The monohydrated sodium salt of 1-β-(p-toluene-sulfonamidoethyl) - 4 - p - toluenesulfonylpiperazine was obtained by filtration of the precipitate which appeared in the reaction mixture before acidification; m.p. 213-215°.

Anal.—Calcd. for $C_{20}H_{28}N_4NaO_6S_2 \cdot H_2O$: C, 50.-20; H, 5.90. Found: C, 49.5; H, 5.9.

1 - β - Benzenesulfonamidoethyl - 4 - benzene-sulfonylpiperazine.—This compound was prepared in a manner similar to that described in the previous procedure. A yield of 89% of colorless needles was obtained which melted at 144–146°.

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Prediction of Stability
in Pharmaceutical Preparations VIII

Oil-in-Water Emulsion Stability and the Analytical Ultracentrifuge

By EDWARD R. GARRETT†

An oil-in-water emulsion clears in a centrifugal field to form a packed, semirigid "cream." Subsequently, a true oil or continuous phase is spun-out of the "cream." It is shown that rates of emulsion clearing can be stated as a function of the ultra-centrifugal r.p.m. and that the rate of clearing under simple gravity can be predicted for the oil-water emulsion as initially constituted. "Bad" emulsion can be differentiated from "good" emulsion by the ready formation of a separate oil phase in the former. In the latter case, an induction period exists before a continuous oil phase is spun out at an accelerating rate, which rate is a function of the centrifugal force.

THE PREDICTION of stability in pharmaceutical preparations has largely dealt with chemical transformations (1, 2). The basic philosophy has been the application of stress or energy to promote decomposition and the following of degradation or of some property of the degradation as a function of time. This function has been linearized and the slopes of such linear plots have been used as estimates of specific rates (*k*). The reproducibility of such functions at varying degrees of stress would validate their use in prediction of rates under marketing or storage conditions. There are classical relations that describe the variation of such rate parameters with the degree of stress. In the cases previously discussed, a rate at a given temperature is linearized on the basis of it being first, second, etc., order and the apparent rate constant (*k*) or property proportional to rate

constant is correlated with the absolute temperature by means of the Arrhenius expression, which in its logarithmic form is

$$\log k = -(\Delta H_a/2.303\ R)(1/T) + \log P \quad \text{(Eq. 1)}$$

Thus the accelerated reactions can be used to evaluate the parameters of Eq. 1, i.e., ΔH_a and the resultant quantitative expression may be used to predict specific rates or functions thereof at lower temperatures.

Since the nature of the function is known from the reproducibility among the various accelerated studies, the predicted rate constants may be used in such a function to predict thermal stability at lower temperatures.

The same philosophy may be used in predicting physicochemical stability of pharmaceutical formulations where preservation of the pharmaceutical elegance is of primary interest rather than the integrity of the drug.

A case in point is a colloidal suspension or emulsion. An admirable example of an oil-water emulsion[1] (3, 4) is available commercially. It is a

[1] Marketed as Lipomul I.V. by Upjohn.

clinically useful fat emulsion in an aqueous continuous phase which is well tolerated on intravenous administration and has therapeutic utility (4) since it is a high caloric material for intravenous alimentation.

The primary criteria for the stability of the preparation is the preservation of the emulsion or the retention of the complete dispersion of fat in water. A classical evaluation of such stability is vigorous shaking for 72 hours at 5° with essentially no change in particle size. Particle size may be estimated from hemocytometer particle counts. It has been shown that well over 90% of the fat is present in particles which were submicroscopic with not over 0.02% of the visible particles larger than 1.5 μ in diameter (3).

The importance of the maintenance of stability of such a preparation is obvious. Not only would nondispersed oil be conducive to embolism, but unstable oil particles would resist metabolism where the particulate nature of the fat is considered mandatory. Solvolytic degradation would tend to decrease emulsion stability. Phosphatide hydrolysis would diminish dispersing agent and increase solvolysis rates. Such a model of degradation would be autocatalytic in nature.

There are two aspects of the stability prediction of colloidal suspensions or emulsions. The one relates to the shelf life of the emulsion when gravitational influences alone are to be considered, i.e., oil flotation of the emulsion.[1] The other is the stability prediction of emulsion when chemical degradation produces an inherent emulsion instability or tendency for oil coalescence. This paper primarily reports on studies of the former or physical instability, but also considers the implications of the latter.

EXPERIMENTAL

Analytical Ultracentrifuge.—The data presented in this paper were obtained from quantitative measurement of photographs of sector cells filled with the oil-water emulsion.[1] The sector cell was counterbalanced in the rotor of the Spinco analytical ultracentrifuge, model E (5) which may be operated at speeds up to 60,000 r.p.m. The optics are a Schlieren optical system (5, 6) but may also be used to measure light transmittance in different levels of the cell. The operating temperature was maintained within 2° of the initial temperature of 29° for the duration of a run.

The oil-water emulsion[1] was prepared as specified in the literature (3, 4). It was opaque and initially the photographic film was sensitized only by light which passed through (a) transparent air above the emulsion, i.e., toward the center of the rotor, and (b) a reference hole in the counterbalance. This latter is manifested in the photographic negative by a dark

reference bar from which the distance to the center of the rotor is 7.30 cm. (see Figs. 1b and 5b).

