

errors become excessive since the agreement between duplicate analyses of commercial preparation containing acetophenetidin is generally satisfactory.

### CONCLUSION

Eq. 9 is fundamental to this general type of analysis. All the basic advantages and disadvantages associated with this method are found therein. It is important, therefore, to prepare a plot of  $K_m$  vs. relative concentration before attempting an analysis based on controlled partial separation. The importance of this is evident from Fig. 2. If such a curve shows that a simultaneous analysis of the components of a particular binary mixture is possible, then the method commends itself to the analyst. This method is particularly useful in those cases where the usual spectrophotometric methods of simultaneous analysis are not possible because of the similarity of the spectrophotometric curves of the compo-

nents and where the usual solvent-solvent extraction techniques are not capable of completely separating the two components. Table I shows that the method is accurate and precise. The method, therefore, provides another approach to the basic problem of the analysis of complex pharmaceuticals.

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## Investigation of the Sedimentation Behavior of Dispersions

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Using a modification of the method of Greiner and Vold, suspension isotherms were obtained for dispersions of zinc oxide, calcium carbonate, and bismuth subcarbonate in sodium lauryl sulfate, dioctyl sodium sulfosuccinate and sodium salts of polymerized alkyl naphthalenesulfonic acids (Daxad 11) solutions. For zinc oxide and bismuth subcarbonate systems maximum suspendability was reached at surfactant concentrations somewhat beyond the critical micelle concentration and extended over a relatively short concentration range. In the case of calcium carbonate, limited suspendability was observed with all three surfactants. Previous workers attribute the reduction in suspendability at higher surfactant concentrations to a reduction in zeta potential, thus permitting increased aggregation. Suspension isotherms obtained at constant and varying ionic strengths of sodium chloride indicate that aggregation is facilitated by the presence of excess surfactant through some additional mechanism.

THE SEDIMENTATION behavior exhibited by a dispersion has long been recognized as being of interest and importance pharmaceutically. Separation of phases in a polyphase pharmaceutical product can result in failure to provide uniform doses of the drug or drugs suspended.

One phenomenon which may occur and contribute to increased rates of sedimentation in these dispersions is aggregation (1). Thus, a number of investigations of sedimentation or creaming rates have been made and aggregation behavior

deduced in a qualitative or semiquantitative fashion (1-5).

Further interest in the phenomenon of aggregation arises from the observation that in addition to the effect on physical stability, aggregation may also contribute to the flow properties exhibited by emulsions and suspensions (6). Recently, W. I. Higuchi, Okada, and Lemberger (7) reported on the reversible aggregation-deaggregation of hexadecane-in-water emulsions containing dioctyl sodium sulfosuccinate (AOT). In this study a procedure involving rapid counting and sizing of droplets as a function of time was employed, thus permitting direct determination of aggregation in the system.

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Sedimentation studies in which ionic surface-active agents have been employed reveal that in a given system, suspendability of the dispersed phase passes through a maximum at a given concentration of surface-active agent something in excess of its critical micelle concentration (2, 3, 5, 8). Increasing suspendability to the maximum is generally accepted as being due to selective adsorption of the anion (2, 3, 5, 8, 9). As the anion is adsorbed, the zeta potential of the particles increases which leads to deflocculation of aggregates. As a result of deflocculation, effective particle size is decreased and the rate of sedimentation under gravitational effects is reduced.

Two possible explanations for the observed decrease in suspendability beyond the maximum have been offered. Greiner and Vold (2) and Vold and Konecny (3) propose that the decrease in suspendability at higher concentrations of surface-active agent results from a decrease in zeta potential caused by the increased concentration of counter ions. However, Doscher, in his sedimentation studies (5), showed that sedimentation rates increased markedly at a concentration in excess of the critical micelle concentrations, while zeta potential decreased only slightly. Both he and Cockbain, reporting on the creaming of emulsions systems (1), suggest that adsorption of poly-molecular aggregates occurs at higher concentrations, and that interaction of hydrophobic surfaces results in bridging between particles leading to aggregation. Higuchi, Okada, and Lemberger (7) recognized that both London dispersion forces, rendered more effective by decreased zeta potential, and film to film interactions may be important in aggregation phenomena. It is the purpose of this study to lend further support to this position.

### EXPERIMENTAL

**Materials.**—The insoluble powders employed were zinc oxide U.S.P., calcium carbonate, reagent grade, and bismuth subcarbonate U.S.P. (light powder). These particular powders were chosen because of their widespread use in pharmaceutical suspensions.

