

Review Article

Stability of Oil-in-Water Emulsions

By EDWARD R. GARRETT

AN EMULSION can be defined as one liquid dispersed in the form of droplets in another liquid (11). The particle sizes of the dispersed phase in operationally usable emulsions may lie within the arbitrary limits of 0.01 and 10 μ (11, 92).

For particle sizes above 1 μ the mixture may be considered a coarse dispersion, whereas below 1–10 μ the mixture is in the region of molecular dispersions, *viz.*, true solutions.

In general, one phase of the emulsion may be referred to as the "oil" and is some organic compound. The other phase is most frequently water. Of primary interest in pharmaceuticals and biological systems is the oil-in-water emulsion which will be considered in this review. Similar concepts can be applied to other systems.

An operationally stable emulsion would have an unchanging amount of oil dispersed in a given amount of continuous phase when subjected to expected stresses of temperature, agitation, and gravitational influences. This does not establish requirements for the maintenance of particle size distribution and may not be considered satisfactorily stable in circumstances where maintenance of a minimum particle size is necessary. In the case of an emulsion which is to be intravenously administered, a minimum particle size must be maintained to prevent embolism (37, 81, 85, 111, 112, 135), and changes in physico-

chemical properties can be correlated with physiological effects (16).

A perfectly stable emulsion would maintain the same number and sizes of particles of the dispersed phase per unit of volume or weight of the continuous phase. The total interfacial energy per unit of emulsion volume or weight must be invariant with time to conform to this definition.

Emulsion instability may be initiated by aggregation of the droplets of the discontinuous phase. These aggregates may remain dispersed or flocculate. Eventually flotation (or sedimentation if the oil is heavier than water) would result in a clearance of the continuous phase. This process is referred to as "creaming." The aggregates may coalesce to form aggregates of larger droplets of the dispersed phase, and a well-defined layer of oil may eventually result, the ultimate in "coalescence." An alternative process that may occur within an emulsion that by gross measurements is stable is the redistribution of particle sizes of a dispersed phase by an aging process, *i.e.*, an accretion by larger particles of the molecules of the dispersed phase which may exist monomolecularly in the continuous phase, *i.e.*, in "solution." This process may originate by "evaporation" of oil molecules from the smaller droplets through the droplet interface into the body of the continuous phase.

Any of these phenomena may occur by the natural process of aging, *i.e.*, as a function of time. The purely physical processes of these phenomena in a given emulsion could be: (a)

Received from the College of Pharmacy, University of Florida, Gainesville.

This article was prepared in conjunction with investigations supported by grant GM-12099-01, 02 from the National Institutes of Health, U. S. Public Health Service, Bethesda, Md.

by collision of particles, maintenance of cohesivity by van der Waals or London forces with sufficient thermal energy available to promote coalescence and to overcome the energies of repulsion which may be electrostatic or mechanical; (b) by the inherent vapor pressure of oil molecules which permits evaporation from droplet "membrane" into the continuous phase of the emulsion wherein the energetics favor transfer into the membranes of larger particles; (c) by gravitational influences which favor flotation/sedimentation and creaming with subsequent greater probability of contact of dispersed particle. Such flotation may favor graduation of particle sizes and preferentially place large particles in contact with large particles which may be energetically predisposed to coalescence.

Since a dispersing agent is used to lower surface tension and may solubilize the oil in micelles, the process of chemical deterioration may reduce the surfactant concentration and thus the micellar concentration and may change the environment in the continuous phase to favor any one of the above physical processes of instabilization. Oxidative, photolytic, or solvolytic degradation of either the dispersing agent or the oil may reduce the available surface-active agent and change the pH or the chemical composition of the dispersed phase.

Since the repulsion of dispersed particles may be on the basis of charge and electrostatic energies, changes in salt and/or hydrogen- and hydroxyl-ion concentrations of the aqueous phase should vary the energetics. Considerations of the Helmholtz double layer (136) and the zeta potential (22, 42, 136) are undoubtedly as important as the chemical instabilities of these systems.

As this introduction demonstrates, the factors which lead to the thermodynamic inevitability of emulsion instability are complex and interacting. This review of the literature considers the information that is available to quantify these basic models. The reader is also referred to texts (11, 15, 23, 30, 46, 88, 92, 152).

DEFINITIONS AND CHARACTERIZATIONS OF EMULSION INSTABILITY

Gravitational influences may permit the separation of the dispersed phase from the body of the emulsion with maintenance of its particulate character. This involves a change in the prepared emulsion and, in this sense, may be considered as a manifestation of instability. If the primary characteristic of emulsion stability is maintenance of particulate character, *i.e.*, the lack of coalescence into larger particles or to form

a distinctly homogeneous second phase, then creaming and instability are not the same thing (61-63). Creamed emulsions can be reconstituted readily by gentle shaking (37, 62, 106). Coalesced systems where the components were chemically stable also can be reconstituted as emulsions by the same methods that were used in their manufacture in the first place. However, since these methods are not so readily available to the laity as gentle shaking, it must obviously be a more aristocratic order of instability than mere creaming.

It follows that the changes in the emulsion properties that may be considered undesirable depend on the prospective use of the emulsion and the operational ease of reversibility of these changes.

Types of instability that may be manifested are: (a) creaming with or without aggregation and increase in particle diameter, (b) aggregation (with or without creaming), (c) increase in particle diameter or lowering of interfacial area, and (d) the ultimate in coalescence, the production of a separate and continuous oil phase.

Notwithstanding the fine points made in the literature as to what does or does not constitute instability, it is apparent that any observable change in the emulsion with time is a valid measure of emulsion transformation. Whether such changes can serve as quantitative measures for the comparison of stabilities of dissimilar systems or whether they can be used as tools to predict changes in other observable emulsion parameters are questions of importance.

Emulsion parameters that can be measured as a function of time include visually observed rates of creaming which may be postulated to increase with droplet size (52) or with the extent of droplet aggregation (24). A modern approach is to use radioisotopically labelled oil or water phases (7). This procedure is claimed to be less time-consuming than the conventional visual (94), microscopic (62), or analytical methods (71). The change of radiation with time of the appropriately soluble radioisotopes can be measured at various heights in a tube to ascertain creaming rate (7). If the oil is so labelled, a linearity exists between the logarithm of the ratio of counts at the top of the tube to the counts at the bottom and the logarithm of time (7). Rates of creaming can be accentuated by the use of centrifugal stress which can be observed visually (80) or photographically in the modern analytical ultracentrifuge (37, 48, 90, 101, 143-146). Rates of amounts of separation of phases in a given time can also be used (37, 80, 81, 101, 143-146, 151).

A method of evaluating emulsion stability is the determination of a mean particle size or the number of globules formed from a given quantity of oil (26, 108, 126, 137, 138) or the rate of change of particle diameter and particle numbers under centrifugal stress (26). A classical technique is the determination of size-frequency distribution of oil particles and the derived interfacial area based on volume estimates from measured particle diameters (14, 36, 47, 57, 59, 61, 62, 64, 86, 87, 99, 108). These measurements are usually effected through the microscope with the aid of a hemocytometer, although reflectance measurements have been used (74). Propylene glycol has been suggested as a suitable diluent (62). Mathematical representations of size distribution are, in general, empirical (2, 35, 57, 59, 97, 108).

Arguments have been presented, however, that it is not the area of the interface that defines emulsion stability, but the change of this quantity with time (62, 63).

Increases in particle diameters or decreases in numbers of particles do not appear to depend on the coarseness (61) or fineness (26) of particle sizes in an emulsion. King and Mukherjee (62) have shown that the rate of decrease of interfacial area in a given emulsion is reasonably constant with time. This method has found wide application in the estimation of emulsion stabilities (47, 61, 62, 64, 86, 87). Its superiority over mean particle size measurements has been claimed (47, 86) on the premise that changes in size-frequency distribution are reflected in the derived specific interfacial area, whereas a mean particle size may be relatively invariant. It has been stated (87) that the rapid deterioration of an emulsion followed in this manner can be correlated with that ultimate in instability, coalescence, and separation into two continuous phases since there is an increased frequency count of relatively large oil globules. It is of interest that in several emulsions studied, a discontinuity in particle sizes was observed above 7.5μ , and free oil accumulated. It is tempting to conclude that soap-stabilized (62) and nonionic-stabilized (86) emulsions are stable only when particles are of diameters below 7.5μ . The maximum error in the estimated specific interfacial area is 5% with an average error of 2-3% (86). A count of 1000 globules is considered to have a high probability of characterization in the size-frequency method of analysis (73, 86), although counts of 4000 (64) have been made. The large counts are considered mandatory since large particles, although few in number, have large effects on the estimation of specific interfacial areas.

