alkyl substituted nitrosoureas, *i.e.*, NNMU, NNEU, NNBU, etc. Compounds with large groups in the R and R′ positions (Table V), *i.e.*, the disubstituted nitrosoureas, show deviations in this respect and imply that steric factors may affect the reduction reaction. Apparently both nitroso groups in SRI-1631 are equivalent and are reduced simultaneously, producing a current about twice that expected for a molecule of this size.

In the adsorption controlled region (phosphate buffer) the changes in the half-wave potentials and the limiting currents due to different substituents are not so pronounced as in the diffusion controlled region. However, many of the nitrosoureas, *i.e.*, NNBeU, SRI-1834, and those disubstituted derivatives with large groups in the R or R′ positions, exhibit a double wave in phosphate buffer (Table VI), indicating that the adsorbed species may be reduced more easily than the free form. Again steric factors may assume a role in the reduction of these particular compounds.

The relationship between the half-wave potentials and the apparent first-order rate constants (k, sec.$^{-1}$) for the solvolysis of various *N*-alkyl-*N*-nitrosoureas (6) in the neutral pH region is shown in Table V and in Fig. 9. In this case large discrepancies are noted when the substituents contain a double bond close to the electroactive site, *i.e.*, allyl and benzyl.

No correlation (Table VI) could be demonstrated between the half-wave potentials of the *N*-nitrosoureas and the available biological activity data (2). However, the biological data are limited and those which are available may not be entirely reliable due to the instability of these compounds in the neutral pH region.

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Rheological Study of Selected Pharmaceutical Semisolids

By JAMES C. BOYLAN

Rheograms were obtained with a Ferranti-Shirley cone and plate viscometer at 20, 25, 30, and 35° for 13 pharmaceutical semisolids. As the temperature was raised, all the products studied showed a decrease in viscosity, thixotropy, and yield value. For many of the semisolids there appears to be a straight line relationship between thixotropic area and temperature. For ointments whose base is predominately white ointment, the viscosity is reduced by a factor of 0.5 for every 5° rise in temperature. At 35° many of the products studied showed similar values for thixotropy and viscosity.

A GREAT VARIETY of test procedures have been utilized over the years for the evaluation of the spreading and flow characteristics of pharmaceutical semisolids. Today, even widely used test equipment, such as the cone penetrometer, leave much to be desired as to the amount and type of data obtained. At the present time no single instrument can provide all the information required for complete product evaluation. However, this situation can be improved by the use of a viscometer capable of obtaining the complete hysteresis profile of non-Newtonian pharmaceutical semisolids.

Schulte and Kassem (1–6) have recently published an excellent series of papers dealing with the flow properties of several semisolid systems including silicone gels, triglyceride gels, polyethylene gels, polyethylene glycol gels, various vaselines, and carbohydrate gels. In addition,

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TABLE I.—SEMISOLIDS STUDIED AND THEIR INGREDIENTS[a]

