Rheological Evaluation of Lipophilic Suspending Agents I

Dimethyl Dialkyl Ammonium Hectorite

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A modified Brookfield viscometer was used to evaluate dispersions containing various concentrations of dimethyl dialkyl ammonium hectorite (DDAH) and ethanol in light mineral oil. The optimum amount of ethanol needed to disperse the DDAH in the oil was found to be an amount equal to the weight of the DDAH. A new method of determining the static yield value was used as one of the rheological parameters in the evaluation. The static yield value (Y_s) in dynes/cm.^{2} was found to be related to the percentage concentration (C) of the DDAH as follows: log $Y_s = mC + \log b$ in which the constants m and b equal 1 and 2, respectively, for dispersions containing an ethanol content equal to the DDAH; and equal to 0.6 and 3.5, respectively, for dispersions containing an ethanol content twice that of the DDAH. A 1.25 per cent DDAH–1.25 per cent ethanol dispersion was evaluated for its ability to suspend several drugs. It was postulated from the sedimentation data that the small amount of supernatant liquid which occurred in these suspensions was due to syneresis.

THE EVALUATION of hydrophilic suspending agents as stabilizers for aqueous suspensions has been the subject of numerous investigations. However, there are no such lipophilic suspending agents in use for preparing pharmaceutical oil suspensions with the exception of aluminum monostearate. Aluminum monostearate is used to gel the oil in the preparation of oily suspensions of procaine penicillin G, not for the purpose of stabilizing the suspension (even though it does this), but for the purpose of prolonging the absorption of the penicillin.

Oily mediums still serve a need as vehicles for dermatological drugs as attested to by the number of U.S.P. XVII (1) and N.F. XII (2) ointments that use the petrolatums as the base. Rheologically, petrolatum has a high yield value at room temperature. The yield value becomes greater as solid substances are incorporated. This makes the resulting ointment difficult to spread and the excessive pressure needed for its application may be painful. It would seem that a liquid vehicle, such as mineral oil, might serve the same purpose as an ointment prepared with petrolatum and be easier to apply.

Mineral oil is a viscous liquid but is not a good suspending medium because of its Newtonian character. A good suspending medium should have a yield value, yet it should be capable of being poured from a bottle (3–6). The evaluation of a substance that would alter the flow properties of mineral oil to produce such an effect is of interest here. Previous reports indicate that dimethyl dialkyl ammonium hectorite[1] (DDAH) might be a likely candidate to produce this effect. For example, it has been used to prepare ointments with heavy mineral oil (7) and with hexamethyltetracosane (8). Viscous dispersions of DDAH in volatile organic solvents have been tested as granulators and binders in the production of tablets (9).

DDAH is a finely divided light cream-colored powder. Unlike hectorite, which is highly hydrophilic, this organic derivative of hectorite is hydrophobic and organophilic. As a result, it produces gels with organic liquids. The mechanism of the gelling process has been investigated by Jordan and co-workers (10–12). Although they worked with organic derivatives of bentonite, their results and interpretations can be applied to DDAH because both bentonite and hectorite have the same montmorillonite lattice structure (13). In the gelling process it is necessary for the solvating liquid to first penetrate between the small primary particles and effect a separation of them before solvation can occur. The liquid must possess some degree of polarity which is needed to overcome the attractive forces that hold these particles together and allow its penetration. Liquids consisting primarily of hydrocarbons, such as mineral oil, do not possess sufficient polarity to accomplish this. The use of polar additives and mechanical shear can be used to overcome these forces and allow the penetration of the oil. The low molecular weight alcohols, such as methanol and ethanol, are recommended as polar additives for this purpose.

[1] Made by the National Lead Co. under the name of Bentone 38. The alkyl groups are a mixture of C_{18} and C_{16} in a ratio of approximately 70 to 30, respectively.

TABLE I.—DIMENSIONS OF CYLINDRICAL SPINDLES

Spindle No.	Radius (R_b), cm.	Ht., cm.	Effective Ht. (h),[a] cm.
1	0.942	6.510	7.493
2	0.513	5.395	6.121
3	0.294	4.288	4.846
4	0.159	3.101	3.396

[a] The effective height is the actual height plus the correction for the end effect.

It is also suggested that the alcohols contain 5% water (14).

