TABLE I.—CALCULATED MATERIAL CONSTANTS OF THE PSEUDOPLASTIC AGENTS STUDIED

Suspending Agent	Material Constants K	Material Constants b
Kelcosol	2.7042	−1.4533
Kelmar	2.7271	−1.5443
Kelzan	7.5840	−2.4834
Kelgin	2.2744	−1.6153
Keltone	2.7046	−1.4424
Tragacanth	2.2858	−3.6653
CMC-7 MP	1.4222	−2.1351
Methocel 1500 cps.	1.8363	−2.0426

determined from the intercept, log $1/\eta'$, of the log-log plots (Fig. 2), using the least squares method.

A first-order relationship existed between the apparent viscosity of the pseudoplastics and their concentration (Fig. 4) and may be expressed mathematically

$$\eta' = e^{KC+b} \quad \text{(Eq. 4)}$$

where η' = apparent viscosity, and C = concentration of the suspending agents.

In Eq. 4, b and K are constants depending upon the suspending agent (Table I). The value b can be calculated from the graph as the interception point, while the constant K is the slope. Once K and b are calculated for a suspending agent, then these values are the fixed constants for that particular suspending agent according to the method of viscosity determination. The effect of lot to lot trace chemical variation or processing variation on these constants was not determined. The concentration required to produce the desired apparent viscosity for a material can thus be computed by using the above constants in Eq. 4 or by the standard curve.

SUMMARY AND CONCLUSIONS

Eight pseudoplastic suspending agents, including five alginates, a vegetable gum, and two synthetic cellulose derivatives, were rheologically evaluated. The apparent viscosity was calculated using the equation $F^N = \eta' G$. This equation was expressed in logarithmic form in order to obtain a straight line relationship of shearing stress and shearing rate.

The exponential constant N was calculated using the least squares method, and these values varied from one material to another and were related (zero-order function) to the concentration of each suspending agent studied.

The N values for all of the suspending agents used for this study were greater than 1 and increased with the concentrations of the suspending agent. This further demonstrates the pseudoplastic natures of the suspending agents.

A first-order relationship between apparent viscosity, η', and concentration, C, was exhibited by all of the mucilages prepared for this study, and is expressed as $\eta' = e^{KC+b}$ where K and b are material constants.

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Rheology and Suspension Activity of Pseudoplastic Polymers II

Comparison of Suspension Activity of Pseudoplastic Polymers at Fixed Apparent Viscosities

By SHIVACHANDRA P. KABRE, H. GEORGE DEKAY, and GILBERT S. BANKER

According to a previously described method of expressing the apparent viscosity of pseudoplastic materials and of relating this parameter to concentration, eight pseudoplastic suspending agents were prepared at four levels of apparent viscosity and were studied for their suspension activity for two insoluble drugs (zinc oxide U.S.P. and sulfamethazine U.S.P.). The drug which was compatible with the suspending agents studied was stabilized in the various suspension media at an apparent viscosity of 10 or above. Both insoluble drugs demonstrated an exponential sedimentation rate, while zinc oxide showed a zero order and sulfamethazine an exponential separation rate in the various pseudoplastic suspension media.

A PRECEDING REPORT (1) described a method of characterizing pseudoplastic materials according to calculated values derived from their rheograms. The relationship between the resulting apparent viscosity (pseudoplastic viscosity) and concentration of the suspending agents required to produce that viscosity has also been determined and reduced to a mathematical expression. In this study the suspension activity of

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eight pseudoplastic suspending agents which have been rheologically characterized was studied for two insoluble drugs at four apparent viscosity levels.

EXPERIMENTAL

The formula for the suspension vehicles (mucilages) was:

Concentration of the suspending agent yielding the desired apparent viscosity	(see Table I)
Methylparaben as preservative (in all algins)	1.5 Gm.
(in CMC-7 MP and Methocel 1500 cps.)	0.5 Gm.
Amaranth solution U.S.P.	10 ml.
Distilled water......q.s. to	1000 ml.

The weighed amount of preservative was dissolved in 90% of the final volume of distilled water in a 1-L. beaker, and the concentration of suspending agents required to produce the desired apparent viscosity (Table I) was added. A lightnin mixer was used to mix the preservative solution during the gradual addition of the suspending agent. After formulation of the mucilage, the amaranth solution U.S.P. was added. The dye was used to facilitate the observation of sedimentation and/or separation of the insoluble drugs in these latter studies. The tragacanth and methylcellulose solutions were prepared according to the U.S.P. method.