The size-frequency method with its reflected estimation of specific interfacial area also has been criticized by Knoechel and Wurster (64), who observed an increase in specific interfacial surface prior to the subsequent decrease that was expected from aging. They attributed this phenomenon (which in accordance with the proponents of the size-frequency analysis would indicate *increased* emulsion stability) to the presence of subvisual particles (*i.e.* $<0.5 \mu$) which ultimately coalesced to give visual particles under microscopic observation. The technological limitation of this technique thus should result in erroneous estimates of specific interfacial area. The method has also been criticized (143) as being insensitive to small but important changes occurring in the emulsion.

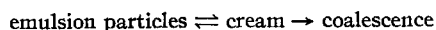
The advent of modern instrumentation has introduced the use of the Coulter counter (28) in the determination of size-frequency relations (50, 53-55, 69, 70, 149) which can conserve much of the time and energy expended in microscopic counts. However, the same criticisms are applicable. The error is large in the estimation of large particles. The lower limit of particle sizes that can be measured are of similar magnitude to the microscopic method.

Other properties of emulsions that may be measured are surface or interfacial tensions (56), electrophoretic mobility (32, 45, 98), or interfacial tension (20, 61, 77, 125). The lifetime of drops at an oil/water interface may be measured (21, 25, 100). Merrill (80) has listed a great number of methods. Some of the testing methods applied to emulsions in industrial pharmacy have been reviewed recently (133).

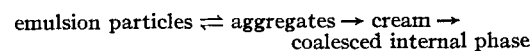
PHYSICAL FACTORS AFFECTING EMULSION STABILITY

If a chemically stable emulsion of specified composition and particle size distribution may be assumed, several sequences of events may occur with time, *i.e.*, with the "aging" of the emulsion.

(a) The emulsion may cream and the creamed particles may coalesce. The creaming process may be reversible with agitation:

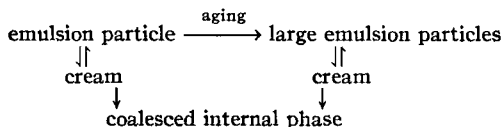


(b) A preliminary equilibria may occur to form aggregates of dispersed particles prior to the creaming process:



(c) A growth process may occur in the emulsion due to collision factors: van der Waals and London forces may overcome the energy barriers

of the interfacial films so that within the body of the continuous phase there is a growth process due to coalescence of drops or the growth of 1 drop at the expense of another:



Gravitational influences permit the separation or creaming of the dispersed phase from the body of the solution. The force, F , on a particle in a gravitational field is (41)

$$F = V(\rho - \rho')a \quad (\text{Eq. 1})$$

where V is the volume of the particle, ρ and ρ' are the densities of the particle and medium, respectively, and a is the acceleration due to the field (41). When steady-state conditions are reached, there is a constant particle velocity, v , and the gravitational force equals that applied to the particle by Stokes' law so that

$$V(\rho - \rho')a = k\eta v \quad (\text{Eq. 2})$$

where k is the shape constant, and η is the coefficient of viscosity of the fluid medium (41).

In the special case where the droplet is considered spherical and of radius, r , Eq. 2 can be modified to

$$v = \frac{2ar^2(\rho - \rho')}{9\eta} \quad (\text{Eq. 3})$$

If the density of the dispersed phase is less than that of the continuous phase, *i.e.*, $\rho > \rho'$, the phenomenon observed is flotation, and the resultant creaming is due to the lessening of the interparticle distance by the effects of gravitational field. If $\rho' > \rho$, sedimentation results.

T. Higuchi (49) has criticized the application of the simplified Stokes equation since it may be based on the oversimplified assumptions of (a) spherical particles, (b) similar sizes for all dispersed particles, (c) sufficient distance between particles so that the movement of one particle is independent of the other, and (d) that the rate is governed solely by hydrodynamic factors.

Nevertheless, since it may be anticipated that rates of coalescence may be dependent on the ability of dispersed particles to lessen the distance between them (42), it may follow that factors that would increase rates of creaming and aggregation would lead to changes in rates of coalescence and to the ultimate separation into homogeneous phases. It has been demonstrated that centrifugal stress does significantly increase the mean particle diameter (26).

Effect of Density Differences.—It is ap-

parent from Eqs. 2 and 3 that the velocity of creaming should be dependent on the differences in the density of the oil used as the dispersed phase and the density of the continuous medium.

Small density differences promote ease of emulsification unless polarities of the oil are excessive (61). However, the initial specific interfacial areas of emulsions similarly prepared are not necessarily inversely proportional to the magnitude of these density differences (87). It is interesting to note that changing density differences between the oil and water do not have significant practical effects on emulsion stability as based on time changes of size-frequency analysis (47, 62, 87). Although creaming was inhibited when brominated oils were blended to equate the specific gravity of dispersed oils and the external phase, the effects on stability as measured by the change of specific interfacial area with time were indeterminate, since these minor increases on stability could also be attributed to the nature of the brominated oils used (87).

The application of centrifugal stress to induce coalescence, the rate of which was considered a measure of stability, did not correlate coalescence rate with the differential densities (80). In fact, castor oil, which possesses a density closest to that of water of all the oils studied, gave evidence of the most rapid separation under the stress of centrifugation. Merrill (80) also asserts that factors other than density difference must be considered in comparing different oils in an oil/water emulsion even for creaming purposes. This is readily understandable when it is considered that creaming is also dependent on the volume, V , of the suspended material and/or the radius, r , of the dispersed particle and/or the viscosity, η , of the medium and/or the shape constant, k (Eqs. 2 and 3). It thus follows that if creaming is implicated in coalescence, other factors may be of greater significance than phase density differences. Aggregate formation where the factor V is increased occurs at higher surfactant concentrations (49).

Aggregates are probably not spherical, and thus the shape constant, k , may be modified (101). The magnitude of particle size which is reflected in increased r and the magnitude of the viscosity, η , which is a function of particle size and oil concentrations may also be of greater significance than phase density difference (118).

It must be appreciated also that the ultimate resistance to coalescence arises from the existence of extremely thin water films between creamed droplets and the presence of an ionized emulsifier adsorbed on particle surfaces (101).

Effect of Properties of Dispersed Oil.—If

oils of large polarities are excluded so that specific interactions with surfactants would be negligible, it appears that the nature and viscosity of the oil is of negligible practical importance in all aspects of emulsion stability.

Changes in oil viscosity had no significant effect on droplet size distribution, although a slight increase in the number of large droplets was observed (47). In an attempt to rank emulsifier efficiency of various soaps, there was no quantitative or qualitative difference in results between such widely divergent oils as kerosene and olive oil (62). King (61) has concluded that the viscosity of the internal phase is of little importance in determining the viscosity or stability of the emulsion it forms. Toms (134) and Sherman (116) have found no correlation between emulsion viscosity and the viscosity of the internal phase. The chemical nature of the oil internal phase was of greater significance in the specific case where carbon black was incorporated into dispersed sorbitol.

In other studies (86) it has been shown that the viscosity of the internal phase has no influence on particle size distribution in prepared emulsions. The same modal value of 0.5μ was obtained for various oils when prepared by the same method. No difference among oils was observed when the emulsions' ingredients were subjected to various homogenization pressures. Sherman, in a complete review (118) on the flow properties of emulsions, has come to a similar conclusion concerning the negligible effects of internal phase viscosity. Any influence exerted by the internal phase was attributable to its interaction with the emulsifier film around the particles (120, 134).