The amount of ethanol recommended as a polar additive for organic derivatives of montmorillonite clays is about 45% based on the weight of the clay derivative (14). It is likely that the amount of ethanol would vary, depending on the particular derivative and the polarity of the vehicle. The purpose of this investigation was to determine the optimum concentration of DDAH and ethanol and the most efficient procedure for the preparation of an oily suspending medium. Rheological evaluations of the dispersions were used to select the combination of DDAH and ethanol in light mineral oil that could be used as a suspending medium. Various rheological parameters were used in the evaluation for the purpose of correlating concentrations with a rheological parameter.

EXPERIMENTAL

Instrumentation.—A Brookfield viscometer (LVT model)[2] was modified so that it would function as an absolute rheometer. The No. 2 and No. 3 disk shaped spindles were replaced with cylindrical spindles. The dimensions of the spindles are given in Table I. The guard that is supplied with the viscometer was removed to prevent the guard from interfering with shearing and also to facilitate the use of a cup having a smaller diameter and volume than the cup recommended for use with the guard attached to the instrument. These modifications were similar to those of Wood *et al.* (15) with the exception of the cup. The cup used in this investigation was a 100-ml. graduated cylinder having a diameter of 2.6 cm. and cut at the 70-ml. mark to reduce its height.

The shearing stress (F) was calculated utilizing the following equation

$$F = \frac{M}{2 \pi R_b^2 h} \qquad \text{(Eq. 1)}$$

in which M is the torque, R_b is the radius of the spindle, and h is the effective height of the spindle (16). The effective height of the spindle is the actual height plus a correction factor for the end effect of the spindle. The torque is obtained by multiplying the dial reading of the instrument by 6.737. Each unit division of the dial is equal to 6.737 dynes-

cm. for the Brookfield LVT model. The equation for calculating the shearing stress for this instrument is then

$$F = \frac{6.737D}{2 \pi R_b^2 h} \qquad \text{(Eq. 2)}$$

in which D is the dial reading.

The rate of shear (G) was calculated at the wall of the spindle by the following equation

$$G = \frac{2 \omega R_c^2}{R_c^2 - R_b^2} \qquad \text{(Eq. 3)}$$

in which ω is the angular velocity, R_c is the radius of the cup, and R_b is the radius of the spindle (16).

Rheograms could now be prepared by plotting rate of shear in sec.$^{-1}$ *versus* shearing stress in dynes/cm.^{2}. These flow curves would visually describe the flow character and relative viscousness of the liquid. However, a mathematical description of the curve would be more useful.

Plastic Viscosity and Bingham Yield Value.—The rheogram of a Newtonian liquid is a straight line which passes through the origin. The reciprocal of the slope of this line is the coefficient of viscosity in poises. Theoretically, the rheogram for a plastic liquid is a straight line which does not pass through the origin but intercepts the shearing stress axis at zero rate of shear. The reciprocal of this line is the plastic viscosity in poises and the intercept is known as the Bingham yield value in dynes/cm.^{2}. Both parameters, the plastic viscosity and the Bingham yield value, are needed to describe a plastic liquid. In an actual experimental determination the rheogram of a plastic liquid will not be a straight line throughout the whole range of shear rates but will curve toward the origin at the lower rates of shear. This curve is due to an instrumental characteristic. The low angular velocity of the spindle is not great enough to cause the liquid to flow throughout the annular space between the walls of the spindle and cup. The straight line portion of the curve can be projected to the shearing stress axis for the determination of a Bingham yield value, the reciprocal of the straight line being the plastic viscosity. In this study these parameters were calculated from the straight line connecting the two highest shear rates of the rheogram.

Power Law Equations.—Two power law equations have been used to describe the flow curve for non-Newtonian liquids. Equation 4 has been used by a number of investigators (17–19).

$$F^N = \eta' G \qquad \text{(Eq. 4)}$$

Written in logarithmic form the equation is

$$\log G = N \log F - \log \eta' \qquad \text{(Eq. 5)}$$

Equation 6 has also been frequently used (20–22).

$$F = K G^{1/N} \qquad \text{(Eq. 6)}$$

The logarithmic expression for this equation is

$$\log F = 1/N \log G + \log K \qquad \text{(Eq. 7)}$$

While both equations have shearing stress (F) and rate of shear (G) in common, Eq. 4 utilizes the slope (N) of the curve and Eq. 6 uses the reciprocal of the slope ($1/N$). The slope or its reciprocal indicates deviation from Newtonian behavior. The

slope and the reciprocal of the slope are equal to one for Newtonian liquids; $N > 1$ and $1/N < 1$ for pseudoplastic (shear thinning) liquids; $N < 1$ and $1/N > 1$ for dilatant (shear thickening) liquids. The η' in Eq. 4 is the reciprocal of the intercept on the rate of shear axis, while the K in Eq. 6 is the intercept on the shearing stress axis at a rate of shear of 1 sec.$^{-1}$. Therefore, K is the apparent viscosity in poises at a shear rate of 1 sec.$^{-1}$. The relationship between K and η' is given in Eq. 8.

