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Viscoelastic Properties of Pharmaceutical Semisolids II: Creams

S. S. DAVIS

Abstract ☐ Oil-in-water and water-in-oil pharmaceutical creams have been examined using creep testing. Particular attention has been paid to systems stabilized by long-chain alcohol–surfactant complexes and the effect of temperature on their viscoelastic spectrum. The results show that there is a distinct difference between the behavior of complexes made from ionic and nonionic soaps.

Keyphrases ☐ Viscoelastic properties—creams ☐ Creams—creep testing ☐ Temperature effect—viscoelastic parameters, creams ☐ Ionic, nonionic soap complexes—creams

In the second part of this investigation the viscoelastic properties of some pharmaceutical creams of the B.P. and B.P.C. are investigated. A number of them are made by mixing a molten ointment base with water, *e.g.*, aqueous cream from emulsifying ointment (o/w) and oily cream from wool alcohols ointment (w/o). Creams may be considered as high-volume fraction oil-in-water or water-in-oil emulsions of high viscosity.

Recently much interest has been shown in creams that are stabilized by long-chain alcohol–surfactant complexes which, besides forming a protective film at the oil-water interface, provide a considerable "self-bodying" effect. Continuous-shear studies on such systems have been described by Talman *et al.* (1) and Groves (2), while Barry (3–5) has used creep and continuous-shear methods to investigate the ternary system: sodium lauryl sulfate–cetyl alcohol–water, with and without the addition of oil.

In the present work four pharmaceutical creams and the ternary system described above have been investigated using creep and continuous-shear methods over the temperature range 24–51°. The theory of creep testing and model representation for viscoelastic materials have been discussed in Part I(6). The limitations of continuous-shear methods for semisolids have previously been dealt with fully by Davis *et al.* (7).

EXPERIMENTAL

Materials—The creams were commercial samples of B.P. and B.P.C. formulations. Details are given in Table I. The ternary System R8 was prepared using the materials and method of Barry and Shotton (3).

Apparatus—Details of creep and continuous-shear apparatus and procedure have been given by Davis (6). During testing the samples were enclosed in a saturated water vapor atmosphere to minimize effects due to evaporation.

RESULTS

The creams were examined in creep over the temperature range 24–54° while continuous-shear rheograms were obtained at 25° only. All the systems studied were viscoelastic in nature. The creep curves were analyzed as before (8) and the viscoelastic parameters at the different temperatures are given in Table II.

(a) **Oily Cream**—In continuous shear the rheogram for oily cream (Fig. 1) demonstrates a yield value and a hysteresis loop and there is no evidence of expulsion of material from the measuring surfaces of the viscometer (7). The curve, however, is unusual in that the up curve lies to the left of the down curve implying some kind of dilatant behavior. Creep studies show (Table II) that there is a progressive fall in viscoelastic parameters over the temperature range 26–45°. At
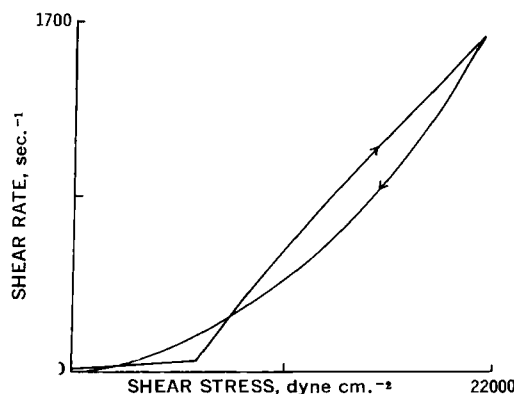

Figure 1—*Rheogram for oily cream. Temperature, 25°C.; sweep time, 240 sec.*

Table I—Composition of Creams

System	Liquid Paraffin	White Soft Paraffin	Hard Paraffin	Wool Alcohols	Water	Cetostearyl Alcohol	Cetyl Alcohol	Sodium Lauryl Sulfate	Cetrimide	Ceto-macrogol
Oily cream	30	5	12	3	50	—	—	—	—	—
Aqueous cream	6	15	—	—	70	8.1	—	0.9	—	—
Cetrimide cream	50	—	—	—	44.5	5	—	—	0.5	—
Chlorhexidine cream	10	—	—	—	65	20	—	—	—	5
System R8 (3)	—	—	—	—	91	—	8	1	—	—
System E9 (5)	22.9	—	—	—	68.8	—	7.43	0.83	—	—
System E10 (5)	22.7	—	—	—	68.2	—	8.18	0.91	—	—
Cetomacrogol cream (1)	50	—	—	—	47.5	2.0	—	—	—	0.5

