lease aspirin tablet was developed. The tablets were evaluated by three methods *in vitro*. Absorption studies were made comparing the salicylate plasma level from the sustained-release tablets with that obtained from the regular commercial aspirin tablets.

The base polyvinyl chloride appears to be non-toxic according to extensive data available. Further *in vivo* evaluation by a double blind technique would be valuable in predicting the clinical efficacy of the developed sustained-release tablet.

## REFERENCES

(1) "Remington's Practice of Pharmacy," 12th ed., Mack Printing Co., Easton, Pa., 1961, p. 499.
(2) Swedish patent 808,014.
(3) Simoons, J. R. A., "Oral Sustained Release Medication," Drukkerij Wed. G. Van Soest N. V., Amsterdam, 1962.
(4) Levy, G., THIS JOURNAL, **50**, 388(1961).
(5) Lazarus, J., and Cooper, J., *ibid.*, **50**, 716(1961).
(6) Teorell, T., *Arch. Intern. Pharmacodyn.*, **57**, 205(1937).
(7) Boxer, G. E., and Jelinek, V. C., *J. Pharmacol. Exptl. Therap.*, **92**, 226(1948).
(8) Swintosky, J. V., Bondi, A., Jr., and Robinson, M. J., THIS JOURNAL, **47**, 753(1958).
(9) Wagner, J. G., *ibid.*, **50**, 359(1960).
(10) Hogben, C. A. M., Shanker, L. S., Tocco, D. J., and Brodie, B. B., *J. Pharmacol. Exptl. Therap.*, **120**, 540(1957).
(11) Truitt, E. B., Jr., and Morgan, A. M., *Toxicol. Appl. Pharmacol.*, **2**, 237(1960).
(12) Weikel, J. H., Jr., and Lish, P. M., *Arch. Intern. Pharmacodyn.*, **119**, 398(1959).
(13) Maney, P. V., and Kuever, R. A., THIS JOURNAL, **30**, 276(1941).
(14) Souder, J. C., and Ellenbogen, W. C., *Drug Stds.*, **26**, 77(1958).
(15) Pankratz, R. E., and Bandelin, F. J., THIS JOURNAL **41**, 267(1952).
(16) Mellon Institute, Special Report "Vinylite" Resin VYNU to Rats (1947).
(17) Trinder, T., *Biochem. J.*, **57**, 30(1954).
(18) Lazarus, J., and Cooper, J., *J. Pharm. Pharmacol.*, **11**, 275(1959).

# Rheology and Suspension Activity of Pseudoplastic Polymers I

## Quantification of Pseudoplastic Viscosity as a Second Order Function of the Rheogram and the Relationship of This Parameter to Concentration

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

**The apparent viscosity (pseudoplastic viscosity) was determined for a number of natural and synthetic gums in aqueous solution, based on flow curves obtained with a multiple point instrument. The power expression $F^N = n'G$ was used to calculate the apparent viscosity from the rheograms. The relationship between the resulting apparent viscosities and the concentrations of the suspending agents studied which were required to produce these viscosities was determined and reduced to the mathematical expression, $n' = e^{KC+b}$, where $n'$ is apparent viscosity, $C$ is concentration, and $K$ and $b$ are material constants. The usefulness of the concentration–apparent viscosity relationship to formulation and product development is discussed.**

Two approaches to the attainment of suspension stability have been discussed recently. Martin and Haines (1) have suggested that controlled flocculation is an approach to the problem of suspension stability, and Samyn (2) suggests that suspensions may be stabilized by preventing phase separation through the careful selection of the rheological properties desired in the suspension media. To achieve this latter goal, Samyn advocated the use of a combination of pseudoplastic and plastic suspending agents in the formulation of suspensions.

A knowledge of the flow properties and rheological parameters of pharmaceutical suspending media is of interest from at least three stand points: (*a*) effect on suspension stability, *i.e.*, ability to retain insoluble particles in a suspended or substantially suspended easily redispersed state; (*b*) effect on the flow, pourability, and measurability of the final product required for pharmaceutical use; and (*c*) effect on process design and methods of manufacture in large scale production.

