

A Rheological Study of Topical Vehicles

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Abstract □ To find out the rheological characteristics of several pharmaceutical semisolid products, experiments were carried out over the temperature range of 20 to 30°C. From continuous shear rheograms obtained with a Ferranti-Shirley cone and plate viscometer, loop area, shear rates, yield values, limiting viscosities and activation energies were calculated. The systems were metastable and their viscosity decreased with time. As the temperature was raised, products studied showed a decrease in viscosity and yield value.

Keywords □ Topical vehicles—Rheological characteristics—semisolid products—effects of temperature—Shear rheograms.

The consistency of the non-Newtonian materials is attributed to the summation of many complex properties such as elasticity, yield value, texture, and viscosity, and cannot be expressed adequately by any single index. However, several fundamental rheological properties which are indicative of consistency can be determined and an inspection of the complete consistency curve of rate of shear vs. shear stress gives an indication of the behavior of the material when it is subjected to manipulation.

An important category comprises the se-

misolids which are the most difficult to characterize rheologically because they combine both liquid and solid properties within the same material.

In recent years significant progress has been made in the area of rheologically defining the spreading and expulsion properties of pharmaceutical ointments and lotions. A great variety of test procedures has been utilized for the evaluation of the spreading and flow characteristics of pharmaceutical semisolids. No single instrument can provide all the information required for complete product evaluation. Although the loop test method of analysis using the Ferranti viscometer has a number of disadvantages and limitations^{1~3)}.

The Ferranti-Shirley cone and plate viscometer has instrumental advantages that make it worth while to evaluate its usefulness in studying the spreading properties of semisolid materials.

Schulte and Kassem^{4~9)} published a series of papers dealing with the flow properties of a wide range of gels and ointment bases by continuous shear method.

Boylan^{2,10)} also evaluated the spreading properties of semisolid material of petrolatum and several kinds of ointment bases. Barry

et al.^{11,13)} examined the rheological properties of soap, water amphiphile mixtures and FAPG base using Ferranti-Shirley viscometer.

The purpose of this paper is to report the rheological characteristics of several pharmaceutical semisolid products in the temperature range of 20–30° and to show how these results can be valuable to the formulator and manufacturer of these products.

EXPERIMENTAL

Materials

The reagents used were: Cetyl alcohol (Sipon products Ltd.), liquid paraffin(B.P.), Span 80 (Atlas Chemicals), Tween 80(Atlas Chemicals).

Equipments

Kenwood Homogenizer (Kenwood), Ferranti-Shirley cone and plate viscometer with automatic flow curve recorder unit (Ferranti Ltd.), Constant temperature water bath, Cone (2.0cm, 0.0064 radians).

Preparation of System

The systems were prepared according to the general formula. The formulations of ointment base were as follows:

Group I. Cetyl alcohol 10 – 25%, Liquid paraffin 15 – 30%, Span 80 0.5%, Tween 80 4.5%, Water 55.0%.

Group II. Cetyl alcohol 15 – 25%, Liquid paraffin 15 – 25%, Span 80 0.5%, Tween 80 4.5 %, Water 45 – 65%.

Group III. Cetyl alcohol 20%, Liquid paraffin 20%, Span 80 0.4 – 0.6%, Tween 80 3.6 – 5.4%, Water 53 – 56%.

As seen in the above formulation the ratio of cetyl alcohol and liquid paraffin was varied in group I, and in the second group the ratio of cetyl alcohol and liquid paraffin was kept constant and the total oil phase was varied. In group III, the amount of total emulsion was changed by varying water content and emulsifying agents concentration. Cetyl alcohol, liquid paraffin, Span 80 and Tween 80 were melted in the beaker at approximately 70°C. Water heated to 70°C was poured in a thin stream into the oil phase solution. Mixing of the ingredients was carried out with a Kenwood homogenizer. The rate of stirring was adjusted to ensure good mixing without entrapping air. The contents were cooled to room temperature. Formulation systems of topical vehicles were shown in Table I.

Rheological Evaluation

This was made using a Ferranti-Shirley cone and plate viscometer equipped with an automatic gap-setting device an X-Y recorder, and a constant temperature water bath. The

Table I: Formulation systems of topical vehicles.