The clearing of the oil-water emulsion on ultracentrifugation was demonstrated by an increasing transparency in the bottom of the cell, i.e., away from the center of the rotor. The recording of this phenomenon on the photographic negative which magnifies the actual cell 2.21 times radially (or along the vertical length in the figures) was by an increasing band of darkness. The difference between the distance, x in cm. corrected for magnification, of the leading edge of this band to the near edge of the reference bar and 7.30 cm. is the distance of the slowest floating oil particles from the center of the rotor (Fig. 5b). The measurements of the x distance were performed in two ways: (a) by magnification in a photo enlarger and projection on a system of coordinates with a selection of scale such that 10 times the magnification of the original cell geometry resulted, and (b) by use of the Spinco Analytrol to determine the optical absorbance of the photographic film as a function of the distance across the film (Fig. 6b). This latter technique gave a good sharp line at the water-emulsion or water-cream interphase. Both methods gave data in good agreement.

Specific Emulsions.—Freshly prepared emulsion,[1] maintained at 5°, preparation A, and a similar material, preparation B, maintained for one-half year at 37°, were ultracentrifuged at speeds ranging from 12,590 to 52,640 r.p.m. and the clearing of the emulsions was measured (see Figs. 1-6). The log (7.30 − x) cm. values (Fig. 5b) were plotted against time for each r.p.m. and the constant slopes, k, were determined. These values are listed in Table I.

The preparation B was considered as an example of unsatisfactory emulsion in that its acidity had increased; it gave grossly observable oil and significant changes in particle size when subjected to vigorous shaking for 72 hours at 5°.

The flotation rates of oil particles were extreme at the higher r.p.m. values. Thus, most of the maximum possible clearing of the emulsion had occurred in the time necessary to bring the ultracentrifuge up to the desired r.p.m. setting. Since the valid flotation rate for a given r.p.m. could only be estimated from measurements made at constant r.p.m., the largest error of estimate of k is at the larger r.p.m. values.

TABLE I.—SLOPES, k, OF PLOTS OF LOGARITHM OF POSITION OF CLEARING EMULSION FROM CENTER OF ROTOR IN CM. AGAINST TIME IN SECONDS FOR VARIOUS R.P.M. OF ULTRACENTRIFUGATION

R.P.M.	Prepn. A*a*	Prepn. B*b*
12,590	2.34,*c* 2.35*d*	2.39
15,220	3.96, 3.68	3.67
20,410	5.95	6.03
24,630	7.21	6.53
29,500	9.31	9.67
35,600	13.4	16.9
39,460	19.8	17.9
44,770	31.8	...
52,640	39.1	...

a "Good" emulsion. *b* "Bad" emulsion. *c* After the "cream" formed, i.e., when no change in emulsion clearing was observed with time, material was resuspended using a Burrell wrist-action shaker at high speed for 20 minutes. *d* k Values obtained for resuspended material described in footnote*c*.
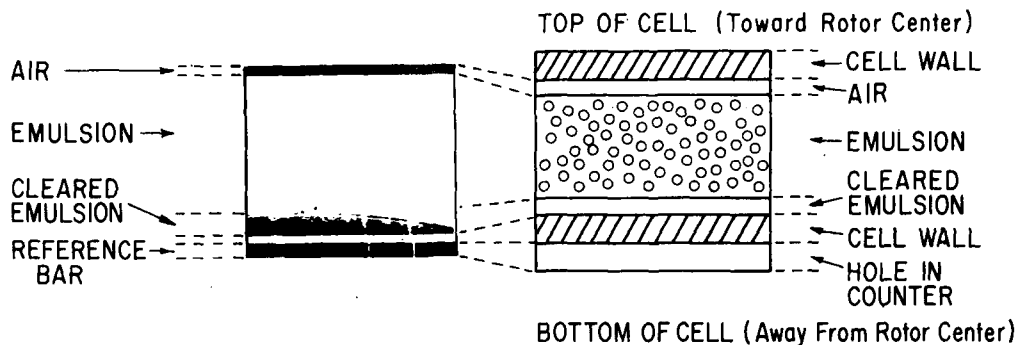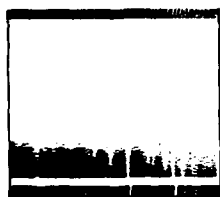
TOP OF CELL (Toward Rotor Center)

AIR

EMULSION

CLEARED EMULSION

REFERENCE BAR

CELL WALL
AIR
EMULSION
CLEARED EMULSION
CELL WALL
HOLE IN COUNTER

BOTTOM OF CELL (Away From Rotor Center)

FIG. 1a
338 sec.

FIG. 1b

FIG. 2
559 sec.

FIG. 3
779 sec.

FIG. 4
1,039 sec.

