

Rheometric Study of Particle-Particle Interactions in Suspensions

By W. I. HIGUCHI and R. G. STEHLE

Gillespie's development of the Goodeve impulse theory of suspension viscosity leads to a relationship that explicitly gives the particle-particle interaction energy as a function of a number of variables. Studies with a concentric cylinder rotational viscometer have demonstrated the usefulness of this theory in providing quantitative insight into the roles played by the dispersed phase, the solvent phase, and the interface in the aggregation behavior of suspensions. Silica suspensions in dibutyl phthalate, hexadecane, mineral oil, ethylene glycol, and mixtures of these solvents have been investigated with and without varying amounts of different surface-active agents, including water. In some cases, the data have been correlated with the sedimentation behavior of the suspensions.

BOTH THE stability and the flow behavior of suspensions are expected to be strongly dependent on particle-particle interactions. Depending on the nature of these interactions, the particles in an initially peptized suspension may or may not aggregate, and, if they do aggregate, may or may not be redispersed upon moderate agitation. Such aggregation-deaggregation characteristics have direct bearing on the modern concepts of pharmaceutical suspension formulation and have been recently discussed by Haines and Martin (1) and by Hiestand (2, 3).

A search of the literature shows that until recently there were no direct methods for determining particle-particle binding energies in suspensions. Recently, Gillespie (4, 5), employing the arguments of Goodeve (6), deduced a relationship for the pseudoplastic behavior of concentrated suspensions and applied it to a number of different situations. The relationship permitted the author to obtain binding energy values for suspension particles that were physically reasonable.

It appeared that Gillespie's method of interpreting shear-stress data for suspensions might be particularly useful in determining quantitatively the effects of solvents, surfactants, and moisture on the particle-particle interaction tendencies in suspensions. This report presents the results of a study on the silica suspension system.

THEORY

The following equation, based on an approximate physical model (4, 5), may be written for the limiting situation at high shear rates:

$$S = \eta^*G + C \quad (\text{Eq. 1})$$

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where S and G are the shear stress and shear rate, respectively, η^* is the Newtonian viscosity, and C is the ultimate dynamic yield value. According to the model

$$C = \frac{E_A K N^2}{2} \quad (\text{Eq. 2})$$

where E_A is the particle-particle interaction energy, K is the shear induced rate constant for collision, and N is the number of suspension particles per milliliter. The magnitude of K may be estimated from (7)

$$K = \frac{32}{3} a^3 \quad (\text{Eq. 3})$$

where a is the particle radius.

Strictly, these relations were deduced for the case of a suspension of monodisperse spheres. However, for suspensions that have a relatively narrow particle-size range and where the particles are relatively isometric, the method should be useful.

EXPERIMENTAL

The silica powder used in this work was Super "L" Neo-Novacite (Malvern Minerals Co., Hot Springs, Ark.). The particles of this material are relatively isometric. The number average radius determined with the Coulter counter was found to be about 1.3μ , and the mass mean radius was found to be about 2.1μ . More than 90% of the mass was in the size range 0.8 to 3.2μ . From the Coulter counter data and assuming that the particles were spheres, the specific surface area was estimated to be $6.0 \times 10^8 \text{ cm}^2/\text{Gm}$.

The powder was washed with water several times by shaking the water suspension, allowing it to settle, then decanting. The material then was dried in an oven for several days at 100 - 105° and stored in a desiccator until ready for use.

The suspensions containing silica from 10% to 35% by volume were prepared in a Waring Blendor with various solvents. In some cases, surfactants or water were added to the solvents prior to mixing with the silica.

The suspensions were run then in a concentric cylinder type rotational viscometer with an automatic recording attachment designed by Mattocks and associates. The particular model used in this work has been described by Sheth (8). Sucrose solutions were used as standards. Shear stresses were determined up to shear rates of about 2400 sec^{-1} . All runs were at 30° .

