

Rheology of Thixotropic Montmorillonite Dispersions II

Kinetics of Structural Recovery

By GERHARD LEVY

Methodology has been developed to study the kinetics of the structural recovery (build-up) of thixotropic montmorillonite dispersions. The recovery process can be described by means of a coefficient of thixotropic recovery with time, R . Thus: $R = (T_2 - T_1) / (\log t_2 - \log t_1)$, where T_2 and T_1 are the torques necessary to overcome the resistance encountered by a special spindle which is simultaneously rotated and lowered into the dispersion at times t_2 and t_1 , respectively, after breakdown of structure by agitation. The effects of aging, concentration, method of preparation (hot process, cold process, ultrasonic treatment), and addition of polysorbate 80, zinc oxide, or glycerin upon structural strength (static yield value) and coefficient of thixotropic recovery have been determined.

THE USEFULNESS of thixotropic systems in pharmacy is based upon their ready conversion from a rigid gel to a fluid sol upon shaking or shearing, and their reversion to the gel state when shaking or shearing is discontinued. The sol to gel transformation or structural recovery is not instantaneous since the particles in random motion are required to approach one another from the proper direction and to overcome an energy barrier before interparticle association can occur. The structural recovery rate of thixotropic systems is probably the most important variable with respect to their pharmaceutical usefulness. For example, if recovery occurs too quickly, thixotropic suspensions will not remain fluid for a sufficient time after agitation to permit pouring. On the other hand, if the time required for structural recovery is too long, the suspended particles will descend to the bottom of the container instead of becoming immobilized within a structural network. This would result in a "stabilized sediment" rather than a well-dispersed, physically stable suspension.

The lack of investigation by pharmaceutical scientists of this important aspect of the rheology of thixotropic systems may be due partly to the long-prevailing misconception regarding the significance of the conventional yield value (1). Usually defined as the minimum tangential force necessary to initiate flow, it has been determined in dynamic systems rather than in static or nonflowing systems. The conventional definition of the term as well as the method

used to measure it imply that the yield value remains the same regardless of the amount of shear to which the thixotropic system is subjected. Thus, there would be no reason to assume that yield value will decrease upon shearing and increase during rest, and any logical basis for studying structural recovery rates would be nonexistent.

Redefinition of the conventional yield value as dynamic yield value (which is considered to be indicative of the energy input required to prevent structure reformation), and postulation of a static yield value as the tangential force necessary to break structure to the point of initiating flow (1), provide a logical foundation for a study of thixotropic recovery rates.

Determinations of thixotropic recovery rates require repeated measurements of static yield value in a resting system as a function of resting time. In the early studies of thixotropic phenomena, the so-called "inverted tube method" was most commonly used to determine gelation or setting time (2), and the reciprocal of this value was taken as the rate of gelation (3).

The setting time of a thixotropic system was defined as the time between liquefaction, by mechanical action, and its resetting upon standing at rest. A sample, kept in a test tube, was considered to have set if it did not flow within a minute or so upon turning the tube upside down (4). Apart from various technical difficulties such as the need for a standardized inversion procedure (5), it was soon realized that the setting time is just an arbitrary point on the gel-strength vs. time curve, and that it does not reflect any sudden change in slope or other unique characteristic of such a curve (3, 6). It was also found that the diameter

Received March 22, 1962, from the University of Buffalo School of Pharmacy, Buffalo 14, N. Y.

Accepted for publication May 31, 1962.

Presented to the Scientific Section, A.Ph.A., Las Vegas meeting, March 1962.

The author acknowledges the technical assistance of J. M. Rutowski.

of the tube had a very large effect on setting time. For example, a bentonite dispersion with a setting time of 30 seconds in a tube of 13 mm. diameter, exhibited a setting time of over 3 hours in a tube having a diameter of 40 mm. (2). The container wall apparently has an organizing effect upon the clay particles, as has been suggested by Houwink (7). This wall effect also limits the usefulness of the standard rotational viscometers for the determination of thixotropic recovery rates, although several investigators have used such instruments to determine what is here defined as static yield value as a function of resting time (8, 9). Evidently these workers did not consider the effect of annular diameter upon thixotropic recovery rate or they felt that this factor was not important relative to the objective of their studies. For pharmaceutical purposes, however, it is desirable to obtain a realistic indication of recovery rates of the material under study when contained in vessels of relatively large diameter. Data to be presented here indicate that recovery rates under these conditions differ by several orders of magnitude from those in which the thixotropic material was situated within a narrow annular space.

