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Structural Rheology of a Model Ointment

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A model ointment consisting of white petrolatum, mineral oil and microcrystalline wax was studied using rheology, microscopy and thermal techniques. Rheograms studied over a temperature range of 25–40°C indicated that the overall rheogram shape changed little as the temperature increased. However, two inflections gradually disappeared as the temperature increased. Thermal optical analysis showed that the temperature range over which these inflections disappeared correlated with the melting transition of the components forming the secondary structure. Another series of rheograms obtained from ointments with different combinations of the raw materials showed the rheology of the ointment is primarily controlled by the white petrolatum and mineral oil and that the microcrystalline wax acts to build-up the structure by incorporating itself into the existing white petrolatum structure. Thermal optical analysis of comelts of the raw materials proved that the ointment network structure is essentially a recombination of the naturally occurring components in differing ratios. The knowledge obtained from these studies is applied to a discussion of the thermal and mechanical stresses encountered in the filling operation.

KEY WORDS: ointment; rheology; petrolatum; videomicroscopy; thermal optical analysis; hot stage microscopy.

INTRODUCTION

Ointments are primarily composed of white petrolatum with waxes and oils added to stiffen and reduce tack. Kostenbauder and Martin (1) studied the effect of waxes and oils on the rheology of white petrolatum and Davis (2) determined the viscoelasticity of white petrolatum and a number of ointment bases; however, these authors offered no structural explanation. The colloidal structure of white petrolatum has been well characterized by a number of authors (3–6) and the structural components of microcrystalline wax are known (7). The present study uses this information, rheometry and thermal optical videomicroscopy to determine the structural rheology of a model ointment and to interpret rheological changes in the ointment during the tube filling operation.

MATERIALS AND METHODS

A model ointment having a composition of white petrolatum, mineral oil and microcrystalline wax in a ratio of 19/5/1 was prepared by heating the components above the liquefaction point with mixing followed by force cooling with a water ring and mixing until congealed. The ointment also contained methyl and butyl paraben as preservatives as well as a suspended, insoluble drug for other experimental purposes. The white petrolatum and mineral oil were USP quality and the microcrystalline wax and parabens were NF quality. All materials were used as received from the supplier. Comelts of white petrolatum and other excipients were prepared in formulation ratios using the same manufacturing techniques as the model ointment.

A Ferranti-Shirley cone and plate viscometer was used for rheological measurements. Unless otherwise specified, samples were tested with the instrument in low gear using the 7cm truncated cone, a 60 second sweep time, and the 2× scale expansion on the recorder. The 25°C samples were tested with the same instrument parameters except a 4× expansion on the recorder was necessary to keep the pen on scale. A shear rate range of 0–164 $\sec^{-1}$ was achieved with these instrument settings. Measurements were obtained at 25°, 30°, 35° and 40° C.

Photomicrographs for Figure 5 were obtained with a Zeiss Universal microscope using polarized light and a 25× normal working distance pol objective to give a 312× magnification. Melting behavior was observed using a Mettler FP82 hot stage at a heating rate of 5°C/minute over the range 25°C to slightly above the melting point. In order to accommodate the size of the hot stage, it was necessary to switch to a 20× long working distance pol objective which resulted in a final magnification of 193×. The hot stage was equipped with a recorder and photomonitor which, when inserted in the eyepiece of the microscope, monitors changes in light levels of the field as melting progresses. The melting point was defined as the temperature at which the photomonitor recording formed an arrest and/or the temperature at which flow began. Samples were monitored by videotaping and with the photomonitor. A Panasonic WV-D5000 CCD color video camera mounted directly on the microscope was used to record melting transitions in real time using a Panasonic AG-6050 time lapse VHS recorder. The video signal was displayed with a Panasonic CT-1330 13″ color video monitor. A Leightronix CG-1000 temperature-monitoring character generator was interfaced between the hot stage and the video monitor to provide on-screen display of the temperature as melting progressed. Videophotomicrographs at the 193× magnification were obtained with a Polaroid FreezeFrame camera initially and at various points during the melting sequence. Samples of the ointment, white petrolatum and comelts could be monitored directly from the initial slide preparation. However, in order to obtain a thin film suitable for microscopy, the microcrystalline wax required premelting on the slide prior to monitoring its melting behavior.

RESULTS AND DISCUSSION

Formula

As mentioned above, the model ointment is composed of white petrolatum, mineral oil and microcrystalline wax in a ratio of 19/5/1, respectively. Since the rheology of the ointment is controlled by the white petrolatum/mineral oil/microcrystalline wax matrix, a discussion of the chemical composition and structure of each component is in order.