Viscosity and Emulsion Stability.—The viscosity of emulsions is linearly related to the volume concentration of dispersed rigid spherical particles in dilute emulsions as per Einstein (33, 34) when no interaction exists among the particles and the magnitude of particle separation exceeds the particle diameters. This basic relation should be modified when the droplets are deformable and increase in number (76, 83, 118, 122). In the former case, the viscosity of the emulsion should not increase with an increase in dispersed volume as much as it would with rigid spheres since the particles are more elastic to tangential stress (118). In the latter case the viscosity of the emulsion should increase more than the ideal systems of the Einsteinian postulates due to the necessity of shearing aggregates and bulk interference with slippage. In concentrated emulsions, hydrodynamic interference takes place between particles and is dependent on particle size (107). Sherman's (118) recent

excellent review discusses these models and cites references so that details are not needed in the present review.

There are two aspects to the consideration of the rheological properties of emulsions. The one is their effects on emulsion stability, and the other is the effects of changes in the emulsion due to its deterioration on the rheological properties.

The presence of a viscosity factor in Eqs. 2 and 3 is applicable in the consideration of creaming instability. Entrained air at an interface stabilizes oil particles that would normally readily cream and coalesce (62). This is attributed to its effect on the viscosity of the emulsion. However, Knoechel and Wurster (64), in an experimental attempt to determine if viscosity played a decisive role in the gross stability of emulsions, were unable to conclude that viscosity played more than a minor part in affecting rates of coalescence.

It is considered to be generally true that viscous emulsions are more stable than mobile ones due to retardation of coalescence. However, high viscosity may be a symptom rather than a cause of stability since emulsion viscosity is usually a function of added stabilizers (61) and emulsifiers (8, 86, 153). The viscosities of some studied emulsions (86) were not influenced by changes in specific interfacial area nor with constituents of the internal phase. In many cases little effect of globular size on the viscosity of oil/water emulsions was observed (8, 72, 121). Conversely, no significant effects on rates of coalescence or changes in specific interfacial area were observed over long periods for wide ranges of emulsion viscosity, *i.e.*, 34 to 1800 cps. (64). However, it has been noted that with emulsions that exhibit thixotropic plastic flow the yield value, *i.e.*, the force to be applied before streamline flow commences, increases with surfactant and oil concentrations (8). In addition, the aggregation-deaggregation equilibria may effect rheology and thixotropy (52). In the specific case of insoluble solid emulsifiers at low concentrations, the viscosity did decrease with the aging of the emulsion (60). At higher concentrations of these emulsifiers, a slight increase in viscosity was first noted which then decreased. The explanation was that there is an initial slow rate of hydration of the solid prior to the previously observed aging effects (60).

In Sherman's recently published review article (118) on rheological properties of emulsions, the various factors such as particle size, emulsifying agent composition and concentration, pH, electroviscous effects, and stabilizers which may influence emulsion viscosity are covered in detail.

In general, the effects on the viscosity of the continuous phase are reflected in the oil/water emulsion prepared from the continuous phase so modified. Such factors as particle size and size distribution may not have significant effects on viscosity under the limited conditions of some of the cited literature, *i.e.*, at low volume concentration of the dispersed oil phase (72). However, under conditions of narrow size ranges around a mean particle size the measured non-Newtonian viscosity may be shown to be a function of the mean particle diameter (102, 103).

A major model for emulsion rheology is that the viscosity of oil/water emulsion decreases with shear (*i.e.*, the system is non-Newtonian) until a minimum value is reached (118). This may be attributed to aggregate destruction. At any rate of shear there is an equilibrium size for the aggregates.

Surface Tension and Particle Films.—On the basis of energetics, surface tension lowering may be considered conducive to emulsification since it is obviously easier to micronize a liquid bounded by such a surface. However, it is not this property *per se* but the interfacial adsorption that accompanies it that is considered to promote stable emulsions (61). There are several instances of high electrophoretic mobilities due to surface-active ions under conditions which give rise to little or no lowering of interfacial tension (98). Surface-tension measurements have been used to evaluate the properties of surface-active substances at a liquid/liquid phase boundary using coalescence of mercury spheres as a model (127). Many emulsifying agents are without appreciable influence on the surface tension of water, although it is axiomatic that low surface tension may favor ease of emulsification to the extent of spontaneity (61). However, the energy input to form an emulsion is surprisingly small. The energy required to form 1 L. of emulsion of 10% of discontinuous phase where the interfacial tension is 1 dyne/cm. is 0.7 cal. This value is quite low compared with the energy necessary to heat the emulsion 1° (42). Electrolytes increase the rigidity of surface films and thus may increase capillary activity and lower surface tension (20, 22). However, this latter may be the very factor that promotes coalescence. Oils with interfacial tensions against water of less than 42 dynes/cm. more readily form oil/water emulsions, but are not necessarily of the highest stability (77). Again, the interfacial film with the proper surfactant is most important. Alexander (4, 5) has surveyed the possible methods of measuring changes in the interfacial tension, viscosity, and potential at oil/

water interfaces and has considered the structure of such films (6).

The available evidence does not indicate that any of the soap films on dispersed particles are thicker than monomolecular (47). Calculations of surface areas and total numbers of molecules adsorbed yield an average area per molecule highly consistent with a monomolecular film (77, 114). The stability of emulsions with respect to the presence of adsorbed films at interfaces is attained by the formation of a coherent, mechanically strong gel oriented in a unimolecular layer (or tightly packed solid particles) (1, 6, 61, 62, 96) which also acts as a barrier to emulsion degradation by molecular diffusion (52). Intermolecular complexes at the oil/water interface between one component in the oil and one in the water can stabilize such interfaces (58, 113).

Phares (95) has recently proposed that reductions in water/oil interfacial tensions produced by hydrophilic and lipophilic surfactants acting simultaneously can be successfully predicted from the separate actions using a modified form of the Langmuir adsorption equation. The data indicated that the surfactants do not interact and that all interfacial adsorption sites behave alike.

The Gibbs adsorption isotherm has also been applied to obtain concentrations of surfactants at interfaces on the premise that the interfacial tension depends on the surfactant concentration (136, 150).

Optimum salt concentrations exist to stabilize the Gouy layer (20, 22).

At the critical micelle concentration (CMC) the maximum emulsifier concentration exists per unit surface area with the retention of a monolayer (101), and the emulsion stability is greatest. It may be assumed that polymolecular adsorbed films are formed when the soap concentration exceeds the CMC, and aggregation then occurs (24). The increase in CMC values of nonionic dispersants on urea addition has been attributed to the increased hydration of the ethylene oxide chain caused by a reduction of the "ordered" structure of water about the macromolecule (110).

Alexander (5) has reviewed the literature for the experimental methods for determining changes in the oil/water interfacial tension, interfacial viscosity, and interfacial potential. He also states that the achievement of interfacial tension equilibrium values at an oil/water interface is not a time-dependent process (4). Thus aging of emulsions may not be considered dependent on a lag time for orientation of dispersants at the oil/water interface of particles.

Effects of Preparative Methods.—There are many methods available for the preparation of emulsions. In addition to classical pharmaceutical practices, there are some exotic techniques. One such is ultrasonics (52, 78, 123) for which finer emulsions have been claimed than by more conventional techniques. Reproducible emulsions have been claimed by using a series of vibrating rollers in contact (155). Electrical dispersion may produce emulsions of more homogeneous particle sizes (89). An elegant modification was the passing of electrically charged monodispersed aerosols through a liquid medium containing an emulsifier (149). The more classical emulsifying equipment has been compared by preparing similar emulsions with varied emulsifiers (124). When the more common methods of shaking or stirring are varied, there are only slight changes in median particle diameters (47). Finer and more stable emulsions have been claimed from the formation of soaps *in situ*, viz., fat in oil, alkali in water, than from dissolution of soap in the water phase and subsequent shaking with the oil (61, 62). Specific interfacial area, as based on size-frequency distribution calculations, increased linearly with homogenization pressure (86, 87). When equidensity oil emulsions were prepared in the homogenizer, there was an increased frequency of large oil particles. It is believed that preparation of emulsions at higher temperatures will yield smaller particle sizes. However, the distinction between ease of formation of an emulsion and its subsequent stability is well recognized (25, 77), although homogenization procedures which produce smaller particles more resistant to coalescence than larger particles are considered to enhance emulsion stability (59). Plastic viscosity, thixotropy, and yield values of emulsions were altered by the temperatures of emulsification and the rates of cooling (17). Slow cooling minimized variations among emulsions. In contrast to the previous observation cited (59), the small particles favored by fast cooling produced emulsions that were more unstable (17). There were no significant differences visually, microscopically, or rheologically, regardless of whether the phase temperatures of the emulsion preparations were the same (17).

