid Co., Pearl River, N. Y.
† Present address: School of Pharmacy, University of California, San Francisco.

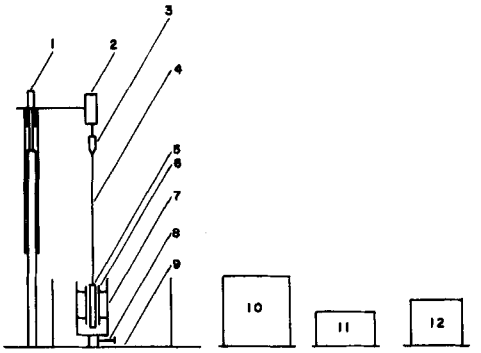

Fig. 1.—Shear-stress relaxation apparatus. Key: 1, micrometer head; 2, force transducer, Statham model G.I. 8; 3, pin vise; 4, bob connecting rod; 5, bob 6.350 × 0.4313 cm.; 6, cup 5.080 × 0.4763 cm.; 7, sample holder; 8, set screw; 9, water bath; 10, amplifier, Ellis Associates model BAM-1; 11, voltage divider; 12, recorder, Varian model G-10.

TABLE I.—COMPUTER CONSTANTS FOR FORMULATIONS WITH VARYING GLYCERIN–GELATIN RATIOS

Glycerin–Gelatin Ratio	Melt Age, hr.	Exponentials for all Curves $\alpha = 0.0350$, $\beta = 0.244$, and $\gamma = 0.750$ sec.$^{-1}$ Pre-exponentials × 10^{-2}, dyne cm.$^{-2}$ A	B	C	D
21–40	10	19.1	8.84	8.16	3.63
21–40	22	11.1	9.06	6.42	2.40
21–40	30	11.2	8.55	5.25	1.68
21–40	46	12.6	2.14	0.99	0
18–43	10	18.5	17.7	21.8	21.4
18–43	22	12.1	10.9	12.3	9.18
18–43	30	10.1	9.72	10.1	6.20
18–43	46	9.45	11.4	7.81	3.30
15–46	10	15.3	21.0	25.9	31.8
15–46	22	9.18	18.4	24.9	30.7
15–46	30	12.2	10.3	17.5	15.4
15–46	46	8.90	12.3	15.0	13.0
12–49	10	6.38	17.8	45.6	130.2
12–49	22	16.9	18.2	34.3	56.6
12–49	30	13.8	13.6	29.7	50.4
12–49	46	12.9	17.4	25.2	27.2

$$G(t) = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t} + D \quad \text{(Eq. 7)}$$

This equation describes a Wiechert model with four Maxwell elements connected in parallel, the fourth having a dash pot with infinite viscosity. Any changes in the constants of this equation may then be used to evaluate the viscoelastic changes occurring in the melt.

EXPERIMENTAL

All formulations were prepared and aged in a water-jacketed 1.2-L. stainless steel vessel fitted with a 0.5-in. o.d. gate valve at its base and a Plexiglas top that was sealed to the vessel by means of an O-ring. The top was equipped with a propeller-type stirrer ($^5/_{16}$-in. shaft mounted at a 45° angle through a Teflon bushing) and an entrance port (1.5-in. i.d.) which was fitted with a threaded cap. Water at the desired temperature was circulated through the jacket by a centrifugal pump.[1]

[1] Precision Scientific Co., 1/4 h.p. centrifugal pump.

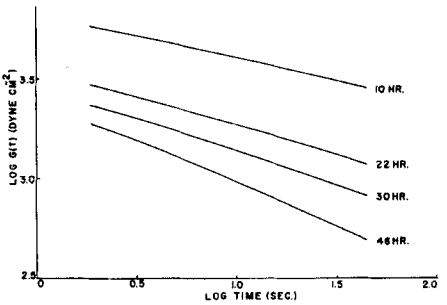

Fig. 2.—Stress relaxation modulus from a typical aging study.

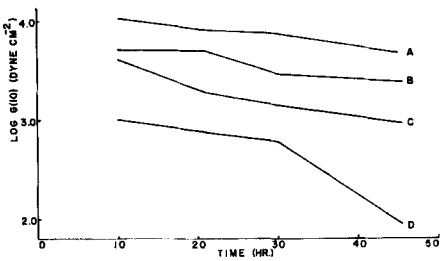

Fig. 3.—Aging studies for formulations with varying ratios of glycerin to gelatin. These curves were obtained from formulations with the following glycerin to gelatin ratio: A, 12:49; B, 15:46; C, 18:43; and D, 21:40.