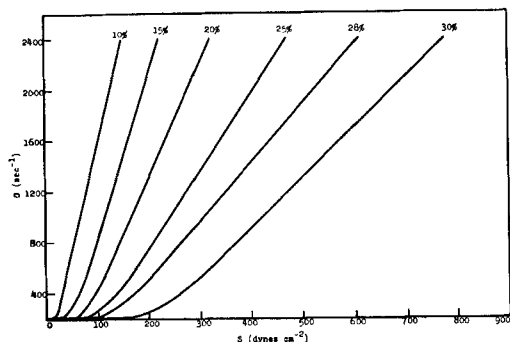


Fig. 1.—Shear-stress curves at 30° for silica suspensions in a 60-40% hexadecane-dibutyl phthalate solvent mixture. Percentages refer to volume percentage of silica phase.

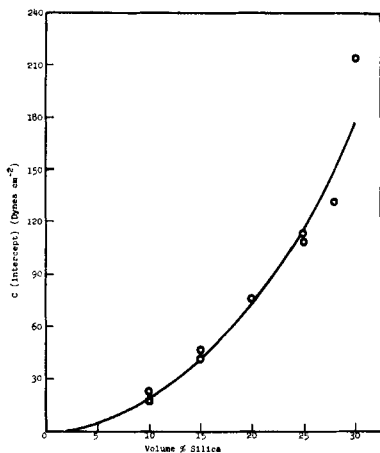


Fig. 2.—Plot of the intercept values as a function of the volume percentage of silica. Solvent is 60% hexadecane-40% dibutyl phthalate.

Sedimentation studies were carried out in some instances. Sediment heights of the suspensions were followed as a function of time in 100-ml. graduate cylinders.

RESULTS

Effect of Solvents.—Figure 1 shows the results of runs with a solvent mixture of 60% hexadecane-40% dibutyl phthalate. At high shear rates, the curves are indeed linear in accordance with Eq. 1. Values for the intercept, C , were determined by extrapolation of the linear portions of these curves. The reproducibility of the C values was about 10 dynes/cm^2 in these, and in other experiments when the C values were in the low ranges. The absolute precision was poorer when the C values were larger ($\approx 500 \text{ dynes/cm}^2$). For example, in the mineral oil studies the reproducibility of the intercept was about 10%. Part of the difficulty in this instance was that the curves were only approaching linearity at the highest shear rates; consequently, the uncertainties in the extrapolations were relatively large.

Figure 2 gives a plot of C versus per cent by volume of the dispersed phase for the 60% hexadecane-40% dibutyl phthalate case. The smooth curve is the best fit parabola. At least approximately the C values follow a square dependence on particle concentration in accordance with Eq. 2.

Suspensions made with a 50% hexadecane-50% dibutyl phthalate mixture gave results similar to the 60-40 mixture. With pure dibutyl phthalate, however, the S versus G curves were nearly Newtonian, even at high suspension concentrations. Ethylene glycol as the solvent also gave essentially Newtonian curves.

In Fig. 3, the η^* values obtained from the linear (Newtonian) portions of the curves are presented as a function of the volume percentage of the silica phase. Actually, the results are presented in reduced form, the η^* value for the particular solvent divided by the η^* value at 10% by volume silica. The approximate coincidence of the results indicates that again Eq. 1 must be approximately valid here. The slightly lower values for the pure dibutyl phthalate results do indicate, however, that particle-particle interaction effects, which are more impor-

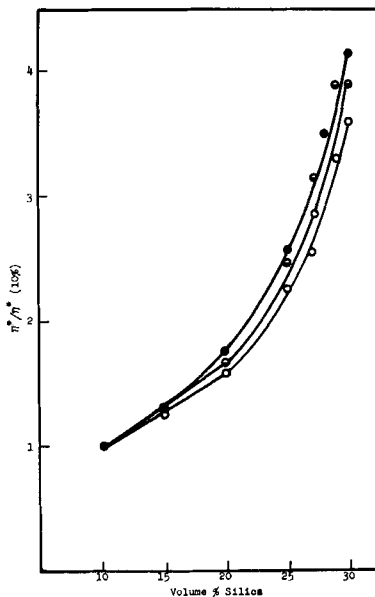


Fig. 3.—Plots of the Newtonian viscosities as a function of silica concentration for different dibutyl phthalate (DBP)-hexadecane (H) solvent mixtures. Key: O, 100% DBP; \odot , 50% DBP-50% H; \bullet , 40% DBP-60% H.