Two suspensions were prepared, one containing 16% zinc oxide and the other 10% sulfamethazine U.S.P., in the mucilages of each suspending agent at each of the four apparent viscosity levels. The zinc oxide and sulfamethazine suspensions were passed through a Tri-Homo-Disperser[1] at a setting of 0.002 in. to obtain a more uniform particle size of the dispersed solid.

Storage of the Samples.—Separate 100-ml. samples of each suspension product were stored in two glass tubes, 2 cm. in diameter and 45 cm. in length, for the determination of sedimentation and separation. In addition, 100 ml. of each suspension sample was stored in a 4-ounce bottle for the resuspendibility evaluation.

Reproducibility.—The concentrations required to produce the four selected apparent viscosities for each material were determined from the standard curves (1). The measured viscosities of the samples thus prepared were within a range of $\pm 10\%$ of the expected values. The apparent viscosity is dependent on the value *N*, which is the slope of the curve of the log of shearing stress *versus* the log of shearing rate. The apparent viscosity is calculated from the interception point, log $1/\eta'$. The shearing stress-shearing rate curves should be carefully prepared using an adequate number of points, since a slight change in the slope produces a substantially different interception point from which apparent viscosity is calculated.

The apparent viscosity of the mucilages prepared by the hand shaking bottle method in the previous study (1) was initially slightly greater (10 to 15%) than the viscosity of the mucilages prepared using a laboratory propeller mixer in this study. After storage for 2 to 3 days, however, the rheological replication was good (no appreciable difference in apparent viscosity according to the method of preparation). This also indicated that the preservative used had no significant effect on the viscosity, since no preservative was used in the first study.

[1] Tri-Homo Corp., Salem, Mass.

Table I.—Per Cent Concentration of Suspending Agents Used for the Study of Suspension Activity at Four Selected Apparent Viscosities

Suspending Agents	Apparent Viscosity 1	5	10	20
Kelcosol	0.53	0.80	0.90	1.00
Kelmar	0.57	0.82	0.94	1.05
Kelzan	0.33	0.42	0.46	0.50
Kelgin	0.70	1.00	1.15	1.28
Keltone	0.54	0.78	0.89	1.00
Tragacanth	1.60	1.90	2.05	2.17
CMC-7 MP	1.50	2.00	2.20	...
Methocel 1500 cps.	1.10	1.50	1.65	...

RESULTS AND DISCUSSION

Evaluation of Pseudoplastic Suspension Vehicles

In an attempt to evaluate the advantages of more precisely describing the rheology of the pseudoplastic suspension vehicles, the following parameters of the suspension activity of the various systems were determined: (*a*) sedimentation rate, (*b*) separation rate, and (*c*) resuspendibility.

In all preparations containing alginates and CMC, the sulfamethazine separated very rapidly. The sulfamethazine suspensions in alginates and Methocel foamed considerably with processing. Channeling was observed in all of the sulfamethazine suspensions. Coagulation of the zinc oxide was observed in the suspensions in the Kelzan vehicle. The particles of zinc oxide appeared as agglomerates upon visual observation in Kelzan; this phenomenon was also noticed in the zinc oxide–tragacanth preparations with apparent viscosities of 1 and 5. The comprehensive summary of the evaluation of the suspending agents is shown in Table II.

Sedimentation Rate (2).—Sedimentation was observed in all zinc oxide suspension series and in the sulfamethazine suspensions prepared in the Methocel vehicles.

The sedimentation rate can be defined as the accumulation of the solid below the bulk suspension in the form of a dense cake, per unit time.

The sedimentation ratio is defined as the ratio between the sedimented column length and the length of the original total suspension column (diameter of the columns are the same). The observations for sedimentation were made daily for the first week and then weekly for 12 weeks. The sedimentation ratios were calculated using

$$\text{Sedimentation ratio} = \frac{Hs_1}{Ho}$$

where Hs_1 = height of sedimented volume in mm., and Ho = original height of sample column in mm.