A new methodology to determine thixotropic recovery rates, which permits measurements in containers of relatively large diameter where recovery rates become essentially independent of vessel diameter, has been developed for this study. It has also been possible to follow the change in static yield values over long periods of time since the thixotropic material could be stored in regular containers until and during the time of measurement. Apart from a description of the method, this communication deals with a mathematical characterization of the thixotropic recovery process, and a survey of the effect of different preparatory procedures and additives on the static yield value and thixotropic recovery rate of aqueous dispersions of magnesium aluminum silicate (MAS), a representative clay of the montmorillonite group.

EXPERIMENTAL

Preparation of Dispersions.—Dispersions, 3% w/w, of colloidal magnesium aluminum silicate (Veegum)¹ were prepared by adding 15 Gm. of the clay to 485 ml. of distilled water and mixing these vigorously for 3 minutes in an Arnold automatic mixer, model No. 15. The individual portions were combined and agitated with a Brookfield counter-

rotating mixer in a 2-gal. beaker at a rheostat setting of 80 for 5 minutes, followed by 25 minutes of agitation at a rheostat setting of 50. The dispersion then was weighed and water lost by evaporation was replaced.

Dispersions of 4, 3.5, and 2.5% concentration were prepared in the same manner as the 3.0% dispersion, except for the necessary changes in amounts of the clay and water.

For dispersions prepared by the "hot" process, the MAS was dispersed in water previously heated to 80°, while water at room temperature was used in the "cold" process. For ultrasonic treatment, 200-ml. portions of dispersion were cooled to 15° and insonated in a General Electric ultrasonic generator, model G 3, at a frequency of 750 kc./sec. for 5 minutes. The temperature of the dispersions did not rise above 25° during insonation. The individual portions of dispersion were subsequently combined. Dispersions containing zinc oxide were prepared in the usual manner, but the zinc oxide was incorporated just 3 days before rheologic measurement, *i.e.*, 9.5 weeks after preparation of the plain dispersion. The zinc oxide was passed through a 60-mesh sieve prior to use.

Polysorbate 80 was added either to the completed dispersion immediately after preparation or it was dissolved in the water prior to addition of the clay.

Glycerin-containing dispersions were prepared by dispersing MAS in water in the usual manner, and adding glycerin just 3 days prior to rheologic measurement, *i.e.*, after 9.5 weeks of aging the plain dispersions.

All dispersions were stored in 8-oz. glass jars (5.5 cm. diameter, 13 cm. height) at room temperature ($24 \pm 2^\circ$). With the exception of the aging experiment (Fig. 3), the dispersions were aged for 10 weeks prior to rheologic evaluation.

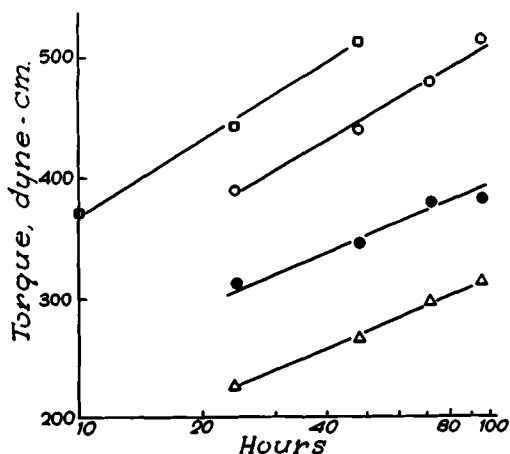


Fig. 1.—Effect of age on static yield value and thixotropic recovery rate of 3.0% MAS dispersions. Δ, 2 Weeks; □, 6 weeks; ○, 11 weeks; ■, 17 weeks.