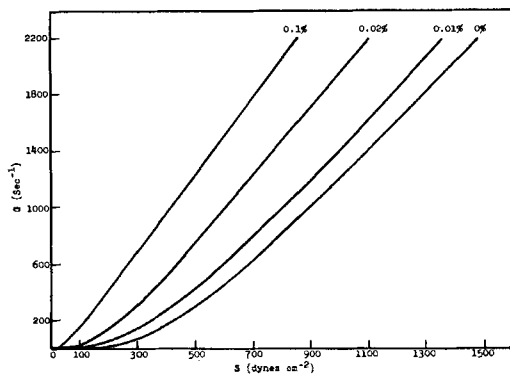


Fig. 4.—Effects of n -decyl amine on the shear-stress behavior of 15% by volume silica in mineral oil. Percentages indicated are per cent by weight n -decyl amine in the mineral oil.

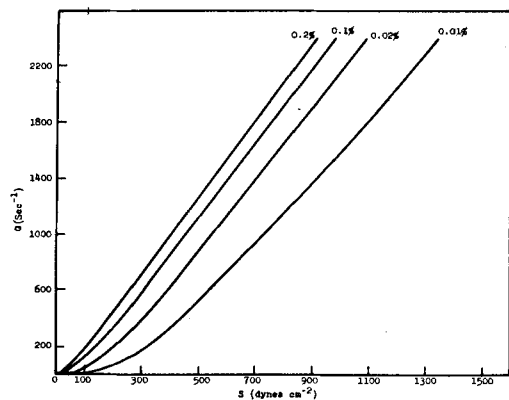


Fig. 5.—Effects of decanoic acid on the shear-stress behavior of 15% silica by volume in mineral oil. Indicated percentages are per cent by weight decanoic acid in mineral oil.

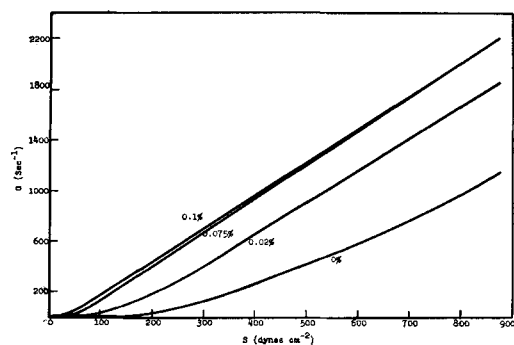


Fig. 6.—Effects of AOT on the shear-stress behavior of 15% silica by volume in mineral oil. Percentages indicated are AOT in mineral oil.

tant for the mixed solvents, cannot be separated entirely from the Newtonian or purely hydrodynamic effects.

Effects of Surfactants.—The marked effects of surfactants are illustrated in Figs. 4–6. Light mineral oil¹ was used as a solvent in these studies because a large yield value was observed with this solvent in the absence of surfactants. With all three surfactants, large reductions in yield values were observed. Only about 0.02% surfactant was required for reducing the yield value by about 50%. At 0.1% to 0.2% surfactant, the suspensions became essentially Newtonian in all cases. As mentioned above, the linear portions of these curves are not exactly parallel. With decreasing surfactant concentration at constant silica concentrations, η^* increases somewhat.

Effect of Moisture.—Figures 7 and 8 illustrate the effect of small amounts of water on the yield values for the mineral oil and dibutyl phthalate suspensions. As indicated, only small amounts of water added to the suspensions were sufficient to cause significant change in the yield values.

Results of Sedimentation Studies.—Figures 9 and 10 illustrate the sedimentation behavior of those suspensions containing *n*-decyl amine and Aerosol OT (AOT). Similar results also were obtained with decanoic acid.