	White Petrolatum U.S.P.	Petrolatum N.F.	White Ointment U.S.P.	Zinc Oxide Paste U.S.P.	Neomycin Sulfate Ointment U.S.P.	Ammoniated Mercury Ointment U.S.P.	Boric Acid Ointment	Sulfur Ointment U.S.P.	Bacitracin Ointment U.S.P.	Ichthammol Ointment N.F.	Cyclomethycaine Ointment	Cyclomethycaine Cream	Cyclomethycaine Jelly
Active ingredient	...	...	...	25.0	5.0	5.0	10.0	10.0	1.0	10.0	1.0	0.5	0.75
White petrolatum U.S.P.	100.0	...	95.0	50.0	90.3	87.4	80.7	76.0	53.0	...	80.1	...	...
Petrolatum N.F.	...	100.0	...	...	...	...	...	...	...	80.0	...	...	...
Mineral oil U.S.P.	...	...	...	...	4.7	3.0	5.0	10.0	23.0	...	...	...	...
White wax U.S.P.	...	...	5.0	...	...	4.6	4.3	4.0	...	...	3.0	...	...
Anhydrous lanolin U.S.P.	...	...	...	...	...	...	...	...	23.0	10.0	15.0	...	...
Stearic acid U.S.P.	...	...	...	...	...	...	...	...	...	...	...	15.0	...
Cetyl alcohol N.F.	...	...	...	...	...	...	...	...	...	...	...	3.0	...
Polypropylene glycol	...	...	...	...	...	...	...	...	...	...	...	...	30.0
Sodium phosphate N.F. (dried)	...	...	...	...	...	...	...	...	...	...	...	0.4	0.3
Sodium lauryl sulfate U.S.P.	...	...	...	...	...	...	...	...	...	...	...	0.5	...
Polysorbate 80 U.S.P.	...	...	...	...	...	...	...	...	...	...	...	...	0.3
Polysorbate 60	...	...	...	...	...	...	...	...	...	...	...	1.0	...
Sorbitan monostearate	...	...	...	...	...	...	...	...	...	...	...	1.5	...
Hydroxypropyl methylcellulose 1500	...	...	...	...	...	...	...	...	...	...	...	...	3.3
Fluid benzoin	...	...	...	...	...	...	...	...	...	...	0.9	...	...
Glycerin U.S.P.	...	...	...	...	...	...	...	...	...	...	...	15.0	...
Purified water U.S.P.	...	...	...	...	...	...	...	...	...	...	...	63.1	65.3
Starch U.S.P.	...	...	...	25.0	...	...	...	...	...	...	...	...	...

[a] All figures are expressed as per cent w/w. Preservative materials are also present in some of the semisolids.

Van Ooteghem (7) has written a helpful review of the methods currently used to measure rheological properties of ointments.

The purpose of this paper is to report the rheological characteristics of several pharmaceutical semisolid products in the temperature range 20–35° and to show how these results can be valuable to the formulator and manufacturer of these products.

EXPERIMENTAL

Materials.—Except for white petrolatum, petrolatum, and white ointment, the semisolid products studied were in commercial 1-oz. tubes.[1] Table I lists the products studied and their component ingredients. The age of the semisolids varied from 4 to 21 months, with most of the samples being from 7 to 14 months in age. Storage was, in all cases, at room temperature.

Rheological Evaluation.—The viscometer used in this study was a Ferranti-Shirley cone and plate viscometer[2] equipped with a 1200-Gm. cm. spring, an automatic gap-setting device, an x–y recorder,[3] and a constant-temperature water bath.[4] The use of this viscometer has been described elsewhere (8). Calibration of the instrument was carried out using N.B.S. standard viscosity oils. The temperature region 20–35° was studied because this range includes the normal range of temperatures encountered during storage or application to the skin (see *Results and Discussion*). The water bath maintained the sample temperature at ±0.1° of the reported temperatures.

The sample to be evaluated (about 1 ml.) was gently squeezed from a tube onto the plate of the viscometer. The plate was immediately raised into position with the cone. The sample then remained undisturbed for 5 min. in this position (to allow temperature equilibration) before obtaining the rheogram. All rheograms were obtained using a truncated cone having an angle of 33 min., 26 sec., and a radius of 2 cm. The instrument was set at an upsweep time of 120 sec., a downsweep time of 120 sec., a maximum r.p.m. of 100, and a scale expansion of 4×. In the case of a few 20 and 25° determinations it was necessary to use a scale expansion of 5×.

The method of reporting a meaningful value for viscosity presented a problem. The products studied were plastic and pseudoplastic materials, all exhibiting thixotropy. It is normally necessary to use different equations when reporting viscosity values for plastic and pseudoplastic materials. Debate continues on whether a satisfactory equation exists for pseudoplastic materials, although the equation of Farrow *et al.* (9) seems to serve adequately for most purposes. Cross (10) has recently discussed the mathematical representation of pseudoplastic flow in some detail.

For the purposes of this study, the viscosity values reported were calculated as follows (11).

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[1] Eli Lilly and Co., Indianapolis, Ind.

[2] Ferranti Electric Co., Plainview, Long Island, N. Y.

[3] Houston Instrument Co., Bellaire, Tex. (model HR-92).

[4] Brinkmann Instrument Co., Westbury, N. Y. (Haake model F).

