_____Review Article___

Particle-Size Analysis of Emulsion Systems

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BECHER (1) reviewed the definitions of an emulsion and suggested the following as a basis for discussion: "An emulsion is a heterogeneous system, consisting of at least one immiscible liquid intimately dispersed in another in the form of droplets, whose diameters, in general, exceed 0.1 μ. Such systems possess a minimal stability, which may be accentuated by such additives as surface active agents, finely divided solids, etc." Becher's definition is satisfactory on most counts. His limitation on the lower size of the disperse phase particles is clearly not intended to be anything other than a broad generalization. Indeed, Becher himself recognized this since in a later section (p. 44) he stated that: "Emulsions are essentially unstable heterogeneous systems; they are partly dispersions, partly colloids"; the use of the term, colloid, inferring submicron sizes.

The influence of particle size upon the physical properties of emulsions and suspensions has been reviewed by others (1-6). It is generally agreed that stability, viscosity, rate of heat transfer, and optical properties of emulsions are dependent upon the particle size or the particle-size distribution of the disperse phase. However, there is at present no satisfactory correlation of the relationship. For example, Rutgers (5) reviewed the literature (up to 1962) on the relationship between relative viscosity and dispersion concentration. He concluded that absolute particle size was of importance, but not one of the 97

equations discussed by this author contained an expression for size or distribution of size. Sherman (6) also concluded that the bulk of the published literature on the viscosity of emulsions contained little or no reference to the state of the dispersion beyond broad statements to the effect that an emulsion was "fine" or "coarse."

Reexamining the published work that attempts to derive a correlation between some physical property of an emulsion and the state of dispersion, it was noted that many of the size measurements had been obtained by optical microscopy (Table I). However, it is widely accepted that this method of size analysis cannot adequately differentiate between particles of less than 1μ diameter owing to the limited resolution of the light microscope as the particles approach the wavelength of the incident radiation (7-9). Thus even if one accepts Becher's definition of an emulsion and his arbitrary limitation to disperse phase particles exceeding 0.1μ diameter, the accuracy of measurement of the smaller particles that could be present in a system, and the assessment of the significance of the results must at least remain suspect. The purpose of this review is to consider the particle size of emulsion systems and the alternative methods at present available for its measurement.

MEANING OF PARTICLE SIZE

In practice it is rarely found that all the particles in a system under examination have the same size parameter. Accordingly, size measurements on polydisperse particle systems indicate the probability that a given particle picked at random has a specified size. Thus the particle sizes re-

ported for any material are associated with their frequency of occurrence; being the number of particles, or the weight greater or smaller than a stated size, or range of sizes. The purpose of a particle-size measurement technique is to discover the true frequency distribution of particle size, either as a number distribution or a weight distribution.

Form of Size Distribution for Emulsion Systems

Jellinek (10) suggested that it was unlikely that emulsions prepared by different methods and with different materials would have similar mathematical forms of distribution. Nevertheless, Herdan (11) noted that many systems appeared to obey some standard forms of distribution function such as arithmetical or logarithmic forms of normal (Gaussian) distribution, or exponential distributions of the Boltzmann law type.

The earliest attempt to derive a statistical function of this type was by Rossi (12) who considered the mechanism of subdivision as a random process. Rossi's model had certain deficiencies which Dobrowsky (13), van den Tempel (14), and Lederer (15) attempted to overcome. Jellinek found that Rossi's equation fitted experimental data for homogenized bitumen except for the largest particles present.

Troesch (16) applied statistical theory to the breakdown of droplets under turbulent flow conditions, and deduced that the droplet-size frequency followed a normal Gaussian distribution. Brodnyan (17), considering emulsion polymerization processes, found that in some cases radii were distributed normally although in other examples a log-normal distribution occurred.

A Gaussian distribution is absurd in many ways since it implies that a fraction of the particles, even though a small one, has to be expressed as having negative diameters (18). Nevertheless, the concept is useful since moments can be calculated by the use of algorisms (11). Cooper (7, 8) found that the Rossi equation appeared to apply only to the main drops in the emulsion. The presence of small daughter droplets always means that the size distribution is skewed and this also applies to a Gaussian plot. However, empirically, one method of removing this skewness (that is, make the distribution more evenly spaced out) is to plot it as a function of the logarithm of the particle size. Kottler (19), in 1952 reviewed the use of a logarithmicro-normal distribution and cited examples back to 1924. Although Kottler's analysis of the statistical aspects of the log-normal distribution was confined to photographic emulsions, he demonstrated

TABLE I—AUTHORS WHO HAVE EXAMINED THE RELATIONSHIP BETWEEN EMULSION AND SUSPENSION PROPERTIES AND PARTICLE SIZE, SHOWING METHOD OF PARTICLE-SIZE ANALYSIS

Authors	Reference[a]	Particle-Size Analysis Method
Axon	(161, 162)	Microscope
Becher	(291)	Microscope
Bredee and de Booys	(163, 164)	Microscope
Chessman and King	(165)	Microscope
Eilers	(166, 167)	Microscope
Elworthy and Florence	(290)	Microscope
Eveson	(168, 169)	Microscope
Gillespie	(170–173)	Microscope, electron microscope
Groot	(289)	Adsorption
Johnson and Kelsey	(174)	Electron microscope
Kelsey and Johnson	(175)	Electron microscope
Knoechel	(54)	Microscope
Knochel and Wurster	(55)	Microscope
Lawrence and Rothwell	(176)	Microscope
Leviton and Leighton	(177)	Microscope
Lyttleton and Traxler	(178)	Microscope
Manley and Mason	(179)	Microscope
Matsumoto	(151–154)	Sedimentation
Mima and Kitamori	(145)	Coulter counter
Nawab and Mason	(180, 181)	Microscope
Orr and Blocker	(182)	Microscope
Rajagopal	(183)	Microscope
Richardson	(3, 184)	Microscope
Rowe	(144)	Coulter counter
Saunders	(185)	Electron microscope
Sherman	(56–58, 186–196, 292, 293)	Microscope
Sheth	(197)	Microscope
Sheth *et al.*	(198)	Microscope
Shotton and Davis	(284)	Coulter counter
Shotton and White	(199, 200)	Microscope
Sibree	(201, 202)	Microscope
Simpson	(203)	Microscope
Srivastava	(204)	Microscope
Sweeney and Geckler	(205)	Microscope
Takano and Kambe	(206, 207)	Electron microscope
Talman *et al.*	(217)	Microscope
Taylor	(208, 209)	Microscope
Traxler	(210)	Microscope
Vand	(211)	Microscope
van den Tempel	(212, 213)	Microscope
Wachtel and La Mer	(127)	Coulter counter
Williams	(214, 215)	Microscope, Centrifuge
Wilson and Parke	(216)	Microscope

[a] Papers not necessarily discussed in the text.

that if a distribution were not linear when plotted on log-probability paper it was an indication that

the sample contained at least two different populations.

Mugele and Evans (20) critically compared Rossin-Rammler and Nukiyama-Tanasawa distributions with log-probability plots and showed that the first two were largely unsatisfactory. They found that the log-probability equation predicted the general distribution trend correctly for most data and gave good results for the mean diameter calculations. These authors showed that the emulsion data of Harkins and Beeman (21) and of Cooper (7, 8) fitted this presentation satisfactorily despite the extremely small size of the emulsion particles.

Gwyn, Crosby, and Marshall (22) considered bias in particle-size analyses resulting from the use of a log-normal distribution. Many analyses indicate the existence of maximum size classes but the log-normal distribution is in fact infinite in extent. Thus, the results tend to be biased, an occurrence implicitly recognized by Mugele and Evans. Gwyn *et al.* assumed that the sample was taken from a population with a true log-normal distribution and adjusted the data for bias. They suggested that the analysis could be carried out in two parts, a few particles being first counted to establish the central portion of the distribution, and a larger number of particles falling above, say, 5% of the total distribution based on the central portion. As noted by Gwyn *et al.*, if a single distribution applies over the entire range of sizes the curve for the upper range will exactly, or very nearly, coincide with the extension of the curve for the central portion of the distribution.

Rajagopal (23) derived a rigorous proof of the log-normal distribution by considering the randomness due to violent break-up of the interface during cavitation, the formation of daughter droplets, the disruption due to collisions, and coalescence due to the same cause. The process was considered as a Markoff chain and the empirical applicability of a log-probability law to emulsion particle-size distribution was placed on a firm theoretical basis.

Schwarz (24) introduced a so-called universal distribution law and this was later amplified and confirmed in two papers by Schwarz and Bezemer (25, 26). This equation, derived on statistical grounds, is also a variation upon the truncated log-normal distribution. From the data supplied by these authors, the equation appears to be less universal in application than their claims suggest. However, Sprow (27) found that the equation was useful when investigating droplet sizes produced in turbulent liquid-liquid dispersions.

There are a number of advantages in utilizing a distribution law of the log-normal type to describe a particle-size distribution, as discussed by Smith and Jordan (28). Thus, on a number basis a particle-size distribution is defined uniquely by two parameters, M, the geometric mean particle diameter, and σ_g, the geometric standard deviation. Both these parameters can be readily obtained by plotting the size-distribution data as a cumulative undersize curve on log-probability paper, a point also brought out by Kottler (29). In establishing line of best fit Kottler pointed out that preference should be given to those points lying closest to the midvalue of 50 cumulative percent. Due to the distortion of the probability axis, the distance by which points are displaced from a straight line becomes increasingly significant as one considers points progressively closer to the 50% mark. For this reason some investigators such as Drinker and Hatch (30) fit the best line to those points within the 20–80% limits, ignoring points outside these marks.

Espenscheid *et al.* (31) criticizes the use of log-normal distribution functions obtained from light-scattering data. They suggested that this was a new distribution function with different parameters and physical properties. However, Honig (32) pointed out that the suggested distribution function was readily reduced to the usual log-normal distribution function and this was the only one which could be determined experimentally.

One other approach deserves mention since the method of presenting the size analysis is unique. Broadbent and Callcott (33) suggested that a size analysis could be presented in the form of a matrix, leading to the derivation of a single parameter, the breakage function (π), which was defined as the proportion of particles that are broken during a grinding process. This approach, requiring distributions at different times, was developed in a series of papers (34–36) in the context of coal grinding and assumes that the chance of breakage is the same irrespective of the particle size. Furthermore, in its suggested form it could not be applied to emulsion systems since no account is taken of coalescence which always occurs during an emulsification process. Nevertheless, the concept of presenting the size analysis as a matrix is an attractive mathematical model since it is not necessary to assume any "law" controlling the emulsification process, and it might be possible to derive a single parameter to describe any one distribution. Arbiter and Harris (37) extended the concept to include a time relationship in grinding, but the approach

does not appear to have been used in the context of emulsions and might be a fruitful approach for a future investigation.

To summarize, there is considerable agreement that a size distribution follows a log-normal distribution, being characterized by the mean size and the slope, or standard deviation. This distribution can be plotted on log-probability paper and, although a relatively insensitive method of presenting results, it must be regarded as satisfactory when considering such factors as sampling error and repeatability of a particular size analytical method.

METHODS OF PARTICLE-SIZE ANALYSIS

The Society for Analytical Chemistry in 1963 published a classification of methods for determining particle size (38). This, supplemented by the standard textbooks on the subject by Herdan (11), Orr and Dallavalle (39), Rose (40), and Cadle (41), and review articles such as that by Scarlett (42), are sufficient background. It is not proposed therefore, to discuss the methods in general but rather to select certain aspects for comment and deal with two methods, the Coulter counter and the centrifugal photosedimentometer, in detail.

MICROSCOPE MEASUREMENT OF EMULSION PARTICLES

Most of the work carried out on correlation of properties of emulsions to the particle size of the disperse phase has relied upon optical microscopy for the particle-size measurement (Table I). The microscope has the advantage that it is direct and inexpensive, but the measurements in themselves may be extremely lengthy and tedious.