¹ Marketed as White Mineral Oil No. 9 by the Standard Oil Company of Indiana.

DISCUSSION

As indicated by the results shown in Fig. 2 and by the experiments in other solvents, the silica particles in the micron size range approximately obey Eq. 1 in the range of shear rates encountered in these studies. According to theory, it should be permissible to set C proportional to the particle-particle interaction energy, E_A , if the volume fraction of the silica is maintained constant.

The yield value, C , decreases with increasing solvent polarity for silica suspensions containing no other additives. For example, at 15% by volume silica, the C values are about 500 dynes cm.^{-2} for mineral oil, 40 dynes cm.^{-2} for the 60% hexadecane–40% dibutyl phthalate solvent mixture, and zero for both pure dibutyl phthalate and ethylene glycol. The behavior is consistent with the idea that a more polar solvent can interact better with the polar surface groups of silica. This results in a lyophilic interfacial region with a relatively low interfacial tension and perhaps with an interfacial film that is not easily displaced during a collision. Both of these factors allow for the more polar solvent a smaller interaction energy when two particles collide, then separate.

It is instructive to estimate E_A for the 60% hexadecane–40% dibutyl phthalate case by Eqs. 2 and 3. Taking any point on the smooth theoretical curve in Fig. 2 and with $a = 1.3 \times 10^{-4}$ cm., one obtains E_A

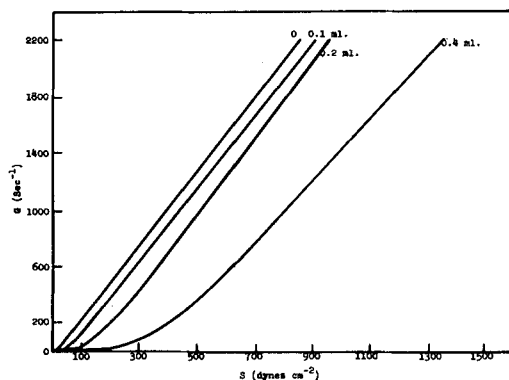


Fig. 7.—Effects of water added to 25% silica by volume in dibutyl phthalate. Indicated value for each curve refers to volume of water added to suspension of 270 ml. volume.

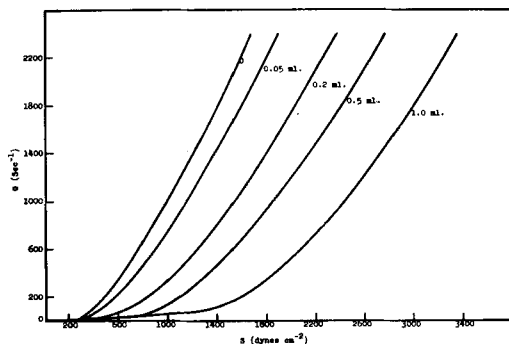


Fig. 8.—Effects of water added to 15% silica by volume in mineral oil. Volumes of water added to 270 ml. of suspension are indicated.

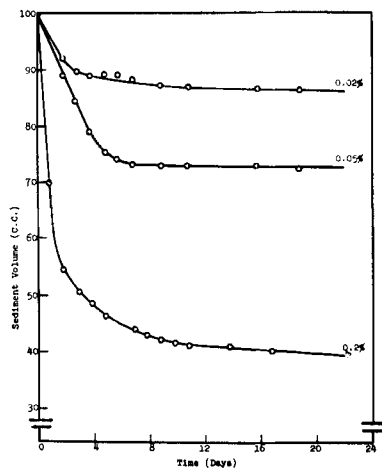


Fig. 9.—Sedimentation behavior of 15% silica suspensions in mineral oil in the presence of *n*-decyl amine. Indicated percentages refer to amount of amine in mineral oil.

$= 1.2 \times 10^{-8}$ ergs. If it is assumed that the specific surface interaction energy is somewhere between 10 and 100 ergs/cm.², this value for E_A gives for effective particle-particle contact area a value somewhere between 6×10^{-11} and 6×10^{-10} cm.², which is physically reasonable for the present situation.