Instrumentation and Methodology.—The Brookfield Synchro Lectric viscometer, model LVT, mounted on a Brookfield Helipath stand, was used. The spring tension (torque) of the instrument is 673 dyne-cm. at full scale, with a linear relation between

¹ Manufactured by R. T. Vanderbilt Co., New York, N. Y.

scale readings. A No. 5 Helipath spindle, consisting of a 11.4-cm. long stem having a diameter of 0.16 cm. with a 3.6-cm. long, 0.07-cm. diameter crossbar, 0.6 cm. from the end, was used for the measurements. This spindle was rotated at 6 r.p.m. while the platform of the Helipath stand descended at a rate of 2.2 cm. per min. Consequently, the crossbar of the spindle passed through the system being measured in a helical path, continuously contacting a different and previously undisturbed region.

A jar containing 200 ml. of the dispersion was opened carefully in a manner which avoided jarring, and placed on a micro Lab-Jack beneath the viscometer. The instrument was lowered manually until the crossbar of the spindle just touched the dispersion. The Lab-Jack was then raised 1 cm., so that the crossbar was immersed in the dispersion to that distance. Both viscometer and Helipath stand were then switched on, and torque readings were taken at every revolution of the spindle for a total of 16 revolutions. At no time was the spindle stopped or the torque indicator clutch engaged during the period of measurement. The 4th to the 13th readings were averaged and are reported here. Thus, the data represent the structural strength found in the body of the dispersion rather than that found close to the surface or bottom.

To determine structural recovery rate, jars containing the dispersion were placed on a reciprocating shaker with a shaking excursion of 3.8 cm., and shaken at 280 oscillations per min. for exactly 1 minute. The jars then were stored and left undisturbed until time of measurement. Five jars were used at each measurement period, and their average individual readings were averaged to yield the experimental values for the torque *vs.* time plots reported here.

RESULTS AND DISCUSSION

The method used for the determination of structural strength satisfies the requirement for measurement of undisturbed structure, since the crossbar of the inverted *T* spindle continuously encounters a new region as the spindle descends in the dispersion. The structural resistance met by the spindle is indicated continuously by the instrument pointer in terms of scale units, which can be changed to conventional torque units. The instrumental design does not, however, permit this value to be expressed in terms of dynes/cm.². Thus, the static yield value determined by the instrument cannot be expressed in conventional units, but this presents no undue disadvantage with respect to the present studies. Since the dispersion can be measured in the container in which it is stored, it is possible to utilize a large number of samples at all time intervals without inconvenience. The reproducibility of the method is high, as indicated by the data shown in Table I, which were selected at random from the total tabulation of experimental results. It is desirable that the rate of application of force by the spindle be high compared with the relaxation time of the system. Reference to the relaxation time of a MAS suspension reported by McVean and Mattocks (10) indicates that this is the case. While it usually is desirable to carry out rate studies at constant temperature, the present studies were

TABLE I.—STATIC YIELD VALUE^a OF A 3% MAS DISPERSION^b AT 4 HOURS

Jar No.	Average	Range
1	28.64	28.6–28.7
2	28.40	All readings identical
3	28.79	28.6–29.0
4	28.90	All readings identical
5	29.84	29.8–29.9
Overall	28.9	28.6–29.9

^a Expressed in instrument scale units. ^b Ten weeks old, prepared by the "hot" method.

made at room temperature since storage of the jars in an oven or water bath would subject the dispersions to vibration and motion. It is known that oscillations and similar slight motion can increase the recovery rate of bentonite dispersions as much as several hundredfold (5), so that it is important not to expose the dispersions to such effects. The usual ambient temperature fluctuations ($\pm 2^\circ$) did not have a significant effect on the recovery rates of MAS dispersions.