Mounting techniques for emulsions have been discussed and described by Simmonite (43). The emulsion under examination must first be diluted before mounting, and care is required to ensure that the system is not affected by this treatment. Various dilution media have been proposed including aqueous gelatin, acacia solution, and diluted polyols such as glycerin or propylene glycol (9). Various techniques have been described for examining the particles and classifying them into size groups. The simplest form utilizing a micrometer eye-piece or calibrated graticule has been widely employed (44). Harkins and Beeman (21) used a projection microscope, thereby reducing eye strain and improving the accuracy of the method. Smith and Grinling (45) introduced a counting technique using a hemocytometer slide and Cockton and Wynn (46) improved this by using a shallow *Helber counting chamber*. Levius and Drom-

mond (9) criticized the previous papers and suggested a camera lucida method which they found to be an improvement over the counting techniques. Photographic methods were employed by, for example, Cooper (7, 8) who measured the particle size from prints. Photomicrography of emulsions is difficult since particles in the micron range exhibit Brownian movement, necessitating very short exposure times with subsequent loss of contrast.

Automatic scanning methods have been described (294) in an attempt to reduce the tedium of microscope analysis and improve speed and accuracy. Collins (295) investigated the sources of error using a Mullard type L188 "flying-spot" analyzer. Fisher (296) described a new scanning instrument which includes a computer to produce secondary information such as total projected area, total numbers of particles, or parameters such as mean Feret's or Martin's diameter.

The necessity of sizing large numbers of particles to obtain meaningful results has received some attention, the most serious attempt being probably that of Fischer and Harkins (47) who counted 50,000 particles in each of their systems However, as discussed by Becher (1), statistically significant counts can be obtained with only 300 particles. A count of 300 particles will result in a cumulative distribution in which the error at any value will be less than 8% ($p = 0.95$) and to lower this to 5% would require a count of 2,960 particles. Kaye (48) also discussed this point and showed that errors arising from sampling were such that a 10-fold increase in count only produced a slight increase of accuracy. The statistics of sampling are discussed (49).

Cooper (7, 8) carried out the classical critical evaluation of microscope sizing methods for emulsions. He pointed out that photographic methods were limited by the depth of focus since no lens is available which can give a clear image of particles of 1 μ or less and yet have a depth of focus of 20 μ, the thickness of a hemocytometer cell. Direct visual counting, in which the focus of the microscope can be continually varied, was found always to show a higher value for the number of particles in the smallest size range, confirmed by van Kreveld (50). As the particle approaches the wavelength of the incident light, the resultant halo makes estimation of the actual particle diameter extremely difficult so that sizing of particles below, say, 2 μ cannot be carried out with 100% efficiency, a point also confirmed by Saylor (51). Lucas (52) noting that rubber lattices contained particles well below 0.5 μ, attempted to improve the light microscope by reducing the wavelength of the radiation to the

ultraviolet range ($\lambda = 2573$ Å). The technique was extremely difficult since the source was not stable. van den Tempel (14) showed from Lucas's data that there are a considerable number of particles present in his system below the visibility limit of 0.12 μ, probably more than 60% being below the limit. van den Tempel considered the use of the light microscope for such small particles to be meaningless and favored the ultramicroscope which can be used to detect and count particles down to 0.02 μ diameter but is unable to differentiate particle sizes.

Although Cooper showed that microscope measurement of particles below 2 μ was of limited value, the method has continued to be used up to the present. King (53) implied that misleading results were occasionally obtained when correlating emulsion stability with particle sizes of 0.5-1 μ diameter. Knoechel (54) and Knoechel and Wurster (55), investigating o/w emulsion stability, discussed the inability of the microscope to take into account submicron particles, concluding: "The experimental evidence indicates that the presence of sub-visual particles could lead to unreliable values for various diameters and interfacial areas during the period in which minute globules coalesce to a visible size." This conclusion was echoed by Sherman (56, 57, 292, 293) who proposed that the only way out of this dilemma was to allow all the minute particles to coalesce until they could be measured microscopically. The value of this suggestion for unstable systems may be doubted, but the idea clearly cannot be applied to those which are stable or in which the particles do not coalesce. Sherman pointed out in the discussion of a later paper (58) that submicroscopic particles are "cancelled out" when determining a mean size. He made a tentative proposal for utilizing a reciprocal mean diameter, thereby bringing out the importance of submicron particles in a system.

ELECTRON MICROSCOPE

The early development of electron microscopy and its application to the investigation of materials below the limits of light-microscope discrimination was reviewed by Anderson (59). Walton (60) and Watson (61) reviewed the application of the instrument to particle-size measurement and described some of the limitations of the technique. The method has some advantages compared with light scattering, sedimentation, and other methods. In particular any peculiarities in shape can be observed directly (62). As noted by Walton (60), major difficulties are sampling and the effects of drying under vacuum. Local heating effects in the electron beam are often important when examining soft materials such as emulsion particles. Cravath *et al.* (63) improved the sampling of suspensions by depositing small droplets of the suspension from a mist (aerosol) onto a specimen film treated to promote wetting. The entire residue left by a single droplet could then be examined. Nixon and Fisher (64) used an aerograph gun to produce droplets and dispersed their material in bovine serum albumin which dried out to yield a transparent matrix supporting the particles. The basic technique of Nixon and Fisher was later improved by Craik who used a more concentrated albumin solution and stained the protein with osmium to improve contrast at the edges of the particles where the maxtrix was thickest, described by Groves and Scarlett (65).

Other methods of supporting suspensions for examination have been reported (66, 67). Soft polymeric materials which distort in vacuum have been hardened before examination by bromination (68) or cross-linking with hard polymers using high energy irradiation (62, 69, 70). However, in general these hardening techniques have not been applied to the electron microscopy of liquid-liquid emulsion systems.

Particle-size analysis using the electron microscope requires the measurement of a large number (at least 3,000) of particles by a photographic method since the image is often not sufficiently stable for more than a few minutes. The problems associated with this aspect of the method were described by Crowl (71) who proposed a mechanical method for sizing from photographic plates. The alternative approach of image shearing proposed by Rippon (72) may also offer a solution for future development.

However, the use of electron microscopy for measuring the particle size of emulsion particles below about 1μ diameter would appear to be the only direct method at present available.

ULTRAMICROSCOPE AND LIGHT-SCATTERING METHODS

Recent work on ultramicroscope methods has been devoted to either counting particles in a flow cell (73) or using a flow method to separate particles out according to their size and counting in a flow ultramicroscope (74–76).

Particle sizes can also be measured in principle by optical methods depending on the measurement of the reduction of light directly transmitted through a dispersion (turbidimetric or nephelometric methods) or by light scattered at some definite angle (usually 90°) from the light path.

Krishnan (77) appears to have been one of the first workers to investigate the light scattering in dilute emulsion systems, and Sing (78) showed that for small particles secondary scattering could no longer be neglected. This author utilized the Mie theory and the approach was investigated theoretically by van der Hulst (79).

The relationship between the scattering of light, the wavelength of the light, and particle size is complicated, but for particles small relative to the wavelength of light it assumes the simplified form originally derived by Rayleigh:

$$S = 24\pi^3 \left[\frac{m^2 - 1}{m^2 + 2}\right] \frac{V^2}{\lambda^4} \qquad \text{(Eq. 1)}$$

where S = total amount of light of wavelength, λ, scattered by a sphere of volume, V, and relative refractive index, m, per unit intensity of illumination.

This equation holds for spherical transparent particles when $r \leqslant 0.1\lambda$. When a particle is comparable in size or large relative to the wavelength of the incident radiation the scattered light will be the resultant of light waves originating from various parts of the particle. The phase and intensity of such waves are related in a complicated manner, predicted by the Mie equation (80, 81), written in the form:

$$S = \frac{\lambda^2}{2\pi} \sum_{v=1}^{\infty} \left(\frac{a_v^2 + p_v^2}{2v + 1}\right) \qquad \text{(Eq. 2)}$$

where S = total scattering by one spherical particle per unit intensity and the a_v's and p_v's are functions of X $(2\pi r/\lambda)$ and β $(2\pi rm/\lambda)$, r being the particle radius.

This equation has been discussed in detail by van der Hulst (79) and numerous tables of solutions to the Mie series have been published (80).

When S is divided by πr^2, the scattering per unit cross-sectional area of the particle, known as the scattering coefficient K, is obtained. Equation 2 then becomes

$$K = \frac{s}{\pi r^2} = \frac{\text{light obscured by particle}}{\text{light obscured if laws of geometric optics were valid}}$$

$$= \frac{2}{X^2} \sum_{v=1}^{\infty} \left(\frac{a_v^2 + p_v^2}{2v + 1}\right) \qquad \text{(Eq. 3)}$$

Thus, K is a function of r/λ and when the scattering coefficient is known for a particular value of r and λ its value is established for the ratio regardless of the individual values.

Equations 1–3 have been derived for scattering from single particles, but unless the number concentration of particles in a suspension is very high the scattering from a suspension can be considered to be the sum of the scattering by the individual particles. In practice, fine particles usually have a range of size as well as being of irregular shape. Thus, although the total scattering is the sum of the scattering by individual particles, the scattering coefficient may vary widely from one particle to another. If the ratio of r/λ is greater than 50, the value of K is constant and can be taken as unity. For smaller ratios the value of K becomes a complex function of r/λ. The effect of adding the scattering from a number of particles of varying size would be expected to damp out the wide fluctuations in scattering coefficient with varying size that occur for single particles. Gumprecht and Sliepcevich (82) considered the problem and proposed a quantitative relationship between Mie theory and K which enabled them to obtain a size-frequency distribution. The approach was simplified and does not appear to have gained wide acceptance. Goulden (84) used scattering-coefficient data calculated by van der Hulst (79) to apply the Mie equation to determining the particle size of homogenized milk (85–89). However, his method can only yield a mean particle size, and although useful for control purposes, cannot be employed for other than relatively monosized systems.

When a measure of total scattering is desired, it is much more convenient to measure the percent transmission than to attempt to integrate the intensity of the scattered light. Transmission methods have been used in many fundamental studies of light scattering and form the basis of a number of methods of particle-size determination.

When a beam of light is passed through a suspension of particles, the intensity of the beam is attenuated as a result of the scattering, and the decrease in intensity obeys the exponential law:

$$I/I_0 = \exp. (-\tau 1) \qquad \text{(Eq. 4)}$$

The initial intensity = I_0, the intensity after the light has traversed distance 1 is I and τ is the absorptivity, $\tau 1$ being termed the absorbance.

Equation 4 can be rewritten for monosized systems as

$$I/I_0 = \exp. (-K\pi r^2 n 1) \qquad \text{(Eq. 5)}$$

where n = the numbers of particles of radius, r, per unit volume of suspension, and K is the scattering coefficient as defined in Eq. 3. For very small particles which obey the Rayleigh relationship Eq. 1 can be rewritten as

$$I/I_0 = \exp. \left[-\frac{128 \pi^5 r^6}{3\lambda^4} \left(\frac{m^2 - 1}{m^2 + 2}\right) \right] n 1 \qquad \text{(Eq. 6)}$$

On the other hand, when the particle diameters

are large K approaches a value of 2. Lothian and Chappel (83) discussed the fractional loss of intensity of a beam of light passing through a layer of emulsion particles, and showed that the absorbance of a dilute suspension of spheres was a function of their particle size. After strong criticisms of turbidimetric methods by Skinner and Boas-Traube (90), an improved instrument was described by Branson and Dunning (91). This device was further developed by Rose (40) who narrowed the angle of acceptance to reduce forward scattering. Other investigations were carried out by Kaye (48) and by Hodkinson (92). The latter made measurements of the angular scattering distribution over the range of 0.5–90° using suspensions of powdered flint, diamond, anthracite, and bituminous coal. Smooth curves were obtained which were quite unlike those for single particles or monodispersed spheres. Mie theory was therefore not applicable to these irregular particles, and K was found to rise slowly from 0 to 2. Kaye, and later Kaye and Allen (93) investigated the optical scattering cross-sections of small particles using white light and a wide angle of acceptance. Under these conditions, they also found that fluctuations of K were much reduced and for many purposes it was sufficient to take it as unity. Thus, the claim by Bolton and Marshall (94) that a simple turbimeter could be used to measure wax particles down to 0.06 μ diameter must be viewed with caution. It is not clear if these authors used a white light source, but it is of interest to note that they found values for K as low as 0.04 for their smallest particles.

Trice and Rodger (95) measured interfacial areas using a light-transmittance method similar to that used earlier by Langlois *et al.* (96) for coarse, unstable emulsions.

