Throughout the extractions, vigorous shaking was avoided to control emulsion formation.

SUMMARY

A GLC procedure was presented that is capable of determining atropine/hyoscyamine and scopolamine in the presence of phenylpropanolamine and chlorpheniramine, and also where the scopolamine is less than 9% of the belladonna present. Interfering excipients were removed with chloroform from acid, adjustment to pH 8.0 and extraction with cyclohexane removed chlorpheniramine, and further adjustment to pH 9.0 with methylene chloride extraction isolated the belladonna alkaloids. The final extract was concentrated and gas chromatographed. Homatropine was used as the internal standard. The method was sensitive, highly specific, and reasonably precise.

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ACKNOWLEDGMENTS AND ADDRESSES

Received October 16, 1972, from *Smith Kline & French Laboratories, Philadelphia, PA 19101*

Accepted for publication February 27, 1973.

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PHARMACEUTICAL TECHNOLOGY

Sensory Assessment of Spreadability of Hydrophilic Topical Preparations

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Abstract □ The rheological conditions operative during spreading of topical preparations on the skin were determined for series of aqueous gels and oil-in-water emulsions. Master curves were derived from the rheological data obtained using a sensory test with a panel of 24 members. Rates of shear varied from 350 to 10,000 sec.$^{-1}$, depending on the consistency and the type of preparation being spread. Two preference scoring techniques were used to assess the series of preparations in terms of spreadability. From the preference data, the shearing conditions with optimum patient acceptance potential were derived. An indication is given for the use of such master curves with their preferred regions for the determination of instrumental rheological conditions for use in routine and innovative industrial control procedures. Where relevant, all results were compared with previously reported work on lipophilic formulations.

Keyphrases □ Spreadability—sensory tests correlated to rheological conditions, hydrophilic topical preparations □ Rheological master curve—shear rate variation, spreadability of hydrophilic topical preparations, sensory tests □ Skin, sensory perception of spreadability of hydrophilic topical preparations—correlation of rheological conditions, master curves derived

In the pharmaceutical and cosmetic industries, it is important that formulations, besides possessing the correct physicochemical and biopharmaceutical properties, should have maximum patient and consumer acceptability. Spreadability plays an important role in the patient's assessment of a topical product. The correct consistency for such a preparation helps to ensure that a suitable dose is applied to the skin. This is particularly important with vehicles that incorporate potent drugs such as corticosteroids; excessive doses may lead to collagen atrophy and other undesirable side effects. Previous authors have assessed spreadability in terms of shear rate, either by a correlation with non-Newtonian viscosities (1–4) or by assuming that the spreading procedure can be likened to plane laminar flow between parallel plates (5–7) and thus can be described by the equation:

$$\dot{\gamma} = V/d \qquad \text{(Eq. 1)}$$

where $\dot{\gamma}$ is the rate of shear, V is the relative velocity of the plates or skin surfaces, and d is the distance between them. *Estimates* of V and d were used to find the shearing conditions operative during spreading.

In contrast, Wood (8) developed a method which involved comparing Newtonian liquids with pseudoplastic liquids to determine the approximate rate of shear developed in the mouth. This procedure, which has the advantage that V and d need not be known to determine the shearing conditions occurring *in vivo*, was modified by Barry and Grace (9) to investigate the rheological conditions that operate during the spreading of lipophilic preparations on the skin.

In the present work, the techniques used by Barry and Grace (9) were extended to investigate the shearing con-

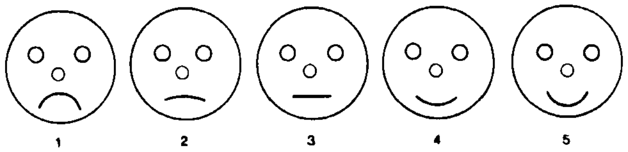

Figure 1—*Preference Scoring System 2. Faces represent degrees of agreeableness during spreading, with numerical scores as shown.*

ditions that operate during the spreading of aqueous gels. Oil-in-water emulsions were similarly tested to ascertain whether an internal lipophilic phase affected these conditions.

Preference scaling techniques were used to obtain the optimum consistency for spreading and, thus, the maximum patient acceptability potential for a preparation.