Kinetics of Structural Recovery.—It was found that a linear relationship exists between static yield value of MAS dispersions and the logarithm of resting time (Fig. 2). This linear relationship can be expressed as

$$T = \frac{T_2 - T_1}{\log t_2 - \log t_1} \log t + \text{constant} \quad (\text{Eq. 1})$$

where *T* is the torque on the spindle at time *t*, *T*₁ the torque at time *t*₁, and *T*₂ the torque at time *t*₂. The structural recovery rate, therefore, is reflected by a coefficient of thixotropic recovery with time, *R*, which can be defined as

$$R = \frac{T_2 - T_1}{\log t_2 - \log t_1} \quad (\text{Eq. 2})$$

and is the slope of the line which correlates torque and logarithm of resting time. Differentiation of Eq. 1 yields

$$R' = \frac{dT}{dt} \cdot t \quad (\text{Eq. 3})$$

where

$$R' = 0.434 R \quad (\text{Eq. 4})$$

From Eq. 3 it is evident that the rate of change of torque is inversely proportional to the time and that *R'* is the proportionality constant.

The definition of *R* in the above equations is identical with that of Chong and co-workers for a coefficient of increased resistance to shear with time, as applied to the increase in yield value with shearing time of antithixotropic systems (11). Thus it is possible to express the rate of structure formation in thixotropic systems at rest and in antithixotropic systems during shear by means of the same coefficient *R*. This lends added justification to the term "antithixotropy" as applied by Chong, *et al.*

It would seem reasonable to assume that the structural recovery process ceases after a certain maximum static yield value is attained. The maximum was not reached in the present studies during periods considerably longer than 100 hours. Measurements over even longer periods of time are com-

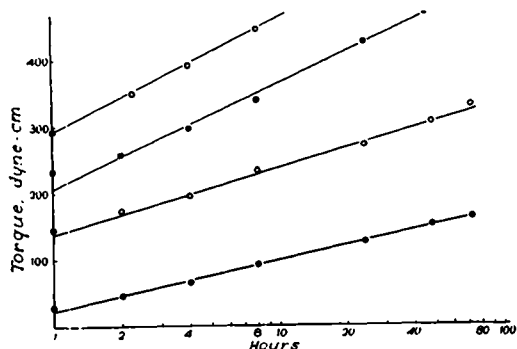


Fig. 2.—Structural recovery of aqueous dispersions of MAS. ●, 2.5%; ○, 3.0%; ■, 3.5%; □, 4.0% w/w.

pliated by the superimposed irreversible rheological changes due to aging, as described in the previous paper (1), which begin to overshadow and distort the now very small changes due to structural recovery. It has also been found that the initial stage of the thixotropic recovery process does not follow the kinetic scheme described. Reference to Figs. 2 and 3 will show that 1-hr. values were occasionally higher than theoretically indicated. Ten-minute values, not reported here, were always much higher than indicated by extrapolation of the straight line. This suggests that structural buildup occurs in two consecutive processes, analogous in part to von Smoluchowski's theory of fast and slow flocculation, for which assumption considerable evidence is available. Hauser and Reed have observed the structural build-up of bentonite dispersions with the ultramicroscope and have found that individual particles first form clusters which subsequently join together to form a continuous network throughout the dispersion (5). This two-step sequence has been observed also in other types of thixotropic dispersions. For example, Voet has found that structure formation in a dispersion of channel black in mineral oil occurred by association (formation of aggregates) followed by reticulation (interlinking of aggregates into a continuous network) (12). The data of Braune and Richter (8) also indicate that the initial rate of structural recovery of bentonite dispersions is higher than the rate in the subsequent

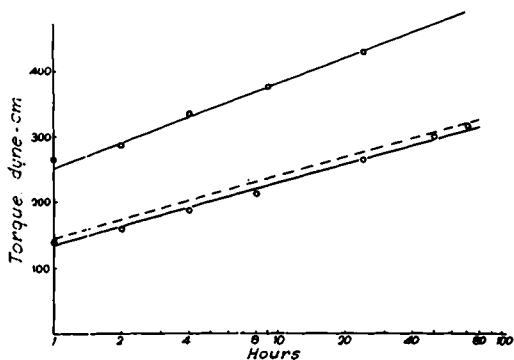


Fig. 3.—Effect of glycerin on static yield value and thixotropic recovery rate of 3% MAS dispersions. - - -, No glycerin; ○, 10% glycerin; □, 30% glycerin.

period. While the present studies deal with the kinetic aspects of structural recovery of MAS dispersions after the first hour of rest, the kinetics of the initial recovery process are currently under investigation and will be dealt with in a subsequent communication.