The calculated sedimentation ratios were plotted on linear coordinate graph paper *versus* time of

TABLE II.—COMPREHENSIVE SUMMARY OF THE EVALUATION OF SUSPENDING AGENTS

		After 3-Mo. Storage Period				
Suspending Agents	Apparent Viscosity	Sedimentation Ratio	Separation Ratio	Shakes for Resuspension, No.	Appearance[a]	Vehicle Suspendibility[b]
Zinc Oxide Suspensions						
Kelcosol	1	0.0935	0.2569	15	Fair	U
	5	0.0800	0.1444	35	Good	Q
	10	0.0700	0.0475	35	Good	A
	20	0.0549	0.0262	35	Good	A
Kelmar	1	0.0985	0.2433	25	Fair	U
	5	0.0601	0.1445	50	Good	A
	10	0.0268	0.0354	35	Good	A
	20	0.0412	0.0072	35	Good	A
Kelzan	1	0.2394	0.7581	5	Poor	U
	5	0.2581	0.7441	5	Poor	U
	10	0.3431	0.6525	5	Poor	U
	20	0.3651	0.6258	20	Poor	U
Kelgin	1	0.0952	0.2150	30	Poor	U
	5	0.0554	0.0459	80	Good	A
	10	0.0303	0.0303	70	Good	A
	20	0.0093	0.0116	55	Good	A
Keltone	1	0.0926	0.2537	20	Fair	U
	5	0.0750	0.1573	45	Good	A
	10	0.0666	0.0860	55	Good	A
	20	0.0547	0.0642	55	Good	A
Tragacanth	1	0.0000	0.3743	15	Poor	U
	5	0.0000	0.0779	45	Fair	Q
	10	0.0000	0.0318	10	Fair	Q
	20	0.0271	0.0169	10	Good	A
CMC-7 MP	1	0.0227	0.0579	20	Good	Q
	5	0.0160	0.0114	15	Good	A
	10	0.0162	0.0093	15	Good	A
Methocel 1500 cps.	1	0.2185	0.1115	20	Fair	U
	5	0.1649	0.0318	20	Fair	Q
	10	0.0000	0.0314	20	Fair	Q
Sulfamethazine Suspensions						
Kelcosol	1		0.6481	5	Poor	U
	5		0.6482	5	Poor	U
	10		0.6221	5	Poor	U
	20		0.6299	5	Poor	U
Kelmar	1		0.7171	5	Poor	U
	5		0.6254	5	Poor	U
	10		0.6842	5	Poor	U
	20		0.6223	5	Poor	U
Kelzan	1		0.6564	5	Poor	U
	5		0.5772	5	Poor	U
	10		0.5204	5	Poor	U
	20		0.4541	5	Poor	U
Kelgin	1		0.6595	5	Poor	U
	5		0.6053	5	Poor	U
	10		0.5880	5	Poor	U
	20		0.5689	5	Poor	U
Keltone	1		0.6393	5	Poor	U
	5		0.6369	5	Poor	U
	10		0.6332	5	Poor	U
	20		0.6021	5	Poor	U
Tragacanth	1		0.1813	5	Poor	U
	5		0.1278	5	Poor	U
	10		0.0594	5	Poor	Q
	20		0.0272	5	Poor	A
CMC-7 MP	1		0.5551	5	Poor	U
	5		0.2078	5	Poor	U
	10		0.0164	5	Poor	Q
Methocel 1500 cps.	1	0.1484	0.0653	25	Fair	U
	5	0.1826	0.0201	20	Fair	U
	10	0.2075	0.0165	20	Fair	Q

[a] Good: uniform smooth appearing suspension with some separation possible, but no distinct sedimentation. Fair: suspension may be quite stable with slight or no separation and no distinct sediment, but particles appear to be flocculated; products appeared less smooth than those classified as good. Poor: Samples evidenced considerable separation with sediment formation and possible channeling (vertical clear areas) or layering (horizontal clear areas). [b] Vehicle suspendibility indicates the adequacy of each suspension system at a set apparent viscosity to suspend zinc oxide or sulfamethazine satisfactorily. A, Acceptable: product does not sediment or materially separate and is probably of commercial quality. Q, Questionable: product separates and/or sediments to a moderate degree, and the acceptance of the vehicle for drug suspension is doubtful. U, Unacceptable: product separates considerably and/or sediments.

storage. Table II summarizes the sedimentation ratios calculated for all the preparations studied.

Kelzan was a poor suspending agent for zinc oxide and sulfamethazine and demonstrated both channelling and layering, making the measurement of the sediment portion difficult. In tragacanth and Methocel, no sedimentation of zinc oxide was observed during the storage period.

Figure 1 shows the sedimentation rate as a ratio for the zinc oxide suspensions in Keltone observed for a period of 12 weeks. Similar curves of the sedimentation rate were obtained with zinc oxide suspensions in Kelcosol, Kelgin, Kelmar, CMC, and for sulfamethazine in Methocel (Table II). The sedimentation rate decreased exponentially with the time of storage and equilibrated at a sedimentation ratio of about 0.05 at an apparent viscosity of 20 and at a ratio of about 0.09 at an apparent viscosity of 5 (Fig. 1). The sedimentation ratios of zinc oxide in Kelcosol, Kelgin, Kelmar, and CMC at an apparent viscosity of 5 were all approximately twice the ratio values at an apparent viscosity of 20.