In practically all industrially made pharmaceutical suspensions, including flocculated systems, suspending agents of some type are used to stabilize the suspension product. The mucilages of natural and synthetic gums, which include a large majority of suspending agents, are pseudoplastic. However, for reasons of convenience, cost, or due to a lack of knowledge of a better approach, these mucilages are very often evaluated in pharmaceutical practice using a single

Received May 16, 1963, from the School of Pharmacy, Purdue University, Lafayette, Ind.
Accepted for publication August 8, 1963.
Abstracted in part from a dissertation by Shivachandra P. Kabre presented to the Graduate School, Purdue University, Lafayette, Ind., August 1962, in partial fulfillment of the Master of Science degree requirements.
Presented to the Scientific Section, A.PH.A., Miami Beach meeting, May 1963.

point viscosity measurement, which essentially treats them as if they were Newtonian.

No part of the rheogram curve for a pseudoplastic is linear, and the viscosity cannot thus be expressed as a single value corresponding to a single point on the curve. The single point determinations for two pseudoplastic materials could nearly coincide, even though rheograms for the materials had markedly different curvatures or even crossed each other at higher shearing rates if plotted as superimpositions. In such cases, depending on where the one point determination was taken, entirely different conclusions might be reached in comparing product viscosities. In practice, at the lower shearing stresses, it is not usually possible to obtain reproducible shearing rates with pseudoplastics and a one point measurement.

The hysteresis effects as reflected in the rheogram, particularly in the downcurve where molecular redisorientation is occurring, can be obtained only with the multipoint instrument. Data of this latter type can be expected to be much more valid in predicting the stability of suspension systems than any one point determination.

The following four rheological properties alone and in combination are of primary importance in determining the stability of suspension systems: (*a*) yield value, (*b*) thixotropy, (*c*) elastic components, and (*d*) the decrease of the proportionality factor of shearing stress/shearing rate, with an increase in the applied shearing stress. The third and fourth listed properties, and sometimes thixotropy, are present in all pseudoplastic materials.

The mathematical representation of pseudoplastic flow has been a serious problem to rheologists. No theoretical equation has been derived from physical concepts, but an empirical power function has been proposed by Porter and Rao (3) to fit the flow curves produced by pseudoplastic materials. Their expression, in the form of more than one constant, is

$$F^N = \eta' \frac{dv}{dy} \qquad \text{(Eq. 1)}$$

where $F$ = shearing stress, $dv/dy$ = velocity

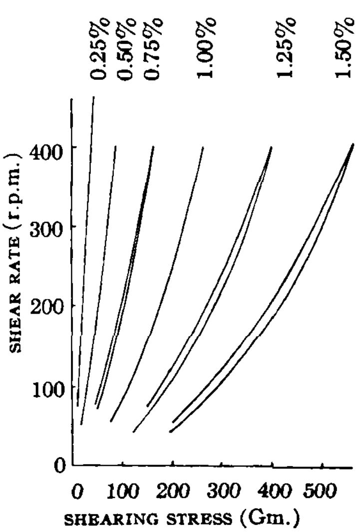


Fig. 1.—Rheograms of Kelcosol mucilages of various concentrations.

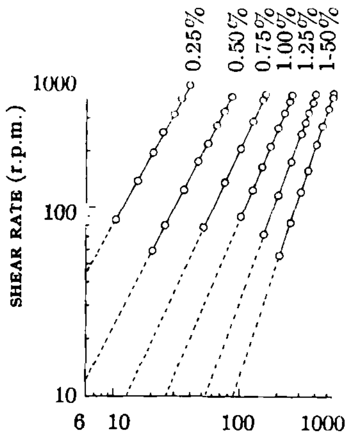


Fig. 2.—Log-log extrapolation of rheograms of Kelcosol mucilages (for calculation of "apparent" viscosity).

gradient per unit area, $N$ = is the constant, and $\eta'$ = is "the apparent viscosity." The apparent viscosity, being different from the coefficient of viscosity, does not have the dimensions of viscosity and is not expressed in poises. $N$ is a characteristic constant which depends on the substance and its concentration and also indicates the structural change.