TABLE II.—RHEOGRAMS: SCALE DEFLECTION IN dynes/cm.^{2} (UPCURVE)

	At 1074 sec.$^{-1}$ (100 r.p.m.)				At 120 sec.$^{-1}$ (11 r.p.m.)			
	20°	25°	30°	35°	20°	25°	30°	35°
White petrolatum U.S.P.	11,600	8,135	4,400	2,665	13,000	8,150	4465	2135
Petrolatum N.F.	14,470	6,000	5,600	3,065	14,735	7,465	4065	1600
White ointment U.S.P.	11,375	8,935	4,265	2,400	15,000	8,935	4265	1600
Zinc oxide paste U.S.P.	...	21,335	13,065	6,735	...	13,065	7000	2935
Neomycin sulfate ointment U.S.P.	14,470	8,000	4,200	2,665	10,265	5,150	3135	1735
Ammoniated mercury ointment U.S.P.	30,000	14,750	7,300	3,735	16,465	9,465	5135	2400
Boric acid ointment	21,865	12,665	6,665	3,465	13,000	7,335	4000	1500
Sulfur ointment U.S.P.	11,335	7,850	4,400	2,265	9,000	5,150	2665	1465
Bacitracin ointment U.S.P.	10,265	6,875	4,665	2,400	5,535	3,625	1465	665
Ichthammol ointment N.F.	21,470	14,750	7,935	5,200	11,735	8,150	3730	1865
Cyclomethycaine ointment	12,200	8,000	4,300	2,800	10,000	6,250	3200	2000
Cyclomethycaine cream	1,335	1,500	1,465	1,335	1,000	1,125	935	935
Cyclomethycaine jelly	11,865	12,500	10,800	10,000	8,000	8,000	5700	5265

The potentiometer scale reading was recorded for the maximum sample shear rate (100 r.p.m. in all cases). The viscosity (in poises) was then calculated from Eqs. 1 and 2.

$$R = \text{scale reading} \times \text{scale expansion} \quad \text{(Eq. 1)}$$

$$\eta = \frac{R}{100} \times C \quad \text{(Eq. 2)}$$

where η is the viscosity in poises, and C is a cone constant. The value of C is determined by Eq. 3

$$C = \left(\frac{3}{2\pi V}\right)\left(\frac{aT}{r^3}\right) \quad \text{(Eq. 3)}$$

where a is the cone angle in radians, T is the torque spring constant in dyne-cm./division (×5 scale), V is the angular velocity in radians/sec., and r is the radius of the cone in cm. The value of C for the truncated cone used in this study was 13.36.

The thixotropic area was measured directly in square inches with a compensating planimeter.[5]

Effect of Aging.—Rheological changes with time have been observed in several pharmaceutical systems (12–15). Consequently, it was necessary to ascertain whether any significant changes were occurring in the semisolids reported here. This was accomplished for a given material by obtaining rheograms of a second production lot of a different age and also by rerunning the original lot at a later date.

RESULTS AND DISCUSSION

Effect of Temperature.—The results obtained are shown in Table II and Figs. 1–14. As the temperature was raised from 20 to 35°, all products studied demonstrated a decrease in viscosity, thixotropy, and yield value. This was expected and agrees with the data of Schulte and Kassem (1–6) for other pharmaceutical semisolids.

Effect of Aging.—There was no evidence that the semisolids studied were undergoing any significant rheological changes during the course of this study. When stored properly, it was felt that if significant changes in the rheograms were going to occur, they would likely occur in the first few weeks after manufacturing. As was noted previously, the most recently prepared material was 4 months old.

Petrolatum.—Although the particular petrolatums studied differ slightly in both viscosity and thixotropy, the rheogram of each has a characteristic initial "spur" at low rates of shear (Table II, Figs. 1 and 2).