Reflectance relationships for emulsions are, if anything, more complex. This was noted by Lloyd (97) who incorporated a red dye in the oil phase and found that the reflectance at wavelengths at which the colored internal phase partially absorbed the incident light was inversely proportional to a power of the surface-area particle diameter. This relationship was claimed to be independent of the particle-size distribution. Schulman and Friend (98, 99), and van der Waarden (100) both used the Rayleigh formula to calculate the mean size of very small droplets (up to 400 Å. diameter). La Mer (101) investigated monodisperse aerosols using the higher-order Tyndall spectra method. Heller *et al.* (102) verified experimentally that Mie theory was applicable to light-scattering methods and tabulated the data required to transform light-scatter-

ing measurements into particle-size distributions (103, 105). Although initially confined to relatively monodisperse polymer lattices, Wallach (104) claimed that the method was applicable to the study of size distributions of dimethylnaphthalene–water emulsions.

Gledhill (106), Wales (107), and Weber (108) have all described methods for measuring particle-size distributions by measurement of turbidity spectra using methods similar to Heller. La Mer and Plesner (109) described a rapid method of sizing a monodisperse suspension by measuring the light scattering as a function of the angle between the incident beam and scattered light and the method was extended by Dezelic and Kratohvil (110, 111). Kratohvil and Wallace (112) reexamined the claims made by Heller and Tabibian (113), and by Wales (107), and found them unreliable.

To summarize, there is general agreement that light scattering and turbidity methods can give a measure of the mean particle size present in a system although there is some disagreement on the method by which the size distribution can be determined. Simplified techniques, making a number of assumptions, have been applied to determining particle-size distributions by a combination of sedimentation methods and turbidity measurements.

COULTER COUNTER

Coulter described his instrument in 1956 (114) and the device has come to be widely accepted as a convenient and valid method of size analysis. The Coulter counter determines the number and size of particles suspended in an electrically conductive liquid. This is done by forcing the suspension to flow through a small aperture having an immersed electrode on either side. If the suspension is sufficiently dilute, the particles will pass through the aperture one at a time. As each particle passes through, it displaces its own volume of electrolyte thus changing the resistance across the aperture. An electrical current passing between the electrodes converts the resistance change into a voltage pulse, whose amplitude for a given current and electrolyte is proportional to the volume of the particle. The voltage pulses resulting from a known volume of suspension passing through the aperture are fed to an electronic counter fitted with an adjustable threshold level such that all pulses above the threshold are counted. In this manner the number of oversize particles is obtained at different levels of particle volume so that a particle-size distribution by number or by weight can be determined. Detailed descriptions of the in-

strument and its principle of operation have appeared in the literature (114-127) and it is not proposed to repeat them here.

As might be anticipated with any new advance the Coulter counter has been subjected to critical evaluation by many workers in recent years (128-137). However, to date no fundamental flaw in the principle or mode of operation has been detected and it is generally agreed that the instrument is a unique and valuable contribution to the science of particle-size analysis.

Theoretical Response of the Coulter Counter

Batch (115) and Gregg and Steidley (279) have considered the theoretical response of the Coulter counter for various shapes of particles. The current between the electrodes is maintained at a constant level so that any change in the resistance of the cell results in a change of voltage across the cell. The presence of a particle of different resistivity in the aperture will therefore result in a change of resistance, the amount of change being in some way proportioned to the value of the particle.

Consider an orifice of cross-sectional area A, diameter D, filled with an electrolyte of resistivity, r_0, and containing a particle of resistivity, r. If a is the projected area of the particle at the portion of an elemental section of length $d1$ then the resistance of this element of the particle in the direction of the orifice axis is $r\,d1/a$, and the resistance of the annulus of electrolyte is $r_0 d1/(A - a)$. The total resistance across the element is

$$dR = \frac{r_0 r\,dl}{ar_0 + r(A - a)}$$

$$= \frac{r_0 dl}{A - a(1 - r_0/r)}$$

and the increase of the resistance of the element due to the particle is

$$d(\Delta R) = \frac{r_0 d1}{A - a(1 - r_0/r)} - \frac{r_0 d1}{A}$$

$$= \frac{(1 - r_0/r)r_0 a d1}{A^2[1 - (1 - r_0/r)a/A]}$$

$$= \frac{ar_0 k d1}{A^2(1 - ka/A)} \quad \text{where } k = (1 - r_0/r)$$

Thus, the total resistance change is

$$R = \frac{r_0 k}{A^2} \int \frac{ad1}{(1 - ka/A)} \qquad \text{(Eq. 7)}$$

For a rod-shaped particle lying along the axis this equation can be solved simply because a is not a function of 1 so that

$$R = \frac{rkv}{A^2 (1 - ka/A)}$$

Batch solved Eq. 7 for spherical and cone-shaped particles by expanding the expression under the integral sign. Gregg and Steidley obtained exact solutions by solving the integral explicitly before expansion. The resulting equations for change in resistance are summarized in Table II.

The equation for a sphere approximates to

$$R = \frac{r_0 v}{A^2} \left[1 + \frac{0.3K^2 + 0.13K^4}{(1 - K^2)^{-1/2}} + + + \right] \quad \text{(Eq. 8)}$$

Thus, for any shaped particle, provided a/A, or d/D, $= K$ is small, the change in resistance is directly proportional to the volume of the particle. Allen (132) has shown that this assumption is valid for particle–tube ratios of up to 20%. The assumption of the linear response for up to 40% ratio can lead to an error in particle diameter of 7.8% for rod-shaped particles, and 3.6% for spherical-shaped particles.

The error term in Eq. 8

$$\frac{1 + 0.3K^2 + 0.13K^4}{(1 - K^2)^{-1/2}}$$

can be used to assess error due to assuming a linear response, as shown in Table III. Thus it will be seen that, strictly, the response of the Coulter counter is not linear with particle volume and the nonlinearity is dependent upon particle

TABLE II—SUMMARY OF THE EQUATIONS[a] RELATING PARTICLE SHAPE AND TOTAL
RESISTANCE CHANGE IN AN ORIFICE CONTAINING AN ELECTROLYTE

Particle Shape	ΔR[b]	ΔR[c]
Rod length $\gg$ dia.	$\dfrac{rkv}{A^2} \left(1 + \dfrac{ka'}{A} + \dfrac{k^2 a'^2}{A^2} + \cdots \right)$	$\dfrac{r_0 v}{\pi^2 D^4} \dfrac{1}{(1 - K^2)}$
Rod length $\sim$ dia.	—	$\dfrac{r_0 v}{\pi^2 D^4} \dfrac{1}{(1 - K^2)} [t\pi r_1^2 + \sigma \pi r_1^3]$
Sphere	$\dfrac{rkv}{A^2} \left[1 + \dfrac{4}{5}\dfrac{ka'}{A} + \dfrac{24}{35}\dfrac{k^2 a'^2}{A^2} + \cdots \right]$	$\dfrac{2r_0}{\pi D} \left[\dfrac{\tan^{-1}[K(1 - K^2)^{-1/2}]}{(1 - K^2)^{1/2}} - K \right]$
Cone	$\dfrac{rkv}{A^2} \left[1 + \dfrac{3}{7}\dfrac{ka'}{A} + \dfrac{3}{7}\dfrac{k^2 a'^2}{A^2} + \cdots \right]$	—

[a] Where A = area of orifice of diameter D, a' = maximum cross-sectional area of particle. The value of k is $(1 - r_0/r)$, where r is the resistivity of the particle and r_0 the resistivity of the electrolyte. Gregg and Steidley assume r/r_0 to be negligible and define K as d/D = particle diameter/orifice diameter, where t is the length of rod and σ is a constant. [b] From *Reference 115*. [c] From *Reference 279*.

TABLE III—MAGNITUDE OF THE ERROR IN ASSUMING A LINEAR RESPONSE
FOR THE COULTER COUNTER (EQ. 8)

d/D	0.1	0.2	0.3	0.4	0.5
$\Delta R \cdot A^2/V$	1.008	1.033	1.077	1.145	1.26
Error in volume, %	0.8	3.3	7.7	14.5	26.0
Error in diameter, %	0.3	1.1	2.9	4.8	8.7

shape. However, it should be emphasized that in practical terms the error is not significant if the largest particle is of the order of 40% of the tube diameter. Particles larger than this can be measured providing the "error" is recognized although blockage of the orifice by such large particles generally means that in practice the size analysis would be carried out using a larger orifice tube. Experimentally Eckhoff (283) has found that spherical and comminuted particles of identical volumes give rise to voltage pulses of identical amplitude; the effect may, therefore, prove to be less significant than was earlier thought.

The resistivity of the particle has a theoretical effect upon the response of the instrument. Thus, from Batch's equations (Table II), if $k = (1 - r_0/r)$ is less than 1, the magnitude of the errors shown in Table III will be increased. However, in practice it has been found that the majority of powders, whether conducting or not, behave in the electrolyte as particles with infinite resistance (116). Thus the assumption that $k = 1$ can generally be assumed to be good. It is interesting to note, however, that if the particles showed the same resistivity as the electrolyte there would be no "size" error.

Lower Limit of Size Measurement by the Coulter Counter

Coulter's Laboratory Manual (1966) claims that, with a 20-μ nominal diameter orifice tube, the instrument will detect particles of 0.4-μ equivalent sphere diameter. Kubitschek (120) claimed to detect particles of 0.2 μ diameter with a resolution of 0.04–0.06 μ^3. This claim must be viewed with caution although Princen (private communication) has confirmed it and suggests that it may be due to instrument idiosyncracy. It is widely accepted that the instrument is useful for particles of diameters down to 1 μ, and will detect particles down to 0.5 μ diameter (138). However, in this range the instrumental background caused by electrical effects, especially heating within the orifice, and cavitation by the passage of material through the small orifices which are required for these sizes make actual detection of submicron particles less certain. In addition, the loss of count caused by "shadowing" of small pulses by larger ones makes the detection of small particles difficult in the presence of large

ones (129). The practical difficulties in obtaining electrolyte free from particulate contamination are also considerable. The instrument is therefore limited to approximately the same size range as optical microscope methods but has the overwhelming advantage that a vastly greater number of particles is actually counted for any one size distribution.

Coincidence Correction and Dilution of the Sample

The theory of the Coulter counter assumes that only one particle will be found in the volume defined by the orifice at any one instant of time. However, even with very dilute suspensions there is a finite possibility of two or more particles passing through at the same time. Clearly the more dilute the suspension the lower the probability of coincidence. Wales and Wilson (130, 131) recognized two forms of coincidence: (a) All pulses from two or more simultaneous particles add so as to produce a single pulse whose maxima is the sum of the two individual pulses, and (b) The pulses from two or more simultaneous particles behave as one pulse whose maximum corresponds to the largest particle.

Princen and Kwolek (280) showed that type a coincidence should predominate and would result in overcounting of large particles. The methods of correction for the coincidence error were discussed by these authors and Edmundson (135, 281) has proposed an alternative method. At low counts, however, the required correction will be approximately 1–3% of the total count and the method of calculating this relatively small error is not likely to be significant. For this reason, it is better to operate the Counter at dilutions which will give low total counts and this itself is sometimes a source of difficulty. Groves (139) pointed out that dilutions of the order of 1 : 50,000 or more are often required for emulsion systems and great care is required when making these dispersions for analysis.

Effect of Electrolyte on Dilute Emulsion Systems

Parfitt (282) has recently described the theoretical background to the preparation of dispersions and their subsequent stability. Emulsion particles are often stabilized with surface-active agents and emulsion systems diluted with water

will sometimes flocculate on standing. However, the addition of electrolyte to such a dilution will frequently cause flocculation because the energy barriers preventing aggregation and coalescence are reduced. Although electrolyte is necessary for a Coulter counter analysis, few authors appear to have encountered this phenomenon when using the instrument to measure the particle-size distribution of an emulsion system. Singleton and Brown (140) found that the count of the systems in their investigation changed with time. They noted the elapsed time to the beginning of counting for each of the sizes being measured; counts were then corrected for the time effect by extrapolation to zero time. Groves (139) reported the same effect for an emulsion stabilized with cetrimide and found that the flocculation could be minimized by carrying out the dilution in sodium chloride solution containing cetrimide at a concentration in excess of the critical micelle concentration. The results obtained in this manner agreed with those obtained independently using other size analysis methods. Some dangers of extrapolating to zero time in the manner suggested by Singleton and Brown are illustrated by the results shown in Fig. 1. The phenomenon has been noted in systems stabilized with other surface-active agents (278). Aggregation of an emulsion system is therefore possible during a Coulter counter size analysis, and the analyst should be at least aware of the possibility.