System	A		B		C		D		E		F		G		H		I	
Component(%)																		
Cetyl alcohol	10.0	15.0	25.0	15.0	20.0	25.0	20.0	20.0	25.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0
Liquid paraffin	30.0	25.0	15.0	15.0	20.0	25.0	20.0	20.0	25.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0
Span 80	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.6	0.7	0.4	0.4	0.4	0.4	0.4
Tween 80	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	5.4	6.3	3.6	3.6	3.6	3.6	3.6
Distilled water	55.0	55.0	55.0	65.0	55.0	45.0	54.0	53.0	56.0	53.0	53.0	53.0	53.0	53.0	53.0	53.0	53.0	53.0

Table II: Areas of hysteresis loops and shear rates at spur point, static yield values, dynamic yield values and limiting viscosities.

System No.	Area of hysteresis loop(cm ⁻¹)	Shear rate at spur point (sec ⁻¹)	Static yield value (dyne cm ⁻¹)	Dynamic yield value(dyne cm ⁻²)	limiting viscosity (poise)
A	14.50	378	5662	1399	3.37
B	15.64	441	6998	1908	4.11
C	16.50	164	4326	3817	7.27
D	3.62	189	2417	1400	3.90
E	16.18	113	3944	1527	4.85
F	38.55	693	13359	3562	7.67
G	9.42	265	2099	191	0.98
H	17.46	504	4962	509	1.68
I	13.87	32	3753	636	1.62

water bath maintained the sample temperature at $\pm 0.1^\circ$ of the reported temperature. The sample to be evaluated was gently put onto the plate of the viscometer. Samples were disturbed as little as possible using a small spatula. The plate was immediately raised into position with the cone.

The sample then remained undisturbed for 10 minutes in this position before obtaining the rheogram. The recorder unit was set to give a maximum shear rate of 1890 sec^{-1} and a sweep time of 120 sec. The calibration of the viscometer was checked using a N.P.L. viscometry standard (Liquid paraffin B.P. 1592 poise at 25°C). Hysteresis loop areas were measured by balance.

RESULTS AND DISCUSSION

All experimental plots showed a common hysteresis effect in that the down curve lay to the left of the up curve. The areas enclosed by the loops and the values of shear stress, shear rate and shear strain at the spur point for the 9 systems are given in Table II. Figures 1~3 show a typical plot of rheogram for each

system at $20 \pm 0.1^\circ\text{C}$.

In general terms, the loop area may indicate the amount of structure break down which has taken place during a shearing cycle. The information obtained from this type of experiment is valuable in many situation, for example, in the formulation of suspension which must be of such a consistency that dispersed solids are maintained in suspension when in the container, but the preparation must become fluid enough on shaking to be poured. It is equally important that disturbed structures should rebuild rapidly upon resting so that sedimentation of the remaining material does not occur. The shear-stress rate relationship near the apex of the loop provides the parameters most useful in controlling high shear rate process such as mixing, milling, pumping, filling, etc.

A characteristic feature of many such rheograms is the presence of a spur point on the ascending curve. System I shows a pronounced spur on the up curve at low rates of shear, and system F shows a pronounced bulge.