26° an eight-unit mechanical model is necessary to describe the system. This consists of three Voigt models in series with a Maxwell model (4, 6). At 45° only a four-unit model, a Voigt model in series with a Maxwell model, is required. The longest retardation time (τ_2) falls linearly with increase in temperature.

(b) System R8—The continuous-shear behavior of this system has been described by Barry and Shotton (3). The rheogram is of the hysteresis-loop type with the down curve lying to the left of the up curve. A yield point and spur are also present (9). The creep behavior is markedly different from that of oily cream as an eight-unit model is required to describe the system throughout the temperature range. The individual creep curves are shown in Fig. 2. It can be seen that as the temperature increases the compliance at any given time decreases until the temperature reaches 43°. After this temperature the compliance increases with temperature. The inset in Fig. 2 shows the change in compliance with temperature for an arbitrary time of 360 sec. A minimum compliance is found in the region of 43°. The viscoelastic parameters G_0 and $J(N)$ (Table II) show a maximum and minimum, respectively, near this temperature but there is little change in η_0 or τ_2.

(c) Aqueous Cream—This is essentially System R8 containing added oil. The continuous-shear rheogram is of the hysteresis-loop type with a yield value (Fig. 3). In creep, as with System R8, an eight-unit model is required over the tempera-

ture range 24–46°. The compliance at 360 sec. (Fig. 4) passes through a minimum around 40° and there is a maximum G_0, η_0, and minimum $J(N)$ at this point.

(d) Cetrimide Cream—In all respects the behavior of this material is similar to b and c above. The rheogram at 25° shows a definite spur effect immediately after the yield point. In creep there is a minimum in the compliance at 360 sec. (Fig. 4) but the minimum/maximum in the G_0, η_0, $J(N)$ relationships is not as pronounced as before. τ_2, however, passes through a maximum and the number of model units required to represent the system increases to a maximum of eight (Table II).

(e) Chlorhexidine Cream—Although the cream is based on a surfactant-alcohol complex and the rheogram is of the hysteresis-loop type with a yield point (Fig. 3), there is no evidence of a minimum compliance at 360 sec. in creep (Fig. 4) or a maximum G_0 and η_0 (Table II).