Use of the Coulter Counter for Sizing Emulsion Systems

Wachtel and La Mer (127) employed the Counter to size o/w emulsion systems, using the device to measure the degree of dispersion
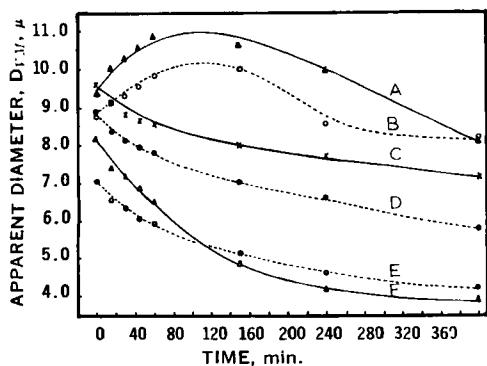

Fig. 1—Change of apparent mean particle size of a cetrimide emulsion measured with a Coulter counter as a function of time. All primary dilutions were made in 0.0003 M cetrimide in normal physiological saline. Key: secondary dilutions were made in saline containing the following concentrations of cetrimide: A, 0.00003 M; B, 0.000015 M; C, 0.0003 M; D, 0.00015 M; E, 0.003 M; F, 0.03 M. [Reproduced with permission from J. Pharm. Pharmacol., 18, 305(1966).]

achieved by the use of a Sinclair aerosol generator for making monodisperse emulsions. Higuchi (141, 142) investigated factors influencing the aggregation of emulsions, followed by Lemberger and Mourad (143), and Swift and Friedlander (125). Shotton and Davis (284) investigated the influence of soap concentration on creaming rates of liquid paraffin emulsions in potassium laurate, and Singleton and Brown (140) used the Counter while investigating i.v. fat emulsions. Rowe (144) and Mima and Kitamori (145) studied emulsion-stability parameters as reflected in changes of particle-size distribution. Princen, Stolp, and Kwolek (146) examined the factors controlling the emulsification of linseed oil and Marshall and Taylor (147) described the use of the counter for following changes produced in an emulsion during the evaluation of different homogenizers. In general terms, Schrenzel (148, 149) discussed the use of the Coulter counter for the size analysis of pharmaceutical emulsions. Whittlestone (285) showed that the counter could be used for determining the size distribution of fat globules in cows milk but found no detectable systematic trends in the distribution pattern. However, later Cornell and Pallansch (286) improved the technique and demonstrated the effects of homogenization, pasteurization, and cream separation. The instrument has therefore been applied to many different types of emulsions.

As noted by Edmundson (281), "although simple in principle and reliable in operation, the Coulter Counter is a highly sophisticated apparatus, not to be regarded as a 'black box' that gives the right answer automatically." To summarize this section, therefore, the instrument covers approximately the same size range as the optical microscope but has the overwhelming advantages of improved speed and accuracy; the proper methods for using the instrument and interpreting its results are still being developed.

GRAVITY SEDIMENTATION METHODS

As noted by Becher (1), if an emulsion creams at an observable rate, measurement of the amount creamed per unit time permits the construction of a distribution curve. Most methods which depend on this principle, such as that of Kraemer and Stamm (150), measure the change of density. More recently Matsumoto (151–154) has described a method in which the viscosity changes in a creaming emulsion are used to build up a particle-size distribution of the system. Following the design of a cell to measure emulsion stability using creaming rate monitored by dielectric measurements (155), Kaye and Seager have described a similar device to measure the particle size of o/w

emulsions (156). The method is confined to systems of mean particle size around 100 μ and does not appear to be useful for diameters below 15 μ; it is therefore of limited application to pharmaceutical emulsion systems which have particles well below the lower limit of the method (1). Figurovskii and his co-workers (157–160) examined sedimentation methods and stated that they offered the fastest and most reliable means of determining the degree of dispersion of dispersed systems. Unfortunately, gravity sedimentation methods are not applicable to particles below about 10 μ diameter since the particles "cream" too slowly. In addition convection and displacement currents as well as Brownian movement all tend to disturb the sedimentation pattern. Hence the use of gravity sedimentation is of limited use for most pharmaceutical systems where particle sizes of 1 μ and below are common.

CENTRIFUGAL SIZING TECHNIQUES

One obvious way to increase the settling rate is to centrifuge the suspension. Orr and Dallavalle (39) described a number of centrifugal sedimentation techniques and other devices have been developed in recent years.

The first attempt to use a centrifuge to obtain a size distribution was that of Dumanskii, Zabotinskii, and Evseyev (218). Using an ordinary centrifuge, they determined the amount sedimented by ultramicroscope counts before and after centrifuging, but obtained poor agreement with the ultramicroscope method. Svedberg and Pederson (219) suggested that this was probably due to convection currents caused by serious deviation from ideal sedimentation conditions. Nichols and Svedberg developed a centrifugal densitometer, a two-arm centrifuge in which the boundary of particles was observed by taking photographs at different stages of the analysis. Nichols and Liebe (220) used a much improved version of this early instrument which rotated at 20,000 rpm and had better balancing and freedom from vibration. The obscuring power, related to the cross-sectional surface diameter of the particles, was measured for six colloidal lithopone samples by measuring the absorbance from light absorption measurements. The method was described in detail later by Bailey, Nichols, and Kraemer, (221) and by Bailey (222), the former group showing how it could be applied to the particle size analysis of emulsions. Nichols and Bailey (223) gave a worked example of how to calculate a size distribution of an emulsion using the so-called "low-speed Svedberg ultracentrifuge."

Nichols and Liebe (220) equated the viscous force due to Stokes' law with centrifugal force, ignoring the Coriolis force or accelerating force which is also present. Robison and Martin (224, 225) were able to demonstrate that this assumption would not lead to any significant error. Cheng and Schachman (226), after an intensive investigation of the ultracentrifugal sedimentation behavior of polymer lattices, concluded that Stokes' law was valid under these conditions.

Marshall (227–229) suggested a two-layer technique in which particles are considered to start from substantially the same position. This technique has a superficial attraction but is fraught with many difficulties, including that of irregular sedimentation, a point noted by Keen and Schofield as early as 1930 (230). This technique and methods for overcoming the problems have been discussed (72,231,232) and the streaming problem for particulate solids subjected to a two-layer sedimentation technique has been effectively overcome. However, the approach is only applicable to materials which are denser than the sedimentation liquid, *i.e.*, the particles are thrown to the outer periphery of the vessel. Since emulsion particles are usually less dense than water and soluble in organic liquids which have a lower density, the use of a centrifugal sedimentation method is mainly confined to a homogeneous technique. Thus emulsion particles move inward from the outer periphery toward the center of the sedimentation vessel. It is therefore necessary to consider in more detail centrifugation techniques and methods for the solution of a homogeneous system.

Centrifugal Techniques

The early techniques as noted above used centrifugal tubes. Martin (233), and later Robison and Martin (224), reviewed breaker-type centrifugal sedimentation and concluded that it had advantages, not the least being that collisions between the particles and the walls of the vessel are minimized. Robison and Martin developed the theoretical approach and described the application of a modified beaker- or sector-shaped centrifuge cell from which samples were withdrawn at the end of a variable time at a fixed depth (225). Brodnyan (17) used a similar method for polymer lattices but with an ultracentrifuge. Kamack (234) improved the theoretical method and described a similar sector-shaped cell to which was attached a sampling device that removed a sample at a fixed depth while the centrifuge was still running, thereby removing the danger of stirring the suspension during the slowing-down phase. Kamack had to use concentrated suspen-

sions of the order of 1% and only one point on the distribution curve could be obtained from each run. Owing to hindered settling (235, 236) the method was also probably inaccurate. Nevertheless, the method of calculating the experimental results was retained when Donoghue and Bostock (237) introduced the complete disk centrifuge. This particular instrument resulted in the introduction of a centrifugal analog of the Andreasen pipet by Slater and Cohen (238), the Simcar centrifuge. Gupta (239) also described a version of the centrifugal Andreasen pipet technique.

Moser and Schmidt (240) described a centrifugal photosedimentometer using a shallow cylindrical tank or disk rotating in the horizontal plane. The absorbance of the suspension was followed as a function of time by passing a thin beam of light through a fixed point on the tank onto a photoelectric cell. The authors used a nomograph to relate the recorder curve to the percentage of particles of a given size calculated from Stokes' law and stress was laid on the fact that an instrument of this type must first be calibrated by some other method owing to variable factors such as particle shape and opacity. Moser (private communication) stated that the instrument was a prototype which was not developed further.

Later Kaye (241) patented a photosedimentometer which was essentially similar to that of Moser and Schmidt. The new instrument employed a servosystem which compared the attenuated light beam with the unattenuated beam, using the difference signal to rotate an optical wedge to cancel the difference. A potentiometer attached to the optical wedge was used to control the recorder so the instrument plotted out the absorbance of the suspension. The instrument was described in more detail by Kaye (48) and evaluated with Burt (242–244). A simplified instrument, omitting the servo unit, was described and evaluated by Groves, Kaye, and Scarlett (245). The light beam was allowed to fall onto an unbalanced photocell after passing through the centrifugal disk. The instrument was used with the two-layer technique and was insufficiently sensitive to detect the streaming later investigated by Rippon (72). A prototype of an improved version has been described and evaluated (246, 247, 231, 278) and is shown in Figs. 2 and 3.

Other disk centrifuges have also been described. Martin, Brown, and de Bruyn (248) used a hollow aluminum disk centrifuge similar to Kaye's design to size analyze submicron powders containing elements of high atomic density such as lead
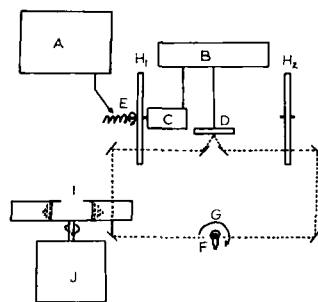

Fig. 2—*Diagrammatic cross-section of the Coulter centrifugal photosedimentometer. Key: A, recorder; B, amplifier; C, servomotor; D, photocell (CdS); E, potentiometer; F, light source; G, chopper, H₁, servo-driven optical wedge, H₂, hand-operated optical wedge; I, centrifuge disk containing liquid; J, constant speed motor. The optical path is shown as a discontinuous line.*
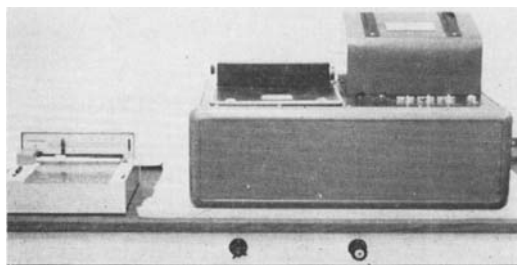

Fig. 3—*Photograph of the prototype of the Coulter centrifugal photosedimentometer. The edges of the optical wedges are seen as projections from the right-hand housing. The rotating disk is horizontal and is situated under the lid seen on the left of the main unit.*

glass, an X-ray beam passing through it and onto a proportional counter.

Hildreth (249, 250) described a simple photoextinction type of disk sedimentometer, similar in principle to that described by Groves *et al.* An initially homogeneous suspension was used on the variable-time system (*vide infra*), the transmittance *versus* time curve being related to transmittance weight curve by obscuration factors. As noted by Rippon (72), this is an oversimplification of the theory and is not a tenable method.

