Continuous shear, viscoelastic and spreading properties of a new topical vehicle, FAPG* base

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The rheology of a new topical vehicle FAPG base was investigated over the temperature ranges of 25–37°. Continuous shear rheograms obtained with a Ferranti-Shirley cone and plate viscometer were hysteresis loops with spur points; loop areas, yield values and apparent viscosities decreased with increase in temperature and an activation energy for viscous flow of 10·4 kcal mol⁻¹ was derived. In creep (concentric cylinder geometry) the base was viscoelastic with a low limit of linearity with respect to strain. Creep compliance curves showed an initial elastic response, a region of retarded elasticity and a viscous region; compliances increased and viscosities decreased with temperature rise. Patient acceptance of skin spreadability of the base was assessed using a master curve concept; the spreading properties were close to the preferred values for maximum patient acceptance. It is concluded that FAPG base deserves further study as a vehicle for dermatological use.

For skin therapy, the vehicle used should have optimum physicochemical properties for assuring drug stability and release besides inhibiting microbial growth and being aesthetically satisfactory. Recently, a new topical vehicle 'FAPG' base was reported to have possible significant advantages over traditional ointments and creams (British Patent No. 1,259,858 and other Patents pending; Garnier, 1971a,b; Rhodes, 1971). We have examined the rheological properties of the material in continuous shear and in creep and have attempted to assess patient acceptance of its spreadability.

METHODS AND RESULTS

Material. A production sample of FAPG base was provided by Syntex Pharmaceuticals Ltd., St. Ives House, Maidenhead, Berks. It is a mixture of propylene glycol, stearyl alcohol, polyethylene glycol and glycerol combined to form a gel-like structure with a crystalline network. The product is a smooth, white, soft, non-aqueous, hydrophilic semisolid with a slight pearly sheen (Garnier, 1971b).

Microscopy. The base was examined with a Kofler Micro Hot Stage attached to a polarizing microscope. At room temperature the material was anisotropic (Fig. 1A) and slight melting occurred between 32–34°. Between 47–49° the preparation melted to form an isotropic solution which recrystallized in a different form on cooling. The flocculated suspension appearance was replaced by a mosaic of thin, flat, anisotropic, polyhedral crystals (Fig. 1B). This implies that FAPG base may change its crystalline form on storage to yield a product with different mechanical properties.

Continuous shear rheology. A Ferranti-Shirley cone and plate viscometer with automatic flow curve recorder unit was used with a large cone (diameter 7 cm,

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* Syntex Pharmaceuticals Ltd.

angle 0·0062584 rad) which accelerated from 0 to 10 rev min⁻¹ and decelerated to 0 rev min⁻¹ in a total sweep time of 1200 s. Temperatures of testing ($\pm0\cdot1°$) were 25° (typical test and storage value) 30°, 34° (average skin temperature) and 37° (body and high storage temperature). Flow curves are illustrated in Fig. 2; duplicate runs were within 5% full scale deflection on the shear stress axis. Apparent viscosities derived from the apex of each loop and static yield values measured at each spur point are plotted as functions of reciprocal temperature in Fig. 3 (Arrhenius-type plots). Loop areas and dynamic yield values (obtained from the intersection of each down curve with the stress axis) are listed in Table 1.

Creep rheology. Viscoelastic measurements were made with concentric cylinder reaction air turbine creep viscometers (Barry & Grace, 1970; Barry, 1971). Samples were loaded at 25° ($\pm0\cdot2°$) and 37° ($\pm0\cdot2°$), temperatures representing the extremes
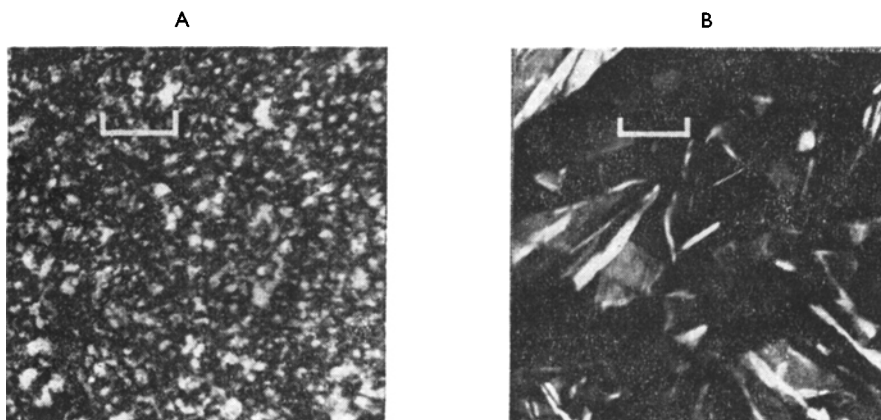