The formulations investigated varied in consistency from mobile liquids to stiff and, in some cases, highly elastic semisolids and, therefore, encompassed the range of consistencies found in hydrophilic topical applications.

EXPERIMENTAL

In general, the theory used and experimental procedures applied were as reported previously (9). Only the essential details and variation in procedure are reported here.

Preparations Used—Fifteen gels, ranging in consistency from mobile liquids to elastic semisolids, were prepared by neutralizing aqueous solutions of carboxypolymethylene 940 or 941[1] with triethanolamine (Table I). Sample 1 was a mixture of starch and Carbopol gel. Samples 17–22 were liquid paraffin in water emulsions stabilized by the mixed emulsifier cetrimide–cetostearyl alcohol in various concentrations. All materials were of BP or BPC quality, except the Carbopols which were commercial samples. Prior to use, samples were stored at 25 ± 1°.

Instrumental Rheology—A range of silicone oils [viscosities determined[2] by Barry and Grace (9) at 34 ± 0.2°] were used as standards. A cone and plate viscometer[3] with automatic flow curve recorder unit and *X–Y* plotter was used in two modes to obtain rheograms for the test preparations at 34 ± 0.2° (approximate skin temperature).

Instrumental Method 1—The samples were continuously sheared from 0.0 to 1754.0 to 0.0 $sec.^{-1}$ in 120 sec. When necessary, the shear rate range was changed either by alteration (by a factor of 10) of the gear train in the cone drive unit or by using cones of different angles.

Instrumental Method 2—The viscometer (with *X–Y* plotter measuring torque as a function of time) was used to determine shear stresses at various constant rates of shear. The "fast-up" control applied the rate of shear within about 1 sec., and the "hold speed" control maintained the shear rate. From the plot obtained at each shear rate, the shear stresses at zero time and after 20 sec. [estimate of average time of spreading (9)] were determined.

Instrumental Method 2 is relevant when the material being tested exhibits time-dependent behavior on shearing. For Carbopol gels, time-dependent effects were negligible (programmed shearing provided negligible hysteresis loops); thus, the data obtained by Method 2 agreed with those from Method 1 and are not included. Since the oil-in-water emulsions provided large hysteresis loops, both sets of data are shown.

Sensory Tests—From a panel of 24, a minimum of 14 and a maximum of 24 persons were selected for any one test. The untrained panel contained both sexes, with an age range of 18–50 years. The panel members were asked to assess the preparations critically, according to the relevant scaling procedure, while spreading the materials onto the inner surface of the forearm. In all sensory tests, three or four samples were presented to each panel member at each session according to a scheme designed to eliminate the sample sequence affecting the results. The reliability of the panel members was confirmed using the method of circular triads (10–12) with Samples 5–12.

Shear Conditions during Spreading—Panel members were asked to indicate for each sample the Newtonian silicone oil that appeared

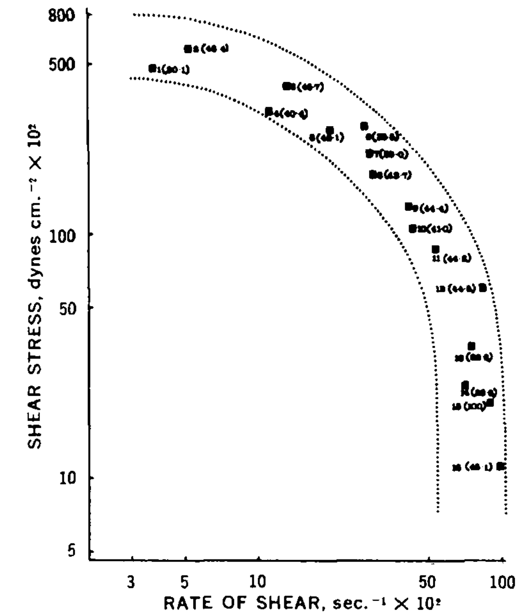

Figure 2—*Master curve of rheological conditions that operate during spreading of aqueous gels on the skin. The data are numbered to identify the samples; in parentheses are the coefficients of variation of the Newtonian viscosity values used to obtain the data.*