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Each material is derived from the refinement of crude petroleum oil and as such is a complex mixture of straight chain, branched chain and cyclic hydrocarbons of varying chain lengths. Petrolatum is chemically related to mineral oil. While mineral oil contains mainly liquid hydrocarbons at room temperature, petrolatum is a mixture of solid and liquid hydrocarbons and is a solid at room temperature (6). Petrolatum may be considered to be a soft-type microcrystalline wax with a high oil content (6). Both petrolatum and microcrystalline wax are obtained from the crude petrolatum which results from dewaxing the residue remaining after distillation (6). The microcrystalline wax fraction (up to 25%) is then isolated by de-oiling the crude petrolatum which contains 5–50% oil (6,8). The resultant microcrystalline wax contains up to 5% oil. Petrolatum and microcrystalline wax both have small irregular crystals. Warth (8) attributes the lack of well-defined crystals to the occluded retained oil. Microcrystalline wax and the microcrystalline fraction of petrolatum are composed primarily of iso- and cyclic paraffins (4,6). Chain lengths range from C_{38}–C_{60} for microcrystalline wax and C_{16}–C_{32} for petrolatum and the melting point increases with increasing chain length (9).

Barry (4) offers a more detailed explanation of petrolatum structure. He indicates that petrolatum is a two-phase colloidal gel of liquid, microcrystalline and crystalline hydrocarbons. Upon cooling a molten sample, the stiffening wax phase forms an amorphous, compact three-dimensional network structure having voids of molecular dimensions while the liquid phase binds to the network via a sorption mechanism. According to Barry, electron microscopy has shown that the crystals consist of fiber-like bundles of colloidal dimensions linked by numerous contact points. He attributes the rheological properties of petrolatum and its formulations to this microscopic and submicroscopic wax matrix. Schulte and Kassem (10) have shown that the rheological properties of white petrolatum are determined by the ratios of n-, iso-, and cyclic paraffin fractions. Structural collapse of the iso-paraffins has been determined to be less than that of the n-paraffins during mechanical stress. Schulte and Kassem attributed this to the finer crystallite gel structure of the iso-paraffins which is less susceptible to mechanical strain than a large crystallite structure. According to their study, as the crystallite size decreased, the viscosity of the petrolatum increased.

Rheology

Figure 1 illustrates the changes in the rheology of the model ointment as the temperature increases. In general, the overall shape of the rheogram remains constant, but the rheogram shifts toward the shear rate axis and the size of the hysteresis loop decreases as the temperature increases. The apparent lack of a spur on the up curve of the 25°C rheogram is an indication that the three-dimensional network structure of the ointment at 25°C is more resilient and more easily withstands the mechanical shearing stresses of the up curve. The significance of the spur formation, its associated static yield value and its relationship to the network structure have previously been proven and discussed (11,12). The static yield values of the model ointment are given in Table IA and reflect a gradual weakening of the three-dimensional network structure as the temperature increases. This would be expected since as a previous works (11) indicated, melting is associated with a reduction in network crosslinks as particle size diminishes.

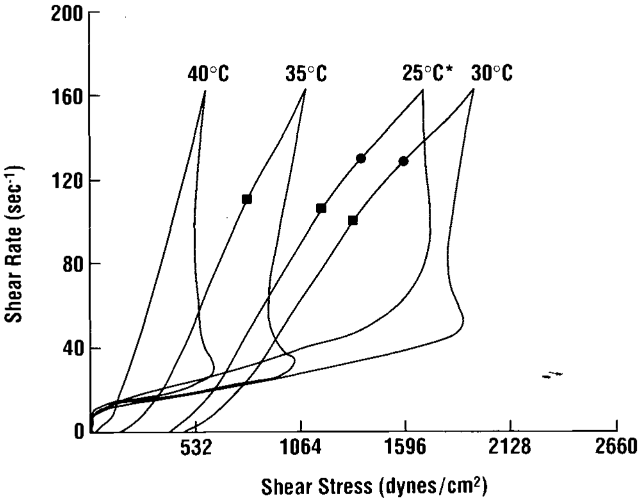

Figure 1. Ointment rheograms at 25°, 30°, 35° and 40°C. ● τ''_D ■ τ'_D. *Recorder at 4× on the abscissa.