DISCUSSION

In continuous shear, the rheograms of all the creams are of the hysteresis-loop type and they all demonstrate a yield point. This indicates that there is some definite minimum shear stress required to cause the materials to flow and that below this point the materials are behaving as solids. In creep, however, a residual viscosity (η_0) is found in all cases. This residual
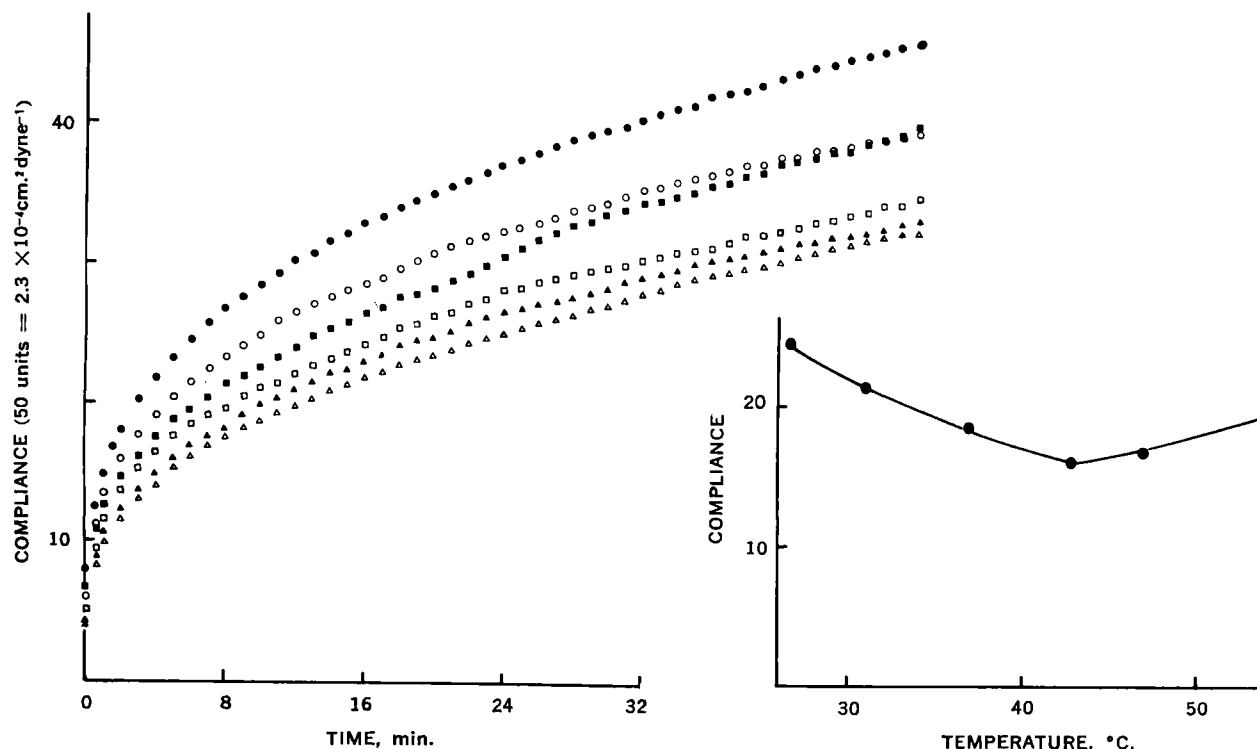

Figure 2—*Creep curves for System R8. Key: (°C.); ●, 26; ○, 31; □, 37; △, 43; ▲, 47; ■, 54. Inset: Creep compliance at 360 sec.*

Table II—Viscoelastic Parameters of Creams[a]