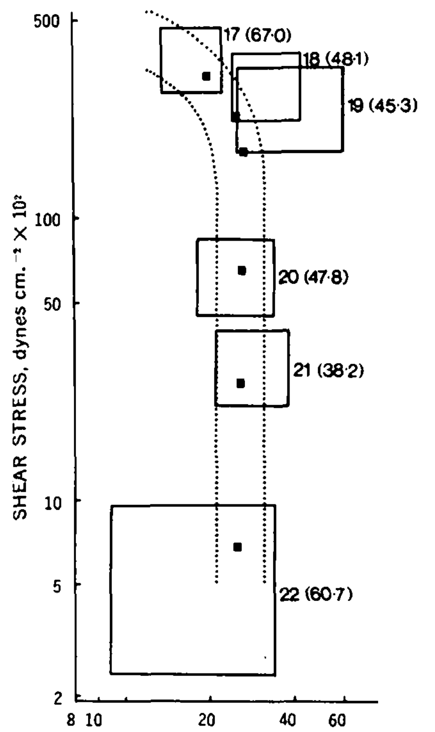

Figure 3—*Master curve of rheological conditions that operate during spreading of oil-in-water emulsions on the skin. The black squares indicate data derived from Instrumental Method 1, and the open rectangles indicate data derived from Instrumental Method 2. The data are numbered to identify the samples; in parentheses are the coefficients of variation of the Newtonian viscosity values used to obtain the data.*

[1] Carbopol, Honeywill and Stein Ltd.
[2] Using a Haake-Rotovisko.
[3] Ferranti-Shirley.

Table I—Formulations of Preparations Used (by Weight)

Sample Number	Carbopol 940 or 941	Starch	Cetrimide	Cetostearyl Alcohol	Water	Liquid Paraffin
1	5	50	—	—	45	—
2–16	20–0.025	—	—	—	80–99.975	—
17	—	—	6.4	57.6	100	300
18	—	—	4.8	43.2	100	300
19	—	—	4.0	36.0	100	300
20	—	—	3.2	28.8	100	300
21	—	—	2.4	21.6	100	300
22	—	—	0.8	7.2	100	300

most similar while spreading on the skin. The shearing conditions operative during spreading are assumed to be those located at the intersection of the rheogram obtained by Instrumental Method 1 or 2, and the flow curve for the Newtonian silicone oil, judged by the panel to be of similar spreadability to the sample under test.

Preference Testing—Panel members were asked to evaluate Samples 4–22 taken in groups of three or four according to two scoring systems (only one scoring system was used per session).

System 1 [Five-Point Semantic Hedonic Scale (5, 8, 9)]—

Score	Sensation during Spreading
1	Too fluid, disagreeable
2	Fluid but all right
3	Agreeable
4	Stiff but all right
5	Too stiff, disagreeable

System 2 [Five-Point Facial Hedonic Scale (13, 14)]—Panel members were asked to indicate the face that most closely agreed with their feeling with regard to the spreadability of each sample. Scores were allocated to their decision (Fig. 1). The faces depict the degree of agreeableness or disagreeableness experienced by the subject, the neutral face being the median interval. System 2 was developed (13) to overcome problems in semantics, which can arise with the use of descriptive rating scales such as System 1. A score of 1 or 5 in System 1 corresponds approximately to a score of 1 in System 2. A score of 2 or 4 in System 1 corresponds approximately to a score of 2 in System 2, and a score of 3 is approximately the same for both systems. Scores of 4 and 5 in System 2 represent degrees of agreeableness not present in System 1; hence, System 2 was considered by one worker to be more sensitive than System 1 when used for tasting tests (13).

Data Analysis[4]—A computer program was used to fit the best straight line or curve to the data obtained from the two preference scoring methods, according to the least-squares criterion. A second program was used to calculate the means, standard deviations, coefficients of variation, and other statistical data used in this work.