TABLE II.—COMPUTER CONSTANTS FOR FORMULATIONS WITH VARYING GLYCERIN–WATER RATIOS

Glycerin–Water Ratio	Melt Age, hr.	Exponentials for all Curves $\alpha = 0.0332$, $\beta = 0.212$, and $\gamma = 0.798$ sec.$^{-1}$ Pre-exponentials × 10^{-2}, dyne cm.$^{-2}$ A	B	C	D
15–42	10	17.2	9.72	8.82	7.29
15–42	22	11.6	7.08	5.13	1.19
15–42	30	12.0	6.90	4.86	1.53
15–42	46	11.2	5.55	5.92	1.43
17.5–39.5	10	17.1	17.3	29.0	41.8
17.5–39.5	22	15.1	12.8	12.2	7.65
17.5–39.5	30	11.1	9.35	8.30	4.27
17.5–39.5	46	10.8	5.90	3.13	0.67
20–37	10	17.3	21.1	30.5	43.3
20–37	22	13.3	15.5	18.2	17.0
20–37	30	12.7	13.6	14.9	9.18
20–37	46	10.3	13.7	12.2	9.90

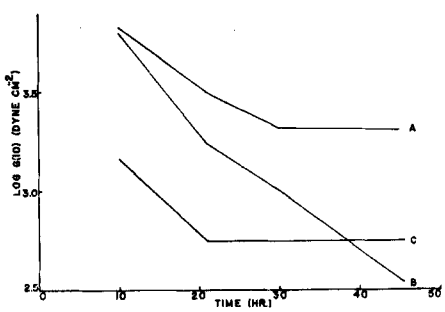

Fig. 4.—Aging studies for formulations with varying ratios of glycerin to water. These curves were obtained from formulations with the following glycerin to water ratios: A, 20:37; B, 17.5:39.5; and C 15:42.

TABLE III.—COMPUTER CONSTANTS FOR FORMULATIONS WITH 1,2,6-HEXANETRIOL SUBSTITUTED FOR GLYCERIN

Hexanetriol, % w/w	Melt Age, hr.	Exponentials for all Curves $\alpha = 0.0318$, $\beta = 0.218$, and $\gamma = 0.764$ sec.$^{-1}$ Pre-exponentials $\times 10^{-2}$, dyne cm.$^{-2}$ A	B	C	D
1.0	10	21.9	17.5	16.2	12.3
1.0	22	15.7	10.5	8.32	3.68
1.0	30	11.4	12.0	8.40	3.46
1.0	46	12.5	9.45	6.48	2.00
2.0	10	23.7	14.8	14.4	7.80
2.0	22	13.9	10.7	8.08	3.13
2.0	30	11.2	12.5	8.08	3.26
2.0	46	10.9	8.85	4.95	1.59
3.0	10	22.2	15.4	10.6	5.46
3.0	22	13.5	8.86	7.84	2.47
3.0	30	13.1	8.67	4.89	0.80
3.0	46	14.1	4.43	2.29	0.56

TABLE IV.—COMPUTER CONSTANTS FOR FORMULATIONS WITH PROPYLENE GLYCOL SUBSTITUTED FOR GLYCERIN

Propylene Glycol, % w/w	Melt Age, hr.	Exponentials for all Curves $\alpha = 0.0318$, $\beta = 0.218$, and $\gamma = 0.764$ sec.$^{-1}$ Pre-exponentials $\times 10^{-2}$, dyne cm.$^{-2}$ A	B	C	D
1.0	10	16.3	19.8	14.2	12.3
1.0	22	15.8	10.9	11.9	6.45
1.0	30	10.0	17.2	11.9	6.70
1.0	46	14.0	6.75	4.86	1.22
3.0	10	30.9	12.7	8.94	3.55
3.0	22	14.7	8.52	4.83	1.61
3.0	30	12.8	10.6	5.74	1.41
3.0	46	12.4	9.99	4.62	1.62

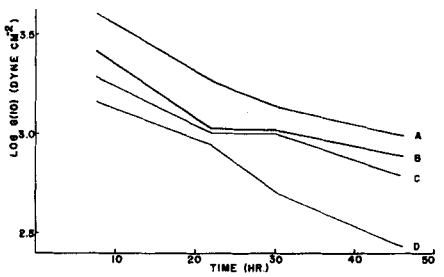

Fig. 5.—Aging studies for formulations with 1,2,6-hexanetriol substituted for glycerin. These curves were obtained from formulation with the following w/w percentage of 1,2,6-hexanetriol: A, 0.0; B, 1.0; C, 2.0; and D, 3.0.