CONCENTRATION AND COMPOSITION FACTORS AFFECTING EMULSION STABILITY

The effect of the nature and composition of the oil phase has been considered previously.

Influence of Emulsifier.—There appeared to be little appreciable change in the distribu-

tion of particle size diameters when freshly made emulsions were prepared from various soap concentrations (47). However, larger numbers of oil particles are claimed to be produced with increased surfactant concentrations (26).

Notwithstanding this minor discrepancy, both studies noted that dilute soap emulsions tend to be more unstable on aging than those prepared with concentrated surfactant solutions. In the latter case (26), stability was considered increased when the rate of reduction in numbers of particles under centrifugal stress is considerably diminished. Increasing surfactant concentration causes decreasing median particle size, and the logarithm of the emulsified concentration is linearly related to the mass median diameter (106). This decrease in particle size and resistance to aging with increased concentrations of emulsifiers (106) is true even for insoluble solid emulsifiers (60, 75). Of course, the concomitant increase of viscosity with increasing emulsifier concentrations which was observed with high ratios of oil to water (134, 153) may favor resistance to creaming and the subsequent particle growth promoted by particle contact.

Increased stability also can be ascribed to the increased surface barrier to emulsion degradation by the molecular diffusion route (52).

In general, emulsion stability, as estimated from correlation with the variously proposed measurements, increases to a maximum with surfactant concentration and then tends to decline. In many cases the stability appears to be maximized at a critical concentration of surfactant (93). In the case of soaps this critical concentration increases with increasing electrolyte concentrations (36, 61).

Rehfeld (101) has demonstrated by ultracentrifugal techniques that increasing the surfactant concentration gives maximum stability at a concentration corresponding to the CMC of the surfactant. The rate of coalescence of the dispersed phase increases with decreasing surfactant below this CMC value. At the CMC, the area per adsorbed emulsifier molecule approaches the actual molecular cross section, and the mechanical stability of the adsorbed emulsifier is expected to be at its greatest (101).

In regard to these observations, it should be noted that the stability of a drop at an oil/water interphase increases with soap concentration to a value just slightly greater than the CMC of the soap (25). These phenomena have been attributed to a minimum in the rate of film drainage slightly shifted by a rate constant necessary for film rupture (25). The increase in surfactant concentration can take a relatively monodis-

persed system (at $<0.1\%$ AOT) and increasingly aggregate it. The aggregation is reversible on dilution of the surfactant (53). Increases have been noted in micellar size of nonionic surfactants in aqueous solution (by light scattering) above the CMC (by surface tension) until a critical concentration of surfactant is reached where the micellar size remains constant (9). The logarithm of the micellar molecular weight may be proportional to temperature. The defining of CMC on the basis of lowering of interfacial tension (88) has been criticized recently (95) on the basis that the effect of surfactant concentration can be explained completely without considering CMC.

The free energy of micelle formation decreases with increases in the chain length of a nonionic detergent. The free energy change per methylene group appears to be constant and is accompanied by a decrease in ΔH and an increase in ΔS (27). The net result is a tendency to larger enthalpy and smaller entropy increments as the chain lengths increase. If the detergent molecule achieves a configuration to minimize the surface volume ratio, a decreasing entropy increase may be expected if the total increase in entropy which governs the micellization process arises from the desolvation of the detergent molecules in the process of aggregation (27).

The effects of kinds of emulsifiers on emulsion preparation have been replete in the literature, especially with regard to mixed surfactants and HLB systems (11, 12, 44, 104, 105) or different mixtures of oil- and water-soluble surfactants (128), so there is little need to review this here. Optimum surfactant blends described for emulsions (44) cannot be explained by producing a minimum surface tension between oil and water (95). However, a brief mention of procedural methods that have been used to determine emulsion stability with variations in emulsifiers may be of interest. No significant difference on particle size distribution of oil/water emulsions was observed when the hydrocarbon chain lengths of several sodium soaps were varied in one study (47), although the stability ranking was oleate $>$ stearate $>$ palmitate $>$ rosin in another (62). The potassium and sodium soaps were similar in stabilization, but the ammonium soaps were much inferior, as determined by changes in particle size distribution (62). It was again observed that ability to disperse is not necessarily related to the maintenance of an emulsion by this criterion of emulsion stability (63). Gelatin does not disperse as well as soap, but the latter deteriorates more readily (61). Gelat-

inous alumina also gives coarser dispersions but more stable ones.

There was no observed difference in stability under ultracentrifugal stress and as monitored by particle size and numbers for several emulsifiers (*viz.*, sodium oleate and nonionics) examined (26). Acacia was poorer than some polysorbates in the preparation of emulsions with better specific interfacial areas (86). Beeswax, a thixotropic emulsifier, was not significantly different than other dispersants in its effects on decreasing specific interfacial area with time (87).

Influence of Addends.—Growth and coalescence of soap-emulsified emulsions may be accelerated by HCl and CaCl_2 addition (62). Salt addition produces coarser and less stable emulsions. When electrostatic repulsion is involved, electrolytes influence flocculation according to the Schulze-Hardy rule (92, 152). Size-frequency measurements show there is an initial decrease in the specific interfacial area on the addition of K_2SO_4 , probably due to the salting out of soap adsorbed at the interface (61). This phenomenon is most marked at lower soap concentrations. Salts lower the soap concentration necessary to initiate aggregation. This aggregation appears to be reversible (24). Salts and alkanols inhibit deaggregation (69, 70). In general, only ionized monolayers are affected by salts, and only ions of opposite sign to the film have an appreciable effect. More complete references on this subject are available (20).

W. Higuchi has shown that an oil that is miscible with the major oil that is dispersed, but highly immiscible with water, diminishes instability by the molecular diffusion route (52). The addition of urea forms complexes with polyoxyethylene surfactants and inhibits the structural formation of micelles which may be considered ordered (110). In this study surface-tension methods obtained the CMC values which increased with urea concentration.

The effect of adding aliphatic alcohols on the CMC was correlated with the aggregation of particles as measured by the visually observed rate of creaming (24). The effects of pH on the electrophoretic mobility of oil/water emulsions have been studied (32, 45). Hydrocarbon and alkyl halide oil/water emulsions demonstrated a small positive charge at low pH and an increasing negative charge until a constant value is reached at pH 9 (32).

Influence of Volume Concentration of the Dispersed Phase.—Increases in the volume concentration of the dispersed phase yield only slight increases in viscosity up to a critical con-

centration. Above this value, there is a sudden rise to a maximum, instability, and inversion (8, 18, 19, 66, 82, 115). No significant effects of phase volume of oil between 10 and 25% were observed on the rate of visual creaming which was used to estimate rate of aggregation (24). However, on theoretical grounds and by experimental observation, it has been shown that electrical charges cannot be expected to stabilize water-in-oil emulsions of more than extremely low concentrations against flocculation (2, 25).

T. Higuchi (49) has argued that when the emulsion has a high volume of dispersed phase, the basic assumptions of the Stokes equation are no longer applicable. He turned the problem around for such concentrated systems and did not consider the suspended particles falling (or rising) in the continuous medium, but considered the medium to flow through a bed of solid immovable internal phase in accordance with the Kozeny expression. The assumptions for this model would include no change in the composition of the dispersed phase due to differential velocities of small and large particles, *i.e.*, the mass of the dispersed phase is relatively closely packed. This model possibly may be modified to include adjustment of particles in the packed bed with time to simulate the sweep-out phenomenon which should be characteristic of the clearance of a concentrated emulsion. The creaming of the finer particles of a dilute (about 14%) oil/water emulsion follows the Stokes relations (37, 41) until the cream is closely packed. It is very possible that the drainage of continuous phase from the closely packed cream would be closer to the Kozeny expression and that the creaming of high ratios of oil/water emulsions would not follow either the Stokes or Kozeny relationships.