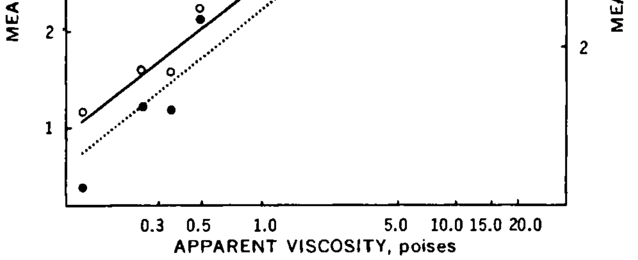

Figure 4—*Data from Preference Scoring System 1 for gels. Key:* —, ○, *a, single-logarithmic plot; and* . . . , ●, *b, double-logarithmic plot.*

[4] Using an I.C.L. 4130 computer with computer instrumentation plotter C4600.

RESULTS

The rheological conditions operative during spreading of the aqueous gels were similar whether derived by Instrumental Method 1 or 2. These conditions, when used in a double-logarithmic plot of shearing stress against shear rate, showed a distinct trend (dotted lines in Fig. 2). The double-logarithmic plot of the oil-in-water emulsions showed a similar trend to the gels but, in general, the oil-in-water emulsions were assessed at lower rates of shear (Fig. 3). The Newtonian viscosity, used to determine the rheological conditions for any sample, was the arithmetic mean of the silicone oil viscosities considered by each panel member to be similar to the topical product during spreading. The coefficients of variation of the panel data are indicated in Figs. 2 and 3.

The data derived from the two preference scaling procedures are listed in Table II. The apparent viscosities quoted were obtained from Instrumental Method 1 data at the rate of shear indicated approximately by the master curve. The mean panel scores were compared graphically with their respective instrumental viscosities. For Scoring System 1, linear plots were obtained using semi- and double-logarithmic axes; for Scoring System 2, parabolic plots were obtained using the same axes (Figs. 4–7). The equations for these lines are listed in Table III. The use of higher order polynomials in the computer analysis gave better fitting curves but were not used owing to the limited accuracy of the experimental data.

The data from Scoring System 2 for Samples 4 and 16 were not included in the computer analysis, because these points would have

Table II—Data Derived from Preference Scoring Procedures[a]

Sample Number	Apparent Viscosity, poises	Preference Scoring System 1[b]			Preference Scoring System 2[b]		
		S	*SD*	*CV*	*S*	*SD*	*CV*
4	29.5	4.9	0.2	4.7	1.4	0.6	41.5
5	13.5	4.4	0.4	10.0	1.9	0.7	37.4
6	10.1	4.3	0.5	11.9	2.3	0.9	37.4
7	7.6	3.7	0.6	17.1	2.9	0.9	32.1
8	6.0	2.9	0.5	14.9	3.5	0.8	24.4
9	3.2	3.0	0.3	11.0	4.1	0.8	19.1
10	2.5	2.9	0.4	13.0	4.0	0.8	19.6
11	1.6	2.7	0.5	19.5	3.7	1.0	26.6
12	0.72	2.4	0.6	24.9	3.3	1.0	32.3
13	0.48	2.2	0.6	29.4	3.5	1.3	36.5
14	0.35	1.6	0.6	36.5	2.4	1.1	47.1
15	0.23	1.6	0.8	47.8	2.0	1.0	47.3
16	0.11	1.8	0.4	33.4	1.7	0.9	54.1
17	15.8	4.2	0.5	13.0	2.4	0.9	39.2
18	9.2	3.7	0.5	14.8	3.0	1.0	33.3
19	6.44	3.4	0.4	12.6	3.6	0.9	24.6
20	2.5	2.9	0.4	12.5	4.5	0.6	14.5
21	1.0	2.5	0.5	18.7	3.7	1.1	29.9
22	0.27	1.5	0.4	27.1	2.0	0.8	38.1

[a] Samples arranged in decreasing order of apparent viscosity, grouped as gels and emulsions. [b] *S* is the arithmetic mean of the data, *SD* is the standard deviation (determined using $n - 1$ degrees of freedom), and *CV* is the coefficient of variation expressed as a percentage.