FIG. 1. Photomicrographs of FAPG base in polarized light (a) room temperature (b) heated to 50° and allowed to cool. One division = 50 μm.
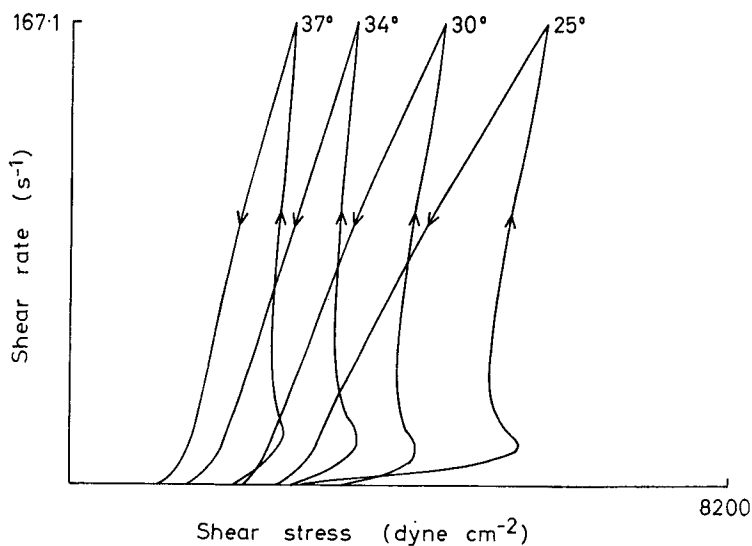

FIG. 2. Continuous shear rheograms; Ferranti-Shirley viscometer used in automatic mode.

Table 1. *Rheological parameters of FAPG base as a function of temperature.*

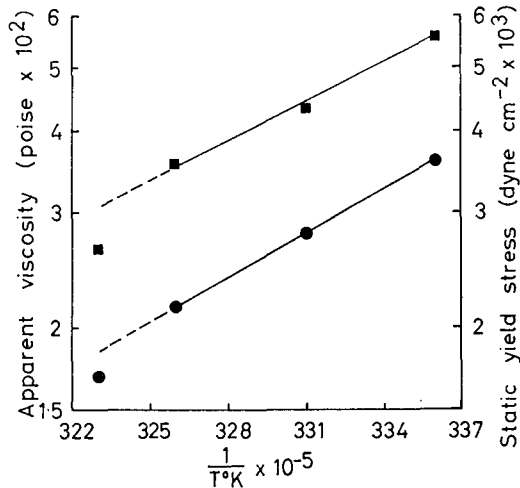| Temperature (°C)	Continuous shear		Creep	
	Loop area* (cm²)	Dynamic yield value (dyne cm⁻² × 10³)	Initial compliance (dyne⁻¹ cm² × 10⁻⁷)	Residual viscosity (poise × 10⁹)
25	61·3	2·54	4·5	1·6
30	51·8	2·17	—	—
34	38·7	1·52	—	—
37	29·2	1·11	13	1·1

* 1 cm² = 7·75 × 10⁵ dyne cm⁻² s⁻¹.

FIG. 3. Arrhenius-type plots of apparent viscosity at apex of loop (—●—) and static yield stress at spur point (—■—).

of the continuous shear range, and were left overnight for stresses to relax and for temperatures to equilibrate. Approximate linearity checks were performed by applying increasing shear stresses and by measuring the resulting instantaneous shear strains. The results are plotted in Fig. 4A. Creep tests were run at the maximum stresses for linearity and the creep curves are illustrated in Fig. 4B.