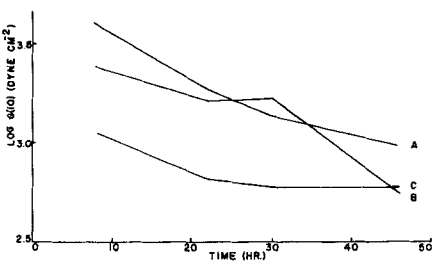

Fig. 6.—Aging studies for formulations with propylene glycol substituted for glycerin. These curves were obtained from formulations with the following w/w percentage of propylene glycol: A, 0.0; B, 1.0; and C, 3.0.

TABLE V.—COMPUTER CONSTANTS FOR FORMULATIONS CONTAINING VARIOUS ADDITIVES

Additive, 10 Gm./Kg.	Melt Age, hr.	Exponentials for all Curves $\alpha = 0.318$, $\beta = 0.218$, and $\gamma = 0.764$ sec.$^{-1}$ Pre-exponentials $\times 10^{-2}$, dyne cm.$^{-2}$ A	B	C	D
$CaCl_2$	10	24.5	10.2	6.17	3.30
$CaCl_2$	22.5	12.2	9.27	4.77	1.65
$CaCl_2$	30	12.8	9.27	4.83	1.87
$CaCl_2$	46	13.4	5.53	2.13	0.62
Na_2SO_4	10	21.3	18.4	22.9	25.1
Na_2SO_4	22	16.3	12.2	15.2	12.7
Na_2SO_4	30	10.2	14.0	16.0	14.2
Na_2SO_4	46	11.4	13.0	10.6	5.56
Na citrate	10	25.6	15.3	14.8	8.84
Na citrate	22	12.9	16.2	14.8	10.5
Na citrate	30	14.7	15.0	14.4	6.71
Na citrate	46	14.6	10.9	5.95	2.42
Na tartrate	10	20.4	14.0	18.8	18.2
Na tartrate	22	18.8	13.9	18.4	15.0
Na tartrate	30	13.9	15.4	15.3	10.9
Na tartrate	46	11.8	11.3	10.2	5.44

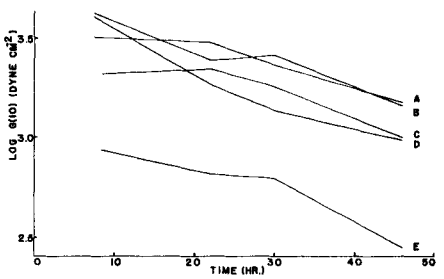

Fig. 7.—Aging studies for formulations containing various additives. These curves were obtained from formulations with 10 Gm./Kg. of the following additive: A, sodium tartrate; B, sodium sulfate; C, sodium citrate; and E, calcium chloride. Curve D was obtained from the basic formulation.

The weighted gelatin[2] sample was placed in the vessel which was maintained at 90 ± 0.1°. After 30 min. the glycerin–water solution (at 25.0°) was added. The time of this addition was designated as zero time. The gelatin was allowed to hydrate for 1.0 hr. without stirring followed by 1.0 hr. of stirring to insure homogeneity.[3] The stirrer was stopped and the water jacket connections were attached to a 60.0° bath for the remainder of the study.

Samples were withdrawn from the valve at the base of the vessel periodically during the aging period (max. 50 hr.). The removal of samples was facilitated by applying 9.0 psig air pressure to the vessel by means of a special attachment at the entrance port. Samples were collected in the sample holder (Fig. 1) which was contained in a small 60.0° water bath. The holder was transferred rapidly to a larger 60.0° water bath, and the bob (0.1698 × 2.5 in.) which had been preheated to 60° was inserted into the cup (9.1875 × 2.0 in.). After covering the sample with approximately 20 ml. of light liquid petrolatum to prevent the loss of water, the bob was rotated slowly for 15 min. by attaching

[2] Swift pork skin gelatin having a bloom value of 200; viscosity, 37–43 millipoise; pH, 4.4–4.8; and moisture 10.4%, was used throughout this study.
[3] Heller model G-21 motor.

it to the Heller motor to assure deaeration of the shearing gap. The sample holder was allowed to remain in the 60° bath for a total of 30 min. and then was installed in the rising cylinder apparatus (Fig. 1). This was accomplished by securing the set screw at the base of the holder to a mounting rod located in the water bath (39.0 ± 0.1°) and attaching the bob connecting rod to the force transducer by means of a pin vise. After allowing the sample to come to thermal equilibrium (3.5 hr.) the measurement was taken by instantaneously rotating the micrometer head located at the top of the apparatus. The distance the bob had risen was read directly from the micrometer head in millimeters ±0.002. The force developed by imposing the shear-strain was measured by the force transducer. The output voltage signal from the transducer was amplified, adjusted by the voltage divider, and continuously recorded by a Varian model G-10 recorder with a chart speed of 16 in./min.