Table III—Equations[a] for the Plots Shown in Figs. 4 and 5 of the Type $y = bx + c$ and in Figs. 6 and 7 of the Type $y = ax^2 + bx + c$

	Mean Score, y	Log Mean Score, y'	Coefficient, a, of (Log Apparent Viscosity)^2, x^2	Coefficient, b, of Log Apparent Viscosity, x	Constant, c
Figure 4	y	—	—	1.54	2.49
	—	y'	—	0.25	0.36
Figure 5	y	—	—	1.43	2.37
	—	y'	—	0.24	0.35
Figure 6	y	—	−2.71	1.37	3.82
	—	y'	−0.41	0.21	0.59
Figure 7	y	—	−2.60	1.83	3.82
	—	y'	−0.37	0.28	0.57

[a] Equations for Figs. 4 and 5 are derived from Preference Scoring System 1; those for Figs. 6 and 7 are derived from Preference Scoring System 2.

unrealistically distorted the curve. This situation arises because the minimum preference score is 1, whereas apparent viscosities may range from near zero to infinity. If such extreme data are added to the graph, the resulting extended tails seriously widen the curve apex. This makes the curve a less sensitive means for assessing the range of acceptable apparent viscosities. For Scoring System 1, the optimum apparent viscosity for spreading corresponded to a score of 3 and the range of acceptable apparent viscosities was given by the score of 2–4. For Scoring System 2 the optimum was given by the highest score obtained and corresponded to the maximum of the parabola; the range was given by a score of 3 or greater. These values were obtained from the plots (Figs. 4–7) and checked by substituting the appropriate scores in the respective equations (Table III). The optimum viscosities were plotted, in terms of shear rate–shear stress, on the master curves, and the intersection of the two plots defined the shearing conditions with maximum patient acceptability for the class of preparations under consideration (Fig. 8). The range of acceptable values were similarly plotted (shaded areas in Fig. 8).

DISCUSSION

Figure 2 shows the approximate rheological conditions that operate during the spreading of aqueous gels on the skin. The master curve obtained for these hydrophilic preparations approximates to a mirror image, about the figure's diagonal axis, of the master curve

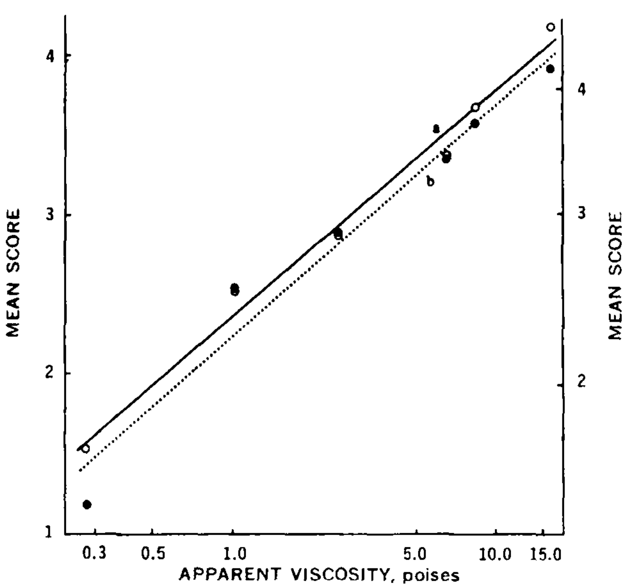

Figure 5—*Data from Preference Scoring System 1 for oil-in-water emulsions. Key: —, O, a, single-logarithmic plot; and . . . , ●, b, double-logarithmic plot.*

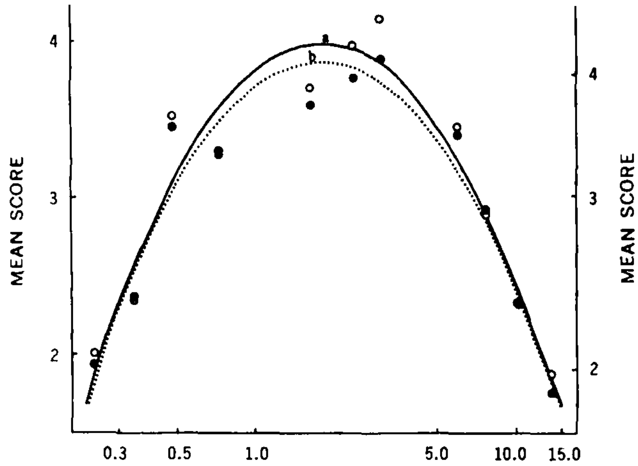

Figure 6—*Data from Preference Scoring System 2 for gels. Key: —, O, a, single-logarithmic plot; and . . . , ●, b, double-logarithmic plot.*

for lipophilic materials (9). This suggests that there is a large general region defining the shear stress–shear rate conditions which operate during spreading of topical preparations and that exact conditions depend on the class of preparations applied.