$$\log K = 1/N \log \eta' \qquad \text{(Eq. 8)}$$

Static Yield Value.—Newtonian liquids flow when acted on by any force, however small. Some liquids, other than Newtonian, do not flow until the applied shearing stress exceeds a certain minimum value. This minimum stress necessary to initiate flow is the yield value of the liquid. The present methods of determining yield value either measure the stress at a very low rate of shear or project a stress at zero rate of shear. These methods are referred to as dynamic since the yield value is determined as a result of shearing.

A method of determining static yield value was reported by Levy (23). The advantage of his method is that a different and previously undisturbed region of the liquid is continuously sheared as the Helipath spindle descends into the liquid. The method has the disadvantage in that the instrumental design does not permit the yield value to be expressed in terms of dynes/cm.^{2}. It is also questioned whether the method is static since the spindle was rotated at 6 r.p.m.

It was noticed in the preliminary rheological evaluations of the dispersions made in this study that the pointer of the Brookfield viscometer did not move immediately after the instrument was turned on, even though the dial moved at the designated r.p.m. The pointer started to move only after some stress value was reached as indicated by the dial reading. This condition did not occur when known Newtonian liquids were tested. It was determined that the spindle did not move until the pointer moved, which meant that the liquid was not being sheared. It was reasoned that the liquid prevented the spindle from moving until the strain on the torsion spring of the instrument overcame the yield value of the liquid. It was also determined that the yield value taken at zero rate of shear was independent of the spindle size used.

It was known prior to this investigation that a yield value could be determined directly with a Brookfield viscometer using cylindrical spindles (24). If the liquid has a yield value the pointer will not drift to zero when the motor of the instrument is stopped. Instead, the pointer will drift and come to rest at some position on the dial before reaching zero. The stress equivalent to the dial reading would be the yield value. This yield value, however, would depend on the shear history of the sample even though the yield value was determined at zero rate of shear.

Methodology.—The method used in this study for taking the static yield value consisted of a repeated on-off technique of operating the instrument. The viscometer was turned on at a speed of 0.3 r.p.m. and then off almost immediately. The pointer would remain stationary after the instrument was turned off until the yield value was

exceeded, then it would drift toward zero, stopping at some distance from zero. The last stationary reading taken before the pointer started to drift toward zero was taken as the static yield value.

It was necessary to control the shear history of the samples since the dispersions were time-dependent; that is, at a constant rate of shear the shearing stress decreased with time. All of the rheological evaluations were made 2 days after the preparation of the dispersion unless otherwise specified. The sample was transferred to the cup. The cup was immersed in a water bath and held in place by a clamp. The temperature of the bath was regulated at 25° ± 0.1° by a constant-temperature circulator.[3] After the spindle was immersed in the sample, a period of 30 min. was allowed to elapse before taking the static yield value. Immediately after taking the static yield value, the sample was sheared for exactly 10 min. at each r.p.m. of the instrument starting at the highest r.p.m. The stress was recorded at the end of each 10-min. shearing period. Preliminary investigations of the methodology and instrumentation of the rheological evaluation indicated that results could be satisfactorily duplicated.

Preparation of the Dispersions.—The dispersions of DDAH were prepared in quantities of 900 Gm. The percentages used to express the concentration of the ingredients are by weight. Light mineral oil N.F. which had a specific gravity of 0.8379 and a viscosity of 25 cps. was used as the vehicle. Alcohol U.S.P. which is referred to in this paper as ethanol was used as the polar additive.

Various orders of mixing were investigated to determine the most efficient procedure for dispersing DDAH in light mineral oil. Dispersions containing 1% DDAH and 0.5% ethanol were prepared by each of the following methods.

Method A.—Add the ethanol to a suspension of DDAH in the oil while mixing with the Dispersator.[4]

Method B.—Add the ethanol to the DDAH contained in a beaker and lightly mix with a stirring rod. Add this damp powder to the oil while mixing with the Dispersator.

Method C.—Add the ethanol to the DDAH contained in a beaker and lightly mix with a stirring rod. Add 100 ml. of the oil to the damp powder. Transfer this thick slurry to the remaining oil and mix with the Dispersator.