Effect of Concentration on Structural Recovery Rate.—Figure 4 shows that the logarithm of the coefficient of thixotropic recovery (R) is related linearly to the logarithm of MAS concentration. This relationship takes the form

$$\log R = a \log c + \log K \quad (\text{Eq. 5})$$

where c is the concentration of MAS, and a and K are constants. From the slope of the line fitted to the experimental data by the method of least squares, $a = 1.9$. It appears therefore, that

$$R = Kc^2 \quad (\text{Eq. 6})$$

since the experimental line deviates only slightly from a slope of 2.

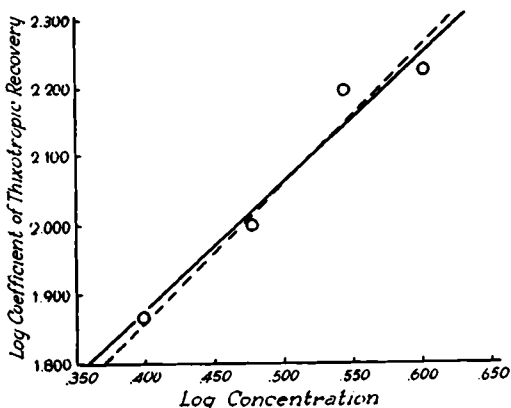


Fig. 4.—Effect of concentration on the coefficient of thixotropic recovery of aqueous dispersions of MAS. —, Fitted line; - - -, line with slope 2.

Effect of Aging.—Figure 1 shows the effect of aging on the recovery rate of 3% MAS dispersions prepared by the "hot" method. Both the recovery rate as well as the static yield value at any time during the measurement period increase as the dispersions age. Structural equilibrium had not been reached even after 17 weeks. The magnitude of the rheological changes on aging are, of course, related to the method of preparation of the MAS dispersions, particularly to the duration and intensity of shear to which the dispersions are exposed. The data presented in Fig. 1 were obtained from dispersions prepared from a different lot of MAS than was used in all other experiments reported here. Consequently, the line representing the structural recovery rate of a 10-wk. old dispersion shown in Fig. 2 does not "fit" into the plot and is closer to the 6-wk. line than to the 11-wk. line. This apparent discrepancy is not unusual since it is known that great lot-to-lot variations occur even in a relatively well-defined clay such as the type of MAS used in this study. The data of Samyn, for example, show a more than twofold difference in apparent viscosity between different lots of MAS hydrated for an equal length of time (13).

Method of Preparation.—No attempt has been made to study the effect of numerous manufacturing variables on MAS dispersions, since these have been described by Wood and co-workers (14) and by Simon and co-workers (15). In this study the structural recovery of MAS dispersions prepared by the "hot" method was compared with the recovery of MAS dispersions prepared by the "cold" method, in order to verify the surprisingly small effect of temperature noted in the first part of this investigation (1). The magnitude of the temperature effect again was found to be small (Fig. 5), which is in agreement with our previous results and also with the data reported by Vogt (16). The effect of ultrasonic waves on montmorillonite dispersions had not been studied by the authors cited previously (14, 15) and was, therefore, investigated. Cavitation heating of the dispersions was minimized by precooling and limiting the insonation period to 5 minutes in order to separate the possible temperature effect from the effect due to ultrasonic waves. The results show that ultrasonic treatment can increase the structural strength of MAS, probably due to greater dissociation of face-to-face particle aggregates (Fig. 5). Since the conditions of insonation were chosen arbitrarily, the results should be interpreted only in a qualitative manner.