The very interesting effects of surfactants (see Figs. 4-6) may be explained on the basis of surfactant adsorption. Taking the decanoic acid case, let us assume that the area occupied by the adsorbed molecule is about 25 sq. Å. at maximum coverage and that all of the surfactant molecules are in the adsorbed state. Then a simple calculation shows that about one-half of full coverage is reached when there is initially 0.02% surfactant in the mineral oil for the 15% by volume silica suspension (density of Neo-Novacite = 2.65, specific surface area = 6×10^3 cm.² Gm.⁻¹). Thus, it appears that the interaction energy may be approximately proportional to the fraction uncovered at low coverages.

Mechanistically, the effect of surfactant adsorption may be attributed entirely to the lowering of the interfacial tension or to the formation of a lyophilic film that prevents the necessary close contact of the particle surfaces. It is reasonable to expect that both are operating. It is a question of whether a secondary minimum type situation (9) is important² or whether direct contact of silica phases is important in determining E_A . If it is a secondary minimum type phenomenon, E_A may be close to the energy corresponding to the depth of the minimum and would be expected to be relatively small in the limiting case of a strongly adsorbed thick lyophilic film. If it is a direct silica phase-phase contact situation, E_A would be expected to be larger but still smaller than the E_A without surfactant. In this case, E_A might be expected to be approximately proportional to the interfacial tension provided that the activation energy for film rupture is small.

² Here electrical repulsion as discussed, for example, in Reference 9 is probably not so important. Instead, the repulsive contribution to the total interaction energy comes mainly from the desorption energy of the adsorbed surfactant.

It is interesting that the sedimentation curves (see Figs. 9 and 10) correlate with the intercept values at the lower surfactant concentrations. The larger sedimentation volumes for those suspensions containing less surfactant shows that stronger binding energies between the particles are necessary for maintaining a relatively porous sediment structure with a relatively small coordination number (2, 3). Here the potential usefulness of rheometric measurements like these is indicated, and future studies are planned to explore in more detail the relationship between the particle-particle interaction energy and sediment structure.

It is also interesting that at the higher surfactant concentrations the rheometric measurements become relatively insensitive to significant differences in the sedimentation behavior. Thus, for example, the sedimentation behaviors of the 0.05% and the 0.20% surfactant in the case of *n*-decyl amine (see Fig. 9) and the 0.075% and the 0.10% AOT cases (see Fig. 10) show significant differences, while their respective rheometric curves were nearly identical. This is not unreasonable, considering that even for an intercept value of 10 dynes/cm.², the corresponding E_A value is calculated to be about 3×10^{-9} ergs, which is still considerably greater than thermal energies ($\sim 4 \times 10^{-14}$ ergs). Therefore, it is not surprising that the aggregation-deaggregation behavior in unsheared suspensions may be quite different, even though the present rheometric measurements were insensitive to such differences.

Examples of the use of water as a liquid-bridging flocculating agent has been recently reviewed by Hiestand (2). In the present situation, a reasonable explanation of the effect of water is that the presence of the interfacial film of water increases E_A by providing a larger effective cross-sectional area of bonding between the particles. By means of Eqs. 2 and 3 and with the C value obtained for the 0.50-ml. water case (see Fig. 8), the cross-sectional area of the water bridge would be about 5×10^{-9} cm.² assuming an oil-water interfacial tension of about 30 ergs/cm.². For the particle sizes involved in the present situation, this is a reasonable figure. The smaller effect of water upon E_A for the dibutyl phthalate case may be explained on the basis of the expected lower oil-water interfacial tension for dibutyl phthalate.