STRESS FACTORS AFFECTING EMULSION STABILITY: HEAT AND TEMPERATURE

It has been well known that the breaking of emulsions has been accelerated by thermal stress. However, size-frequency and specific interface methods show that thermal effects are greater for some systems than for others and that there is no real basis for comparison (16, 61, 62, 86, 154). In many cases the physical instability may be concomitant with chemical instability which is also thermally activated (16, 37). Low temperatures may precipitate emulsifiers and thereby change emulsion characteristics (133).

The stability of large drops that collide with an interface, *i.e.*, a flat liquid-liquid interface, increases with decreasing temperature (21, 91). It has been claimed that with such an interface stability increases with increasing drop size (21),

although arguments have been presented also that stability of a drop can either decrease or increase as the size of the drop changes (91).

There does not yet appear to be any clearly definable relation between temperature and the rates of change of quantifiable parameters used to evaluate emulsion stability (154). Solubilities of each phase in the other may be complex functions of temperature (133). Nevertheless, Levius and Drommond (73) suggest that about 30° is the temperature of maximum stability and that short-time stability tests performed at elevated temperatures will give some reliable information as to the comparative behavior of emulsions under normal storage conditions, and urge further work. Although emulsions stored at higher temperatures show greater deterioration in specific interfacial area (16, 86) it is believed that emulsions prepared at higher temperatures give the smaller particle sizes conducive to higher stability (87). In many instances there exists a phase-inversion temperature above which oil/water emulsions revert to a water/oil type, and this temperature is lowered by the increased solubility of the surfactant in the oil (119). The importance of hydrophilic emulsifiers in preserving emulsion stability in preparations that undergo high-temperature homogenization and sterilization is readily understandable (13).

AGING AND TIME

It appears indisputable that aging of an emulsion, wherein such aging includes normal thermal and gravitational stresses, results in an increase in mean particle diameter and concomitant decreases in specific interfacial area (16, 47, 60, 62, 64, 67, 86, 87). Sherman (117, 118) claims that if the major change is in the mean globular size, there should be an accompanying decrease in emulsion viscosity which should permit prediction of mean globular size with aging. He gives equations for such prediction.

Claims have been made that the logarithm of an emulsion property which changes on aging when plotted against the logarithm of time is sufficiently linear to be used as a predictive method (154).

This relation has been claimed for phase separation (79) and for creaming rates (7) as well as viscosity (154). In some cases, the relationship between average diameters and specific areas with time has been found to be approximately linear (59, 62).

Aging by Molecular Diffusion.—The mean particle-size enlargement on aging could be

by molecular diffusion which is applicable in those instances where the oil has a finite solubility in the water phase (52). When an aqueous phase is not saturated with the oil, the smaller particles dissolve first (50), consistent with the preferential dissolution of smaller size crystals (51). W. Higuchi made the interesting proposal that the incorporation of a small amount of a third component in the internal phase could stabilize particle sizes. Such a component should be highly miscible with the oil but highly immiscible with water (52). This phenomenon is consistent with the observation that mutually saturated phases give longer lifetimes to drop coalescence with an interface than unsaturated phases (91).

Aging and Aggregation.—The extent of equilibrium aggregate formation is time dependent, as is the extent of deaggregation under lessened surfactant concentration (24, 53).

The Coulter counter was used by W. Higuchi (50, 53) in such studies, whereas rates of creaming also have been used as a chief criterion of aggregation (24). Ultracentrifugation can also study aggregation phenomena (101). Rate-dependent aggregation also may affect rheology (53), creaming rates (24), and thus coalescence (54). The sequence of collision, aggregation and coalescence can be formulated as based on an initial bimolecular process for the minimum collision frequency where Brownian motion is involved (54). It is interesting to note (54) that the observed diffusion-controlled rate is somewhat less than that predicted by Smoluchowski (147, 148).

The basis for relations between the numbers of aggregate and time is founded on the concepts of Smoluchowski (147, 148), who assumed that in the rapid coagulation of particles of equal size, one particle becomes permanently fixed to another when the two approach within a certain minimum distance, R . Aggregation occurs when R is less than twice the particle radius, r , *i.e.*, $R < 2r$. The simplest equation which gives the rate of disappearance of simple primary particles by a bimolecular process to obtain doublets when all collisions are effective is

$$n_1 = \frac{n_0}{(1 + \beta t)^2} \quad (\text{Eq. 4})$$

where n_0 is the number of primary particles in a unit volume at zero time, and n_1 is the number of particles at time, t , where β is a constant equal to $4DRn_0$, where D is the diffusion coefficient. The factor, β , can include a factor representing the fraction of collisions that are effective in the slow aggregation process. The expression appears to have experimental validity (59). A modern

review of the experimental verification and modification of the equation has been given recently by Banerjee (10), who has studied the coagulating effects of electrolytes on colloidal sols. Gillespie (39) has considered the effect of size distribution on the rate constants for collisions in disperse systems and points out that polydispersivity increases the rate constant for diffusion-controlled collisions but reduces the rate constant for shear-induced collisions.

As evidenced by creaming or sedimentation rates, the addition of electrolytes to emulsions or suspensions enhances the aggregation tendency of particles (24, 43, 84) due to a reduction in the zeta potential. Consistent with this, deaggregation rates, as measured directly by means of the Coulter counter, were reduced by and directly related to the concentrations of various sodium salts (69). The rates of deaggregation increased as the temperature was increased, but no adherence to the Arrhenius relation was observed in the temperature range studied. Lemberger and Mourad (70) also studied the inhibitory effect of various alkanols and dioctyl sodium sulfosuccinate on deaggregation rate and concluded that both reduction in zeta potential and film-film interactions are important in the enhancement of aggregation.

The maximum in aggregation occurs with the maximum in particle-particle sticking and in many cases occurs at soap concentrations considerably higher than the CMC (24).

Electrical Factors.—Positive and negative ions distribute themselves between the oil phase and the water phase to charge the oil droplets (42, 140). There is an excess of one ionic type in the oil, and the gradient decreases toward the center of the oil droplet. The first layer about the oil droplet, the "solvation layer," consists of strongly bound water molecules and hydrogen atoms which are oriented with respect to their charge. This is considered as the Stern layer and possesses a given potential with respect to a distant point in the aqueous phase (29, 31, 130, 136). A second diffuse double layer surrounds the solvation layer and is the Gouy layer (136). The arbitrary sphere that separates these layers is the surface of shear. A potential difference exists at this surface (136, 140–142). The electrostatic interaction between charged oil globules in water is determined by the potential drop at the aqueous side of the interface. The zeta potential is the electrokinetic potential in the secondary or diffuse layer (152). The calculation of potential functions has been well outlined by Van den Tempel (136), who has calculated the

potential of the Stern layer which is practically independent of soap concentration and decreases nearly linearly with increasing salt concentration. The zeta potential can be calculated from electrophoretic measurements (136) and confirms his estimated potentials of the Stern layer. The amount of adsorbed soap ions had been determined by measuring the dependency of the interfacial tension on the soap concentration (136).

In contrast with these expectations of electrostatic interactions, Albers and Overbeek (1) had not observed any correlation between stability against flocculation or coalescence and electrokinetic potential in rapidly flocculating oil-in-water emulsions. However, their theoretical calculations (2, 3) predict a reduction in energy barrier between charged droplets at higher oil/water ratios, so that a high concentration in the sediment (or cream) should promote flocculation, so that electrical charges cannot be expected to stabilize water-in-oil emulsions of more than extremely low concentration. It is also predicted that such emulsions cannot be protected sufficiently against flocculation by an adsorbed layer of amphipolar molecules, although they can be redispersed by moderate rates of shear as evidenced by viscosity measurements (3).

Aging and Coalescence.—The subsequent rate-determining step is the rapidity whereby the particles can overcome the potential barrier between them (54, 109). This latter may be considered as two processes analogous to the case of a drop at an oil/water interface (25, 91), where the drainage of the continuous phase from between the drops within an aggregate precedes the surmounting of an energy barrier, the rupture of the adsorbed film, and subsequent coalescence (40, 101, 117) which may be expected to be a first-order process (137). It may be expected that coalescence rather than aggregation may be the rate-determining process for emulsion instability in concentrated emulsions with respect to dilute emulsions (137, 145). Since most emulsions are not monodisperse, the size distribution may become progressively broader (117). Since coalescence is related to the rate of drainage of thin films separating globules, the probability of rupture should be directly related to the thickness of the film (40) and the contact surface area (54). Thus, the rate of coalescence should be determined by the average lifetime of the films separating the droplets (139). The coalescence of drops occurs on the localized displacement of stabilizer molecules at the interface and is to be resisted by the viscosity and elasticity of the film (38). The more rigid a film about a drop, as im-

parted by a stabilizer, the more resistant are the drops to coalescence (22, 91, 132).