Numerous workers have obtained similar

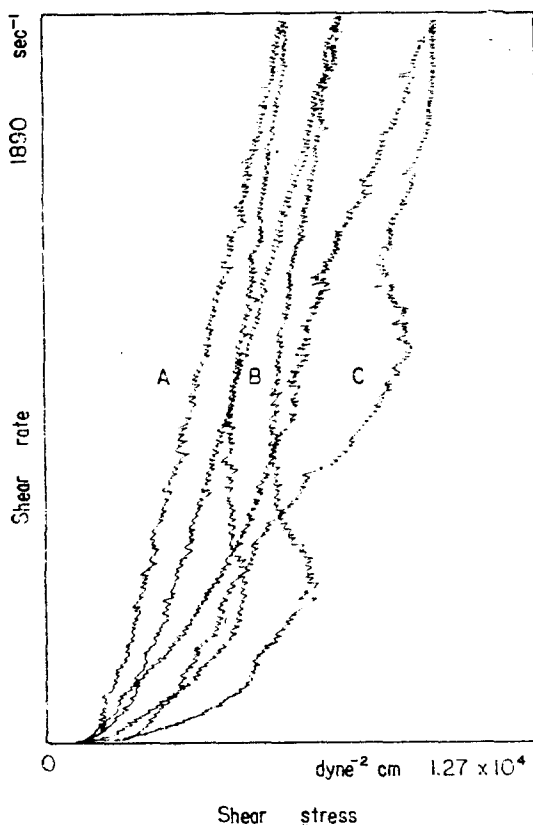


Fig. 1: Flow curves for systems A~C at 20°C

spur for a wide variety of systems, for example, ointments^{2,10}, soft paraffins^{14,15}, FAPG base¹³ and ointment base¹². The causes of such spur and bulges are not certain. When they occur on rheograms of time-dependent materials and are not due to instrumental artifacts, they are thought to arise from the presence of a three-dimensional gel-like structure¹⁶. The spur may be taken as a measure of the strength of a system in which structure must be broken down before a significant amount of deformation can take place and thus when the system is

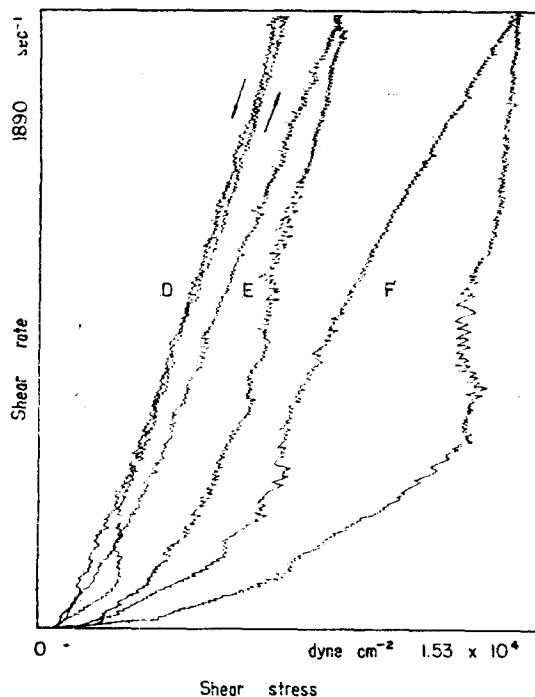


Fig. 2: Flow curves for systems D~F at 20°C

sheared, a spur is formed on the upcurve.

The gel centres are frozen spherulites and the network structure is made up of immersed frozen smectic phase in the form of threads. When the system is at rest these give considerable mechanical strength and provide most of the solid properties. They must be broken before a significant amount of formation can take place and thus, when the systems are sheared, a spur is formed on the upcurve. The static yield stress in each rheogram implies that besides the base being suitable for incorporating drugs which are soluble in base, it may be valuable for suspending insoluble materials. Thus the base has a high consistency when at rest, which