Examination of the rheogram down curves reveals inflections which disappear as the temperature increases. The inflections become evident during determination of the dynamic yield value and can be considered to be intermediate dynamic yield values. Levy (13) associates the dynamic yield value τ_D with the energy input required to maintain a constant ratio of shear rate and shear stress and to maintain the existent degree of structural breakdown. In other words, Levy (13) associates the dynamic yield value with the degree of destruction by a given shear stress and duration of shear. The higher the dynamic yield value, the greater the destruction. Experimentally, the value is obtained by extrapolating the linear portion of the down curve to the shear stress axis. However, in the case of the model ointment, there are as many as three linear portions of the down curve defined by the infections and each has an associated dynamic yield value designated τ''_D, τ'_D, or τ_D corresponding to successive increases in structural breakdown. τ_D relates to Levy's (13) definition and structural breakdown is at a maximum. τ''_D and τ'_D reflect structures which resist the shearing stresses of the up curve to the maximum shear rate, but which break down with the continued duration of the down curve shearing stresses with τ''_D being the weakest structure. Since Schulte and Kassem (10) have shown that the iso-paraffin fraction is more shear resistant than the n-paraffin fraction, the up curve, intermediate and final dynamic yield values probably correspond to an initial destruction of the n-paraffin crosslinks followed by successive destruction of the iso-paraffin crosslinks. The dynamic yield values and associated inflection shear rates are given in Table 1A. Note that the inflection shear rates remain relatively constant regardless of the temperature, thus indicating a constant degree of structural integrity. This would support the suggestion that the dynamic yield values correspond to successively greater destruction of the iso-paraffin network structure. It will become apparent later in this paper that these inflections cor-

Table IA. Rheological Parameters of the Model Ointment as a Function of Temperature

Temperature °C	Static Yield Value (dynes/cm^2)	Dynamic Yield Value (dynes/cm^2)		Inflection Shear Rate (sec^{-1})	Area (cm^2)
25	3474	τ''_D	160	164	46.9*
		τ'_D	665	130	
		τ_D	1027	106	
30	1894	τ''_D	122	164	50.7
		τ'_D	386	128	
		τ_D	638	100	
35	1048	τ'_D	133	164	28.3
		τ_D	293	110	
40	636	τ_D	138	—	18.7

*Data point not entered in the regression analysis because of the change in the scale expansion of the shear stress axis.

respond to melting portions of the ointment structural network.

The series of rheograms in Figure 2 illustrate the role of mineral oil and microcrystalline wax in modifying the rheology of white petrolatum to yield that of the model ointment. The microcrystalline wax not only builds-up the three-dimensional network as is evident from the increased static yield value, it also blends directly into the existing white petrolatum network structure as is evidenced by the maintenance of the overall rheogram shape. Considering the nature and origin of both ingredients as described in the formula section, this behavior might be expected. In other words, the added microcrystalline wax is essentially increasing the existing microcrystalline wax fraction of the white petrolatum. Mineral oil which is present in a higher ratio has a dramatic negative effect on the rheology of white petrolatum. As was discussed in the formula section, white petrolatum is composed of both liquid and solid hydrocarbons with the liquid phase residing in the voids of the three-dimensional network structure formed by the solid phase. Therefore, the observed effect of the mineral oil on the white petrolatum rheology results from expanding the network structure of white petrolatum and reducing the number of effective crosslinks between the solid phase particles. The addition of microcrystalline wax to the white petrolatum/mineral oil combination partially rebuilds the network structure via the mechanism described above, but the greater mineral oil concentration dominates. The rheograms of the model ointment and the three component mixture should ideally be the same, but slight variations in manufacturing cooling rates would account for the slight variation observed.

Videomicroscopy

Figure 3 shows a series of photomicrographs of the model ointment obtained during melting. Three distinct structures are present in the videophotomicrographs. Using thermal optical videomicroscopy, the amorphous background structures will be identified as a combination of white petrolatum and microcrystalline wax while the large needle-like structures will be identified as butyl paraben. The small bright particulates are suspended drug. Ointment melting is gradual and occurs over a broad range with transition points as listed in Table II and pictured in Figure 3. The melting sequence begins with a gradual disappearance of the amorphous background structure. Flow and the start of liquefaction of the background structure begins at 39°C and is completed by 52°C. The needles melt over the range 57°–63°C.

Thermal Optical Analysis

Figure 4 shows the photomonitor recordings of the melting transitions of the model ointment, its structural raw materials and a comelt of these materials. The associated break and arrest temperatures for each recording are given in Table II. Each of the recordings shows a broad, gradual transition. According to McCrone (14), this broad melting range results from liquefaction of successively higher melting eutectics. As the formula section indicated, white petrolatum and microcrystalline wax are complex hydrocarbon mixtures with varying chain lengths and the longer the chain length, the higher the melting point. Therefore, the broad melting transitions would be expected.