Centrifugation.—Although centrifugation has been considered in a casual manner in the evaluation of emulsion stability and properties, little quantitative study and prediction has been effected until recently with the use of the modern analytical ultracentrifuge (37, 90, 101, 143–146).

Centrifugation has been of importance at relatively low centrifugal rates in the creaming of emulsions, such as in the dairy industry, but experimental investigations of emulsions with this tool have been severely limited (11). To quote Becher (11): "To be sure, creaming may be accelerated by centrifugation, indeed the ultracentrifuge has been used, albeit rarely, for this purpose."

Until 1962, the only application of the analytical ultracentrifuge by others to emulsion investigations was a study on the particle-size distribution of a Nujol emulsion by this technique (90).

Greenwald (42) considered the application of the Stokes equation to the creaming of an emulsion and the effect of sedimentation velocity as based on the fundamental equations of sedimentation.

The use of the low-speed clinical centrifuge up to 3600 r.p.m. has been applied by Merrill (80). The results from this applied stress in measurement of the rate of separation of the internal phase was considered as a quantitative index of the mechanical stability of emulsions.

Cockton and Wynn (26) have claimed that spinning of an emulsion at 20,000 r.p.m. with time produced a suitable degree of progressive deterioration and stated that the logarithm of the root mean cube diameter of the particles is linearly related to the time of centrifuging, *i.e.*, the logarithm of the numbers of particles decreases linearly with time.

The classical methods of evaluating emulsion stability included previously mentioned techniques that determined the size of particles and established frequencies of occurrence in various size classifications. A major criticism of such a technique is that in fine emulsions only a small fraction of total amount of the dispersed phase can be characterized, and the distribution of the smaller particles can be estimated only by mathematical correlation of size and frequency with subsequent extrapolation. Such counting techniques are exceedingly tedious.

Methods of measuring the stability of emulsions in terms of changes in interfacial area

or drop volume may be very insensitive to small but important changes occurring in the emulsion and may be useful only in unstable emulsions (143, 144). Emulsion stability frequently has been determined by measuring the formation of cream and the separate oil phase as a function of time, but has been largely restricted to normal gravitational situations (22, 25, 62, 63, 65, 68). The enormous time lags involved and the uncertainties of complete phase separation are definite disadvantages of such methods, and in general they are only applicable to poor and unstable emulsions.

Garrett (37), Vold and Groot (143, 145, 146), and Rehfeld (101) have demonstrated that the analytical ultracentrifuge is an excellent tool for the evaluation of emulsion stability. The determination of rates of flocculation, flotation, or creaming of a dispersed oil phase can be correlated with the Svedberg relations applied to the sector-shaped cell of the analytical ultracentrifuge (129, 131).

The clearing rate of not too concentrated emulsions adheres to the Svedberg equation and is valid for the prediction of such rates at stresses approaching that of normal gravity (37). This rate does not necessarily permit classification as a "good" or "bad" emulsion, however, since it is most probable that the clearing of the smallest particles is what is measured in both emulsion types. Such definitions of emulsions are peculiarly arbitrary and frequently operationally defined. In the case studied (37) the operational definition of a good emulsion was one which with vigorous shaking for 72 hr. at 5° demonstrated no oil phase appearance and essentially no change in particle size of the dispersed phase. However, rates of coalescence under high centrifugal stress were consistent with these criteria for good and bad emulsions (37).

It has also been shown that coalescence rates in ultracentrifugation are relatively independent of dispersing agent concentration after the CMC is reached (101, 143, 146) but are proportional until the equilibrium concentration in the aqueous phase reaches the CMC. This is postulated to be due to the achievement of the potential maximum adsorption of the surfactant at the oil/water interface.

Many emulsions at their time of constitution cannot be coalesced under gravitational effects until the phenomenon of aging occurs (37, 143). At relatively low oil/water ratios (0.14) in one emulsion system, a good emulsion demonstrated an induction period at high r.p.m. values of the ultracentrifuge before a continuous oil phase

could be observed. This may indicate a "yield" value, a definite energy requirement, before the "skin" of the adhered mass of particulate oil, the cream, is fractured (37). In another and different emulsion system of a high oil/water ratio (0.5), the induction period was not apparent (143). The rapid spin-out of a fraction of the oil from the cream in the latter case agreed with that observed in the former for bad emulsions.

After the induction period observed with the emulsion system of the low oil/water ratio (37), the rate of coalescence accelerated (37), and the acceleration rate is a function of the r.p.m. (37, 146) and may be considered a measure of the toughness of particle skin and the ease of coalescence of different particle sizes. This is consistent with prior observations (59, 91) that the greater the force pushing a drop against an interface, the shorter the lifetime of the drop. Also, the large globules in the emulsion separate from the bulk more readily than the smaller ones, so that after a sufficient time interval, the proportion of smaller globules is higher and the emulsion has a finer dispersion than fresh emulsion (59).

A consistent model for these phenomena may be the more ready flotation of large oil particles so that the cream is a grading of large to small oil particles from top to bottom in low oil/water ratios (37). This may not occur in the case of high oil/water ratios (143) where the phenomenon of sweep-out may occur (37). Higher centrifugal speeds for a given oil/water ratio may also promote sweep-out phenomenon, and the cream may not have any stratification (143). The continuous phase has to drain from the packed globules which will be deformed by the centrifugal stress (37, 143). It has been postulated (91) that the more an interface curves away from a drop, the longer the lifetime of a drop. It is consistent with this premise that the more readily deformable large drops should coalesce first.

Vold and Groot (144, 145) have shown that the rate of separation of oil from an emulsion under centrifugal stress decreases linearly with the increasing logarithm of the concentration of sodium ion in solution which was essentially the salt concentration. Concomitantly, the fraction of saturation adsorption of the surfactant of the oil/water interface increases linearly with the logarithm of the salt concentration. The increased stability of these emulsions on addition of salt under ultracentrifugation is attributed to increased coverage of the oil surface with adsorbed surfactant which possibly changes the rheological characteristics of the film (144, 145).

This is not consistent with statements by Albers and Overbeek (1, 2) that the greater the concentration of the sediment or the cream, the less the effect of electrostatic repulsion due to the zeta potential. Vold and Groot (146) also have demonstrated that ultracentrifugal stability to coalescence decreases with decreasing interfacial area at equal equilibrium concentrations of surfactant. An interesting anomaly of a higher stability to coalescence of coarser emulsions may result if the per cent surfactant is held constant since the equilibrium concentrations of surfactant may be greater than in the case of finer emulsions. The rate of separation of oil is directly proportional to the strength of the applied centrifugal field and varies inversely with the specific interfacial area of the emulsion. Vold and Groot have hypothesized that the rate of oil separation is a measure of the rate of coalescence between the deformed drops in the cream and the bulk oil phase, and the great coalescence in general occurs just below the bulk oil-emulsion interface since water separating the dispersed oil is thinnest there.

There is little doubt that ultracentrifugal stress can give insight into the effects of parameters on emulsion stability in a short time with greater quantification and less tedium than the prior methods described. However, many empirical correlations of the results of such experiments with long-term observations are necessary to establish whether the results from ultracentrifugal stress can be used to predict stability under gravitational conditions.