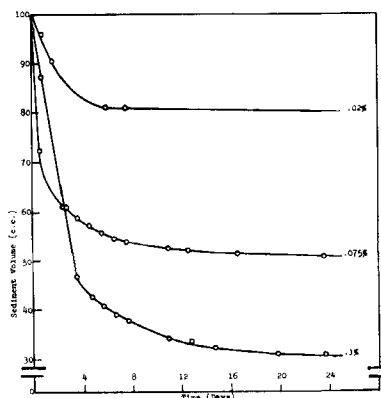


Fig. 10.—Sedimentation behavior of 15% silica in mineral oil in the presence of AOT. Indicated percentages refer to AOT in the mineral oil.

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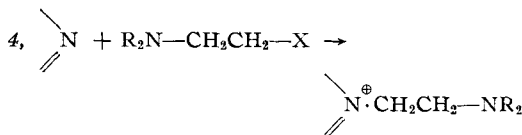
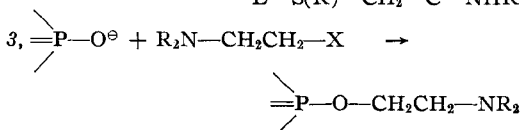
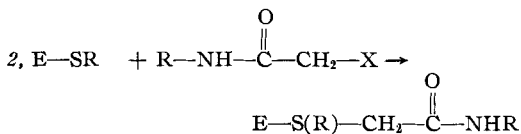
Synthesis of Several *N*-Haloacyl Analogs of α,α -Diphenyl-4-piperidinemethanol as Potential Antineoplastic Agents

By WILLIAM D. ROLL

Eight new derivatives of α,α -diphenyl-4-piperidinemethanol have been prepared to evaluate their anticarcinogenic activity: 1-(3-chloropropionyl)- α,α -diphenyl-4-piperidinemethanol, 1-(2-chloropropionyl)- α,α -diphenyl-4-piperidinemethanol, 1-chloroacetyl- α,α -diphenyl-4-piperidinemethanol, 1-(3-bromopropionyl)- α,α -diphenyl-4-piperidinemethanol, 1-(2-bromopropionyl)- α,α -diphenyl-4-piperidinemethanol, 1-bromoacetyl- α,α -diphenyl-4-piperidinemethanol, 1-(3-iodopropionyl)- α,α -diphenyl-4-piperidinemethanol, and 1-iodoacetyl- α,α -diphenyl-4-piperidinemethanol.

A SERIES OF derivatives of α,α -diphenyl-4-piperidinemethanol were synthesized to evaluate their possible antineoplastic activity. This report describes the synthesis of some *N*-haloacyl analogs of this amine.

Based on the report by Carbon and co-workers (1) that various bis-haloamides demonstrate antitumor activity, a group of diphenamide derivatives have been reported previously (2). The compounds reported herein are halopropionyl and haloacetyl derivatives of a 4-alkylpiperidine. Theoretically, it is possible that such compounds might interfere with vital enzymatic systems or nucleic acids within a cancer cell through reversible and/or irreversible bonding by one of the following mechanisms (3-8):



Baker *et al.* (9, 10) presented evidence for the inactivation of lactic dehydrogenase (LDH) and glutamic dehydrogenase (GDH) by 4-(iodoacetamido)salicylic acid by active-site-directed irreversible inhibition. It is known that LDH occurs in glycolyzing cells (11-13), and it has been studied extensively to establish some relationship to neoplastic disorders. Elevated levels of LDH have been reported in many cancerous conditions. Hill and Levi (14) and Bodanski (15) reported abnormal LDH levels in leukemia; Bierman *et al.* (16) reported abnormal levels in relation to lymphomas and leukemia; and Schenker (17) and Wroblewski (18) reported abnormal lactic dehydrogenase levels in body fluids in gastric cancer and central nervous system involvement by metastatic carcinoma. Busch and Nair (19) and Papaconstantinou and Colowick (20) have proposed that chemotherapeutic agents which would inhibit lactic dehydrogenase activity might be a factor in cancer chemotherapy, since lactic acid formation is a characteristic of neoplastic tissue. Potter (21) stated that the inhibition of some enzymes leads to the failure of hydrogen transport within the internal structure of the malignant cell. Wheeler and Alexander (22) re-