In their comprehensive paper on petrolatum from various sources, Schulte and Kassem (4) pointed out that petrolatum is a mixture of *n*, iso, and isocyclic paraffins. They show that the ratio of these constituents to each other determines the rheological properties of the particular petrolatum studied. *n*-Paraffins form the characteristic structure network and petrolatums with a low content of *n*-paraffins are considered good for ointments. The change of structure involution is greatly dependent upon the isoparaffin content. A gel network built up of large crystallites is more susceptible to mechanical strain than a gel whose network is built up of very small crystallites. In the presence of isoparaffins a finer gel structure forms. With a decrease in crystallite size, the viscosity of the petrolatum increases also.

White Ointment Series.—The addition of 5% white wax to white petrolatum when preparing white ointment increases the thixotropy somewhat and modifies the shape of the "spur," but has only a slight effect on the viscosity (Table II, Figs. 2 and 3).

Ammoniated mercury, sulfur, and boric acid ointments are composed of white ointment, mineral

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[5] Keuffel and Esser Co. (model 3636).

oil, and medicament (Table I). Neomycin ointment and ammoniated mercury ointment basically differ only in the lack of white wax in the neomycin product (Table I). This lack, combined with the slight increase in mineral oil and white petrolatum in the neomycin ointment, results in a less viscous and less thixotropic product with a smaller yield value (Table II, Figs. 4 and 5). The base for sulfur ointment and boric acid ointment differ in that the sulfur ointment contains 5% more mineral oil (and, consequently, 5% less white petrolatum). As a result, the viscosity of sulfur ointment is less than that of boric acid ointment, although the thixotropy and the shape of the rheograms of the two products vary only slightly (Figs. 4 and 5).

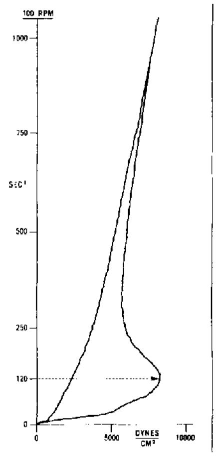

Fig. 1.—Rheogram of white petrolatum U.S.P. at 25°.

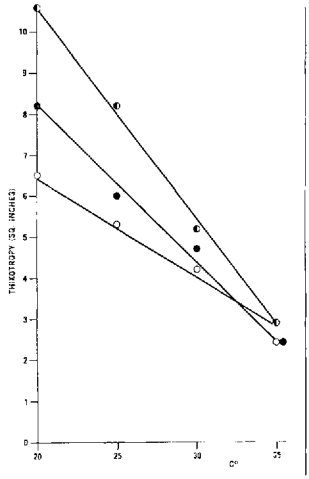

Fig. 2.—The effect of temperature on the thixotropy. Key: O, white petrolatum; ●, petrolatum; ◐, white ointment.

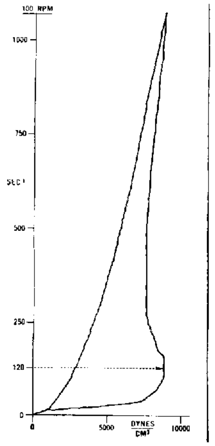

Fig. 3.—Rheogram of white ointment U.S.P. at 25°.

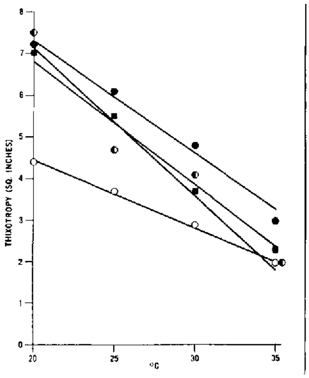

Fig. 4.—The effect of temperature on thixotropy of ointments. Key: O, neomycin; ●, ammoniated mercury; ◐, boric acid; ■, sulfur.

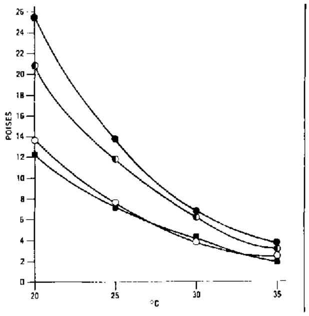

Fig. 5.—The effect of temperature on the viscosity of ointments. Key: O, neomycin; ●, ammoniated mercury; ◐, boric acid; ■, sulfur.