The Carbopol gels containing more than 5% polymer (Samples 2–4) were highly elastic semisolids, which tended to roll up rather than to spread when applied to the skin. It was considered possible that this dominant elasticity was mainly responsible for the shape of the curve at high stress values and that very viscous preparations which lacked substantial elastic properties would not fit on the curve. To resolve this point, it was necessary to prepare and test a hydrophilic preparation of high consistency but minimal elastic recoil. This was achieved by blending starch with gel (Sample 5) to provide Sample 1. The position of the experimental point for this sample (Fig. 2) confirms the general curvature of the graph. In addition, gels containing 5% polymer or less (Samples 5–12), although they exhibited little rolling-up behavior, still defined the curved portion of the graph. Thus, it was considered valid to use elastic gels (Samples 2–4) as aids in defining the general shape of the curve, which then would be applicable to hydrophilic, elastic, and nonelastic gels.

The master curve for aqueous gels is approximately vertical at high shear rates, indicating that mobile materials are applied to the skin at a constant high rate of shear, with shear stress being the variable assessed subjectively by the patient. However, as consistency increased, the applied shear rate decreased so that both rheological

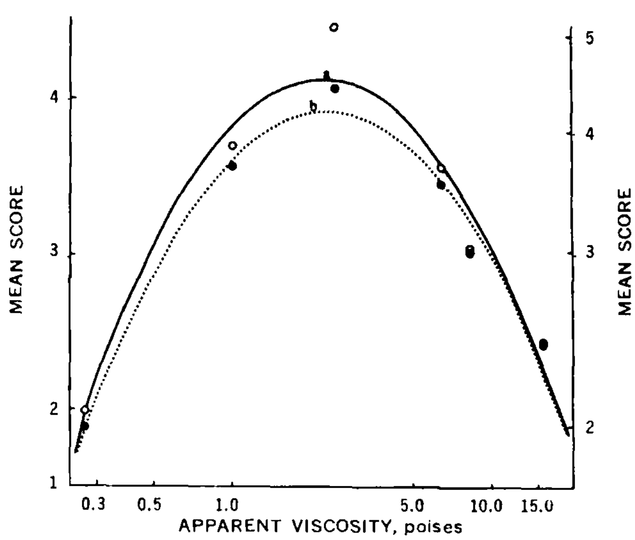

Figure 7—*Data from Preference Scoring System 2 for oil-in-water emulsions. Key: —, O, a, single-logarithmic plot; and . . . , ●, b, double-logarithmic plot.*

Table IV—Optimum and Range of Acceptable Apparent Viscosities (poises) Derived from Single- (A) and Double- (B) Logarithmic Plots of Preference Scoring Data

Type of Material	Preference Scoring System 1				Preference Scoring System 2			
	A		B		A		B	
	Optimum[a]	Range[b]	Optimum[a]	Range[b]	Optimum[c]	Range[d]	Optimum[c]	Range[d]
Gels	2.1	0.5–9.5	3.0	0.6–9.4	1.8	0.4–7.3	1.8	0.5–6.8
Oil-in-water emulsions	2.8	0.6–13.9	3.4	0.5–11.7	2.2	0.5–10.7	2.3	0.6–9.9
Lipophilic materials[e]	6.8	3.9–11.8	7.4	3.8–11.8	—	—	—	—

[a] Corresponding to a preference mean score of 3 (Figs. 4 and 5). [b] Corresponding to a preference mean score of 2–4 (Figs. 4 and 5). [c] Corresponding to parabola maximum (Figs. 6 and 7). [d] Corresponding to a preference mean score of 3 (Figs. 6 and 7). [e] Derived from *Reference 9*.

parameters varied from gel to gel. The shear rate variation was caused by two factors: (*a*) the more mobile the gel, the faster the rubbing cycle used (*V* increases in Eq. 1); and (*b*) the stiffer the material, the thicker the layer applied (*d* increases in Eq. 1).