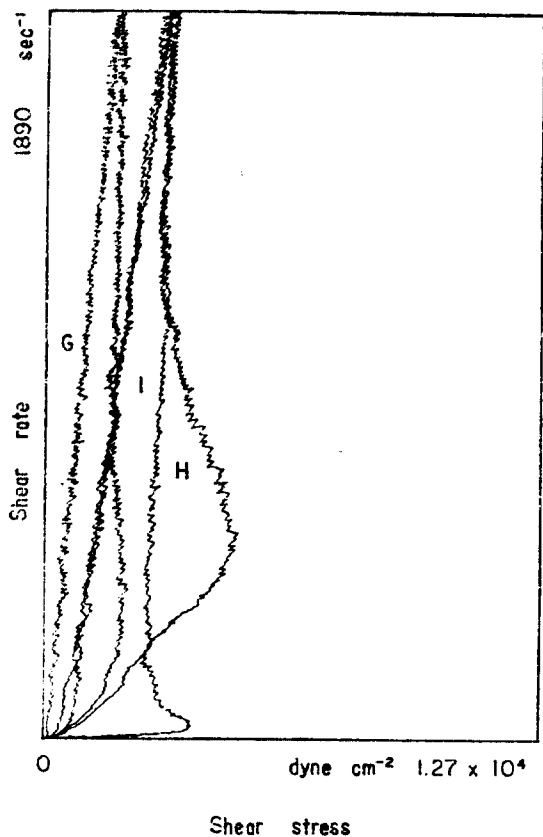


Fig. 3: Flow curves for systems G~I at 20°C

would minimize or prevent drug sedimentation on storage, yet decreases in consistency on working, as shown by the hysteresis loop.

In group I, the area enclosed by the loop increased with increase of cetyl alcohol and decrease of liquid paraffin content. As pointed out in the above the area of the hysteresis loop is a measure of the amount of breakdown which has taken place, as well as a function of the total solid content of the system. This is in accordance with the results obtained.

Materials which exhibit a reversible, isothermal, time-dependent loss of consistency

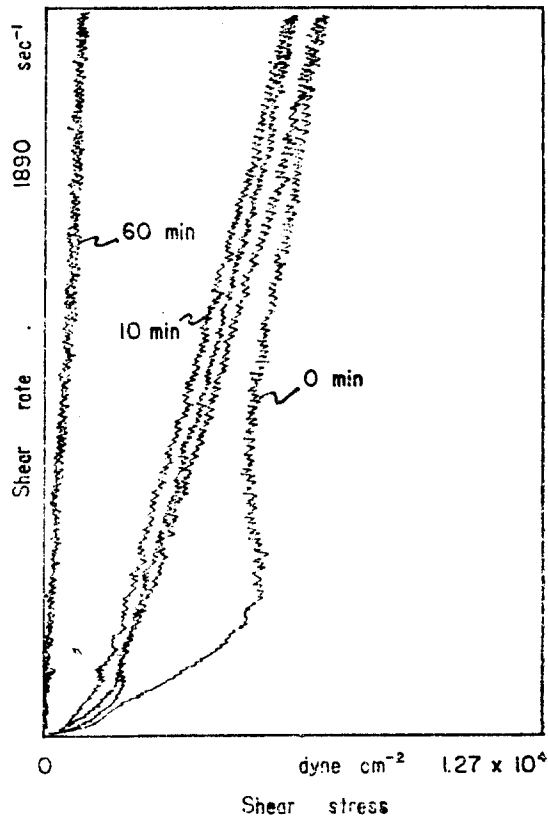


Fig. 4: The effect of time on system A

when sheared are thixotropic. A clear distinction should be made between this and irreversible shear breakdown (irreversible work softening) as in the latter process structure does not reform on standing. To distinguish between the two phenomena, it is necessary to test for the recovery of structure on resting. A series of experiments is performed in which a flow curve is obtained and is repeated with the same sample, varying the time for which the sample is allowed to rest. A typical series of rheograms is illustrated in Figure 4.

The loops of subsequent rheograms are displaced towards the shear rate axis, the displacement increasing in the order in which the runs are made. There is an initial large decrease in loop area from the first to the second sweep (as the majority of structure disruption occurs during the first cycle) subsequent decreases are much smaller in magnitude. As the time elapses, the loop area and shear values decrease until the behavior approximates to Newtonian flow. It may be concluded that the structure breakdown by shear in the viscometer

rebuilds to a negligible extent on standing. Therefore, as structural breakdown is irreversible, the system does not exhibit true thixotropy within the time scale of the experiment. This is in accordance with the view that the systems are in a metastable state and the fragile structure which lends strength to the material is readily broken down although a heating, mixing and cooling cycle will rebuild it. Figures 5~7 illustrate the effect of increase in temperature on the continuous shear rheograms. The rheogram is an anticlockwise hysteresis loop with a spur point. An increase