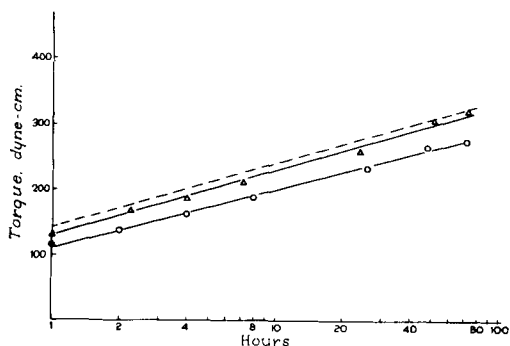


Fig. 5.—Effect of method of preparation on static yield value and thixotropic recovery rate of 3.0% MAS dispersions. O, "Cold" process; Δ , "cold" process and ultrasonic treatment; - - -, "hot" process.

Effect of Additives.—The effect of glycerin on the structural recovery rate and static yield value of MAS dispersions is shown in Fig. 3. In order not to superimpose a possible aging effect, glycerin was added to the MAS dispersions only 3 days prior to measurement, *i.e.*, after 9.5 weeks of aging. Glycerin had no significant effect at a concentration of 10%, but in the presence of 30% glycerin, both recovery rate and static yield value were considerably increased. Since the viscosity of a 30% aqueous glycerin solution is about 2.5 times higher than the viscosity of pure water, it was thought that the structural recovery rate would be lowered by glycerin due to the decreased mobility of dispersed MAS particles in a medium of higher viscosity. Such was not the case and the data suggest an increase in interparticle forces which may overshadow the viscosity effect. It is known that glycerin adsorbs on montmorillonites even from dilute aqueous solutions (17), and it has been suggested recently that the glycerin-bentonite structure differs from

the structure of bentonite in water (18). Unfortunately, details of the latter study are not yet available and cannot be considered at this time.

It was of interest to study the effect of polysorbate 80 on MAS dispersions by the present method in view of the profound effect of this surfactant on the nature of the classical rheogram as noted in the first part of this investigation (1). Figure 6 shows the increased recovery rate and static yield value of MAS dispersions upon addition of 0.1% polysorbate 80. The increase in static yield value reflected by increased torques on the inverted T spindle parallels the increase in static yield value as determined with the standard rotational viscometer (1). The higher recovery rate of the dispersions containing the surfactant explains why rheograms of these dispersions had smaller thixotropic areas (1). In order to establish whether the surfactant effect could be enhanced by adding this agent to the medium prior to dispersion of the clay, dispersions of MAS were prepared to which polysorbate 80 was added, either before or after preparation. The more consistent data obtained from dispersions to which the surfactant had been added prior to MAS suggest that such dispersions are more homogeneous with respect to polysorbate 80. The results do not suggest, however, that lowering of interfacial tension during the mechanical dispersion process results in significantly greater lattice expansion or dissociation of face-to-face particle aggregates than lowering of interfacial tension subsequent to preparation of the dispersions.

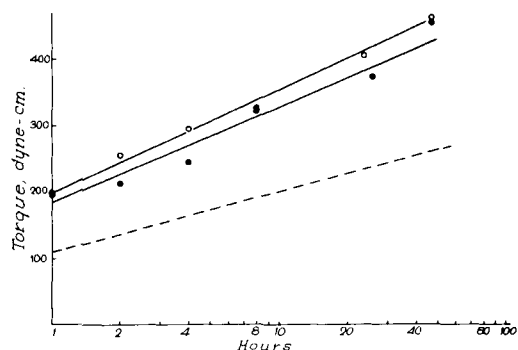


Fig. 6.—Effect of polysorbate 80 on static yield value and thixotropic recovery rate of 3% MAS suspensions. - - -, Prepared by the "cold" method without polysorbate 80; \bullet , 0.1% polysorbate 80 added after preparation; O, 0.1% polysorbate 80 added before preparation.