Method D.—Mix the ethanol intimately with the DDAH in a mortar. Incorporate 100 ml. of the oil with this mass. Transfer this mixture to the remaining oil and mix with the Dispersator.

The mechanical mixing was uniform for all of the above methods. The high viscosity head of the Dispersator was used for 5 min. with a Powerstat setting of 45 which was equivalent to approximately 4500 r.p.m. The use of this head was necessary in order to disperse the large clumps of DDAH resulting from the preliminary mixing in methods *C* and *D*. The Simplex head was then used to shear the dispersion for 10 min. at a full Powerstat setting 120 which was equivalent to approximately 13,000 r.p.m. The sample prepared by method *D* was sheared for an additional 10 min. with the

TABLE II.—RHEOLOGICAL PARAMETERS OF DISPERSIONS PREPARED BY VARIOUS METHODS[a]

Method	Static Yield Value	Bingham Yield Value	Plastic Viscosity	K	1/N
A	None	0.77	0.36	0.57	0.89
B	0.3	3.1	0.39	1.5	0.67
C	2.	6.2	0.79	4.9	0.47
D	3.	12.	1.18	10.	0.39

[a] Spindle No. 2 used to collect data.

Simplex head at the full Powerstat setting. No change in the rheological properties of the sample was detected. No attempt was made to find the minimum time or shearing rate necessary to prepare an equivalent sample. Since method D produced the most viscous sample, this method was used throughout the rest of this investigation.

In order to remove the air entrapped by the mixing, the dispersions were subjected to reduced pressure for 1 hr. at approximately 35 mm. of mercury immediately after their preparation. It was reasoned that some ethanol would be removed in the process of removing the air and it was of interest to determine what effect this alcohol would have on the dispersion if allowed to remain for a longer period of time before evacuating. A 1% DDAH dispersion was prepared using 2% ethanol. Half of this dispersion was subjected to reduced pressure immediately after preparation and a rheological evaluation was made 2, 6, and 8 days after preparation. The other half was subjected to reduced pressure 4 days after preparation and a rheological evaluation made 6 and 8 days after preparation.

Various concentrations of ethanol were used to prepare 1% dispersions of DDAH. The concentrations of ethanol used were 0.25, 0.5, 0.75, 1, 2, and 3%. A sample was also prepared without ethanol.

Dispersions of various concentrations of DDAH were then prepared with ethanol concentrations equal to that of the DDAH and with ethanol concentrations twice that of the DDAH.

RESULTS

Methods of Preparation.—The results of the rheological evaluation of the dispersions which were prepared by the various methods and which contained 1% DDAH and 0.5% ethanol are recorded in Table II. All of the rheological parameters indicate that maximum gellation occurred in the sample prepared by method D.

Although the various methods of preparing the dispersions appear to be similar, it should be emphasized that the principal difference is in the manner of incorporating the ethanol. In method D the ethanol was intimately mixed with the DDAH resulting in a mass that was visibly wet and of a pilular consistency while in methods B and C the mixture was a flowable powder.

In method B the DDAH–ethanol powder was added to all of the oil, while in method C the powder was initially mixed with only a portion of the oil. The greater concentration of ethanol in this preliminary mix of method C is probably the reason

for the greater degree of gellation in the sample prepared by method C as compared to method B.

The least contact of DDAH with ethanol occurred in method A in which the ethanol was added to the mixture of DDAH and the oil. The sample prepared by this method also exhibited the least gellation.

These results seem to substantiate the mechanism of the gelling process proposed by Jordan and co-workers (10–12) in which the polar additive must first effect a separation of the primary particles in order for the oil to penetrate and solvate these particles. The preliminary investigation of these methods of preparing the dispersions indicated that reproducibility could be obtained within an acceptable range of ±10%.

There was no change in any of the five samples of the 1% DDAH dispersion prepared with 2% ethanol during 8 days of storage, regardless of whether the entrapped air was removed immediately after preparation or 4 days after preparation. It was thought that a longer storage period before the air was removed might affect the viscosity of the dispersion. It was possible that some ethanol would be removed in the process of removing the air. A longer storage period before evacuation would mean that the ethanol would be in contact with the DDAH for a longer period of time. Since there were no rheological differences between these samples, it would seem to indicate that the small amount of ethanol lost during the evacuation of the air was too minimal to affect their rheological properties. It is possible that the attraction of DDAH for the ethanol minimized or prevented its removal during the evacuation process.