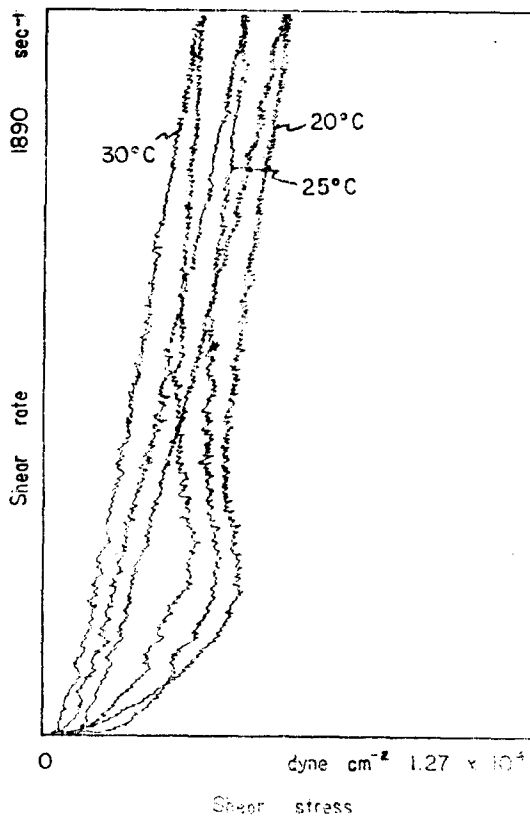


Fig. 5: The effect of temperature on the Hysteresis loop of system A

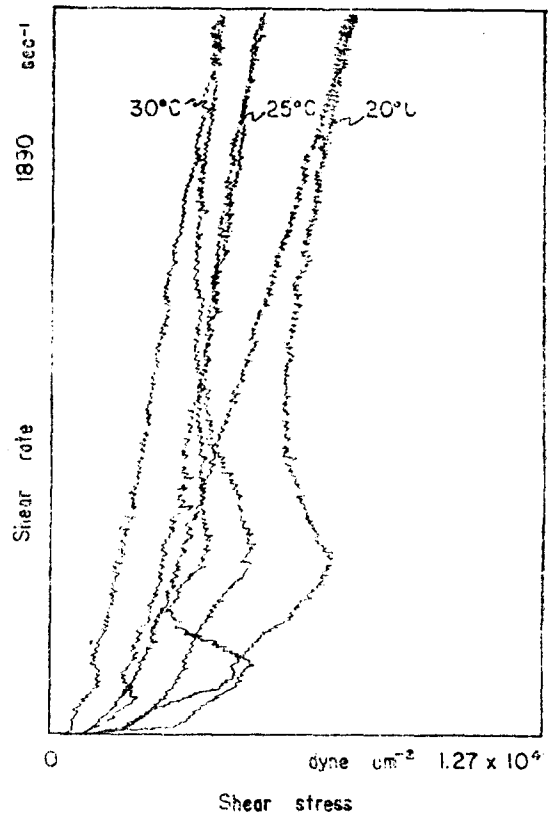


Fig. 6: The effect of temperature on the Hysteresis loop of system B

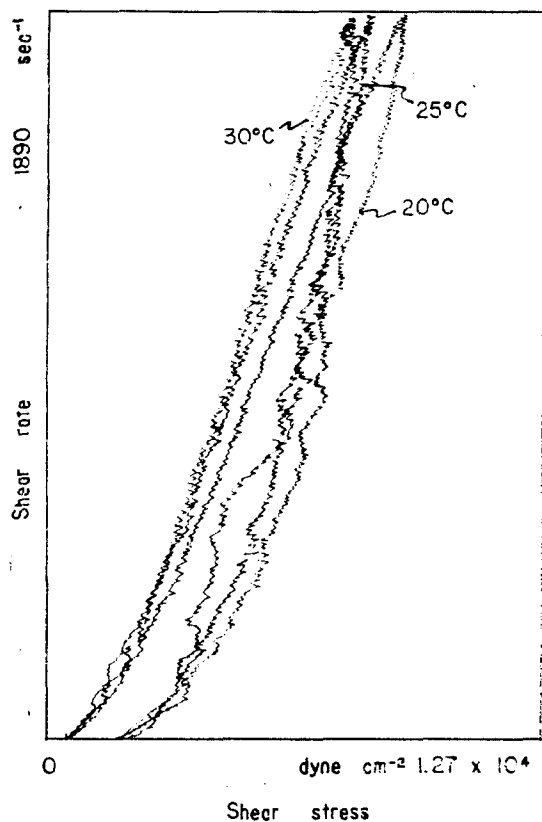


Fig. 7: The effect of temperature on the Hysteresis loop of System E

in temperature causes a decrease in limiting viscosity but there is no significant decrease in expulsion from the gap. Figure 8 shows the change in hysteresis loop area with temperature. There is no significant change in hysteresis loop area within the range of temperature of 20–30°C. Limiting viscosities derived from apex of each loop are plotted as functions of reciprocal temperature in Figure 9. As shown in Figure 9, a linear relationship was found when logarithm of limiting viscosities was plotted against $1/T$. A form of

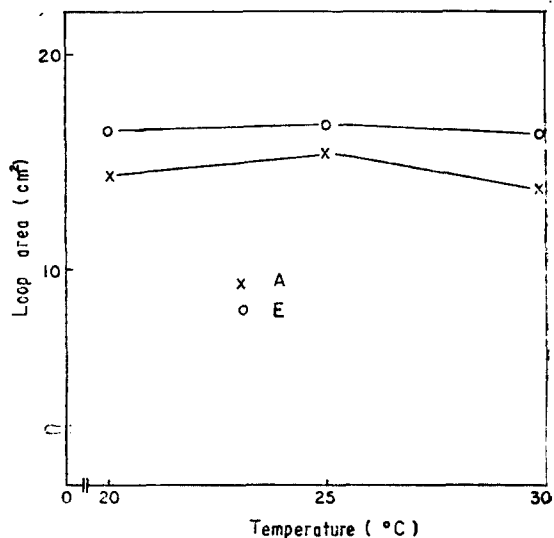


Fig. 8: The change in Hysteresis loop area with temperature