REFERENCES

- (1) Albers, W., and Overbeek, J. Th. G., *J. Colloid Sci.*, **14**, 501(1959).
- (2) *Ibid.*, **14**, 510(1959).
- (3) *Ibid.*, **15**, 489(1960).
- (4) Alexander, A. E., *Trans. Faraday Soc.*, **37**, 15(1941).
- (5) *Ibid.*, **37**, 117(1941).
- (6) *Ibid.*, **37**, 426(1941).
- (7) Appino, J. B., Christian, J. E., and Banker, G. S., *J. Pharm. Sci.*, **51**, 254(1962).
- (8) Axon, A., *J. Pharm. Pharmacol.*, **8**, 762(1956).
- (9) Balmbr, R. R., et al., *Trans. Faraday Soc.*, **60**, 979(1964).
- (10) Banerjee, S., and Bannerjee, J., *Kolloid-Z.*, **190** (1), 57(1963).
- (11) Becher, P., "Emulsions, Theory and Practice," Reinhold Publishing Co., New York, N.Y., 1962.
- (12) Becher, P., *Am. Perfumer Cosmet.*, **7**, 21(1962).
- (13) Benerito, R. R., and Singleton, W. S., *J. Am. Oil Chemists' Soc.*, **33**, 364(1956).
- (14) Berkman, S., *J. Phys. Chem.*, **39**, 527(1935).
- (15) Bikerman, J. T., "Surface Chemistry," Academic Press Inc., New York, N.Y., 1958.
- (16) Boberg, J., and Hakansson, I., *J. Pharm. Pharmacol.*, **16**, 641(1964).
- (17) Boylan, J. C., DeKay, H. G., and Banker, G. S., *J. Pharm. Sci.*, **51**, 742(1962).
- (18) Bredee, H. L., and Booy, J. de, *Kolloid-Z.*, **91**, 39(1940).
- (19) Broughton, G., and Squires, L., *J. Phys. Chem.*, **42**, 253(1938).
- (20) Cassie, A. B. D., and Palmer, R. C., *Trans. Faraday Soc.*, **37**, 156(1941).
- (21) Charles, G. E., and Mason, S. G., *J. Colloid Sci.*, **15**, 236(1960).
- (22) Cheesman, D. F., and King, A., *Trans. Faraday Soc.*, **36**, 241(1940).

- (23) Clayton, W., "Theory of Emulsions," The Blakiston Co., Philadelphia, Pa., 1943.
- (24) Cockbain, E. G., *Trans. Faraday Soc.*, **48**, 185(1952).
- (25) Cockbain, E. G., and McRoberts, T. S., *J. Colloid Sci.*, **8**, 440(1953).
- (26) Cockton, J. R., and Wynn, J. B., *J. Pharm. Pharmacol.*, **4**, 959(1952).
- (27) Corkill, J. M., Goodman, J. F., and Tate, J. R., *Trans. Faraday Soc.*, **60**, 986, 996(1964).
- (28) Coulter Electronics Co., Hialeah, Fla.
- (29) Davies, J. T., *Trans. Faraday Soc.*, **47**, 414(1951).
- (30) Davies, J. T., and Rideal, E. K., "Interfacial Phenomena," Academic Press Inc., New York, N.Y., 1961.
- (31) de Bruyn, H., *Rec. Trav. Chim.*, **61**, 193(1942).
- (32) Dickinson, W., *Trans. Faraday Soc.*, **37**, 140(1941).
- (33) Einstein, A., *Ann. Phys. Leipzig*, **19**, 289(1906).
- (34) *Ibid.*, **24**, 591(1911).
- (35) Espenscheid, W. F., Kerker, M., and Matijevic, E., *J. Phys. Chem.*, **68**, 3093(1964).
- (36) Fischer, E. K., and Harkins, W. D., *ibid.*, **36**, 98(1932).
- (37) Garrett, E. R., *J. Pharm. Sci.*, **51**, 35(1962).
- (38) Gibbs, J. W., "Collected Works," vol. I, London, England, 1928, pp. 300-314.
- (39) Gillespie, T., *J. Colloid Sci.*, **18**, 562(1963).
- (40) Gillespie, T., and Rideal, E. K., *Trans. Faraday Soc.*, **52**, 173(1956).
- (41) Glasstone, S., "Textbook of Physical Chemistry," 2nd ed., D. Van Nostrand Co., Inc., New York, N.Y., 1946, pp. 497-498, 1256-1258.
- (42) Greenwald, H. L., *J. Soc. Cosmetic Chemists*, **5**, 164(1954-1955).
- (43) Greiner, L., and Vold, R. D., *J. Phys. Colloid Chem.*, **53**, 67(1949).
- (44) Griffin, W. C., *J. Soc. Cosmetic Chemists*, **1**, 311(1949).
- (45) Growney, G., *Trans. Faraday Soc.*, **37**, 148(1941).
- (46) Harkins, W. D., "The Physical Chemistry of Surface Films," Reinhold Publishing Co., New York, N.Y., 1952.
- (47) Harkins, W. D., and Beeman, N., *J. Am. Chem. Soc.*, **51**, 1674(1929).
- (48) Hayter, A. J., *J. Soc. Cosmetic Chemists*, **13**, 152(1962).
- (49) Higuchi, T., *J. Am. Pharm. Assoc., Sci. Ed.*, **47**, 657(1958).
- (50) Higuchi, W. I., *J. Pharm. Sci.*, **53**, 405(1964).
- (51) Higuchi, W. I., and Hiestand, E. N., *ibid.*, **52**, 67(1963).
- (52) Higuchi, W. I., and Misra, J., *ibid.*, **51**, 459(1962).
- (53) Higuchi, W. I., Okada, R., and Lemberger, A. P., *ibid.*, **51**, 683(1962).
- (54) Higuchi, W. I., et al., *ibid.*, **52**, 49(1963).
- (55) Higuchi, W. I., Rowe, E. L., and Hiestand, E. N., *ibid.*, **52**, 162(1963).
- (56) Hirose, M., *J. Soc. Chem. Ind. Japan*, **30**, 823(1927).
- (57) Jellinek, H. H. G., *J. Soc. Chem. Ind.*, **69**, 225(1950).
- (58) Jellinek, H. H. G., and Anson, H. A., *ibid.*, **68**, 108(1949).
- (59) *Ibid.*, **69**, 229(1950).
- (60) Jowdy, A. W., and Brecht, E. A., *J. Am. Pharm. Assoc., Sci. Ed.*, **46**, 88(1957).
- (61) King, A., *Trans. Faraday Soc.*, **37**, 168(1941).
- (62) King, A., and Mukherjee, L. N., *J. Soc. Chem. Ind.*, **58**, 243(1939).
- (63) *Ibid.*, **59**, 185(1940).
- (64) Knoechel, E. L., and Wurster, D. E., *J. Am. Pharm. Assoc., Sci. Ed.*, **48**, 1(1959).
- (65) Kraemer, E. O., and Stamm, A. S., *J. Am. Chem. Soc.*, **46**, 2709(1924).
- (66) Kremann, R., Griengl, F., and Schreiner, H., *Kolloid-Z.*, **62**, 61(1933).
- (67) Kremner, L. V., Nerpin, S. V., and Kuibina, N. I., *Doklady Akad. Nauk. S.S.S.R.*, **109**, 1152(1956); through *Chem. Abstr.*, **51**, 13513c(1957).
- (68) Lederer, E. L., *Kolloid-Z.*, **71**, 61(1953).
- (69) Lemberger, A. P., and Mourad, N., *J. Pharm. Sci.*, **54**, 229(1965).
- (70) *Ibid.*, **54**, 233(1965).
- (71) Leviton, A., and Haller, H., *J. Phys. Colloid Chem.*, **51**, 460(1947).
- (72) Leviton, A., and Leighton, A., *J. Phys. Chem.*, **40**, 71(1936).
- (73) Levius, H. P., and Drommond, F. G., *J. Pharm. Pharmacol.*, **5**, 743(1953).
- (74) Lloyd, N. E., *J. Colloid Sci.*, **14**, 441(1959).
- (75) Lucassen-Reynders, E. H., and Van den Tempel, M., *J. Phys. Chem.*, **67**, 731(1963).
- (76) Maron, S. H., and Fok, S. M., *J. Colloid Sci.*, **8**, 540(1953).
- (77) Martin, A. R., and Hermann, R. N., *Trans. Faraday Soc.*, **37**, 25(1941).
- (78) McCarthy, W. W., *Drug Cosmetic Ind.*, **94**, 821(1964).
- (79) Mencil, E., Rabinovitz, M., and Madjor, A., *Am. J. Hosp. Pharm.*, **17**, 613(1960).
- (80) Merrill, R. C., Jr., *Ind. Eng. Chem., Anal. Ed.*, **15**, 743(1943).
- (81) Meyer, C. E., et al., *Metab. Clin. Exptl.*, **6**, 591(1957).
- (82) Monson, L., *Ind. Eng. Chem.*, **30**, 1287(1938).
- (83) Mooney, M., *J. Colloid Sci.*, **6**, 162(1951).