Temp., °C.	G_0	η_1	$J(N)$[b]	τ_2	G_2	η_2	τ_1	G_1	η_1	τ_3	G_3	η_3
					Oily Cream							
26.0	4.33,+5	1.16,+8		11.54	1.02,+5	7.57,+7	1.07	3.86,+5	2.48,+7	2.70,−1	4.19,+5	6.81,+6
30.3	1.75,+5	1.47,+8		9.27	1.05,+5	5.84,+7	2.73	2.53,+5	4.17,+4	9.38,−1	1.83,+5	1.03,+7
35.0	6.98,+4	8.56,+7		8.76	5.05,+4	2.65,+7	5.05,−1	1.72,+5	5.22,+6	3.98,−2	2.28,+5	5.47,+5
39.5	2.77,+3	1.54,+7		5.02	3.11,+3	9.37,+5	2.15,−1	1.05,+5	1.35,+6	—	—	—
45.3	2.49,+3	6.44,+7		2.21	2.18,+3	2.94,+5	—	—	—	—	—	—
					System R8							
26.4	2.73,+4	5.66,+7	1.31,−4	12.54	1.02,+4	7.71,+6	8.92,−1	3.54,+4	4.74,+6	3.48,−1	2.28,+5	4.78,+6
31.0	4.00,+4	5.05,+7	1.03,−4	10.74	1.51,+4	9.72,+6	1.21	4.41,+4	3.20,+6	3.58,−1	6.60,+4	1.42,+6
37.0	4.37,+4	5.30,+7	8.70,−5	12.85	1.96,+4	1.51,+7	1.48	4.18,+4	3.72,+6	4.62,−1	8.32,+4	2.30,+6
42.8	5.46,+4	4.54,+7	7.23,−5	10.45	2.32,+4	1.45,+7	1.19	7.00,+4	4.99,+6	4.03,−1	7.21,+4	1.73,+6
47.0	4.85,+4	4.65,+7	7.37,−5	9.45	2.14,+4	1.22,+7	8.71,−1	4.58,+4	2.39,+6	4.54,−1	1.82,+5	4.95,+6
54.0	3.64,+4	3.63,+7	8.29,−1	9.25	1.79,+4	9.79,+6	5.72,−1	5.60,+4	1.57,+6	4.76,−1	1.93,+5	5.52,+6
25.0	2.22,+4	1.96,+7		17.00	1.12,+4	1.14,+7	3.05	2.39,+4	4.37,+6	4.53,−1	4.36,+4	1.46,+6
					Aqueous Cream							
24.2	5.56,+3	8.26,+6	8.13,−4	13.77	3.14,+3	2.59,+6	1.93	6.97,+3	8.05,+5	5.31,−2	2.10,+4	6.68,+4
26.4	6.24,+3	4.06,+6	6.45,−4	14.00	2.69,+3	2.26,+6	1.94	5.73,+3	6.69,+5	4.18,−2	1.04,+4	2.72,+4
36.4	9.71,+3	3.73,+6	4.00,−4	15.40	1.80,+3	1.66,+6	1.22	6.73,+3	4.95,+5	8.53,−2	1.07,+4	5.38,+4
40.3	1.25,+4	7.72,+6	3.77,−4	16.54	2.38,+3	2.37,+6	1.36	1.04,+4	8.50,+5	6.66,−2	1.90,+4	7.52,+4
46.0	1.09,+4	5.17,+6	5.48,−4	18.40	2.44,+3	2.69,+6	1.52	1.13,+4	1.03,+6	9.82,−1	1.36,+4	8.02,+4
51.8	9.70,+3	4.31,+6	7.37,−4	15.00	2.96,+3	2.66,+6	1.01	6.01,+3	3.61,+5	—	—	—
					E9 (5)							
25.0	1.25,+4	1.5 ,+7		16.5	6.8 ,+3	7.0 ,+6	1.91	1.25,+4	1.8 ,+6	2.06,−1	1.42,+4	2.5 ,+5
					E10 (5)							
25.0	1.42,+4	1.5 ,+7		15.6	6.8 ,+3	7.0 ,+6	4.55	2.50,+4	9.0 ,+6	7.66,−1	1.00,+4	6.0 ,+5
					Cetrimide Cream							
16.6	1.88,+4	3.96,+7	1.78,−4	3.75	1.32,+4	2.96,+6	6.51,−1	9.36,+3	3.64,+5	—	—	—
26.6	1.39,+4	3.13,+7	1.00,−4	11.30	1.66,+4	1.12,+7	1.15	4.30,+4	2.99,+6	6.63,−2	6.10,+4	2.43,+5
33.2	1.29,+4	3.12,+7	1.22,−4	10.23	1.14,+4	7.00,+6	5.64,−1	6.53,+4	2.21,+6	4.19,−2	7.80,+4	1.96,+5
39.0	1.29,+4	5.58,+7	1.00,−4	10.14	1.55,+4	9.41,+6	7.79,−1	4.37,+4	2.06,+6	7.31,−2	8.24,+4	3.65,+5
46.5	1.27,+4	2.58,+7	7.85,−5	7.54	2.39,+4	1.08,+7	5.35,−1	3.82,+4	1.22,+6	—	—	—
50.5	6.72,+3	6.18,+6	7.95,−5	4.51	1.97,+4	5.35,+6	2.21,−1	3.15,+4	6.24,+5	—	—	—
					Chlorhexidine Cream							
23.5	2.73,+3	3.73,+6	3.85,−3	7.82	1.16,+3	5.45,+5	7.35,−1	2.25,+3	9.94,+4	8.17,−2	7.10,+3	3.43,+4
31.5	2.18,+3	1.78,+6	6.66,−3	13.20	6.67,+2	5.28,+5	1.26	2.38,+3	1.81,+5	5.35,−2	4.27,+3	1.37,+4
36.6	1.82,+3	1.62,+6	2.36,−3	14.70	5.26,+2	4.64,+5	8.15,−1	2.37,+3	1.16,+5	—	—	—
41.0	1.82,+3	1.31,+6	2.05,−3	11.35	7.52,+2	5.12,+5	1.06	2.26,+3	1.44,+5	2.25,−1	3.40,+3	4.61,+4
46.5	1.56,+3	1.01,+6	2.28,−3	13.38	6.33,+2	5.08,+5	1.20	1.95,+3	1.41,+5	6.68,−2	3.32,+3	1.33,+4
51.8	6.06,+2	2.06,+6	3.32,−3	9.74	4.36,+2	2.55,+5	9.95,−1	1.04,+3	6.23,+4	—	—	—