Atherton, Cooper, and Fox (251), Atherton and Tough (252), and Murley (253) described a small diameter disk centrifuge in which the two-layer technique is used in conjunction with a rotating-probe sampling device, the I.C.I.-Joyce Loebl centrifuge, Figs. 4 and 5. Thus, liquid and suspended contents are removed for subsequent analysis after predetermined centrifugation times at a known radius while the centrifuge is still rotating. This centrifuge has been investigated in our laboratories using a homogeneous suspension method. Irregular sedimentation behavior was observed at the high concentrations of an emulsion required for subsequent analysis. In addi-
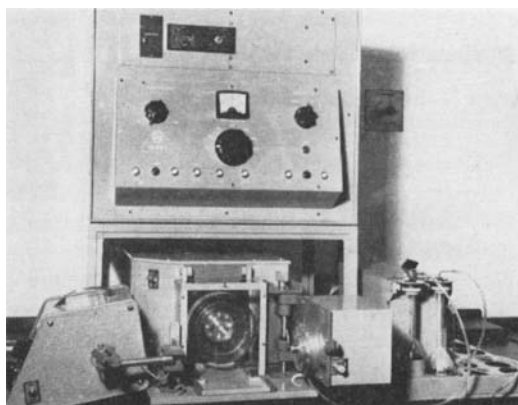
Fig. 4—Photograph of the Joyce-Loebl centrifuge, showing the disk probe, and sampling equipment.
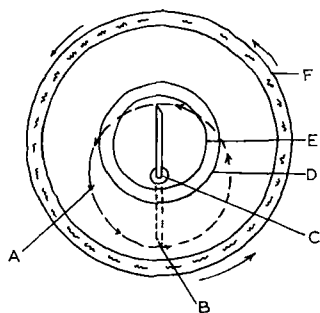

Fig. 5—Sketch of Joyce-Loebl centrifuge disk, showing relationship of probe during sampling. Key: A, path described by probe tip; B, final collection point; C, probe pivot; D, meniscus of liquid before sampling; E, inner edge of disk port; F, outer edge of disk.

tion considerable turbulent disturbance was observed when the sampling probe was inserted into the suspension (Groves, unpublished results). However, Jones (private communication) claims that the instrument has been used to obtain the particle-size distributions of submicron polymer emulsion systems.

Theory of Homogeneous Suspension Methods

When the material to be analyzed is dispersed in the sedimentation liquid to produce a homogeneous dispersion, three main modes of operation are possible as noted by Murley (253). (*a*) The inner radius of the liquid surface and the outer radius of collection are kept constant, samples being collected after varying running times of the centrifuge. (*b*) The running time of the centrifuge is kept constant, as is the inner radius of liquid and the outer collection radius is varied. (*c*) The running time of the centrifuge is kept constant as before, but the outer collection radius is kept constant for successive measurements, while the inner liquid surface radius is varied.

In all cases the centrifuge speed is kept constant. Donoghue and Bostock (237) gave solutions for solving methods *b* and *c*, to which Murley added another proof. However, Donoghue and Bostock also stated that no analytical proof exists for the derivation of the particle-size distribution of a sample when time is varied, unfortunately the precise situation relevant to the centrifugal photosedimentometer. Murley agreed that this was correct but pointed out that iterative methods could now be developed for calculating the required results using modern computer techniques at relatively low cost. The variable time mode of operation offers a number of important experimental advantages and as a result many attempts have been made to find a solution, or the best approximation.

Although the position of a particle relative to its initial position can be described mathematically, it still remains difficult for a distribution function to be derived from the experimental information. This is complicated by the fact that, from the initially homogeneously dispersed particulate system, particles are accelerated proportionally to their position from the axis of rotation. At any given reference or sampling zone, after a certain time t it can be said that all particles greater than a certain size d_t will have passed, where d_t is the Stokes' diameter of the particle which started from the free surface and in time t had transversed to the sampling zone. Subsequently the theory was developed for a disk centrifuge which is an ideal form of a sector-shaped cell since wall collisions are reduced to a minimum. The size distribution is considered to be continuous, containing in an infinitesimal range of diameters a fraction of $F(y)dy$.

Referring to the sector of the disk centrifuge, the distance from the axis to the free surface is S; that to the sampling zone, R.

Hence a particle of diameter d is defined as that particle which will just travel from the surface at S to R during the centrifuging. From a consideration of the centrifugal forces:

$$\ln \frac{R}{S} = \frac{(\rho - \sigma)\omega^2 d^2 t}{18 \eta} \qquad \text{(Eq. 9)}$$

where ω = angular velocity, ρ = density of particle, σ = density of sedimentaion liquid, and η = the viscosity of the liquid. Thus,

$$\ln \frac{R}{S} = kd^2 t, \text{ where } k = \frac{(\rho - \sigma)}{18 \eta} \omega^2 \quad \text{(Eq. 10)}$$

These particles of diameter d and all larger particles will have been sedimented as well as a fraction of the particles smaller than d (*i.e.*, those which were nearer to the sampling zone than those at the surface) in time t.

If p is the total fraction of material deposited, then p is given by the equation

$$p = \int_d^\infty Fy(dy) + \int_0^d \frac{R^2}{(R^2 - S^2)}$$
$$[1 - e^{-2ky^2t}]\ Fy \cdot dy \quad \text{(Eq. 11)}$$

Differentiating Eq. 11 with respect to time gives:

$$\frac{\delta p}{\delta t} = \int_0^d \frac{R^2}{(R^2 - S^2)} - 2ky^2 e^{-2ky^2t}\ Fy \cdot dy \quad \text{(Eq. 12)}$$

This equation is not capable of analytical solution although Romwalter and Vendl (254) obtained Eq. 11 and invalidated their solution by an error. This error was detected by Brown (255) who obtained Eq. 11 but solved it by making $(R - S)$ variable. Robison and Martin (224) used an iterative method to produce a set of approximate solutions which were claimed to give better accuracy than that due to normal experimental errors. Kamack (234) improved the iterative technique to give an approximate general solution to Eq. 12 in recursive form:

$$F_i = \frac{1}{2}\,(S + S_{i-1,i})C_i +$$

$$\sum_{=1}^{i\ =\ 1} \left[\frac{S + S_{i-1,i}}{S_{j+1,i} + S_{j,i}} - \frac{S + S_{i-1,i}}{S_{j,i} + S_{j-1,i}} \right] F_j$$
$$i = 1,2 \ldots n \quad \text{(Eq. 13)}$$

where $F = F(D) = $ fraction by weight of particles smaller than diameter D. $C = $ concentration of suspended solids, as a fraction of the concentration of uniform suspension prior to settling, and $S = (R/S)^2$.

Others have attempted to obtain a solution of the variable-time equation. Nichols and Liebe (220) published a result which would not, however, give a weight-distribution function. Parkinson (256) overcame the variation due to the centrifugal field by the simple process of ignoring it. More practically, Jacobsen and Sullivan (257) employed a very low value of R/S (1.05), but this was experimentally difficult since only small volumes of material were available for analysis. Dana (258) employed a pipet method using an inclined-tube centrifuge for which mathematical analysis was found to be inapplicable. Other attempts were critically reviewed by Robison and Martin (224). It must be concluded that an exact solution of the theory for deriving a distribution function from an initially homogeneous dispersion centrifuged for various time intervals is not possible. As noted by Murley (253) approximate methods of an order of

accuracy better than that due to experimental techniques are, however, available.

Light Scattering as Applied to Centrifugal Techniques

The use of a beam of radiation to measure the concentration of particles in a centrifugal cell has many attractions, especially as it is not necessary to disturb the sedimenting system in order to obtain an analysis which can be made continuous. The pioneer investigations of Svedberg and Nichols and Liebe, and Nichols and Bailey have been mentioned. However, it is usual to employ Schlieren techniques to follow boundary changes in analytical ultracentrifugation, the boundary being detected by changes of refractive index between solvent and suspension. This method was used by Hermans and Ryke (259) to determine the particle size of colloidal silica particles. Bierman et al. (260) used the technique to measure particle-size distributions of the chylomicrons, the submicron lipoprotein particles found in plasma after meals of fat, and found that the turbidity of their suspensions sometimes interfered with observation of the boundary. McCormick (261) noted that by increasing the intensity of the light beam with a mercury arc lamp the Schlieren patterns could still be obtained for concentrations up to 0.05% polystyrene latex particles with diameters of 2500 Å. He was therefore able to adapt conventional analytical ultracentrifugal techniques for the size analysis of a number of polymeric emulsions. Averink et al. (262) criticized McCormick's method since the turbidity forced him to use such low concentrations that the Schlieren peaks were very small, leading to poor accuracy. Averink et al. showed that the applicability of Schlieren optics was restricted to a range of particle diameters ranging from 200 to 2,400 Å. They concluded that with absorption optics the range could be greatly extended and described a method for achieving this. A graphical method was used to relate absorbance to concentration in order to calculate the size distribution. Using monochromatic light this method would appear to be the most satisfactory currently available.

Using a simple beam of light of mixed wavelengths, Groves, Kaye, and Scarlett (245) emphasized that their method could not be absolute for particles whose diameter approximates to the wavelength of the incident light but was useful for the detection of differences between samples. Kaye and Jackson (263) applied a modified centrifuge developed from the earlier models to the size analysis of polymer emulsions of narrow size range, and were able to deduce that these

materials had a wider range than that claimed by the manufacturers.

Thus, although the technique is relatively unsophisticated it may have some use where the particles are still big enough to cause interference with a light beam (>0.01 μ), since these particles are separated according to Stokes' law. The quantitative expression of the actual particle concentration may not be exact and may result in an overemphasis of the fines (277). The relationship between this effect and errors due to, for example, inadequate dispersion of the fine particles remains to be established. An adaptation of the technique described by Schleusener and Read (287) for detecting sedimenting particles with a 6328 Å./He-Ne gas laser may offer some improvement for future investigation.

Other Centrifugal Techniques for Sizing Emulsion Particles

The ultracentrifuge has been used to determine emulsion stability, measuring the free oil and compacted emulsion boundaries as a function of time (264–269). By analogy with gravity sedimentation methods this technique could be applied to particle-size determinations. Pinter and Zilversmit (270), and Zilversmit (271) described a density-gradient method for the ultracentrifugal size measurement of chylomicrons. This technique is used in studies on living materials (272) and the approach might well be applicable to emulsion systems.

ADSORPTION METHODS

Brodnyan and Brown (288) estimated the soap concentration adsorbed onto polymer emulsion particles. Assuming a monolayer of absorbed molecules of known molecular cross-section, they were able to calculate the total interfacial area and an average particle size from a knowledge of the phase volume. A similar method has been described by Groot (289) for paraffin oil emulsions stabilized with sodium lauryl sulfate. Since analytical methods for estimating a wide variety of surface-active agents are now available, the method may be generally applicable.

DISCUSSION AND CONCLUSIONS

The range of particle sizes in operationally usable pharmaceutical emulsions may be within the arbitrary limits 0.01 and 10 μ (297), although some have claimed that particles of up to 100-μ diameter may be found (156). From a practical standpoint it should be pointed out that emulsion droplet sizes well below Becher's (1) limit of 0.1 μ have been reported in the literature. For example, droplet diameters in transparent emul-

sions investigated by Bowcott and Schulman (273) were of the order 100–500 Å. van der Waarden (100) prepared emulsions with particle diameters varying between 250 and 900 Å. Kiyama et al. (274, 275) reported particle sizes varying between 0.08 and 0.2 μ, finding up to 30% w/w of their material below 0.08 μ in some instances. Lucas (52) found that rubber latex particles were generally below 0.1 μ, and chylomicrons have a size range extending down to 150 Å. (260). Schoenholz and Kimball (276) showed that bright-drying wax polish emulsions contained particles in the range of 0.05–0.1 μ, the particle size decreasing if the ratio of emulsifier-wax was increased. Thus, although it seems that emulsion systems may contain particles below the limit of detection by the light microscope, as shown in Table I, many workers have chosen arbitrarily to ignore them. It is true that on a weight basis these particles may only represent a small fraction of the total dispersed phase. On the other hand, when considered in terms of surface area, or number, the small particles could have a disproportionate influence on the behavior of an emulsion system, as noted by Sherman (56, 57, 292, 293). The problem can therefore be resolved into one of deciding which method of particle-size analysis to utilize; it is clear from this review that no one method in isolation is adequate to cover the wide range of particle sizes which occur in emulsion systems.