Closer examination of the recordings shows that white petrolatum has two break points and an arrest as do the

Table IB. Regression Analysis of the Model Ointment Rheological Parameters as a Function of Temperature

Parameter	Static Yield Value	Dynamic Yield Value			Area
	τ_s	τ''_D	τ'_D	τ_D	
Slope	−0.049	−0.024	−0.070	−0.059	−0.043
Intercept	4.77	2.79	4.61	4.53	2.99
Correlation Coefficient	0.999	1.000	0.983	0.995	0.9954

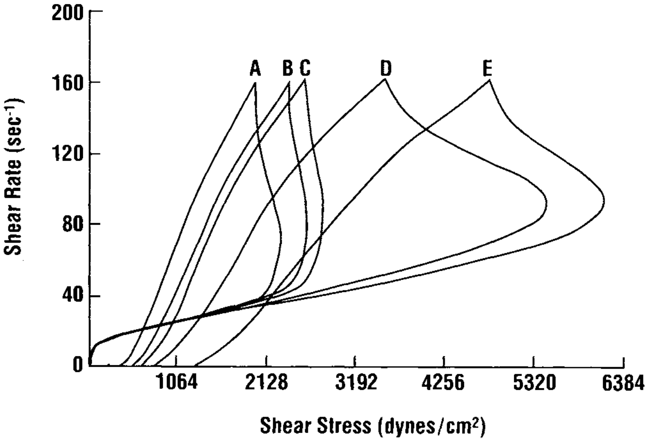

Figure 2. Ointment rheograms as a function of composition. A) White petrolatum and mineral oil B) White petrolatum, mineral oil, and microcrystalline wax C) Complete formula D) White petrolatum E) White petrolatum and microcrystalline wax.

ointment and the comelt, but the microcrystalline wax has only an arrest. This is consistent with the videotapes of the melting transitions. The microcrystalline wax video showed a gradual size reduction of the minute particles as the temperature increased, but no liquefaction occurred until the arrest temperature. The other samples all showed liquefaction and flow at the break temperatures. Based on the description of the white petrolatum network structure, the break and arrest temperatures probably correspond to liquefaction of the short chain crystalline hydrocarbons to release the liquid fraction followed by liquefaction of the long chain microcrystalline hydrocarbons. Addition of microcrystalline wax to the white petrolatum results in a comelt melting transition having breaks correlating with those of the petrolatum and an arrest correlating with the microcrystalline wax. Since the comelt composition is identical to the structural network of the ointment, the similarity of the ointment break and arrest temperatures would be expected.

The gradual slope of the photomonitor recordings rather than abrupt increases in absorbance at the breaks verifies the rheological observation that the microcrystalline wax blends into the existing white petrolatum network structure. In addition, the disappearance of the rheogram down curve inflections at elevated temperatures can be attributed to melting the network structures associated with the break points of the ointment photomonitor recording. In other words, the 35°C rheogram does not have an inflection associated with τ''_D and the 40°C rheogram lacks an inflection for τ'_D because