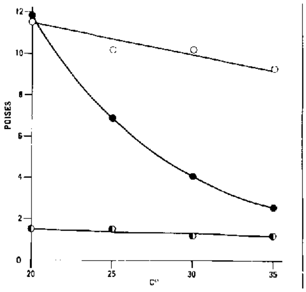

Fig. 6.—The effect of temperature on viscosity. Key: O, cyclomethycaine jelly; ●, ointment; ◐, cream.

Figure 5 and cyclomethycaine[6] ointment in Fig. 6 illustrate a trend of importance to the pharmaceutical formulator—namely, that for every 5° rise in temperature the viscosity is reduced by a factor of 0.5. The viscosity of these ointments, containing predominately white ointment, demonstrate a definite first-order relationship between (loss of) viscosity and temperature (increase).

It may be seen from Figs. 2, 4, and 7 that there appears to be a linear relationship between thixotropic area and temperature (in the region 20–35°) for neomycin, bacitracin, ammoniated mercury,

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[6] Marketed as Surfacaine by Eli Lilly and Co., Indianapolis, Ind.

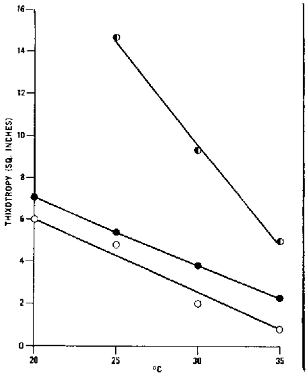

Fig. 7.—The effect of temperature on thixotropy. Key: ○, bacitracin ointment; ●, ichthammol ointment; ◐, zinc oxide paste.

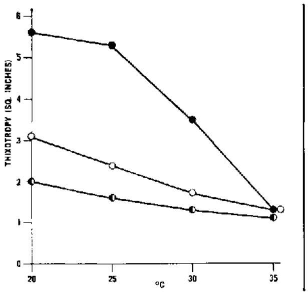

Fig. 8.—The effect of temperature on thixotropy. Key: ○, cyclomethycaine jelly; ●, ointment; ◐, cream.

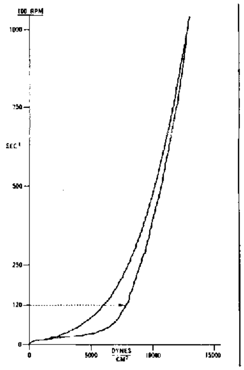

Fig. 9.—Rheogram of cyclomethycaine jelly at 25°.

sulfur, ichthammol, and white ointments, zinc oxide paste, and petrolatum.

Cyclomethycaine Series.—The cyclomethycaine series shows interesting and unique differences (Figs. 6, 8–11). Cyclomethycaine cream exhibits the least viscosity and thixotropy of any of the semisolids studied in this report. The rheograms for cyclomethycaine jelly retain their unique shape (Fig. 9) over the entire temperature range studied. In addition, it can be seen from Figs. 6 and 8 that there is relatively little change in thixotropy and only moderate change in viscosity for this product. This jelly is predominately a polypropylene glycol–water base (Table I) which would suggest a potential use as an all climate vehicle. Cyclomethycaine ointment follows the general pattern established by the other predominately white ointment base products.

Zinc Oxide Paste.—Zinc oxide paste, because it is designed as a protective and adsorptive material, is a deliberately stiff product with poor spreading and melting qualities. These characteristics are borne out by Figs. 7, 12, and 13. Using the Ferranti-Shirley cone and plate viscometer under the test conditions described, it was not possible to obtain data for zinc oxide paste at 20°.

Spreading.—The ease of application of a pharmaceutical semisolid to the surface of the skin is an

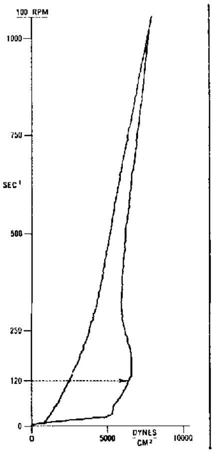

Fig. 10.—Rheogram of cyclomethycaine ointment at 25°.