Separation Rate.—The measurements of phase separation were made at 1-day intervals for the first week and weekly thereafter for 10 weeks for the sulfamethazine suspensions. With zinc oxide suspensions, the measurements of phase separation were made weekly for 12 weeks. The separation ratios were calculated in the same way as the sedimentation ratio, the only difference being in the definition of the numerator, which is the height of clear separated phase in mm. The calculated separation ratios are shown in Table II.

Separation of Suspensions During the First Week.—The suspensions of zinc oxide did not show noticeable phase separations during the first week, while the majority of the sulfamethazine suspensions showed appreciable separation. The pattern of separation obtained for Kelcosol, Keltone, Kelgin, and Kelmar, corresponding to the fixed apparent viscosities 1, 5, 10, and 20, are exemplified by the Kelcosol data in Fig. 2. Sulfamethazine suspensions in tragacanth and Methocel did not show separation during the first week. The curves indicate an exponential decrease in the separation rate over the period of 7 days.

Separation of Suspensions Over a 10 to 12-Week Period.—The rate of separation of the sulfa-

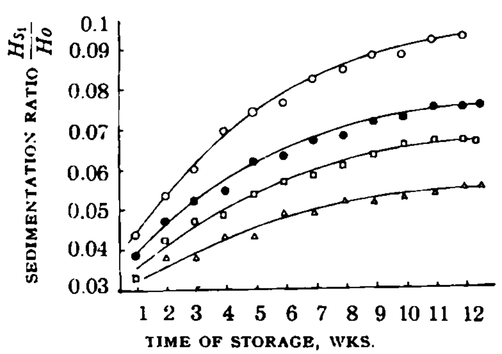

Fig. 1.—Weekly sedimentation rate of zinc oxide suspensions (Keltone as the suspending agent). Key: O, vehicle apparent viscosity, 1; ●, vehicle apparent viscosity, 5; □, vehicle apparent viscosity, 10; Δ, vehicle apparent viscosity, 20.

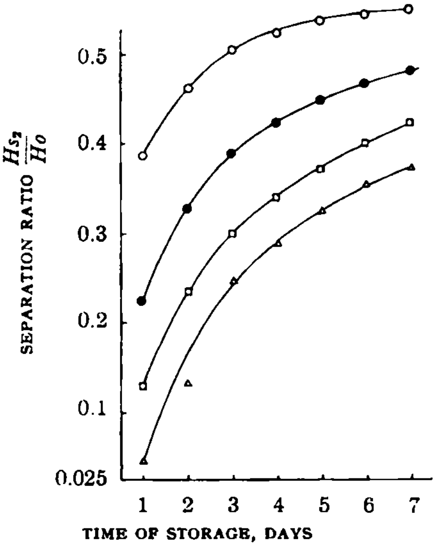

Fig. 2.—Daily separation rate of sulfamethazine suspensions (Kelcosol as the suspending agent). Key: O, vehicle apparent viscosity, 1; ●, vehicle apparent viscosity, 5; □, vehicle apparent viscosity, 10; Δ, vehicle apparent viscosity, 20.

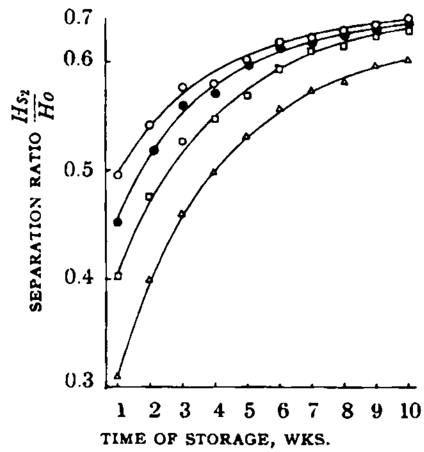

Fig. 3.—Weekly separation rate of sulfamethazine suspensions (Keltone as the suspending agent). Key: O, vehicle apparent viscosity, 1; ●, vehicle apparent viscosity, 5; □, vehicle apparent viscosity, 10; Δ, vehicle apparent viscosity, 20.