The anionic surfactants used were sodium lauryl sulfate (NaLS), Aerosol OT (100% pure sodium dioctyl sulfosuccinate from American Cynamid), and Daxad 11 (sodium salts of polymerized alkyl naphthalene sulfonic acids from Dewey and Almy). The AOT and Daxad 11 were used without alteration. The NaLS was recrystallized twice with hot 95 per cent ethanol before use.

Sodium chloride U.S.P. was used in the experiments concerning electrolytes.

The distilled water used in the dispersions was decarbonated by vigorous boiling for fifteen minutes and cooling in a flask stoppered with a soda-lime tube apparatus.

**Procedure.**—The procedure employed was a modification of the method outlined by Greiner and Vold (2). Surfactant solutions of the desired concentrations were prepared in 250-ml. quantities at specific time intervals before use (3 hours for the AOT solutions and 24 hours for the Daxad 11 and NaLS solutions). The necessity for using solutions of uniform age was demonstrated by Greiner and Vold in their studies of the suspending powers of aged AOT solutions.

A small portion of this solution and 2 Gm. of the insoluble powder were placed in a ground-glass homogenizer and levigated vigorously for 2 minutes. The concentrated suspension was then transferred quantitatively to a graduated 12-in. test tube, using portions of the remaining surfactant solution. All test tubes were calibrated at the 50-ml. and 250-ml. levels. Both the diameter (3.7 cm.) and the distance between calibrations (23 cm.) were identical in every case. The liquid was brought up to volume (250 ml.) with the remaining surfactant solution and the tube clamped on the stirring apparatus. This consisted of an elongated glass spiral terminated with a soft rubber propeller fitted onto a small reduction motor. The suspension was stirred for 18 minutes, effecting a total stirring time of 20 minutes. The tube was then removed from the stirrer, stoppered, inverted slowly by hand several times, clamped in a vertical position, and allowed to stand undisturbed for a 2-hour period. At the end of this time the liquid was withdrawn to the 50-ml. mark, and assayed for the amount of powder which had remained suspended. A special J-tipped siphon and a slow withdrawal rate were employed to minimize the disturbance of the sediment.

The zinc oxide suspensions were assayed according to a modified U.S.P. XVI procedure in which the zinc oxide was dissolved in an excess of 1.0 *N* sulfuric acid in the presence of ammonium chloride, and the resulting solution back-titrated with 1.0 *N* sodium hydroxide.

The 1932 British Pharmacopoeia assay method was employed for calcium carbonate. The calcium carbonate was dissolved in an excess of 1.0 *N* hydrochloric acid, and back-titrated with 1.0 *N* sodium hydroxide. Methyl orange test solution (U.S.P. XVI) was used as an indicator in both of the above cases.

A gravimetric procedure was used for bismuth subcarbonate, whereby the 200 ml. of suspension were centrifuged approximately 20 minutes, or until the supernatant liquid was clear. The liquid was decanted, and the residue was transferred quantitatively to a tared crucible and dried to constant weight.

In the experiments demonstrating the influence of electrolytes on the suspending ability of the surfactants, the salt was dissolved in the surfactant solution before levigation was begun.

Suspension isotherms were obtained by plotting the milligrams per milliliter of insoluble powder remaining suspended after the 2 hours *vs.* the concentration of surfactant solution used.

It has been established that the effects of stirring time (10) and precontact<sup>1</sup> time (2) are critical factors in sedimentation analysis, and, therefore, were carefully controlled. Inasmuch as the suspending power

<sup>1</sup> Precontact time is the length of time which the powder and surfactant are allowed to remain in contact before the actual sedimentation period begins (2).

of detergents is generally independent of temperature (11), no effort was made to maintain a constant temperature experimental environment; all work was done at room temperature.

### RESULTS AND DISCUSSION

The suspension isotherms obtained for the various insoluble powder-anionic surface-active agent combinations employed are given in Figs. 1-5. In accordance with results of previous workers, a maxi-

mum suspendability which extended over a relatively short concentration range was observed at a point somewhat beyond the critical micelle concentration of the surfactant.