Glycerin–Gelatin Ratio Variations.—Aging studies were conducted on four different formulations which contained 39% (w/w) water but had varying ratios of glycerin to gelatin. The stress relaxation curves obtained from these studies were fitted to the following equation on an analog computer:

$$G(t) = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t} + D \quad \text{(Eq. 7)}$$

The constants for these studies are listed in Table I. As a typical example of a single study, log-log plots of the stress relaxation modulus are presented in Fig. 2 for the 43:18 glycerin–gelatin formulation. In Fig. 3, $G(10)$ values (G at t = 10.0 sec.) taken from each curve of all four studies are plotted against time of aging.

Three studies were performed on formulations containing a combined total of 57% water and glycerin (gelatin concentration remaining constant). The computer constants for these studies are listed in Table II. The $G(10)$ values for these studies are plotted against time of aging in Fig. 4.

Glycerin Substitutes.—The computer constants obtained when 1, 2, and 3% 1,2,6-hexanetriol and 1 and 2% propylene glycol replaced an equal weight of glycerin in the basic formulation are listed in Tables III and IV. The $G(10)$ values are plotted in Figs. 5 and 6.

Additives.—Various additives in concentrations of 10 Gm./Kg. of melt were dissolved in the glycerin–water solution used to prepare the melts. The computer constants for these modified formulations are listed in Table V, and the $G(10)$ values are plotted in Fig. 7.

DISCUSSION

To evaluate the method and the instrumentation, and to determine the viscoelastic changes occurring with various formulating modifications, a single gelatin was employed in these studies. In addition to fitting the stress relaxation data obtained from these studies on the computer, these data were plotted as log of stress relaxation modulus *versus* log of time (*cf.* Fig. 2 for log-log plots of a typical aging study). Further, as a method of interrelating the viscoelastic changes occurring with various formulating modifications, values for the modulus at 10 sec. $G(10)$ were taken from each curve and plotted against the time of thermal aging (*cf.* Figs. 3–7).

The first of the formulating variation studies demonstrates that an increase in the glycerin–gelatin ratio (constant per cent water) causes a decrease in stress relaxation modulus (*cf.* Fig. 3 and Table I) which is consistent with theory considering the molecular species which are varied. Figure 4 and Table II illustrate the changes in the stress relaxation modulus when the glycerin–water ratio is varied (constant per cent gelatin). The changes in the viscoelastic properties of the formulation accompanying these variations can be attributed to the changes in the corresponding degrees of solvation of the gelatin.

The glycerin substitute studies (*cf.* Figs. 5 and 6, Tables III and IV) indicate that the magnitude of the stress relaxation modulus is increased as the number of hydroxyl groups capable of hydrogen bonding is increased. A similar relation appears to exist with the hydroxylated organic acids in the additive studies (*cf.* Fig. 7 and Table V). In this case, however, the number of carboxyl groups provided by the additive also must be considered.

The additive studies with the inorganic salts indicate some relation between the viscoelastic properties of the melt and the valence of the ions employed, but further studies are necessary before this relation can be elucidated.

Although it was possible to fit all of the experimental curves using Eq. 7 (*cf.* Tables I–V) the pre-exponential factors are difficult to interpret as was found previously with the film studies (1). The modulus at 10 sec. $G(10)$ was plotted, therefore, as a more convenient means of visualizing changing in the melt. This method has the additional advantage of not requiring the computer.

Inspection of Figs. 2–6 shows that the stress relaxation modulus of the melt is markedly altered by small changes in the concentration of gelatin, glycerin, or glycerin substitutes. It, therefore, may be concluded that these studies are not only consistent with existing viscoelastic theory, but in addition they illustrate that the method provides data which are sensitive enough to be useful for evaluating soft gelatin encapsulating formulations. Preliminary experiments under industrial conditions have shown that the instrument may be useful in predicting some of the technological problems involved in manipulating gelatin melts.

REFERENCES

(1) Castello, R. A., and Goyan, J. E., This Journal, **53**, 777(1964).
(2) Reiner, M., "Lectures on Theoretical Rheology," North-Holland Publishing Co., Amsterdam, The Netherlands, 1960.
(3) Bueche, F., "Physical Properties of Polymers," Interscience Publishers, New York, N. Y., 1962.
(4) Ferry, J. D., "Viscoelastic Properties of Polymers," John Wiley & Sons, Inc., New York, N. Y., 1961.
(5) Kuhn W., *Helv. Chim. Acta*, **30**, 487(1947).