Spreadability. The Ferranti-Shirley viscometer was used to determine shearing stresses at various constant shear rates with the medium cone (diameter 4 cm, angle 0·0059612 rad) at skin temperature of 34° (±0·1°). The "fast-up" control applied the shear rate within about 1 s and the "hold speed" control maintained the shear rate. The shear stress was determined initially (0 s reading) and after 20 s (average time of spreading of topical vehicle on the skin) at each shear rate. A different sample of the base was used for each shear rate. Repeat runs were within 4% full scale deflection on the shear stress axis. The rheograms were superimposed on the master spreadability curve with preferred region (Fig. 5) prepared according to Barry & Grace (1972).

DISCUSSION

The continuous shear rheograms for FAPG base were anticlockwise hysteresis loops, each of which contained a spur point representing a so-called static yield
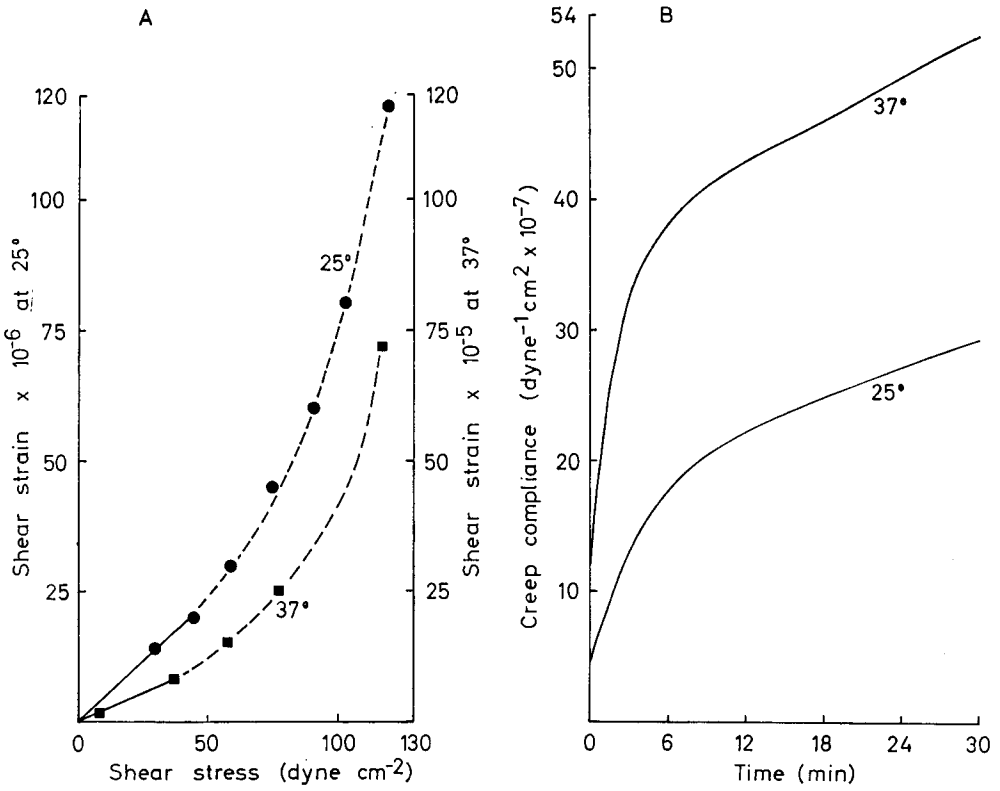
FIG. 4. A. Approximate test for viscoelastic linearity—shear stress versus instantaneous shear strain (full lines represent approximate extent of linearity).

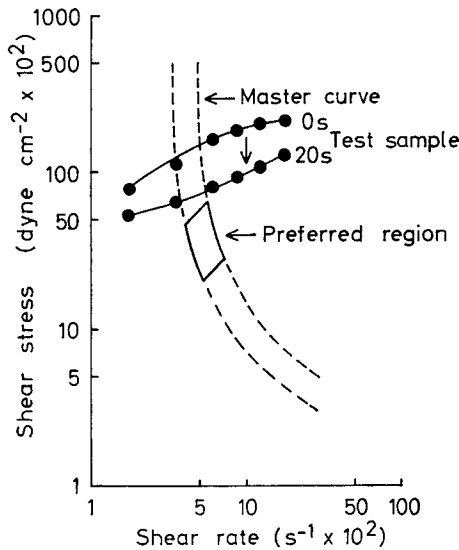B. Creep compliance curves in the linear viscoelastic region.