Rheological Evaluations.—The results of the rheological evaluations of the 1% DDAH dispersions prepared with various concentrations of ethanol are recorded in Table III. All parameters indicate that the dispersion prepared with 1% ethanol was the most viscous. The sample prepared without ethanol does not appear in the table since it had a Newtonian viscosity of 27 cps. which was practically the same as the light mineral oil. Table IV lists the results of the rheological evaluations of the dispersions containing various concentrations of DDAH with ethanol concentrations equal to that of the DDAH and with ethanol concentrations twice that of the DDAH.

Figures 1 and 2 illustrate the flow curves of the dispersions containing various concentrations of DDAH with ethanol concentrations equal to that of the DDAH and with ethanol concentrations

Table III.—RHEOLOGICAL PARAMETERS OF DISPERSIONS[a] PREPARED WITH VARIOUS CONCENTRATIONS OF ETHANOL[b]

% Ethanol	Static Yield Value	Bingham Yield Value	Plastic Viscosity	K	1/N
0.25	2.	7.2	1.05	6.8	0.45
0.50	3.	12.	1.18	10.	0.39
0.75	10.	29.	1.84	21.	0.37
1.00	21.	38.	2.10	29.	0.31
2.00	15.	32.	1.84	26	0.30
3.00	9.	23.	1.71	21.	0.28

[a] One per cent DDAH. [b] Spindle No. 2 used to collect data.

TABLE IV.—RHEOLOGICAL PARAMETERS OF DISPERSIONS PREPARED WITH VARIOUS CONCENTRATIONS OF DIMETHYL DIALKYL AMMONIUM HECTORITE AND ETHANOL[a]

% DDAH	% Ethanol	Static Yield Value	Bingham Yield Value	Plastic Viscosity	K	1/N
1.00	1.00	21.	31.	3.77	25.	0.43
1.00	2.00	15.	30.	2.87	22.	0.42
1.25	1.25	36.	66.	4.83	46.	0.42
1.25	2.50	21.	52.	3.77	41.	0.33
1.50	1.50	61.	84.	10.4	69.	0.42
1.50	3.00	27.	58.	4.83	49.	0.32
1.75	1.75	120.	134.[b]	18.6[b]	102.	0.49
1.75	3.50	38.	60.	6.04	59.	0.28
2.00	4.00	64.	116.	8.45	101.	0.28

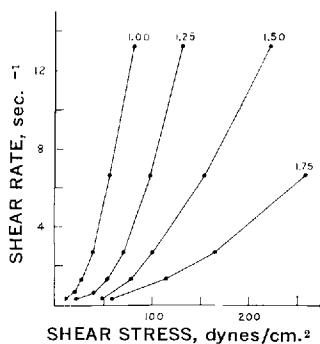[a] Spindle No. 3 used to collect data. [b] Projected value.

Fig. 1.—Rheograms of dispersions prepared with various concentrations of DDAH using an ethanol concentration equal to that of the DDAH.
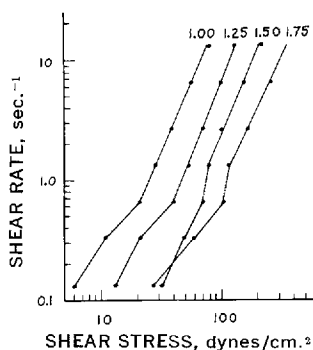

Fig. 3.—Log-log rheograms of dispersions prepared with various concentrations of DDAH using an ethanol concentration equal to that of the DDAH.
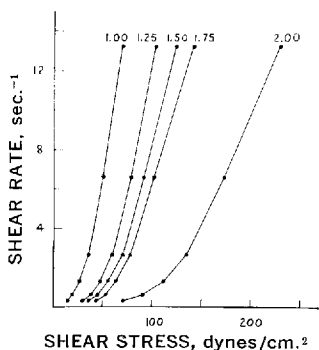

Fig. 2.—Rheograms of dispersions prepared with various concentrations of DDAH using an ethanol concentration twice that of the DDAH.
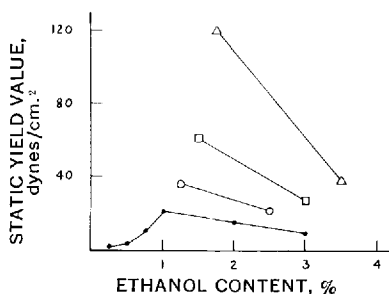

Fig. 4.—Plot of static yield value *vs.* the ethanol content present in dispersions containing various concentrations of DDAH. Key: ●, 1%; O, 1.25%; □, 1.5%; △, 1.75%.

twice that of the DDAH, respectively. The upper portion of the flow curve for the 1.75% DDAH dispersion in Fig. 1 could not be determined because the stress exceeded the upper limits of the instrument for the No. 3 spindle at this high r.p.m. Even though a reading could not be made, the spindle was allowed to revolve at the designated velocity (60 r.p.m.) for the specified time (10 min.) so that the shear history would be the same as the other samples. The upper portion of this curve could be projected on a log-log plot of shear rate *versus* stress (see Fig. 3) to obtain a projected

stress at the rate of shear equivalent to 60 r.p.m. For this reason the plastic viscosity and Bingham yield value given in Table IV for this sample are recorded as projected values.