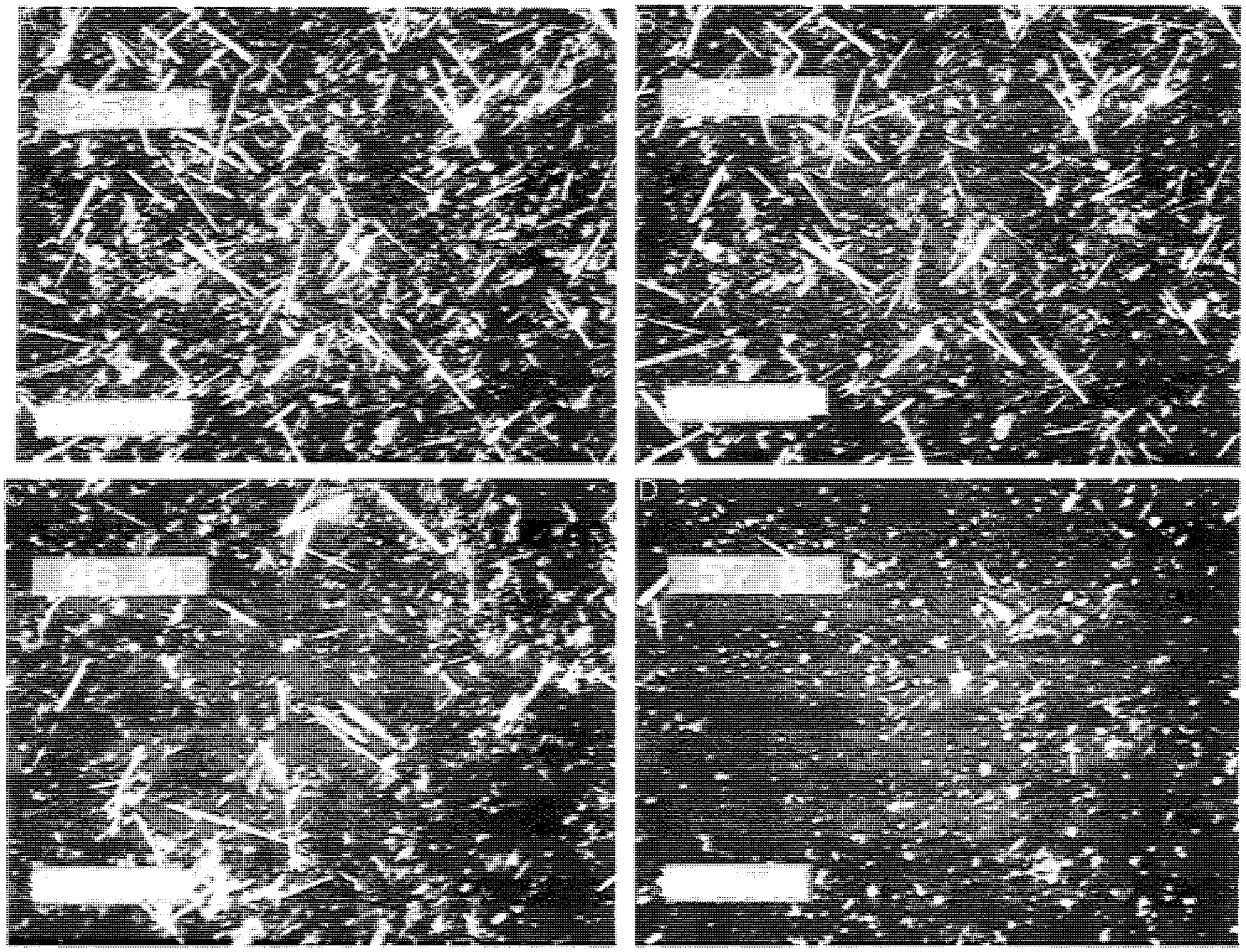

Figure 3. Photomicrographs of the ointment as a function of temperature (193×); reduced to 89% for reproduction.

Table II. Photomonitor Transition Temperatures

Material	Temperature °C
White Petrolatum USP/Microcrystalline Wax 19/1	37, 47 & 58
Microcrystalline Wax	61
White Petrolatum	38, 45 & 48
Ointment	39, 46 & 57

the ointment structures melting at 39°C and 46°C have had sufficient reductions in crosslinks that the residual network can no longer be detected rheologically. A previous paper (11) showed that rheological sensitivity to a network structure is reduced well before its melting point because the particle size reduction associated with melting substantially destroys the network interparticle crosslinks.

Particulate Identification

The videomicroscopy section indicated the presence of three distinct structures in the ointment photomicrographs; an amorphous background, large needles and small bright particulates. Thermal optical analysis proved that the amorphous background structures were the white petrolatum/microcrystalline wax network. The small bright particulates can be identified as the high melting suspended drug since, as Figure 3 shows, it is the only species remaining in the photomicrograph at the melting point of the ointment. The large needle-like structures had the same melting point as both the microcrystalline wax and the butyl paraben. However, neither material appeared to reasonably suit the situation. The needle-like structures were extensive in the photomicrographs, but the butyl paraben concentration in the formula was so small in comparison to the white petrolatum (a ratio exceeding 300/1) that butyl paraben did not appear to be a reasonable assumption. On the other hand, large needles were not consistent with the previously described structure for microcrystalline wax. Therefore, a factorial study was performed in which individual ingredients of the ointment formula were sequentially eliminated. The needle-like structures were present in all the combinations except the ointment made without butyl paraben. Thus, despite the minute formulation concentration, the needles were identified as butyl paraben. Further, this indicated that the butyl paraben must be so insoluble in the ointment that it totally precipitates. Photomicrographs of the ointment with and without butyl paraben are presented in Figure 5. The rheograms in Figure 6 indicate that the presence of the needle-like structures do not significantly impact the rheology of the ointment.

Applications

Changes in the rheological behavior of semisolid dosage forms as a result of temperature variation are a well established fact in their manufacture, filling, storage and dispensing. As an illustration, the effects of the thermal and mechanical stresses of the filling operation on the rheology of the model ointment are discussed and correlated with its colloidal structure. In order to improve flow and ensure fill weight uniformity, ointments are frequently heated during the filling operation. Designated filling temperatures for an ointment generally range from 25–35°C. The ointment rheograms covering this temperature range and the corresponding rheological parameters were discussed in conjunction with Figure 1 and Table IA, respectively. Thermal effects were seen to overwhelmingly dominate all parts of the rheogram and thermal destruction of the network structure exceeded that of mechanical destruction imparted by the viscometer. The magnitude of the separation between the rheograms with respect to temperature also indicated that this destruction was relatively extensive.