FIG. 5. Master curve of rheological conditions which operate during spreading of topical preparations (after Barry & Grace, 1972). Superimposed are the flow curves for FAPG base.

stress. The loops indicated that the material exhibited either thixotropy or irreversible shear breakdown. When rheograms were obtained on the same sample 5 h apart they partly overlapped only at low shear rates and the loop area reduced markedly. The base was therefore only partially thixotropic over the time scale of experimentation and on shearing mainly irreversible disruption of structure occurred. This agreed with the suggestion of a gel-like structure formed from a crystalline network (Garnier, 1971b) which would be susceptible to fracture. In this respect the base was similar to soft paraffin (Barry & Grace, 1971). The possibility exists that the hysteresis loops were in part artifacts caused in particular by expulsion of test material from the viscometer gap (Davis, Shotton & Warburton, 1968; Barry, 1971). However, when the gap was underfilled so that no material could be ejected, the rheogram showed the same characteristic shape as illustrated in Fig. 2 and a repeat flow curve on the same sample behaved as above. The validity of continuous shear methods for examining semisolids will not be discussed in detail in this paper. The problems involved for mechanically similar materials, the soft paraffins, were considered by Barry & Grace (1971a). It was concluded that the rheological behaviour in continuous shear was essentially that illustrated in Fig. 2 and that instrumental artifacts were small. The importance of a valid continuous shear method of control for this material becomes apparent when the difficulties associated with more fundamental viscoelastic measurements are considered (see below).

The static yield stress in each rheogram implies that besides the base being suitable for incorporating drugs such as fluclorolone acetonide (Topilar) which are soluble in the base, it may be valuable for suspending insoluble materials. Thus the base has a high consistency when at rest, which would minimize or prevent drug sedimentation on storage, yet decreases in consistency on working, as shown by the hysteresis loop. This allows easy application to damaged skin. However, a topical vehicle must not become too mobile on working, as its value as a levigating agent will decrease. That satisfactory semisolid properties were maintained after shearing was shown by the presence of dynamic yield values in the flow curves.

Besides the importance of correct rheological behaviour of a topical vehicle at a typical storage temperature, it is relevant that the material should function correctly at skin and general body temperature. The microscopic observations showed that the material softened slightly at 32–34° but did not melt until nearly 50°. Fig. 2 illustrates that up to 37° the flow curves were similar with the usual shift to lower stress values and loop areas with temperature increase (Table 1). The material thus maintained its network integrity within the desired temperature range.

A form of the Arrhenius equation may be expressed as

$$\eta = Ke^{\frac{E}{RT}} \quad .. \qquad .. \qquad .. \qquad .. \qquad .. \qquad (1)$$

where η is the coefficient of viscosity, K is a constant, R is the gas constant and T is the absolute temperature. An estimate of the activation energy for viscous flow, E, for FAPG base was obtained from the apparent viscosity plot of Fig. 3. In this derivation only temperatures lower than 37° were considered because of the microscopic observation of some melting at 32–34°; as can be seen from Fig. 3 the apparent viscosity at 37° was beneath the extrapolated dotted line. Although there are objections to Arrhenius-type plots (Barry & Grace, 1971b) approximate activation energies may be obtained for comparison with other materials. The value for FAPG base was approximately 43 k J mol^{-1} compared to a range of 59–105 k J mol^{-1} for

B.P. grades of white soft paraffin (Barry & Grace, 1970). The base thus spreads more easily than do soft paraffins and like soft paraffins, static yield stresses gave linear Arrhenius-type plots. The linearity of such curves confirms that yield stresses are a function of some property of the material, although they may not be fundamentally significant, and they may be useful in comparative testing procedures such as quality control (Barry & Grace, 1970).