Farrow, *et al.* (4), studied the rheological behavior of starch paste and found that Newton's law could not be maintained. Their modified equation is

$$F^N = \eta' G \qquad \text{(Eq. 2)}$$

where $G$ = shearing rate. This equation is also written

$$\log G = N \log F + \log 1/\eta' \qquad \text{(Eq. 3)}$$

The above equation gives a straight line where $N$ is the slope, and log $1/\eta'$ is the $Y$ intercept. The value $N$ is considered to be an index which describes the behavior of the liquid. When $N = 1$ the flow is Newtonian, when greater than 1 it is pseudoplastic, and when less than 1 the flow is dilatant.

Work which would define a method of expressing apparent viscosity (pseudoplastic viscosity) and which would permit the establishment of the relationship between the apparent viscosity of pseudoplastic materials and concentration would provide (*a*) a systematic method for calculating the apparent viscosity of various suspending agents used in pharmaceutical preparations, and (*b*) a well planned experimental procedure for the evaluation and comparison of the suspension activity of the various pseudoplastic suspending agents.

## EXPERIMENTAL

**Suspending Agents.**—The following pseudoplastic suspending agents were used for the rheological study: Kelcosol,[1] high viscosity sodium alginate; Kelmar,[1] potassium derivative of alginic acid; Kelzan,[1] microbiological polysaccharide derived from glucose; Kelgin,[1] medium viscosity sodium alginate; Keltone,[1] sodium alginate, calcium tartrate, and sodium phosphate; tragacanth (U.S.P. powdered); CMC-7 MP (sodium carboxymethylcellulose); and Methocel 1500 cps. (methylcellulose). The first five of the materials mentioned

[1] Kelco Co., Los Angeles, Calif.

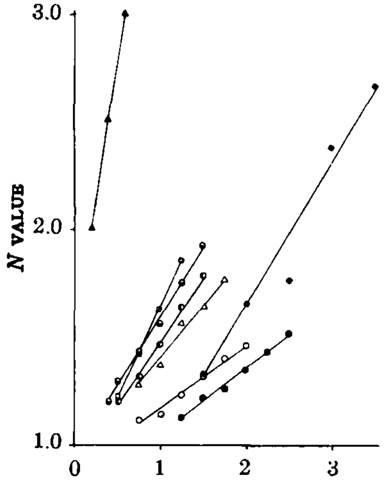


Fig. 3.—Concentration–$N$ value relationship of the various suspending agents. Key: O, Methocel 1500 cps.; ◐, Keltone; ◒, Kelcosol; ●, CMC-7 MP; □, Kelmar; ■, tragacanth; △, Kelgin, and ▲, Kelzan.

above are highly purified derivatives of alginic acid. Tragacanth was selected because it is a U.S.P. natural gum, while CMC-7MP and Methocel 1500 cps. are synthetic gums.

**Preparation of Samples.**—An accurately weighed amount of suspending agent was added to a 4-ounce bottle containing 100 ml. of distilled water, and the bottles were shaken occasionally to produce the mucilages. Six different concentration ranges of the various gums were used to prepare products having approximately the same range in apparent viscosity (0.1 to 480) for each product. The concentration ranges required to produce this viscosity range varied, of course, according to the material used. Preservatives were not added to the mucilages of the suspending agents, and freshly prepared (24-hour-old) samples were used to obtain the initial rheograms.

**Rheological Study.**—The rheology of the mucilages was studied utilizing a modified Stormer viscometer (5) in which the bob or inner cylinder rotated, and the cup containing the sample remained stationary. A constant temperature water bath maintained the sample temperature at 25 ± 0.1°. The cup and solid aluminum bob were calibrated with N.B.S. standard viscosity oils (6). The sample of the mucilage or the suspension was placed in the cup and deaerated by gentle suction. The cup and bob were mounted in the viscometer making certain that no air was entrapped within the sample. The sample was allowed to remain undisturbed for 90 minutes before beginning a run. The rheograms were obtained by adding successively increasing weights to the hanger. A point on the curve was obtained by noting the time required for a given weight to drive the bob through 100 revolutions. This value was converted to revolutions per minute. When a maximum of 380 to 410 r.p.m. was reached, the weights on the hanger were reduced in the same order in which they were increased. An interval of 60 seconds was allowed to elapse between each observation. The data for the downcurve obtained from the above runs were plotted with the shearing stress *versus* shearing rate on log-log paper in instrumental units (grams *versus* revolutions per minute).