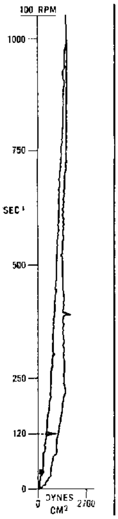

Fig. 11.—Rheogram of cyclomethycaine cream at 25°.

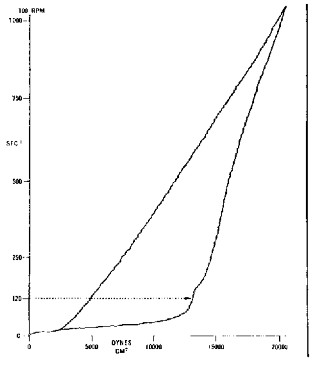

Fig. 12.—Rheogram of zinc oxide paste U.S.P. at 25°.

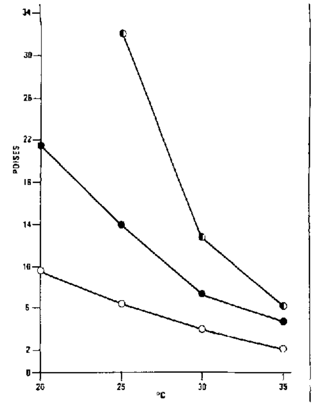

Fig. 13.—The effect of temperature on viscosity. Key: O, bacitracin ointment; ●, ichthammol ointment; ◐, zinc oxide paste.

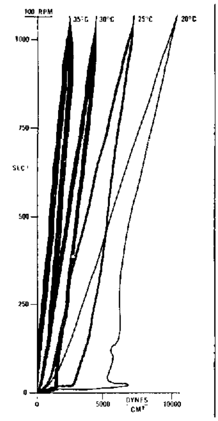

Fig. 14.—The effect of temperature on the rheogram of bacitracin ointment U.S.P.

important factor in consumer acceptance. Each individual applies ointment-like materials to the skin with a slightly different motion, stroke, and rate. Any rheological estimate of this process would, therefore, be limited accordingly. Henderson *et al.* (16) have approximated the rate of shear encountered when spreading an ointment on a surface by assuming a stroke averaging 6 cm., a rate of 4 strokes/sec., and an ointment layer thickness of 1 to 3 mm. Under these conditions they calculated a shear rate of 120 sec.$^{-1}$. If this value is used as a guide, recognizing its shortcomings, an estimate of the spreading resistance can be graphically shown by extending a dashed line through the rheograms at 120 sec.$^{-1}$. On the upcurve of nearly every rheogram 120 sec.$^{-1}$ occurs in a region of great resistance to flow. For example, in the instances of white petrolatum and white ointment (Figs. 1 and 3), 120 sec.$^{-1}$ represents the point of greatest resistance at low rates of shear. In nearly all the rheograms the area between 0 and 250 sec.$^{-1}$ appears to be an extremely important one when characterizing the spreading properties of pharmaceutical semisolids. A rheological investigation of this region has been undertaken and will be the subject of a forthcoming communication.

Relation to Body Temperature.—In his authoritative text, Rothman (17) discusses the temperature of the various regions of human skin under a wide variety of conditions. He clearly shows that there is a great variation in the temperature of human skin depending, *e.g.*, on the region of the body, the quantity and type of clothing worn, the degree of activity and state of health of the subject, environmental conditions, and whether the individual has eaten recently. Under these varying conditions a normal, healthy person's skin temperature will vary from 25 to 35°. If the extremities, especially the toes, are disregarded, the body surface temperature will probably fall between 30 and 35°.

At 35° many of the products studied had nearly the same thixotropy and nearly the same viscosity. This is as expected, since these products are designed to melt at or near the temperature of the human skin surface. An example of a product designed to melt at body temperature is bacitracin ointment U.S.P. (Lilly). As the temperature progresses from 20 to 35° the viscosity, thixotropy, and yield value of this product substantially decrease (Fig. 14). This figure, with minor modifications, is typical of the rheological changes the other semisolids in this study undergo in this temperature range. The curves shown in Fig. 14 also agree with the data of Schulte and Kassem (1–6) for other pharmaceutical semisolids.

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