A 2% DDAH dispersion using 2% ethanol was not prepared since it would have been too viscous to evaluate with the No. 3 spindle. Because of the time-dependency of these systems a comparison could not be made between data collected from two different spindles.

A log-log plot of shear rate *versus* stress for the DDAH dispersions prepared with ethanol concen-
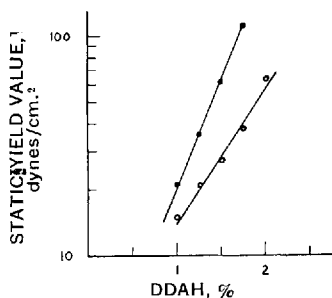
Fig. 5.—Plot of the log static yields value *vs.* the DDAH concentration. Key: ●, dispersions containing an ethanol concentration equal to that of the DDAH; O, dispersions containing an ethanol concentration twice that of the DDAH.

trations equal to the DDAH is presented in Fig. 3. These log-log rheograms are representative of the others encountered in this study and are presented here for the purpose of showing the apparent effect of the static yield value upon them. A straight line relationship was found to exist between log rate of shear and log stress at the higher shear rates but not for the very lowest ones. It is interesting to note that the break in the straight line always occurred near a stress corresponding to the static yield for that particular dispersion. From this observation it is assumed that the straight line relationship between log shear rate and log stress does not exist throughout the whole shear rate range due to interference of the yield value of the dispersion at the low shear rates.

Effect of DDAH and Ethanol Concentrations on the Static Yield Value.—The static yield value of the dispersions containing 1% DDAH and various concentrations of ethanol were plotted against the ethanol concentrations. The results of this plot are presented in the lower portion of Fig. 4. The static yield value increases with an increase in ethanol concentration until a concentration of 1% ethanol is reached. As the concentration of ethanol is further increased a decrease in the static yield value occurs. From these results it is evident that the optimum ethanol concentration for a 1% DDAH dispersion is 1% ethanol which is equal to the concentration of the DDAH.

The static yield value of the dispersions containing various concentrations of DDAH with ethanol concentrations equal to that of the DDAH and with ethanol concentrations twice that of the DDAH are also illustrated in Fig. 4. As can be seen in this figure, the slopes of the lines become greater as the DDAH concentration increases. These slopes represent a decrease in static yield value as the ethanol concentration increases. The slope of each line was determined and the log of the slopes plotted against the DDAH concentrations. This semilog plot produced a straight line represented by the following equation:

$$\log \frac{\Delta Y_s}{E_2 - E_1} = -1.204\ C + \log 0.375 \quad (\text{Eq. } 9)$$

The $\Delta Y_s / E_2 - E_1$ in Eq. 9 is the slope of the lines in Fig. 4 having a negative value; ΔY_s is the decrease in static yield value due to an increase

in the percentage concentration of ethanol from E_2 to E_1; C is the percentage concentration of DDAH.

The log of the static yield value of the dispersions containing various concentrations of DDAH with ethanol concentrations equal to that of the DDAH and with ethanol concentrations twice that of the DDAH were plotted against the percentage concentrations of DDAH. These results, as illustrated in Fig. 5, are represented by the following equation

$$\log Y_s = mC + \log b \quad (\text{Eq. } 10)$$

in which Y_s is the static yield value, m is the slope, b is the intercept on the y axis, and C is the concentration of DDAH. For the dispersions containing an ethanol concentration equal to the DDAH concentration, $m = 1$ and $b = 2$. For the dispersions containing an ethanol concentration twice that of the DDAH concentration, $m = 0.6$ and $b = 3.5$.

The results obtained from the plots in Figs. 4 and 5 indicate the validity of the static yield value as a rheological parameter. Although plots of the other rheological parameters were similar to those in Figs. 4 and 5, they were not so symmetrical and equations were not derived from them. These results also indicate that the ethanol concentration is an important factor in the formulation of a DDAH dispersion and that the optimum amount of ethanol needed to disperse DDAH in light mineral oil is an amount equivalent to the weight of the DDAH.