Assuming a suspension product can be converted to a substantially uniform dispersion by shaking or agitation, the subsequent stability of the product reflected by any change in uniformity of dispersion would depend on the rate and degree of redisorientation of the molecules of the suspension media. Therefore, we would be more interested in redisorientation rheology than orientation rheology from a suspension stability standpoint and any subsequent attempts to relate apparent viscosity and suspension activity. The downcurve of a rheogram represents the redisorientation and the upcurve the orientation of the molecules in the suspension system, and thus in this experiment downcurves were used for the calculation of apparent viscosity. To determine product "pourability," the upcurve would, of course, be of more significance.

## RESULTS AND DISCUSSION

The rheological data obtained with the modified Stormer viscometer were plotted as rheograms of shearing stress (Gm.) *versus* shearing rate (r.p.m.). Characteristic flow curves of one of the alginate suspending agents (Kelcosol) are shown in Fig. 1. In this study a modified Newton's equation (Eq. 3) was used for the calculation of the apparent viscosity of pseudoplastic flow. The rheological data, which were obtained, were plotted on log-log paper for various percentages of suspending agents (Fig. 2). The slopes of the straight lines (Fig. 2) are $N$ and were calculated using the least squares method for each concentration of the suspending agent. The exponential constant (index) $N$ increased as the concentration of the suspending agent increased and was always greater than 1. The relationship between $N$ and concentration (Fig. 3) was a zero-order function for all of the materials studied except tragacanth.

The apparent viscosity, $\eta'$, of each material was

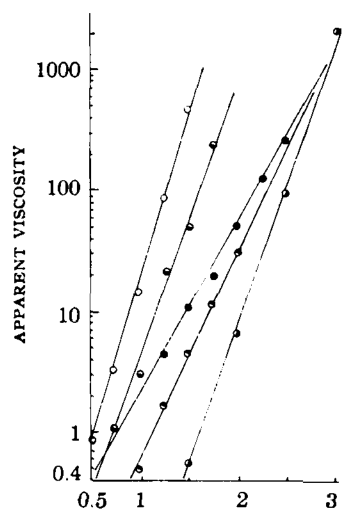


Fig. 4.—Apparent viscosity–concentration relationship. Key: O, Kelcosol; ◒, Kelgin; ●, CMC-7 MP; ◓, Methocel 1500 cps.; and ◑, tragacanth.

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

| Suspending Agent | Material Constants *K* | *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

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

where $\eta'$ = 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, $\eta'$, 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.

## REFERENCES

(1) Haines, B. A., and Martin, A. N., THIS JOURNAL, 50, 228, 753(1961).
(2) Samyn, J. C., *ibid.*, 50, 517(1961).
(3) Porter, A. W., and Rao, P. A. M., *Trans. Faraday Soc.*, 23, 311(1927).
(4) Farrow, F., Lowe, G., and Neale, S., *J. Textile Inst.*, 19, T18(1928).
(5) Fischer, E. K., "Colloidal Dispersions," John Wiley and Sons, Inc., New York, N. Y., 1950, pp. 159–168.
(6) Boylan, J. C., DeKay, H. G., and Banker, G. S., THIS JOURNAL, 51, 742(1962).

# 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

Received June 3, 1963, from the School of Pharmacy, Purdue University, Lafayette, Ind.
Accepted for publication August 8, 1963.
Abstracted in part from a dissertation presented by Shivachandra P. Kabre to the Graduate School, Purdue University, in partial fulfillment of Master of Science degree requirements.
Presented to the Scientific Section, A.PH.A., Miami Beach meeting, May 1963.