An exception to the normal pattern was observed in the case of calcium carbonate. With all three anionic surface-active agents employed in this study only a slight increase in suspendability was noted

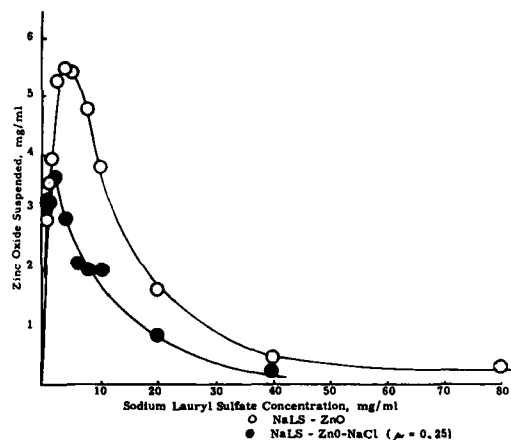


Fig. 1.—Suspension isotherms for zinc oxide-NaLS systems.

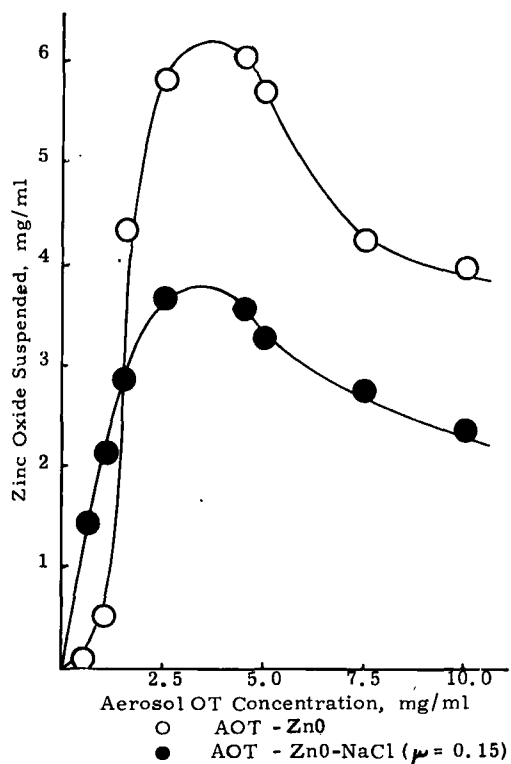


Fig. 2.—Suspension isotherms for zinc oxide-AOT systems.

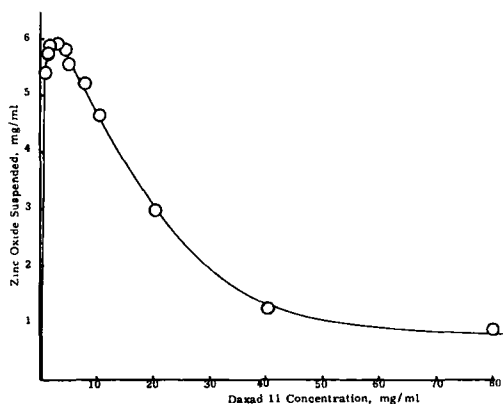


Fig. 3.—Suspension isotherm for zinc oxide-Daxad 11 system.

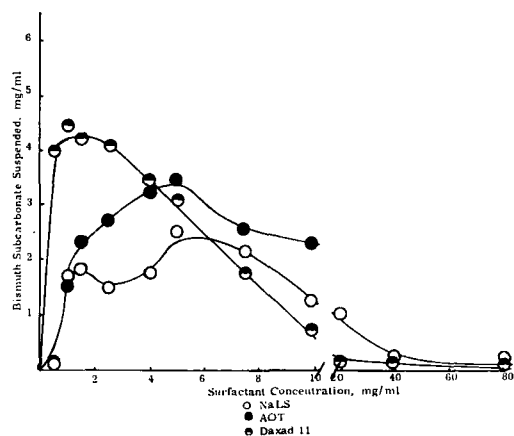


Fig. 4.—Suspension isotherms for bismuth subcarbonate with various anionic surface active agents.

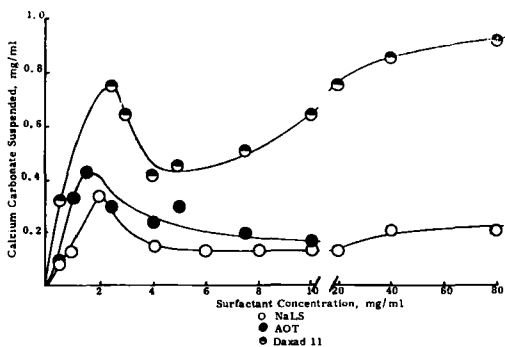


Fig. 5.—Suspension isotherms for calcium carbonate with various anionic surface-active agents.

in the initial portion of the suspension isotherm. With both Daxad 11 and NaLS, whose greater water solubility permitted determination of suspendability at higher concentrations, suspendability was observed to increase once again in the higher concentration range. Qualitative evidence for a high degree of aggregation in these systems which might in part account for their low order of suspendability is furnished by the observation that calcium carbonate sediments were more loosely packed than the other powder sediments.