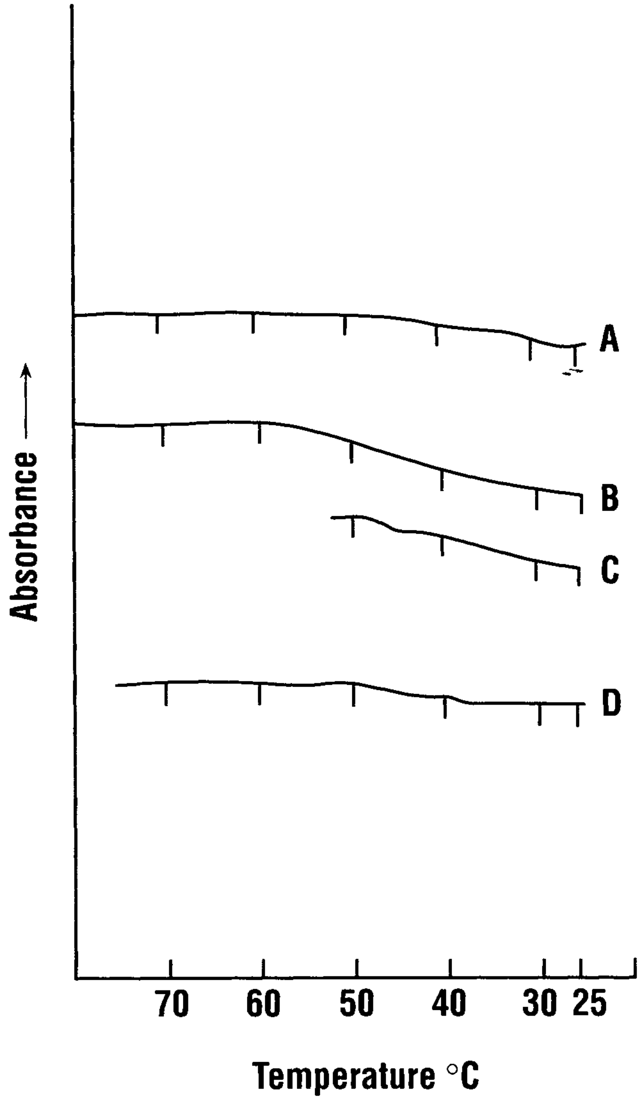

Figure 4. Photomonitor recordings of the ointment and its raw materials. A) White petrolatum/microcrystalline wax 19/1 comelt B) Microcrystalline wax C) White petrolatum D) Ointment.

Each of the rheological parameters in Table IA can be plotted as a function of temperature and fitted to a curve as shown in Figure 7. The slopes, intercepts and correlation coefficients for the regression lines of each parameter are given in Table IB. When analyzed in this fashion, it becomes apparent that the ointment parameters are a logarithmic function of temperature. This suggests that the ointment network structure degrades rapidly as the temperature in-

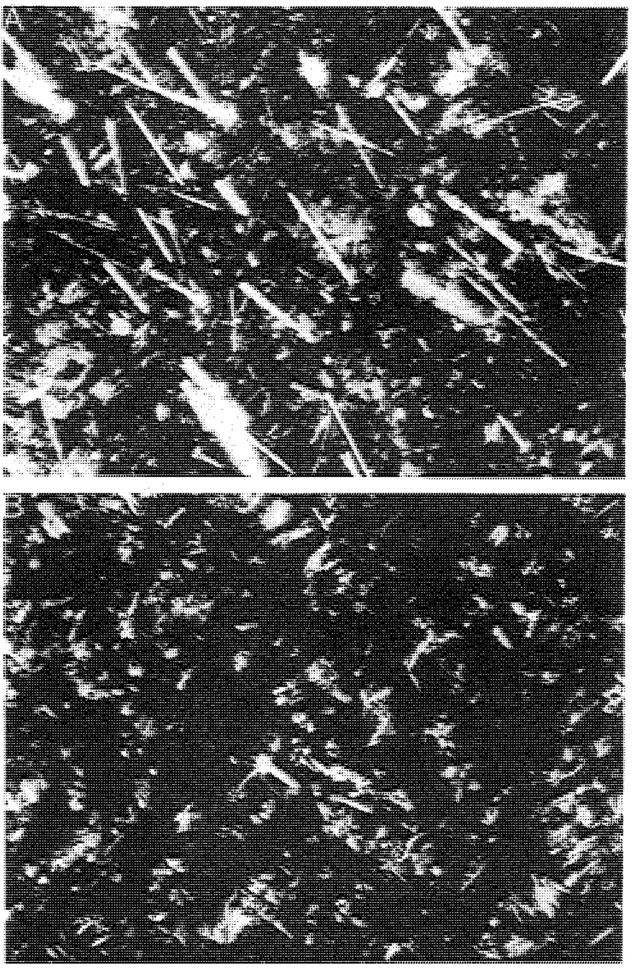

Figure 5. Photomicrographs proving the identity of the needle-like precipitate. A) Ointment B) Ointment without parabens. 312×; reduced to 95% for reproduction.