The dispersion having the highest static yield value would likely be the most effective in suspending insoluble material. However, it would also be impractical as a suspending medium because it would be too viscous to be pourable. Of the dispersions containing an ethanol concentration equivalent to the DDAH concentration, the 1% and 1.25% dispersions could be easily poured from a 2-oz. narrow-mouth bottle having an orifice of 14 mm.

Sedimentation Study.—The effectiveness of the

TABLE V.—SEDIMENTATION RATIO WITH TIME OF VARIOUS DRUGS SUSPENDED IN LIGHT MINERAL OIL

min.	Calcium Carbonate	Zinc Oxide	Ppt. Sulfur	Boric Acid
0	1.00	1.00	1.00	1.00
5	0.96	0.95	0.98	0.35
10	0.94	0.93	0.98	0.27
15	0.92	0.86	0.90	0.23
20	0.90	0.80	0.87	0.23
25	0.88	0.76	0.80	0.22
30	0.86	0.71	0.74	0.22
35	0.86	0.70	0.60	0.22
40	0.84	0.67	0.50	0.22
45	0.83	0.63	0.40	0.21
50	0.82	0.61	0.25	0.21
55	0.81	0.59	0.24	0.21
60	0.80	0.57	0.24	0.21
75	0.78	0.55	0.23	0.21
105	0.76	0.50	0.23	0.21
135	0.74	0.47	0.23	0.21
180	0.73	0.45	0.23	0.21
240	0.71	0.42	0.23	0.21
300	0.71	0.41	0.23	0.21
360	0.71	0.41	0.23	0.21
420	0.71	0.41	0.23	0.21

TABLE VI.—SEDIMENTATION RATIO WITH TIME OF VARIOUS DRUGS SUSPENDED IN LIGHT MINERAL OIL
CONTAINING 1.25% DDAH AND 1.25% ETHANOL

Days	Control	Calcium Carbonate	Boric Acid	Pptd. Sulfur	Zinc Oxide
0	1.00	1.00	1.00	1.00	1.00
1	1.00	1.00	1.00	1.00	1.00
2	1.00	1.00	1.00	1.00	1.00
3	1.00	1.00	1.00	1.00	1.00[a]
6	1.00	1.00	1.00	1.00	0.992
13	1.00[a]	1.00[a]	1.00[a]	1.00[a]	0.984
21	1.00[a]	1.00[a]	1.00[a]	0.992	0.969
24	1.00[a]	1.00[a]	1.00[a]	0.992	0.962
30	1.00[a]	1.00[a]	1.00[a]	0.984	0.954
84	1.00[a]	1.00[a]	1.00[a]	0.977	0.931

[a] A film of light mineral oil, too small to measure, was observed on the surface.

1.25% DDAH–1.25% ethanol dispersion as a suspending medium was determined by comparing the sedimentation rate of various drugs suspended in this medium with the sedimentation rate of drugs suspended in light mineral oil. The drugs used were boric acid, precipitated calcium carbonate, precipitated sulfur, and zinc oxide in 5% w/v concentrations. All were of U.S.P. quality. The suspensions were prepared in a mortar and transferred to 50-ml. glass-stoppered cylinders having an internal diameter of 22 mm. A sample of the DDAH dispersion was also transferred to a cylinder and observed along with the suspensions. The height of the settled phase (H_s) was determined at various intervals of time and compared with the height of the original suspension (H_0). The sedimentation ratio (H_s/H_0) at the various time intervals are given in Table V for the light mineral oil suspensions and Table VI for the suspensions prepared with the DDAH dispersion.

A film of light mineral oil, too small to measure, was observed on the surface of the DDAH suspensions of calcium carbonate, boric acid, and sulfur on the 13th day of aging. At the same time a similar film was noticed on the surface of the DDAH dispersion which served as the control. It is likely that this separation of oil in the DDAH dispersion was due to syneresis. This phenomenon can also be observed in bentonite magma on standing. The fact that this separation occurred in the suspensions of calcium carbonate, boric acid, and sulfur at the same time as the control seems to indicate that syneresis also occurred in these suspensions.

The supernatant liquids of the DDAH suspensions of zinc oxide and sulfur could be measured after the 6th and 21st day, respectively. The supernatant liquids were perfectly clear throughout the 12-week aging period and were obviously light mineral oil. For practical purposes these drugs were considered as settling. However, syneresis cannot be ignored in these suspensions for it is possible that interaction between the DDAH particles and the drugs could occur to increase this effect.