the Arrhenius equation may be expressed as $\eta = K \cdot e^{-E/RT}$, where η is the coefficient of viscosity, K is constant, R is the gas constant and T is the absolute temperature. An estimate of the activation energy for viscous flow A, E, was obtained from the limiting viscosity plot of Figure 9.

Although there are objections to Arrhenius-type plots approximate activation energies may be obtained for comparison with other materials. 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 control¹⁵.

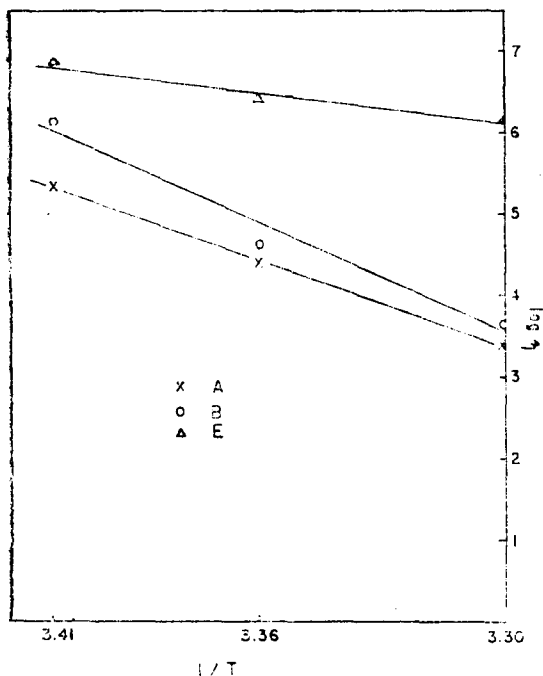


Fig. 9: Arrhenius-type plots of limiting viscosity at apex of loop

CONCLUSION

There was an initial large decrease in loop area from the first to the second sweep, and subsequent decrease was much smaller in magnitude, varying the times for which the sample was allowed to rest. An increase in temperature caused a decrease in apparent viscosity, but no significant decrease in expulsion from the gap was found. A linear relationship was obtained when logarithm of apparent viscosities was plotted against $1/T$ in some vehicle formulations. The base was only partially thixotropic over the time scale of experimentation.

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