This problem was considered by Groves, Scarlett, and Freshwater (277) who determined the particle size of a model emulsion system by a variety of experimental techniques. An appreciable amount of submicron material was found to be present and results obtained are shown in Fig. 6. It is useful to remember when comparing results by different methods that different particle-size parameters are often measured. For example the light and electron microscopes both measure a cross-sectional diameter by direct observation or measurement of a photographic image. The Coulter counter measures the volume of the particle, and the result is derived as the diameter of a sphere of equivalent volume. Similarly, sedimentation methods yield a Stokes' diameter, which is the diameter of a sphere of identical density sedimenting under streamline-flow conditions at the identical velocity. Although it is generally assumed that emulsion droplets are spherical this may not always be the case (65, 298, 299). Nevertheless, emulsion particles are approximately spherical and the different derived parameters representing the particle diameter would be expected to show a reasonable measure of agreement. As will be

seen from Fig. 6, in this system there is general agreement above 1 μ, with the light microscope results tending to give a slightly higher size. This may be due to the difficulties previously noted of resolving and measuring particles below 2 μ. There is good agreement on the size of the largest particles present. The electron microscope results diverge but this was explained by sampling difficulties, the area presented by the electron photomicrograph field being 10 $\times$ 12 μ. The chance of sampling a 4-μ diameter particle is clearly reduced so that it would require an inordinate number of photographs or samples before this method would give results consistent with those from other methods.

However, it is below 1 μ that the methods show their greatest divergence. The system contained particles down to at least 0.02 μ diameter, well below the limiting discrimination level of the Coulter counter or light microscope. Rajagopal (23), recognizing that submicron particles could exist in an emulsion system, suggested that these could be determined by extrapolation of a log-probability plot and Batch (115) suggested a similar process. However, as can be seen from Fig. 6, extrapolation of both the Coulter counter and the light-microscope results yields a serious under estimate of the size of the smallest particles. The extrapolation techniques are clearly untenable for the model system examined by these authors and the validity of the approach was questioned. Comparing all these results with those obtained by the centrifugal photosedimentometer, it will be seen that this instrument

was capable of detecting the majority of submicron particles known to be present in the model system. The size range indicated by the instrument depends upon the particle sedimentation velocity and is therefore probably realistic. On the other hand, the quantitative measurement depends on the light-scattering properties of these small particles which are less predictable as they approach the magnitude of the wavelength of the incident radiation, resulting in overemphasis of the fines. In addition, as pointed out by these authors elsewhere (246), there is a marked tendency for small particles to adhere to the larger ones. Divergence from the electron microscope results may therefore be also due to inadequate dispersion of the system before sedimentation.

From this investigation it was concluded that the Coulter counter and centrifugal photosedimentometer offered the best combination at present available for carrying out an adequate measurement of the relatively wide size distributions that can exist in some emulsion systems. This conclusion has now been explored in more detail (278). The centrifugal photosedimentometer is limited to particles below about 10 μ diameter since above this size sedimentation is no longer under streamline-flow conditions, and a realistic lower limit is approximately 0.05 μ. The Coulter counter was used with a 70-μ orifice tube covering the range 1-25 μ. Using the two methods together on emulsion systems stabilized with a wide range of surface-active agents showed that in most cases on a log-probability plot the results were parallel over the common range of particle size. This enabled a log-probability plot to be built up over the whole of the distribution by a normalization process which was shown to be statistically valid. The particle-size distribution was therefore defined as the midpoint of the log-probability distribution lying between 20 and 80% probability (22, 28-30). As noted earlier, this method is a relatively insensitive method of presenting results. However, when considering such factors as sampling error and repeatability of a particular size analytical method it must be regarded as satisfactory and represents a considerable advance over many methods used before.

Examination of the flow behavior of emulsion systems for which the particle sizes had been determined in this manner suggested that the relationship between these two properties may be more complex than has been indicated from earlier studies (6). The ideal situation has not yet been reached whereby it is possible to predict emulsion behavior from a knowledge of the
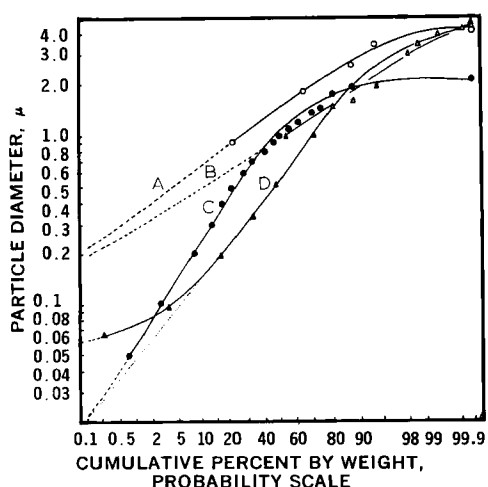

Fig. 6—The particle-size distributions of a model emulsion system determined by: A, light microscope; B, Coulter Counter; C, electron microscope; D, centrifugal photosedimentometer. Extrapolations are shown as broken lines. [Reproduced with permission from Proc. Particle Size Anal. Conf., Loughborough 1966, paper No. 22, p. 281.]

particle-size distribution. However, with improved methods which will give a reasonably accurate picture of the state of dispersion further investigations may well allow prediction of rheological properties with greater precision. Similarly, as noted by Garrett (297), the study of emulsion stability problems would also be assisted by the use of improved methods. The evaluation of emulsification equipment (147) and control of production batches of pharmaceutical emulsion are other examples where, in the long run, a more complete understanding of the quantitative relationship between the particle size and performance may be beneficial. Similarly, emulsion formulation studies would be materially assisted if the effects of surface-active agents, both quantity and quality, and the concentration and type of disperse phase could be predicted with greater accuracy than the rule-of-thumb calculations which are all too prevalent in everyday practice. Becher's excellent text (1) shows that there is a vast fund of knowledge of emulsions; nevertheless there is still room for improvement in many areas and it has been the purpose of this review to highlight just one of these.

"For out of olde fieldes, as men seith
Cometh al this newe corn froe yeer to yere;
And out of olde bokes in good feith,
Cometh al this new science that men lere." (300).

REFERENCES

(1) Becher, P., "Emulsions: Theory and Practice," A.C.S. Monogr. No. 162, 2nd ed., Reinhold, New York, N. Y., 1965.
(2) Martin, A. N., Banker, G. S., and Chun, A. H. C., "Advances in Pharmaceutical Sciences, I," Bean, H. S., Beckett, A. H., and Carless, J. E., Eds., Academic Press, London, England, 1964.
(3) Richardson, E. G., J. Colloid Sci., 5, 404(1950).
(4) Thomas, D. G., ibid., 20, 267(1965).
(5) Rutgers, I. R., Rheol. Acta, 2, 202, 305(1962).
(6) Sherman, P., J. Pharm. Pharmacol., 16, 1(1964).
(7) Cooper, F. A., Doctoral thesis, University of London, England, 1936.
(8) Cooper, F. A., J. Soc. Chem. Ind., 56, 447(1937).
(9) Levius, H. P., and Drommond, F. G., J. Pharm. Pharmacol., 5, 743(1953).
(10) Jellinek, H. H. G., J. Soc. Chem. Ind., 69, 225(1950).
(11) Herdan, G., "Small Particle Statistics," 2nd ed., Butterworths, London, England, 1960.
(12) Rossi, C., Gazz. Chim. Ital., 63, 190(1933).
(13) Dobrowsky, A., Kolloid Z., 95, 286(1941).
(14) van den Tempel, M., Trans. Inst. Rubber Ind., 27, 290(1951).
(15) Lederer, E. L., Kolloid Z., 71, 61(1935).
(16) Troesch, H. A., Chem.-Ing.-Tech., 26, 311(1954).
(17) Brodnyan, J. G., J. Colloid Sci., 15, 563, 573(1960).
(18) Steidl, H., and Vlcek, J., Coll. Czech. Chem. Commun., 25, 291(1960).
(19) Kottler, F., J. Phys. Chem., 56, 442(1952).
(20) Mugele, R. A., and Evans, H. D., Ind. Eng. Chem., 43, 1317(1951).
(21) Harkins, W. D., and Beeman, N., J. Am. Chem. Soc., 51, 1674(1929).
(22) Gwyn, J. E., Crosby, E. J., and Marshall, W. R., Ind. Eng. Chem. (Fund.), 4, 204(1965).
(23) Rajagopal, E. S., Kolloid Z., 162, 85(1959).
(24) Schwarz, N., Proc. 3rd World Petrol. Congr., Sect. 2, 628(1951).
(25) Bezemer, C., and Schwarz, N., Kolloid Z., 146, 145(1956).
(26) Schwarz, N., and Bezemer, C., ibid., 146, 139 (1956).
(27) Sprow, F. B., Chem. Eng. Sci., 22, 435(1967).
(28) Smith, J. E., and Jordan, M. L., J. Colloid Sci., 19, 549(1964).
(29) Kottler, F., J. Franklin Inst., 250, 339, 419(1950).
(30) Drinker, P., and Hatch, T., "Industrial Dust," 2nd ed., McGraw-Hill, New York, N. Y., 1954.
(31) Espensheid, W. F., Kerker, M., and Matijevic. E., J. Phys. Chem., 68, 3093(1964).
(32) Honig, E.P., ibid., 69, 4418(1965).
(33) Broadbent, S. R., and Callcott, T. C., Phil. Trans. Roy. Soc. London, Ser. A, 249, 99(1956).
(34) Broadbent, S. R., and Callcott, T. C., J. Inst. Fuel, 29, 524, 528(1956).
(35) Ibid., 30, 13, 18, 21(1957).
(36) Brown, R. L., Brit. Chem. Eng., 4, 463(1959).
(37) Arbiter, N., and Harris, C. C., ibid., 10, 240(1965).
(38) S.A.C. Classification, Analyst, 88, 156(1963).
(39) Orr, C., and Dallavalle, J. M., "Fine Particle Measurement," Macmillan, New York, N. Y., 1959.
(40) Rose, H. E., "Measurement of Particle Size in Very Fine Powders," Constable, London, England, 1953.
(41) Cadle, R. D., "Particle Size Determination," Interscience, New York, N. Y., 1955.
(42) Scarlett, B., Chem. Process Eng., 1965, 197.
(43) Simmonite, D., Pharm. J., 163, 386(1949).
(44) Fox, C. D., and Shangraw, R. F., J. Pharm. Sci., 55, 318, 323(1966).
(45) Smith, E. L., and Grinling, G. N., Quart. J. Pharm. Pharmacol., 3, 354(1930).
(46) Cockton, J. R., and Wynn, J. B., J. Pharm. Pharmacol., 4, 959(1952).
(47) Fischer, E. K., and Harkins, W. D., J. Phys. Chem., 36, 98(1932).
(48) Kaye, B. H., Doctoral thesis, University of London, 1962.
(49) British Standard, BS 3406, Part I (1964).
(50) van Kreveld, A., Rec. Trav. Chim., 60, 29(1941).
(51) Saylor, C. P., Appl. Opt., 4, 4(1965).
(52) Lucas, F. F., Ind. Eng. Chem., 30, 146(1938).
(53) King, A., Trans. Faraday Soc., 37, 168(1941).
(54) Knochel, E. L., Doctoral thesis, University of Wisconsin, 1958.
(55) Knoechel, E. L., and Wurster, D. E., J. Am. Pharm. Assoc., Sci. Ed., 48, 1(1959).
(56) Sherman, P., J. Phys. Chem., 67, 2531(1963).
(57) Sherman, P., J. Soc. Cosmetic Chemists, 16, 591 (1965).
(58) Ibid., 17, 439 (1966).
(59) Anderson, T. F., "Advances in Colloid Science, 1," Kraemer, E. O., Ed., Interscience, New York, N. Y., 1942.
(60) Walton, W. H., Suppl. Trans. Inst. Chem. Eng., 25, 64(1947).
(61) Watson, J. H. L., Anal. Chem., 20, 576(1948).
(62) Vanzo, E., Marchessault, R. H., and Stannett, V., J. Colloid Sci., 19, 578(1964).
(63) Cravath, A. M., Smith, A. E., Vinograd, J. R., and Wilson, J. N., J. Appl. Phys., 17, 309(1946).
(64) Nixon, H. L., and Fisher, H. L., Brit. J. Appl. Phys., 9, 68(1958).
(65) Groves, M. J., and Scarlett, B., Nature (London), 207, 288(1965).
(66) Atherton, E., ibid., 171, 350(1953).
(67) Schofield, F., Brit. J. Appl. Phys., 2, 18(1951).
(68) Schoon, T. G. F., and van der Bie, G. J., J. Polymer Sci., 16, 63(1955).
(69) Bradford, E. B., and Vanderhoff, J. W., J. Colloid Sci., 14, 543(1959).
(70) Morganson, N. E., ibid., 23, 605(1967).
(71) Crowl, V. T., Proc. Particle Size Anal. Conf. Loughborough, 1966, 36.
(72) Rippon, M., Master of science thesis, University of Loughborough, 1966.
(73) Ottewill, R. H., and Wilkins, D. J., J. Colloid Sci., 15, 512(1960).
(74) Derjaguin, B. V., and Vlasenko, G. J., Dokl. Akad. Nauk. SSSR, 63, 155(1948).
(75) Derjaguin, B. V., and Vlasenko, G. J., J. Colloid Sci., 17, 605(1962).
(76) Winchester, J. M., and Heritage, K. J., The Formulations of Pesticides, S.C.I., Monogr., No. 21, 154(1966).
(77) Krishnan, R. S., Proc. Indian Acad. Sci., 7A, 98(1938).
(78) Sing, D., ibid., 15A, 406(1942).
(79) van der Hulst, H. C., "Light Scattering by Small Particles," Chapman & Hall, London, England, 1957.
(80) Heller, W., J. Chem. Phys., 42, 1609(1965).
(81) Jennings, B. R., and Jerrard, H. G., J. Colloid Sci., 20, 448(1965).
(82) Gumprecht, R. O., and Sliepcevich, C. M., J. Phys. Chem., 57, 90, 95(1953).
(83) Lothian, G. F., and Chappel, F. P., J. Appl. Chem., 1, 475(1951).
(84) Goulden, J. D. S., Dairy Ind., 1958, 558.
(85) Goulden, J. D. S., Trans. Faraday Soc., 54, 941 (1958).
(86) Goulden, J. D. S., J. Dairy Res., 27, 67(1960).
(87) Goulden, J. D. S., Brit. J. Appl. Phys., 12, 456 (1961).
(88) Goulden, J. D. S., Nature (London), 191, 905(1961).
(89) Goulden, J. D. S., and Phipps, L. W., Proc. 3rd Intern. Congr. Surface Activity, 3, 190(1960).
(90) Skinner, D. G., and Boas-Traube, S., Trans. Inst. Chem. Engr., 25, 57(1947).