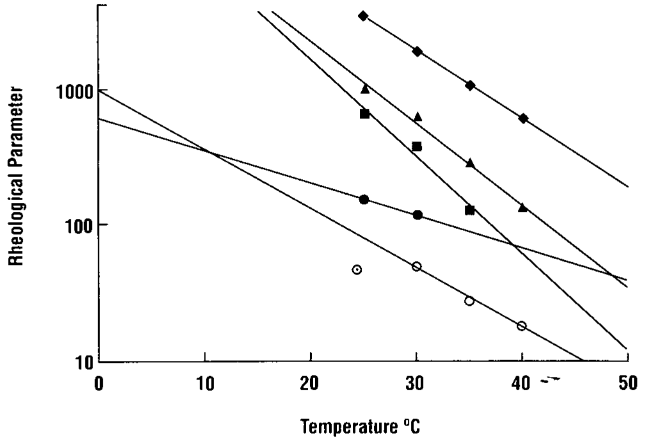

Figure 7. Rheological Parameters vs Temperature. ◆ τ_s ▲ τ_D ■ τ'_D ● τ''_D ○ Area ⊙ Area Outlier.

creases and is consistent with the structural degradation seen in the hot stage microscopy studies. The logarithmic rheology-temperature relationship thus explains why minor temperature adjustments can improve ointment flow during the filling operation to eliminate plug flow and thereby reduce fill weight variation. In addition, these rheology-temperature studies indicate that when an ointment becomes too fluid in response to temperature changes and drips from the filler nozzles, the cause is most likely attributable to approaching or exceeding the critical temperature of one or more of the previously defined dynamic yield values.

Previous discussions indicated that thermal destruction of the rheological network structure occurs via a reduction in the number of crosslinks as a result of particle size reduction associated with the melting process. In comparison, mechanical destruction of the rheological network refers to physically breaking network crosslinks and aligning the network particles in the direction of shear. Figure 8 shows the rheograms of the model ointment before and after a manufacturing filling operation. The data obtained from the rheology parameters of interest are listed in Table III. The overall shape of the rheogram is maintained. However, a number of features indicative of mechanical network destruction are apparent. Chief among these features is the general shift in the rheogram towards the shear rate axis. Also, a decrease in the size of the hysteresis loop is apparent and reflects a

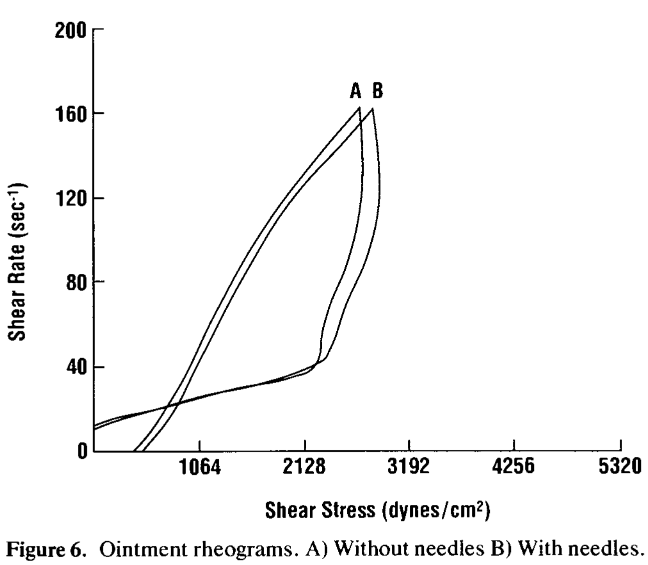

Figure 6. Ointment rheograms. A) Without needles B) With needles.

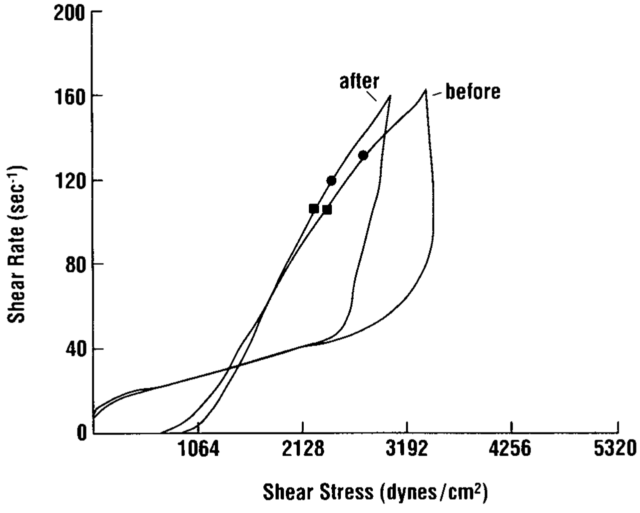

Figure 8. Mechanical Stress Effects on the Ointment Rheogram. ● τ''_D ■ τ'_D.