methazine suspensions (Fig. 3) was of a different order than that of the zinc oxide suspensions (Fig. 4). The sulfamethazine suspensions separated at an exponential rate, while the zinc oxide suspensions separated at a zero-order rate. All the zinc oxide suspensions separated according to the relationship exemplified by the Kelmar data (Fig. 4), except for the Kelzan system which was incompatible. In the zinc oxide systems, exemplified by Fig. 4, there was a great change in the separation rate as the apparent viscosity changed from 1 to 10, with much less change between 10 and 20. The suspensions having an apparent viscosity of 20 were very stable to separation. They usually sedimented the least; except for the most uniform systems on aging (tragacanth, Methocel, and CMC), they were not the easiest to redisperse (Table

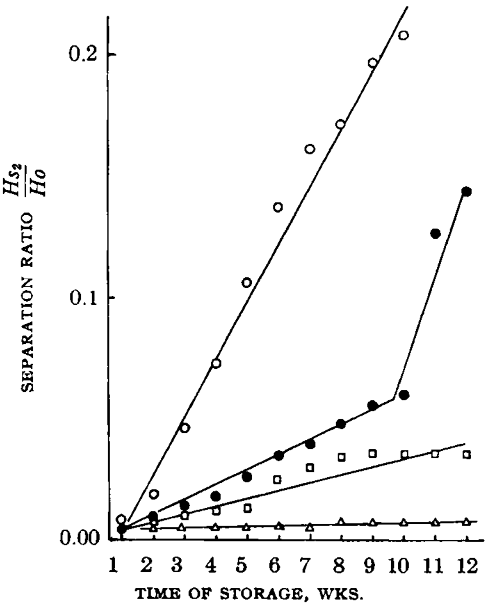

Fig. 4.—Weekly separation rate of zinc oxide suspensions (Kelmar as the suspending agent). Key: O, vehicle apparent viscosity, 1; ●, vehicle apparent viscosity, 5; □, vehicle apparent viscosity, 10; Δ, vehicle apparent viscosity, 20.

II). The resuspendibility of the suspensions was expressed in terms of the number of shakes produced by a mechanical shaker (3) required to resuspend the sediment resulting from a 3-month storage period at room conditions.

The sulfamethazine suspensions separated more rapidly initially and (in general) to a much greater extent than the zinc oxide suspensions, particularly at the higher viscosity levels. However, the zinc oxide suspensions caked, while the sulfamethazine suspensions did not. There are many factors, alone or in combination, which are responsible for dispersed particle behavior in suspension systems. These factors include (*a*) wettability of the insoluble particles, (*b*) electrokinetic properties of the system, (*c*) free surface energy of the system, (*d*) concentration of insoluble material, (*e*) particle size distribution, (*f*) particle interaction, (*g*) flocculation, and (*h*) density of each phase.

The microscopically observed flocculated condition of the sulfamethazine suspensions is probably a major factor in accounting for the difference in the separation and sedimentation behavior between these and the zinc oxide suspensions (which showed no flocculation).

While it is virtually always impossible to make absolute correlations between apparent viscosity and suspension stability due to the complexity of the systems and the numerous physical factors involved, there are advantages to determining apparent viscosity (pseudoplastic viscosity) and the relationship of this parameter to concentration in product development. These advantages include comparing the suspension activity of pseudoplastic polymers at fixed apparent viscosities for any insoluble drug of interest, calculation from the viscosity-concentration relationship of the concentration corresponding to acceptable suspension stability for any extrapolated viscosity value, and better comparisons of vehicle costs based on calculated polymer concentration requirements required to achieve any viscosity level. In addition, certain physical studies of suspension stability would be facilitated by being able to calculate rather precise concentrations of various pseudoplastic polymers to achieve constant apparent viscosity levels.

SUMMARY AND CONCLUSIONS

Pseudoplastic suspension vehicles of natural and synthetic polymeric suspending agents having apparent viscosities of 1, 5, 10, and 20 were used for a study of their suspension activity for zinc oxide and sulfamethazine. The suspension stability was evaluated according to sedimentation and separation rates and resuspendibility. The following conclusions may be made: (*a*) The alginates when used alone are poor suspending agents for sulfamethazine, based on a rapid separation rate. (*b*) The sedimentation rate and separation rate of the sulfamethazine preparations and sedimentation rate of the zinc oxide preparations in this study were exponential. The separation rate of the zinc oxide preparations was zero order. (*c*) The pseudoplastic suspending agents which were compatible with the insoluble materials studied provided adequate particle suspension at an apparent viscosity of 10 and above, according to separation and sedimentation ratio data.

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