A comparison of the sedimentation rates of boric acid and zinc oxide lends support to the theory that zinc oxide increased the syneresis of the DDAH dispersion. Boric acid settled at a much greater rate than zinc oxide in light mineral oil. Yet when suspended in the DDAH dispersion zinc oxide had a greater apparent rate of sedimentation than

boric acid. A similar comparison can be made with boric acid and sulfur. Boric acid settled faster than sulfur in light mineral oil. However, the apparent sedimentation rate of sulfur was greater than boric acid in the DDAH suspending medium. From these observations it appears that the development of the supernatant liquid in the DDAH suspensions was due, not to the settling of the drugs as normally envisioned, i.e., the insoluble particle falling in the suspending medium due to gravity, but rather the squeezing-out of the light mineral oil as the DDAH gel shrinks.

SUMMARY

The ability of dimethyl dialkyl ammonium hectorite (DDAH) to alter the flow properties of light mineral oil was evaluated for the purpose of preparing an oily suspending medium.

Dispersions of various concentrations of DDAH and ethanol in light mineral oil were prepared and rheologically evaluated by the use of a modified Brookfield viscometer. The optimum amount of ethanol needed to disperse DDAH in the oil was found to be an amount of ethanol equal to the weight of DDAH.

A new method of determining static yield value was found to be reliable. The static yield value (Y_s) in dynes/cm.^{2} was found to be related to the concentration (C) of DDAH as follows:

$$\log Y_s = mC + \log b$$

in which the constants m and b equal 1 and 2, respectively, for dispersions containing an ethanol content equal to the DDAH; and equal to 0.6 and 3.5, respectively, for the dispersions containing an ethanol content twice that of the DDAH.

A dispersion containing 1.25% DDAH and 1.25% ethanol in light mineral oil was used to prepare suspensions with several drugs. It was postulated that the formation of the small amount of supernatant liquid which occurred in these suspensions was due to syneresis rather than sedimentation of the insoluble particles.

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Phytochemical Investigation of *Arctostaphylos columbiana* Piper and *Arctostaphylos patula* Greene (*Ericaceae*)

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Improved methods of extraction and new techniques of isolation and identification of 11 components from the title plants were conducted. A solvent mixture of diverse polarity extracted four polycyclic compounds, a hydrocarbon, two flavonoids, and four phenols. Another phenolic, assumed to be widespread in the family, could not be shown to be present. Antibacterial and antifungal activity was found in the extracts obtained from both plants.

ETHNOBOTANICAL and early medical literature have often cited the usefulness of various *Arctostaphylos* species for a variety of medicinal uses. Members of the genus have been used by the Pacific Northwest Indians. These include their uses as healing poultices and as a curative for severe colds (1), as an eyewash and styptic (2), as a food (3–5), and as smoking tobacco (6). In fact, Reagan (7) reported drunken and erratic behavior of Indians who smoked the leaves of *A. uva-ursi* and stated that it was smoked as a medicine and in religious ceremonies.

The most widely known member of the genus, *A. uva-ursi*, reportedly was used by the early Greeks and Romans (8). Griffith (9), however, stated that DeHaen in the 18th century be given credit for its use as a remedy in kidney and bladder diseases. *A. uva-ursi* was official in the first U.S.P. in 1820, remained in the N.F. until

1946, and still is found in a few proprietary urinary tract remedies.

Previous phytochemical examination of the genus has been mainly restricted to *A. uva-ursi*. Arbutin was isolated in 1852 (10). Rosenthaler (11) isolated methylarbutin in 1927 and Britton and Haslam (12) have very recently identified three galloyl esters of arbutin. Two flavonoid compounds, isoquercitrin (13) and hyperin (14), have also been isolated. Hermann (14) reportedly found "*A. uva-ursi* tannin" to consist of gallic acid, ellagic acid, and glucose, whereas Britton and Haslam (12) have reported the tannin to consist of penta- to hexa-*o*-galloyl-β-D-glucose derivatives. Ibrahim (15) recently identified *o*-pyrocatechuic acid in *A. uva-ursi* as well as in other members of the family. The triterpenoid ursolic acid was first isolated from *A. uva-ursi* (10). The corresponding alcohol, uvaol, was also isolated from this plant (16).

Members of the genus have not been thoroughly investigated for biological activity. *A. uva-ursi* extracts were found to inhibit Ehrlich ascites tumor growth (17). Antibacterial activity has also been exhibited against *B. subtilis*, *E. coli*, and *S. aureus* (18). *A. patula*