[a] See *Reference 8*. [b] $J(N)$ = total compliance due to Voigt elements (cm.² dyne⁻¹).

viscosity represents the behavior of the material at long times where the effect of the viscoelastic contribution is complete and the system is flowing as a solid dispersion in a liquid of high viscosity (6), *i.e.*, provided that the time scale is long enough, the material will flow, however low the stress. The yield values found in continuous shear are therefore associated with the time scale of the experiment and are not a true property of the materials.

The change in viscoelastic behavior of oily cream with temperature is very similar to that found with ointment bases (6), in particular wool fat and lanolin. An increase in temperature causes a breakdown in the structure responsible for the viscoelastic properties and the model representation becomes simpler. Oily cream is a water-in-oil emulsion con-
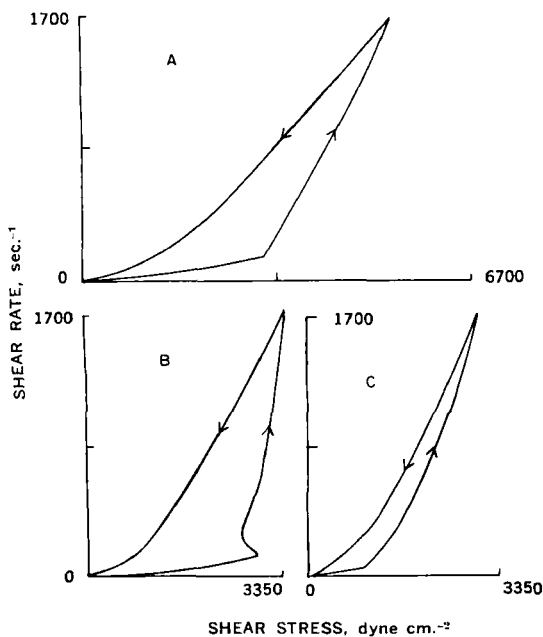

Figure 3—*Rheograms for three creams. Temperature, 25°C.; sweep time, 240 sec. Key: A, aqueous; B, cetrimide; C, chlorhexidine.*
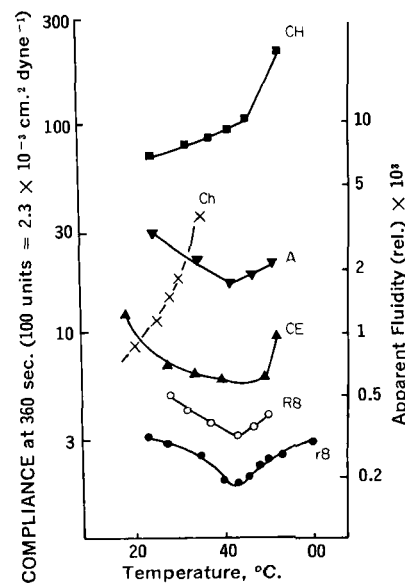

Figure 4—*Creep and continuous-shear behavior of four systems based on a soap-alcohol complex. Key [creep]: R8, System R8; A, aqueous cream; CE, cetrimide cream; CH, chlorhexidine cream. Continuous shear: r8, System R8 (ref. 3); ch, cetomacrogol cream (ref. 1).*

taining very small water droplets that are highly aggregated. The basis of the cream, wool-alcohols ointment, has been shown to be viscoelastic (6) and the presence in this of a network of aggregated water droplets will increase the values of many of the viscoelastic parameters. Aggregated emulsions are known to demonstrate pseudoplastic flow with the formation of hysteresis loops but the presence of dilatancy is unusual. It may well be that the viscoelastic nature of the continuous phase can cause such phenomena. The emulsifier for the cream is thought to be the small quantity of wool alcohols (10–12). The aggregation of water-in-oil emulsions has been discussed in detail by Davies (13) who has concluded that in many cases a macromolecular bridging mechanism was responsible. For oily cream the aggregation is probably due to the wool alcohols, made up of long-chain alcohols, forming a membrane that is lyophobic and which will adhere to itself more strongly than to the continuous phase.