(91) Branson, S. H., and Dunning, W. J., *J. Soc. Chem. Ind.*, **68**, 80(1949).
(92) Hodkinson, J. R., Doctoral thesis, University of London, England, 1962.
(93) Kaye, B. H., and Allen, T., *Analyst*, **90**, 147(1965).
(94) Bolton, M. E., and Marshall, A. W., *Soap Sanit. Chem.*, **25**, 129, 143(1949).
(95) Trice, V. G., and Rodger, W. A., *Am. Inst. Chem. Eng. J.*, **2**, 205(1956).
(96) Langlois, G. E., Gullberg, J. G., and Vermeulen, T., *Rev. Sci. Instrum.*, **25**, 360(1954).
(97) Lloyd, N. E., *J. Colloid Sci.*, **14**, 441(1959).
(98) Schulman, J. H., and Friend, J. A., *ibid.*, **4**, 497 (1949).
(99) Schulman, J. H., and Friend, J. A., *Kolloid Z.*, **115**, 67(1949).
(100) van der Waarden, M., *J. Colloid Sci.*, **9**, 215(1954).
(101) La Mer, V. K., *J. Phys. Coll. Chem.*, **52**, 65(1948).
(102) Heller, W., Epel, J. N., and Tabibian, R. M., *J. Chem. Phys.*, **22**, 1777(1954).
(103) Stevenson, A. F., Heller, W., and Wallach, M. L., *ibid.*, **34**, 1789(1961).
(104) Wallach, M. L., paper presented at 151st American Chemical Society meeting, Pittsburgh, Pa., March 1966.
(105) Wallach, M. L., Heller, W., and Steven on, A. F., *J. Chem. Phys.*, **34**, 1796(1961).
(106) Gledhill, R. J., *J. Phys. Chem.*, **66**, 458(1962).
(107) Wales, M., *ibid.*, **66**, 1768(1962).
(108) Weber, H. H., *Kolloid Z.*, **188**, 40(1963).
(109) LaMer, V. K., and Plesner, I. W., *J. Polymer Sci.*, **24**, 147(1957).
(110) Dezelic, G. J., and Kratohvil, J. P., *Kolloid Z.*, **173**, 38(1960).
(111) Dezelic, G. J., and Kratohvil, J. P., *J. Colloid Sci.*, **16**, 561(1961).
(112) Kratohvil, J. P., and Wallace, T., paper presented at 151st American Chemical Society meeting, Pittsburgh, Pa., March 1966.
(113) Heller, W., and Tabibian, R. M., *J. Colloid Sci.*, **12**, 25(1957).
(114) Coulter, W. H., *Proc. Natl. Elec. Conf.*, **12**, 1034 (1956).
(115) Batch, B. A., *J. Inst. Fuel*, **37**, 455(1964).
(116) Berg, R. H., *A.S.T.M. Publication No. 234*, 1958.
(117) Cartmel, R., and Gerrard, H. N., *Pharm. J.*, **191**, 383(1963).
(118) Coulter Inc., *Theory of the Coulter Counter*, Bulletin T-1, 1958.
(119) Parfitt, G. D., and Willis, E., *J. Colloid Interface Sci.*, **22**, 100(1966).
(120) Kubitschek, H. E., *Nature (London)*, **182**, 234(1958).
(121) Kubitschek, H. E., *Research*, **13**, 218(1960).
(122) Kubitschek, H. E., *Rev. Sci. Instrum.*, **33**, 576(1962).
(123) Neutelings, J., and Polderman, J., *Pharm. Weekblad.*, **99**, 341(1964).
(124) Samartzopoulos, C. G., *Lab. Practice*, **13**, 38(1964).
(125) Swift, D. L., and Friedlander, S. K., *J. Colloid Sci.*, **19**, 621(1964).
(126) Ullrich, O. A., *Instrum. Soc. Am. N. Y. Conf.*, **1960**, 1.
(127) Wachtel, R. E., and LaMer, V. K., *J. Colloid Sci.*, **17**, 531(1962).
(128) Cooper, W. D., and Parfitt, G. D., paper presented at 151st American Chemical Society meeting, Pittsburgh, Pa., March 1966.
(129) Samyn, J. C., and McGee, J. P., *J. Pharm. Sci.*, **54**, 1794(1965).
(130) Wales, M., and Wilson, J. N., *Rev. Sci. Instrum.*, **32**, 1132(1961).
(131) *Ibid.*, **33**, 575(1962).
(132) Allen, T., *Proc. Particle Size Anal. Conf. Loughborough*, **1966**, 110.
(133) Lines, R. W., *ibid.*, 134.
(134) Princen, L. H., *Rev. Sci. Instrum.*, **37**, 1416(1966).
(135) Edmundson, I. C., *Nature (London)*, **212**, 1450 (1966).
(136) Barnes, S., Cheng, D.C-H., and Yarde, H. R., *Brit. J. Appl. Phys.*, **17**, 1501(1966).
(137) Mercer, W. B., *Rev. Sci. Instrum.*, **37**, 1515(1966).
(138) Lines, R. W., *Proc. Particle Size Anal. Conf. Loughborough*, **1966**, 129.
(139) Groves, M. J., *J. Pharm. Pharmacol.*, **18**, 305(1966).
(140) Singleton, W. S., and Brown, M. L., *J. Am. Oil Chemists Assoc.*, **42**, 312(1965).
(141) Higuchi, W. I., Okada, R., and Lemberger, A. P., *J. Pharm. Sci.*, **51**, 683(1962).
(142) Higuchi, W. I., Okada, R., Stelter, G. A., and Lemberger, A. P., *ibid.*, **52**, 49(1963).
(143) Lemberger, A. P., and Mourad, N., *ibid.*, **54**, 229, 233(1965)
(144) Rowe, E. L., *ibid.*, **54**, 260(1965).
(145) Mima, H., and Kitamori, N., *ibid.*, **55**, 44(1966).
(146) Princen, L. H., Stolp, J. A., and Kwolek, W. F., *J. Paint Technol.*, **39**, 182(1967).
(147) Marshall, K., and Taylor, J., *Proc. Coulter Users Meeting, Nottingham*, 1965.
(148) Schrenzel, M., *Pharm. Acta Helv.*, **40**, 635(1965).
(149) *Ibid.*, **41**, 218(1966).
(150) Kraemer, E. O., and Stamm, A. J., *J. Am. Chem. Soc.*, **46**, 2709(1924).
(151) Matsumoto, S., *Soc. Math. Sci. Japan J.*, **12**, 288 (1963).
(152) Matsumoto, S., *J. Chem. Soc. Japan*, **67**, 313(1964).
(153) Matsumoto, S., *Bull. Chem. Soc. Japan*, **38**, 553 (1964).
(154) Matsumoto, S., *Nippon. Kagaku. Zasshi.*, **85**, 741(1964).
(155) Kaye, R. C., and Seager, H., *J. Pharm. Pharmacol.*, **17**, 92S(1965).
(156) *Ibid.*, **19**, 78(1967).
(157) Figurovskii, N. A., *Tr. Vses. Konf. Anal. Khem.*, **2**, 399(1943).
(158) Figurovskii, N. A., *Zavodsk. Lab.*, **12**, 436(1946).
(159) Figurovskii, N. A., *Akad. Nauk SSSR*, **9**, 27(1949).
(160) Figurovskii, N. A., and Futran, M. F., *Kolloid Zh.*, **9**, 392(1947).
(161) Axon, A., *J. Pharm. Pharmacol.*, **8**, 762(1956).
(162) *Ibid.*, **9**, 889(1957).
(163) Bredee, H. L., and de Booys, J., *Kolloid. Z.*, **91**, 39(1940).
(164) *Ibid.*, **99**, 171(1942).
(165) Chessman, D. K., and King. A., *ibid.*, **83**, 33(1938).
(166) Eilers, H., *ibid.*, **97**, 313(1941).
(167) *Ibid.*, **102**, 154(1943).
(168) Eveson, G. F., "The Rheology of Disperse Systems," Mill, C. C., Ed., Pergamon, London, England, 1959.
(169) Eveson, G. F., *J. Oil Colour Chem. Assoc.*, **41**, 150(1958).
(170) Gillespie, T., *J. Colloid Sci.*, **15**, 219(1960).
(171) *Ibid.*, **18**, 32(1963).
(172) Gillespie, T., "The Rheology of Emulsions," Sherman, P., Ed., Pergamon, London, England, 1963.
(173) Gillespie, T., *J. Colloid Sci.*, **18**, 562(1963).
(174) Johnson, P. H., and Kelsey, R. H., *Rubber World.*, **138**, 877(1958).
(175) Kelsey, R. H., and Johnson, P. H., *ibid.*, **139**, 227 (1958).
(176) Lawrence, A. S. C., and Rothwell, E., *Proc. 2nd Intern. Congr. Surface Activity*, **1**, 464(1957).
(177) Leviton, A., and Leighton, A., *J. Phys. Chem.*, **40**, 71(1936).
(178) Lyttleton, D. V., and Traxler, R. N., *Ind. Eng. Chem.*, **40**, 2115(1948).
(179) Manley, R. St. J., and Mason, S. G., *Canad. J. Chem.*, **32**, 763(1954).
(180) Nawab, M. A., and Mason, S. G., *J. Colloid Sci.*, **13**, 179(1958).
(181) Nawab, M. A. and Mason, S. G., *Trans. Faraday Soc.*, **54**, 1712(1958).
(182) Orr, C., and Blocker, H. G., *J. Colloid Sci.*, **10**, 24(1955).
(183) Rajagopal, E. S., *Z. Physik. Chem.*, **23**, 342(1960).
(184) Richardson, E. G., *J. Colloid Sci.*, **8**, 367(1953).
(185) Saunders, F. L., *ibid.*, **16**, 13(1961).
(186) Sherman, P., *J. Soc. Chem. Ind. (Lond.)*, **69**, 570 (1950).
(187) Sherman, P., *J. Colloid Sci.*, **8**, 35(1953).
(188) Sherman, P., *Research*, **8**, 396(1955).
(189) Sherman, P., *J. Colloid Sci.*, **10**, 63(1955).
(190) Sherman, P., *Kolloid. Z.*, **141**, 7(1955).
(191) *Ibid.*, **165**, 156(1959).
(192) Sherman, P., *Proc. 3rd Intern. Congr. Surface Activity*, **B**, 596(1960).
(193) Sherman, P., *Food Technology*, **15**, 394(1961).
(194) Sherman, P., "Rheology of Emulsions," Sherman, P., Ed., Pergamon, London, England, 1963.
(195) Sherman, P., *Rheol. Acta*, **2**, 74(1962).
(196) Sherman, P., "Proc. 4th Intern. Congr. Rheol.," Part 3, Interscience, New York, N. Y. 1965, p. 605.
(197) Sheth, B. B., Doctoral thesis, University of Michigan, 1961.
(198) Sheth, B. B., McVean, D. E., and Mattocks, A. M., *J. Pharm. Sci.*, **51**, 265 (1962).
(199) Shotton, E., and White, R. F., *J. Pharm. Pharmacol.*, **12**, 108T(1960).
(200) Shotton, E., and White, R. F., "Rheology of Emulsions," Sherman, P., Ed., Pergamon, London, England, 1963.
(201) Sibree, J. O., *Trans. Faraday Soc.*, **26**, 26(1930).
(202) *Ibid.*, **27**, 161(1931).
(203) Simpson, G. K., *J. Oil Colour Chem. Assoc.*, **32**, 60(1949).
(204) Srivastava, S. N., *Rheol. Acta*, **2**, 210(1962).
(205) Sweeney, K. H., and Geckler, R., *J. Appl. Phys.*, **25**, 1135(1954).
(206) Takano, M., *Bull. Chem. Soc. Japan*, **36**, 1418(1963).
(207) Takano, M., and Kambe, H., *ibid.*, **36**, 1424(1963).
(208) Taylor, G. I., *Proc. Roy. Soc. London, Ser. A*, **138**, 41(1932).
(209) *Ibid.*, **146**, 501(1934).
(210) Traxler, R. N., *Ind. Eng. Chem.*, **28**, 1011(1936).
(211) Vand, V., *J. Phys. Colloid Chem.*, **52**, 300(1948).
(212) van den Tempel, M., *J. Colloid Sci.*, **16**, 284(1961).
(213) van den Tempel, M., "Rheology of Emulsions," Sherman, P., Ed., Pergamon, London, England, 1963.
(214) Williams, P. S., *Disc. Faraday Soc.*, **11**, 47(1951).
(215) Williams, P. S., *J. Appl. Chem.*, **3**, 120(1953).
(216) Wilson, C. L., and Parke, J. B., *Quart. J. Pharm. Pharmacol.*, **9**, 188(1936).
(217) Talman, F. A. J., Davies, P. J., and Rowan, E. M., *J. Pharm. Pharmacol.*, **19**, 417(1967).
(218) Dumanskii, A., Žabotinskii, G., and Evseyev, E., *Z. Chem. Ind. Kolloid*, **12**, 6(1913).
(219) Svedberg, T., and Pederson, K. O., "The Ultracentrifuge," Claredon, Oxford, England, 1940.
(220) Nichols, J. B., and Liebe, H. C., *3rd Colloid Symp., Monogr.*, **1925**, 268.