The master curves for lipophilic and hydrophilic preparations diverge widely over much of their lengths. This suggests that panel members consciously or unconsciously consider the extent of oiliness of a preparation when assessing its spreadability. This phenomenon is less important at the extremes of the consistency range where the master curves converge at high and low stress values; *i.e.*, at these consistencies, rheological parameters are much more important than a tactile stimulus such as oiliness. If it is true that, for the major portion of the consistency range, patients are influenced in a judgment of spreadability by the proportion of lipophilic material present, it follows that if an oil phase is introduced into a preparation but its overall nature is maintained as hydrophilic, the resulting master curve should lie between the lipophilic and gel curves. As can be seen from Fig. 3, the curve for such materials formulated as oil-in-water emulsions has the same general shape as the gel curve but it is shifted towards the lipophilic curve, thus confirming this view.

When master curves such as those shown in Figs. 2 and 3 have been constructed, it is possible to define preferred areas of acceptability by using the data derived from preference testing (Table IV). Optimum apparent viscosities for spreading, together with the acceptable ranges, are plotted on the master curves. (Figure 8 illustrates arithmetic average values for the two preference scoring methods calculated from both semi- and double-logarithmic plots.) As can be seen from Table IV, both preference scoring procedures gave similar results. However, compared to lipophilic preparations, the preferred regions for gels and oil-in-water emulsions were enlarged, caused mainly by the low limit corresponding to the "fluid but all right" rating. The difficulty that the panel experienced in scoring hydrophilic preparations as "too fluid, disagreeable" was possibly because they were conditioned from birth to accept very mobile, aqueous solutions for spreading on the skin (*i.e.*, washing with soap and water). Such conditioning would not significantly affect the rating for oily preparations; hence, a definite, relatively high, limit was obtained for lipophilic preparations. This conditioning effect is also illustrated in the way in which the optimum apparent viscosity for spreading increases in the order of: gels, oil-in-water emulsions, and lipophilic preparations, *i.e.*, in the order of decreasing hydrophilicity (Table IV). The upper limits for lipophilic and hydrophilic formulations were similar, although shearing conditions were higher in the latter case (*i.e.*, higher shear stresses and shear rates operate for hydrophilic materials).

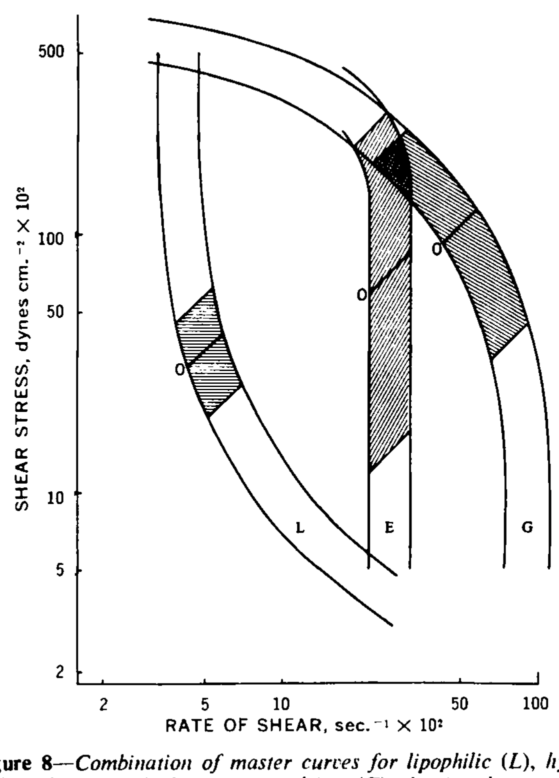

Figure 8—*Combination of master curves for lipophilic (L), hydrophilic gels (G), and oil-in-water emulsions (E), showing the acceptable range of viscosities for spreading on the skin (shaded area) and the optimum values (solid line O).*

In the context of this conditioning effect, it was thought possible that there might be a difference in the location and extent of the preferred regions, based on whether these were derived using an all male or all female panel. For example, it might be that women, due to their experience with cosmetics, would be more critical than men of the spreadability of a preparation and would report a more condensed preferred region. Therefore, the preference results were divided into two subsets, male and female; the data were computed and graphed as before; and the subsets were compared with each other and with the total panel. However, any differences based on sex were found to be nonsignificant when compared by an *F* test and, thus, only total panel results have been reported here.