Table III. Mechanical Stress Effects on the Rheological Parameters of the Model Ointment

Sample	Static Yield Value (dynes/cm^2)	Dynamic Yield Value (dynes/cm^2)			Area (cm^2)
		τ''_D	τ'_D	τ_D	
Before filling	3474	160	665	1027	46.9
After filling	2554	638	931	1170	31.6
% Change	−26.5	+299.0	+40.0	+14.0	−32.6

reduction in the three-dimensional network structure. The increase in the dynamic yield values further indicates crosslink destruction and that the network is being reduced to primary particle sizes. A quantitative examination of the data in Table III indicates that the greatest changes occur in the static and dynamic yield values and the area of the hysteresis loop. Furthermore, the ointment structural network appears to undergo irreversible shear breakdown, as defined by Barry (12), rather than true thixotropy since the sample obtained after filling was allowed to age for one week prior to measurement to allow structural rebuilding to occur. It should also be noted that to minimize shear stresses during preparation, samples were obtained by cutting the tubes open rather than by expression from the tube. The irreversible shear breakdown exhibited by the ointment suggests that previous shear history is important in defining the flow properties of the final product and may provide an explanation for the lot to lot variation in flow sometimes experienced during the filling operation. In other words, excessive shear during manufacture or from transfer operations to the filler will result in an ointment of a thinner consistency. The logarithmic rheology-temperature effects would be more pronounced on a thinner consistency ointment and problems with fill weight variation and dripping from the filler nozzles would be more apparent. Since mechanical and thermal effects on a product can be assessed rheologically and correlated, it is feasible that better control of the filling operation can be realized by adjusting the filling temperature in response to the rheological measurements of a given ointment lot.

REFERENCES

1. H. B. Kostenbauder, and A. N. Martin. A Rheological Study of Some Pharmaceutical Semisolids. *J. Am. Pharm. Assoc. Sci. Ed.* 43:401–407 (1963).
2. S. S. Davis. Viscoelastic Properties of Pharmaceutical Semisolids I. Ointment Bases. *J. Pharm. Sci.* 58:412–417, (1969).
3. F. Gstirner. Composition and Rheological Properties of Vaseline. *Indian J. Pharm.* 32:73–81, (1970).
4. B. W. Barry and A. J. Grace. Structural, Rheological and Textural Properties of Soft Paraffins. *J. Texture Studies,* 1:259–279, (1971).
5. B. F. Birdwell, and F. W. Jessen. Crystallization of Petroleum Waxes. *Nature* 209:366–368, (1966).
6. E. Meyer. *White Mineral Oil and Petrolatum and Their Related Products Petroleum Sulfonates and Microcrystalline Waxes,* Chemical Publishing Co., Inc., New York, 1968, pp. 16–28 and 193–202.
7. H. Bennett. *Industrial Waxes,* Vol. 1, Chemical Publishing Co., Inc., New York, 1975, pp. 97–100.
8. A. H. Warth. *The Chemistry and Technology of Waxes,* 2nd ed., Reinhold Publishing Corp., New York, 1956, pp. 377–442.
9. M. G. DeNavarre. *The Chemistry and Manufacture of Cosmetics,* Vol II, 2nd ed., D. Van Nostrand Co., Inc., Princeton, 1962, pp. 359–370.
10. K. E. Schulte and M. A. Kassem. Rheologische Studien an Salbengelen. *Pharm. Acta Helv.,* 38:358–370, (1963).
11. L. E. Pena, B. L. Lee and J. F. Stearns. "Secondary Structural Rheology of a Model Cream". Paper presented at the Midwest Regional Meeting of the American Academy of Pharmaceutical Scientists, Chicago, Illinois, May 15, 1989.
12. B. W. Barry. Rheology of Pharmaceutical and Cosmetic Semisolids. In H. S. Bean, A. H. Beckett and J. E. Carless (eds.), *Advances in Pharmaceutical Sciences,* Vol.4, Academic Press, New York, 1974, pp. 1–72.
13. G. Levy. Rheology of Thixotropic Montmorillonite Dispersions I. Changes on Aging of Plain and Polysorbate 80 Containing Dispersions. *J. Pharm. Sci.,* 51: 947–951, (1962).
14. W. C. McCrone. *Fusion Methods in Chemical Microscopy,* Interscience Publishers, New York, 1957, p. 53.