A further objective of this study was to show experimentally that the zeta potential of the particles exerts a significant influence on the sedimentation characteristics of a dispersion. Since zeta potential is reduced or lost in the presence of high concentrations of electrolyte, suspension isotherms were obtained for zinc oxide–NaLS and zinc oxide–AOT systems in the presence of swamping electrolyte. For the zinc oxide–NaLS system, ionic strength was maintained at 0.25 and for the AOT system, at 0.15 with sodium chloride. For calculation of ionic strength, 100% dissociation of the surface-active agent was assumed. Although at higher concentrations the ionic strength would be somewhat less, it was felt that electrolyte concentration was sufficient to assure flooding of the system. Results of these experiments are given in Figs. 1 and 2.

In both instances maximum suspendability of the zinc oxide was significantly decreased indicating that zeta potential plays an important role in the suspendability of insoluble powders by contributing to the formation of a deaggregated system. It seems reasonable to expect the appearance of maxima in the suspension isotherms even though zeta potential is minimal because the NaLS and AOT could act as weakly ionic or nonionic surface-active agents in these systems. For the zinc oxide–NaLS system, the position of the maximum was shifted to a slightly lower concentration of NaLS and the width of the peak reduced. A possible explanation of this observation would be the greater ionic strength and/or an increased sensitivity to the presence of electrolyte in the case of NaLS.

Also of interest in suspendability behavior is the decrease observed beyond the maximum. At higher concentrations of anionic surfactant, the concentration of counter ions increases and results in a decreased zeta potential. If the aggregation responsible for the increased sedimentation rates observed in this portion of the suspension isotherm is entirely due to London dispersion forces, rendered more effective because of the closer approach of particles under a decreased zeta potential, any source of counter ions should produce equivalent behavior in the system. For this reason suspension isotherms were obtained where the concentration of surface-active agent at which maximum suspendability was observed held constant (4 mg./ml.) and varying amounts of sodium chloride were added. The resulting suspension isotherms are shown in Fig. 6, where zinc oxide suspended is plotted as a function of total ionic strength of the system. Dotted and broken lines represent the suspension isotherms for zinc oxide–

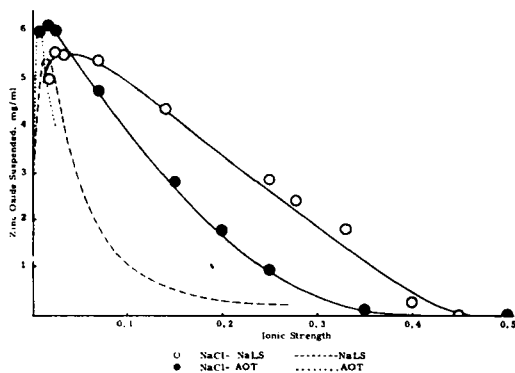


Fig. 6.—Influence of ionic strength on the suspendability of zinc oxide in NaLS and AOT solutions.

AOT and zinc oxide–NaLS, respectively, in the absence of sodium chloride. In order to plot these curves 100% dissociation of the surface-active agent was assumed for the calculation of ionic strength, thus these curves are displaced slightly to the right along the ionic strength axis.

It is seen that although suspendability decreased upon addition of increasing amounts of electrolyte, it did not fall off as rapidly as in the case of addition of excess surface-active agent. The major effect brought about by the presence of electrolyte would be the reduction in zeta potential and, perhaps at higher ionic strength, some dehydration of the interfacial film. It would thus appear that excess anionic surface-active agent in the system facilitates aggregation by some mechanism in addition to reduction of zeta potential. It seems reasonable to expect this mechanism to be film to film interactions enhanced by multilayer adsorption of surface-active agent at concentrations in excess of the critical micelle concentration.

As a result of these studies it may be deduced that both reduction in zeta potential and the presence of excess surface-active agent contribute to the deaggregation and aggregation of suspended particles. The relative significance of each in the total behavior shown can only be determined through direct measurement of aggregation in these systems under controlled environmental conditions.

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