- (84) Moore, A., and Lemberger, A. P., *J. Pharm. Sci.*, **52**, 223(1963).
- (85) Mueller, J. F., and Canham, J. E., *J. Clin. Nutr.*, **16**, 1(1965).
- (86) Mullins, J. D., and Becker, C. H., *J. Am. Pharm. Assoc., Sci. Ed.*, **45**, 105(1956).
- (87) *Ibid.*, **45**, 111(1956).
- (88) Mysels, K. J., "Introduction to Colloid Chemistry," Interscience Publishers, Inc., New York, N.Y., 1959.
- (89) Nawab, M. A., and Mason, S. G., *J. Colloid Sci.*, **13**, 179(1958).
- (90) Nichols, J. B., and Bailey, E. D., in Weisberger, A., ed., "Techniques of Organic Chemistry," 2nd ed., vol. I, Part I, International Publishers, Inc., New York, N.Y., 1949, pp. 673-679.
- (91) Nielsen, L. E., Wall, R., and Adams, G., *J. Colloid Sci.*, **13**, 441(1958).
- (92) Osipow, L. I., "Surface Chemistry," Reinhold Publishing Co., New York, N.Y., 1962.
- (93) Osipow, L., Birsan, S., and Snell, F. D., *J. Am. Oil Chemists' Soc.*, **34**, 34(1957).
- (94) Peck, G. E., DeKay, H. G., and Banker, G. S., *J. Am. Pharm. Assoc., Sci. Ed.*, **49**, 75(1960).
- (95) Phares, R. E., *J. Pharm. Sci.*, **54**, 408(1965).
- (96) Pink, R. C., *Trans. Faraday Soc.*, **37**, 180(1941).
- (97) Powney, J., and Jordan, D. O., *ibid.*, **34**, 363(1938).
- (98) Powney, J., and Wood, L. J., *ibid.*, **37**, 152(1941).
- (99) Rajagopal, E. S., *Kolloid-Z.*, **167**, 17(1959).
- (100) Rehlinger, P. A., and Wenström, E., *ibid.*, **53**, 145(1930).
- (101) Rehfeld, S. J., *J. Phys. Chem.*, **66**, 1966(1962).
- (102) Richardson, E. G., *J. Colloid Sci.*, **5**, 404(1950).
- (103) *Ibid.*, **8**, 367(1953).
- (104) Riegelman, S., and Pichon, G., *Am. Perfumer*, **77**, (2), 31(1962).
- (105) Ross, S., et al., *J. Phys. Chem.*, **63**, 1681(1959).
- (106) Rowe, E. L., *J. Pharm. Sci.*, **54**, 260(1965).
- (107) Saunders, F. L., *J. Colloid Sci.*, **16**, 13(1961).
- (108) Sasaki, W., and Malone, M. H., *J. Pharm. Pharmacol.*, **12**, 523(1960).
- (109) Schenkel, J. H., and Kitchener, J. A., *Trans. Faraday Soc.*, **56**, 161(1960).
- (110) Schick, M. J., *J. Phys. Chem.*, **68**, 3585(1964).
- (111) Schubert, O., *Nutr. Dieta*, **5**, 387(1963).
- (112) *Ibid.*, **6**, 43(1964).
- (113) Schulman, J. H., and Cockbain, E. G., *Trans. Faraday Soc.*, **36**, 651(1940).
- (114) Schulman, J. H., and Hughes, A. H., *Biochem. J.*, **29**, 1236(1935).
- (115) Sherman, P., *J. Soc. Chem. Ind.*, **69**, 570(1950).
- (116) Sherman, P., *Kolloid-Z.*, **141**, 6(1955).
- (117) Sherman, P., *J. Phys. Chem.*, **67**, 2531(1963).
- (118) Sherman, P., *J. Pharm. Pharmacol.*, **16**, 1(1964).
- (119) Shinoda, K., and Arai, H., *J. Phys. Chem.*, **68**, 3485(1964).
- (120) Shotton, E., and White, R. F., *J. Pharm. Pharmacol.*, **12**, 108T(1960).
- (121) Sibree, J. O., *Trans. Faraday Soc.*, **27**, 161(1931).
- (122) Simka, R., *J. Appl. Phys.*, **23**, 1020(1952).
- (123) Singiser, R. E., and Beal, H. M., *J. Am. Pharm. Assoc., Sci. Ed.*, **49**, 482(1960).
- (124) Siragusa, J. M., Husa, W. J., and Becker, C. H., *Am. J. Pharm.*, **129**, 152(1957).
- (125) Smith, R. C., and Dow, I. C., *J. Phys. Chem.*, **31**, 1263(1927).
- (126) Smith, E. L., and Grinling, G. N., *Quart. J. Pharm. Pharmacol.*, **3**, 354(1930).
- (127) Sonntag, H., *Z. Physik Chem. Leipzig.*, **221**, 365(1962).
- (128) Sonntag, H., and Klare, H., *ibid.*, **223**, 8(1963).
- (129) "Spinco Ultracentrifuge Technical Manual, Model E," Spinco Division, Beckman Instrument Co., Inc., Fullerton, Calif., October 1953.
- (130) Stern, O., *Z. Elektrochem.*, **30**, 508(1924).
- (131) Svedberg, T., and Pederson, K. O., "The Ultracentrifuge," Clarendon Press, New York, N.Y., 1940.
- (132) Taubman, A. B., and Korestskii, A. F., *Kolloidn.-Zh.*, **20**, 676(1958); through *Chem. Abstr.*, **53**, 11948e(1959).
- (133) Tingstad, J. E., *J. Pharm. Sci.*, **53**, 955(1964).
- (134) Toms, B. A., *J. Chem. Soc.*, **1941**, 542.
- (135) U.S. pat. 2,945,869.
- (136) Van den Tempel, M., *Rec. Trav. Chim.*, **72**, 419(1953).
- (137) *Ibid.*, **72**, 433(1953).
- (138) *Ibid.*, **72**, 442(1953).
- (139) Van den Tempel, M., in "Second International Congress of Surface Activity," Schulman, J. H., ed., vol. I, Academic Press Inc., New York, N.Y., 1957, p. 439.
- (140) Verwey, E. J. W., *Chem. Rev.*, **16**, 363, 388(1935).
- (141) Verwey, E. J. W., *Trans. Faraday Soc.*, **36**, 192(1940).
- (142) Verwey, E. J. W., and Niessen, K. F., *Phil. Mag.*, **28**, 435(1939).
- (143) Vold, R. D., and Groot, R. C., *J. Phys. Chem.*, **66**, 1969(1962).
- (144) Vold, R. D., and Groot, R. C., *J. Soc. Cosmetic Chemists*, **14**, 233(1963).
- (145) Vold, R. D., and Groot, R. C., *J. Colloid Sci.*, **19**, 384(1964).
- (146) Vold, R. D., and Groot, R. C., *J. Phys. Chem.*, **68**, 3477(1964).
- (147) Von Smoluchowski, M., *Physik. Z.*, **17**, 557, 585(1916).
- (148) Von Smoluchowski, M., *Z. Physik. Chem.*, **92**, 129(1917).
- (149) Wachtel, R. E., and La Mer, V. K., *J. Colloid Sci.*, **17**, 531(1962).
- (150) Weiner, N. D., and Zograf, G., *J. Pharm. Sci.*, **54**, 436(1965).
- (151) White, M. G., and Marsden, J. W., *J. Phys. Chem.*, **24**, 619(1920).
- (152) Wieser, H. B., "Colloid Chemistry," John Wiley & Sons, Inc., New York, N.Y., p. 2.
- (153) Wilson, C. L., and Parke, J. B., *Quart. J. Pharm. Pharmacol.*, **9**, 188(1936).
- (154) Wood, J. H., and Catacalos, G., "Prediction of the Rheologic Aging of Cosmetic Lotions," Presented to the Society of Cosmetic Chemists, New York City, September 1962.
- (155) Zettlemoyer, A. C., Buckingham, J. S., and Schaeffer, W. D., *J. Colloid Sci.*, **18**, 104(1963).