The results for the viscoelastic gel R8 at 25° are similar to those obtained by Barry and Shotton (4) (Table II). The viscoelastic spectrum for this material does not show the rapid change with temperature as shown by oily cream. In fact the creep compliance becomes *smaller* as the temperature rises until it passes through a minimum around 43°. Similar behavior is shown in the values of the calculated viscoelastic properties. Barry and Shotton (3) found, in continuous-shear studies, that the apparent relative viscosity passed through a maximum at 42.5°. Their results have been plotted as fluidities (qualitatively equivalent to compliance) in Fig. 4, demonstrating the similarity between their results and those of the present work.

The System R8 is made up of threads of frozen liquid crystal (smectic phase) and solid alcohol dispersed in aqueous solution to give a submicroscopic network that can entrap both solid alcohol and frozen spherulites to give a viscoelastic gel-like structure (3). The minimum at 43° is thought to be the transition temperature from frozen smectic to liquid smectic phase. This occurs at a temperature a little lower than the penetration temperature (14) of sodium lauryl sulfate in pure cetyl alcohol (46°). At temperatures above the transition temperature the liquid crystal phase will tend to round up into globules which will cause less disturbance to flow.

Aqueous cream and cetrimide cream are similar to System R8 in the manner in which their viscoelastic behavior changes with temperature. A minimum compliance occurs in the region 40–45°. The change of some of the viscoelastic parameters with temperature is somewhat different from R8. These differences may be attributed to the presence of oil in the systems and the nature of the emulsifying agents. Barry (5) concluded that in such systems migration of alcohol from the oil phase to the continuous phase gives a gel-like structure that links the emulsion droplets and entraps the continuous phase.

The results for aqueous cream can be compared with those of Barry (5) (Table II) for systems of similar formulation. The only major difference is the presence of 15% white soft paraffin in aqueous cream, however, this should have little effect on the resultant emulsion for it is well known that the nature of the oil phase of an oil-in-water emulsion has very little effect on the emulsion viscosity (15, 16). The values of all the viscoelastic parameters for aqueous cream are in general smaller than for Barry's systems E9 and E10. These, however, were examined by Barry when the systems had been freshly prepared, whereas the aqueous cream had been stored for a period of time since manufacture. It is known that systems based on the alcohol-surfactant complex using pure-agents are metastable and that the consistency falls rapidly with time (5). Systems made with impure agents (such as

aqueous cream) are far more stable. The differences between E9 and E10 and aqueous cream can therefore be accounted for by the difference in the storage time after preparation. Although a freshly prepared system using pure agents has higher viscoelastic parameters than a stored system made from impure agents, the position would soon be reversed, due to the metastable nature of the foamer.

Chlorhexidine cream, based on nonionic soap (cetomacrogol)-alcohol complex shows no minimum in the compliance temperature relationship. Talman *et al.* (1) studied the effect of temperature on the relative viscosity of a system of similar formulation (Table I). Their results have been plotted in Fig. 4 as fluidities. Unlike the fluidity results for R8 (3) there is no evidence of a minimum. It therefore appears that the nature of the cetomacrogol-alcohol complex is different from that formed by anionic and cationic soaps. This is probably due to the formation of a weaker molecular complex due to the bulky nature of the nonionic soap molecule (17). This difference in behavior is reflected in the B.P.C. formulation of chlorhexidine cream (Table I) where the quantities of alcohol and soap are far greater than for the anionic/cationic soap-alcohol creams. In addition Talman *et al.* (1) have found that for a standard formulation of oil, cetyl alcohol, and 5% soap the calculated viscosity parameters for sodium lauryl sulfate and cetrimide were much higher than for cetomacrogol.

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