To obtain a fundamental insight into the rheological behaviour of a viscoelastic material such as a topical semisolid the material should be tested in its rheological ground state, i.e. when the method of analysis does not significantly alter the static structure (Barry, 1971). In this work creep techniques were used and it became apparent that FAPG base was a difficult substance with which to work. This was because for a valid test the material must react to an applied stress in a linear viscoelastic manner. Then the ratio of stress to strain is a function of time alone and not of the stress magnitude. Thus a plot of stress against strain at some fixed time after the onset of the stress is a straight line. When this preliminary test designed to reveal the extent of viscoelastic linearity was applied to the base, the results in Fig. 4A were obtained. The important feature of this diagram is the low limit of linearity illustrated by the unbroken straight lines. The limit with respect to strain was of the order of 2×10^{-5} at 25° increasing to 1×10^{-4} at 37°. It is difficult to measure accurately deformations of this order. Thus any creep runs performed in this linear region must be looked upon as approximate measurements to which it would be invalid to apply a full analytical treatment.

Fig. 4B illustrates creep curves obtained at 25 and 37° derived by plotting creep compliance (strain per unit stress) as a function of time, the applied stress being in the linear region. From the shapes of these curves we may deduce that the creep compliance may be defined by an equation of the type

$$J(t) = J_0 + \sum_{i=1}^{n} J_1 (1 - e^{-t/\tau_1}) + \frac{t}{\eta_0} \quad .. \quad .. \quad .. \quad (2)$$

$J(t)$ is the total creep compliance at any time t, J_0 is the initial elastic compliance, J_1 is an elastic compliance associated with a viscous element, τ_1 is a retardation time and η_0 is the residual Newtonian viscosity. A mechanical model for this equation comprises a Hookean spring in series with n Voigt units and a Newtonian dashpot. J_0, represented by the residual spring, measures the strength of bonds which stretch elastically and correlates with the consistency of the material at rest.

The retarded elastic region represented by the summation term in equation (2) and by the n Voigt units in the mechanical model corresponds to that part of the structure in which secondary bonds were breaking and reforming during the test. The final linear portion represents viscous flow, provides the value for η_0 in equation (2) and is represented by a residual dashpot in mechanical models.

The value for J_0 at 25° (Table 1) was of the same order as those of white soft paraffin samples with and without emulsified water (Barry & Grace, 1970, 1971b,c) but was much smaller than those of oil in water creams stabilized by mixed emulsifiers of the surfactant-long chain alcohol type (Barry, 1968; Barry & Saunders, 1970, 1972). The residual viscosity was similar to those of the lipophilic group but was higher than the self-bodied creams. Thus the consistency of FAPG base under low shear rate conditions was similar to traditional lipophilic topical vehicles. When

the temperature was increased from 25 to 37° the consistency decreased as shown by creep compliance values increasing on warming. However, as in the continuous shear experiments, the crystalline network remained intact as shown by the creep curve remaining within the same decade of compliance.

For the evaluation of the spreadability of the base on the skin the method of Barry & Grace (1972), developed to determine the rheological conditions operative during spreading, was used. These authors found that the rheological conditions depended on the consistency of the preparation. Patients spread stiff semisolids at an approximately constant shear rate and the authors presumed that shear stress was the subjectively assessed variable. With decrease in material consistency they found that the rate of shear during spreading increased while shearing stress decreased.

A master curve of the rheological conditions was determined (Fig. 5). The optimum conditions for maximum patient acceptance of the spreadability were evaluated by a preference test. The flow curves for FAPG base when superimposed on the master curve illustrated several features. On initial application of shear, the material was stiff but consistency readily decreased on shearing, as illustrated by the arrow. The area between the two test sample rheograms is occupied by a family of curves derived at increasing times of shearing. The final curve at 20 s represents the average time in which a panel of ten persons arrived at a decision on the spreadability of a test material. This shear thinning behaviour with respect to time correlates well with the continuous shear rheograms of Fig. 2. The 20 s curve, although it did not intersect the preferred region, lay close to it at slightly higher stress values, suggesting that the consistency is just too high for maximum acceptance, and that it might be beneficial to reformulate the base to a slightly lower consistency although not at the expense of physical or chemical stability or reduced bioavailability.

In conclusion it is seen that FAPG base possesses many of the rheological properties desirable in a topical vehicle. This, coupled with the advantages of the base for dermatological use compared to traditional formulations (Garnier, 1971a,b; Rhodes, 1971) suggests that it may prove suitable as a vehicle for a wide range of therapeutic agents.

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