(221) Bailey, E. D., Nichols, J. B., and Kraemer, E. O., *J. Phys. Chem.*, **40**, 1149(1936).
(222) Bailey, E. D., *Ind. Eng. Chem. Anal.*, **18**, 365(1946).
(223) Nichols, J. B., and Bailey, E. D., "Physical Methods of Organic Chemistry," 2nd ed., Weissberger, A., Ed., Interscience, New York, N. Y., 1949.
(224) Robison, H. E., and Martin, S. W., *J. Phys. Colloid Chem.*, **52**, 854(1948).
(225) *Ibid.*, **53**, 860(1949).
(226) Cheng, P. Y., and Schachman, H. K., *J. Polymer Sci.*, **16**, 19(1955).
(227) Marshall, C. E., *Proc. Roy. Soc. London, Ser. A*, **126**, 427(1930).
(228) Marshall, C. E., *J. Soc. Chem. Ind.*, **50**, 444T(1931).
(229) Marshall, C. E., *Trans. Ceram. Soc.*, **30**, 81(1931).
(230) Keen, B. A., and Schofield, K. R., *Nature (London)*, **126**, 93(1930).
(231) Bailey, R. J., Lines, R. W., and Wood, W. M., *Proc. Particle Size Anal. Conf. Loughborough*, **1966**, 222.
(232) Jones, M. H., paper presented to Particle Size Analysis Group, Bradford, 1966.
(233) Martin, S. W., *Ind. Eng. Chem. Anal.*, **11**, 471(1939).
(234) Kamack, H. J., *Anal. Chem.*, **23**, 844(1951).
(235) Johne, R., *Chem.-Ing.-Teck.*, **38**, 428(1966).
(236) Kaye, B. H., and Boardman, R. P., *Proc. Symp. Inst. Chem. Eng.*, **1962**, 17.
(237) Donoghue, J. K., and Bostock, W., *Trans. Inst. Chem. Eng.*, **33**, 72(1955).
(238) Slater, C., and Cohen, L., *J. Sci. Instrum.*, **39**, 614(1962).
(239) Gupta, A. K., *J. Appl. Chem.*, **9**, 487(1959).
(240) Moser, H., and Schmidt, W., *Das Papier*, **11**, 189 (1957).
(241) Kaye, B. H., Brit. Pat. 895, 222 (1962).
(242) Burt, M. W. G., *Atomic Weapons Research Establishment Rept.*, No. 0-76/64, 1964.
(243) Burt, M. W. G., and Kaye, B. H., *Analyst*, **91**, 547(1966).
(244) Burt, M. W. G., *Powder Technol.*, **1**, 103(1967).
(245) Groves, M. J., Kaye, B. H., and Scarlett, B., *Brit. Chem. Eng.*, **9**, 742(1964).
(246) Freshwater, D. C., Groves, M. J., and Scarlett, B., *Proc. 25th Inst. Congr. Pharm. Sci. (1965)*, **2**, 307(1967).
(247) Freshwater, D. C., Scarlett, B., and Groves, M. J., *Am. Perfumer*, **81**, 43(1966).
(248) Martin, J. J., Brown, J. H., and De Bruyn, P. L., "Ultrafine Particles," Kuhn, W. E., Ed., Wiley, New York, N. Y., 1963.
(249) Hildreth, J. D., Doctoral Thesis, University of Leeds, 1962.
(250) Hildreth, J. D., and Patterson, D., *J. Soc. Dyers Colourists*, **80**, 474(1964).
(251) Atherton, E., Cooper, A. C., and Fox, M. R., *ibid.*, **80**, 521(1964).
(252) Atherton, E., and Tough, D., *ibid.*, **81**, 624(1965).
(253) Murley, R. D., *Nature (London)*, **207**, 1089(1965).
(254) Romwalter, A., and Vendl, M., *Kolloid Z.*, **42**, 1(1935).
(255) Brown, C., *J. Phys. Chem.*, **48**, 246(1944).
(256) Parkinson, D., *Trans. Inst. Rubber Ind.*, **16**, 87(1940).
(257) Jacobsen, A. E., and Sullivan, W. F., *Ind. Eng. Chem. Anal.*, **18**, 360(1946).
(258) Dana, S. W., *J. Sediment. Petrol.*, **13**, 21(1943).
(259) Hermans, J. S., and Ryke, A. M., *J. Colloid Sci.*, **13**, 508(1958).
(260) Bierman, E. L., Haynes, T. L., Hawkins, J. N., Ewing, A. M., and Lindgren, F. T., *J. Lipid Res.*, **7**, 65(1966).
(261) McCormick, H. I. V., *J. Colloid Sci.*, **19**, 173(1964).
(262) Averink, J. W. A., Reerink, H., Boerma, J., and Jaspers, W. J. M., *J. Colloid Interface Sci.*, **21**, 66(1966).
(263) Kaye, B. H., and Jackson, M. R., *Powder Technol.*, **1**, 81(1967).
(264) Garrett, E. R., *J. Pharm. Sci.*, **51**, 35(1962).
(265) Rehfeld, S. J., *J. Phys. Chem.*, **66**, 1966(1962).
(266) Vold, R. D., and Groot, R. C., *ibid.*, **66**, 1969(1962).
(267) Vold, R. D., and Groot, R. C., *J. Soc. Cosmetic Chemists*, **14**, 233(1963).

(268) Vold, R. D., and Groot, R. C., *J. Colloid Sci.*, **19**, 384(1964).
(269) Vold, R. D., and Groot, R. C., *J. Phys. Chem.*, **68**, 3477(1964).
(270) Pinter, G. C., and Zilversmit, D. B., *Biochim. Biophys. Acta*, **59**, 116(1962).
(271) Zilversmit, D. B., "Biochemical Problems of Lipids," Frazer, A. C., Ed., Elsevier, London, England, 1963.
(272) Oster, G., *Sci. Am.*, **1965**, 70.
(273) Bowcott, J. E., and Schulman, J. H., *Z. Elektrochem.*, **59**, 283(1955).
(274) Kiyama, R., Kinoshita, H., and Suzuki, K., *Rev. Phys. Chem. Japan*, **21**, 82(1951).
(275) *Ibid.*, **22**, 46(1952).
(276) Schoenholz, D., and Kimball, C. S., *Soap Sanit. Chem.*, **23**, 131(1947).
(277) Groves, M. J., Scarlett, B., and Freshwater, D. C., *Proc. Particle Size Anal. Conf. Loughborough*, **1966**, 281.
(278) Groves, M. J., Doctoral thesis, University of Loughborough, England, 1967.
(279) Gregg, E. C., and Steidley, K. D., *Biophys. J.*, **5**, 393(1965).
(280) Princen, L. H., and Kwolek, W. F., *Rev. Sci. Instrum.*, **36**, 646(1965).
(281) Edmundson, I. C., "Advances in Pharmaceutical Sciences, 2," Bean, H. S., Becket, A. H., and Carless, J. E., Eds., Academic Press, London, England, 1967.
(282) Parfitt, G. E., *J. Oil Colour Chemists' Assoc.*, **50**, 822(1967).
(283) Eckhoff, R. K., *J. Sci. Instrum.*, **44**, 648(1967).
(284) Shotton, E., and Davis, S. S., *J. Pharm. Pharmacol.*, **19**, 130S(1967).
(285) Whittlestone, W. G., *Aust. J. Dairy Technol.*, **17**, 108(1962).
(286) Cornell, D. G., and Pallansch, M. J., *J. Dairy Sci.*, **49**, 1371(1966).
(287) Schleusener, S. A., and Read, A. A., *Rev. Sci. Instrum.*, **38**, 1152(1967).
(288) Brodnyan, J. G., and Brown, G. L., *J. Colloid Sci.*, **15**, 76(1960).
(289) Groot, R. C., *Abhandl. Deut. Akad. Wiss. Berlin*, **6B**, 567(1966).
(290) Elworthy, P. H., and Florence, A. T., *J. Pharm. Pharmacol.*, **19**, 140S(1967).
(291) Becher, P., *J. Colloid Interface Sci.*, **24**, 91(1967).
(292) Sherman, P., *ibid.*, **24**, 91(1967).
(293) *Ibid.*, **24**, 97(1967).
(294) Hawksley, P. G. W., Blackett, J. H., Meyer, E. W., and Fitzsimmons, A. E., *Brit. J. Appl. Phys.*, **1954**, 165.
(295) Collins, G. F., *Proc. Particle Size Anal. Conf. Loughborough*, **1966**, 65.
(296) Fisher, C., *ibid.*, **1966**, 77.
(297) Garrett, E. R., *J. Pharm. Sci.*, **54**, 1557(1965).
(298) Lissant, K. J., *J. Colloid Interface Sci.*, **22**, 462(1966).
(299) Groves, M. J., and Freshwater, D. C., *J. Pharm. Pharmacol.*, **19**, 193(1967).
(300) Chaucer, G., *The parlement of foules*, **1**, 22(1380).

🔑 *Keyphrases*

Emulsion systems—particle size

Particle size—analysis methods

Instruments—particle-size determination

Homogeneous suspensions—theory

Light scattering—particle concentration measurement