The data obtained from Scoring System 1 for hydrophilic preparations are similar to those obtained for lipophilic preparations (9), in that the regression lines derived from the data can equally well be represented by either single- or double-logarithmic equations as proposed by Weber and Fechner (15) and Stevens (16). In addition, the data obtained by Scoring System 2 (represented by second-order polynomials) provide similar curves when plotted on either single- or double-logarithmic axes (Figs. 6 and 7). According to Stevens' definition of stimuli (16), preference testing should be metathetic (qualitative—agreeable or disagreeable) and should thus be represented by a single logarithmic equation of the type:

$$\theta = K \log S \qquad \text{(Eq. 2)}$$

where θ is the sensory response to a stimulus, S, and K is a constant. Thus, as pointed out by Barry and Grace (9), the classification proposed by Stevens is probably invalid for the type of test considered in this paper. Treisman (17, 18) questioned Stevens' work and claimed that no experiment can distinguish between the two equations and that the relationship obtained will be a function of the method of scaling.

The correlation coefficients and the other data quoted tend to suggest that individual panel members react similarly when evaluating spreadability. However, the data used in the diagrams are arithmetic means. The coefficients of variation (Figs. 2 and 3 and Table II) show the variability of a sensation produced by the same stimulus on different people. One main disadvantage of preference testing in this case is that only a limited number of samples can be tested on a single occasion and no really effective means of cross-linking the data exists (20). The types and causes of other such variable factors were fully discussed by other authors (15, 20, 21).

The present work gives a broad picture of the type of laboratory screening procedure that may be utilized in innovative work on topical preparations prior to field trials. The new formulation, whether it be lipophilic (anhydrous or water-in-oil emulsion) or hydrophilic (aqueous gel or oil-in-water emulsion) can be tested using Instrumental Method 2 to obtain its rheogram. The instrumental data are then plotted onto the combined master curves (Fig. 8). Depending on the type of formulation under test, the new product curve should intersect the appropriate master curve in the preferred region. To achieve the maximum patient acceptance potential, this intersection should occur at the optimum value of the preferred region.

In addition, manufacturers often wish to standardize a product by a simple rheological test involving a single shear rate. At present, this parameter is often selected arbitrarily. It would be an improvement if selection were made relevant to the individual consistency of the product, taking into account its nature as an ointment, cream, gel, *etc*. This could be done as discussed here, and a shear rate between 350 and 10,000 $sec.^{-1}$ would be obtained. The particular shear rate, selected from such a wide range, would at least be relevant as a quality control parameter in that it would approximate that used by the patient when applying the medicament.

SUMMARY

The work reported here is an extension of that performed by Barry and Grace (9) on the rheological conditions operative during spreading of topical preparations. A master curve for aqueous gels was obtained, which was an approximate mirror image of that obtained previously for lipophilic preparations. To investigate the effect of the introduction of a lipophilic phase into an aqueous preparation, a master curve was similarly obtained for oil-in-water emulsions. This curve, although similar in shape to the gel master curve, was displaced toward the lipophilic plot.

The gels and emulsions were assessed for spreadability by two preference scoring techniques. These data gave the optima and ranges of acceptable apparent viscosities for spreading of the topical preparations used. These values were superimposed on the master curves to show the "preferred regions" (shearing conditions with maximum patient acceptance potential). A combination of these master curves and preferred regions may be used in the design of instrumental tests for industrial quality control procedures concerned with preparations for topical use.

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ACKNOWLEDGMENTS AND ADDRESSES

Received December 11, 1972, from the *School of Pharmacy, Portsmouth Polytechnic, Park Road, Portsmouth, Hants., England.*

Accepted for publication March 13, 1973.

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