The addition of 10% zinc oxide greatly increased the static yield value of a 2.5% MAS dispersion and also increased the recovery rate (Fig. 7). The difference in static yield value is tenfold at 1 hour, and about threefold in 50 hours.² Zinc oxide particles are evidently capable of participating in the scaffolding structure of MAS particles in dispersion. While a possible zinc ion effect due to ion exchange cannot be excluded, it was minimized by incorporat-

² It must be realized that recovery rate is measured in terms of absolute increase in torque units per unit of time rather than in relative terms. Thus, a dispersion having a low initial static yield value and a low coefficient of thixotropic recovery can exhibit, nevertheless, a greater relative increase in static yield value with time than a dispersion with a higher initial static yield value as well as a higher coefficient of thixotropic recovery.

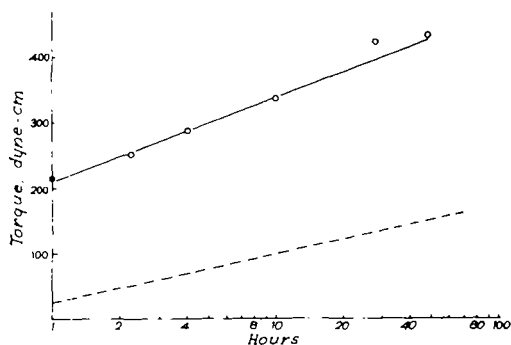


Fig. 7.--Effect of zinc oxide on static yield value and thixotropic recovery rate of 2.5% MAS dispersions. ---, Plain suspension; O, with 10% zinc oxide.

ing zinc oxide in the aged MAS dispersions only 3 days prior to measurement. The results of this experiment may explain the lack of correlation between certain rheological properties of dispersions of two clays, bentonite and activated attapulgite, and their ability to suspend zinc oxide. Foerzler and co-workers indicate that the suspending ability of these dispersions, as reflected by the sedimentation velocity of zinc oxide, is directly related to the thixotropic area of the clay dispersion without zinc oxide (19). Wood could show subsequently, using the same data, that a similar or better correlation seems to exist between the sedimentation velocity and the reciprocal of yield value (20). Regardless of the treatment of the experimental data, however, the two clays yielded different proportionality constants and, thus, no absolute relationship of yield value or thixotropic area and suspending ability could be shown. While this may be due in part

to differences in plastic viscosity as well as recovery rate of the two clays (a variable not considered in the experimental design), it is apparent from the present data that the static yield value of a pure clay dispersion differs greatly from the static yield value of a dispersion containing zinc oxide. Any attempt to correlate rheologic parameters with suspending ability should be based on the rheologic values of the final suspension, and not on those of the pure dispersion containing only the suspending agent.

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Automated Dissolution Rate Studies of Capsules and Tablets

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Automation of dissolution studies of solid dosage forms has been achieved through the use of a timer-controlled sampling and dilution system which automatically removes filtered samples from the dissolution apparatus, makes reproducible dilutions, and records the absorption of the diluted sample as a function of time. The U.S.P. tablet disintegration apparatus was employed to provide constant, reproducible agitation. Versatility and reliability of the apparatus has been demonstrated by comparing automated dissolution rate results with values obtained by independent, manual analyses. Design requirements and specifications of individual components have been discussed in detail so that other functionally equivalent units may be employed to achieve comparable results with those reported in this study.

DISSOLUTION characteristics of solid dosage forms such as tablets or capsules may be determined by agitating the dosage form in a suitable fluid and periodically assaying the solution for drug content. Reproducible agitation is essential to the test. Widespread avail-

ability of the standardized U.S.P. disintegration apparatus (1) makes it ideally suited for providing constant and reproducible agitation of the tablet or capsule since both design and operation of the apparatus are exactly prescribed. Periodic withdrawal of filtered, small aliquots of test fluid provides samples containing varying percentages of dissolved drug. Ultraviolet spectrophotometry serves as a rapid

Received January 10, 1962, from the Pharmacy Research Section, Product Research and Development, The Upjohn Co., Kalamazoo, Mich.

Accepted for publication January 29, 1962.