AIR
CREAM
CLEARED EMULSION
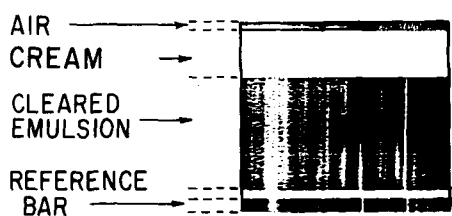REFERENCE BAR

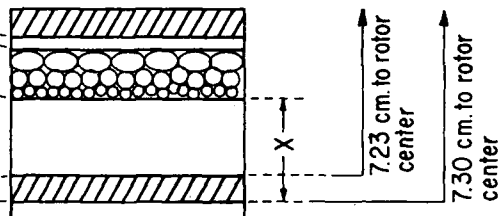7.23 cm. to rotor center

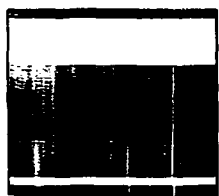7.30 cm. to rotor center

FIG. 5a
1,931 sec.
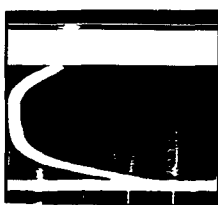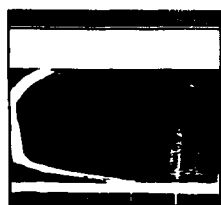
FIG. 5b

3,001 sec.
FIG. 6a

ABSORBANCE
FIG. 6b

Figs. 1a–6b.—Clearing of oil-water emulsion at 24,630 r.p.m. The ultracentrifugal pictures were taken at 2.21 magnification of the i.v. emulsion at 32°. The rotor reached full speed at 158 seconds. The times in seconds of ultracentrifugation are given below the appropriate figures. Figs. 1b and 5b interpret the photographs as to the clearing of the emulsion to the flotation of oil particles as a "cream, "Fig. 6b shows a plot of the absorbance of the film.

Inspection of the material in the sector cell after ultracentrifugation showed a clear liquid at the bottom and a resilient white creamy froth or "cream" at the top of the cell with semisolid or plastic attributes which readily redispersed in the aqueous phase on agitation to give the same k constant as before (see Table I).

The formation of an oil phase occurred at higher r.p.m. values (see Figs. 7–16). Runs were conducted on both preparations A and B from 39,460 to 59,780

TOP OF CELL (Toward Rotor Center)

BOTTOM OF CELL (Away From Rotor Center)

FIG. 7	FIG. 8	FIG. 9
868 sec.	1,652 sec.	2,847 sec.

AIR
OIL
CREAM
CLEARED EMULSION
REFERENCE BAR

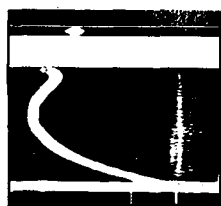7.30 cm. to rotor center

y

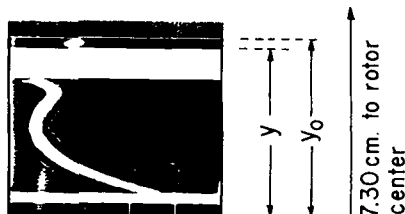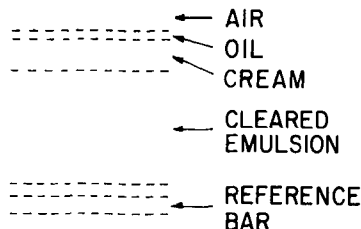y_0

FIG. 10	FIG. 11
4,996 sec.	6,076 sec.

Figs. 7–11.—Flotation of oil in a "poor" oil-water emulsion at 52,640 r.p.m. from the "cream" of adhered oil particles. The times in seconds of ultracentrifugation are given below the appropriate figures. Figs. 10 and 11 are labeled for identification of the layers. The geometry of cell with respect to the center of the rotor is given in Fig. 11. The rotor reached full speed in 6 minutes.

r.p.m., and the depth of the oil phase was correlated with the time of ultracentrifugation (see Fig. 11 for $y - y_0$). The nature of the oil phase was demonstrated by its immiscibility with water and miscibility with oil.

Thermal instability was checked by subjection of emulsion[1] A to 75° and removal of aliquots on the third and subsequent days. These samples were toxic and on gross observations showed poor dispersivity and high acid titer. On ultracentrifugation at 52,640 r.p.m. no band on the photographic negative appeared that could be assigned to formation of an oil layer (see Figs. 10 and 11). However, inspection of the cell after centrifugation did show that the oil had separated but was now opaque.

CALCULATIONS AND RESULTS

Sedimentation of particles heavier than the suspending medium and flotation of particles lighter than the suspending medium follow the same laws on ultracentrifugation except for sign. The former sediment away from the axis of rotation; the latter float toward the axis of rotation. The theory of convection-free sedimentation in centrifugal fields as developed by Svedberg (5–7) applies to a sector-shaped cell whose side walls are in the direction of the centrifugal force so as to provide an unobstructed path to the floating particles.

The classical expression relating the distance, x, of a particle from the axis of rotation with the time, t,

of centrifugation and the r.p.m. of the rotation is

$$\log x_2/x_1 = \frac{V(\rho - \rho')\,(\text{r.p.m.}2\pi)^2\,(t_2 - t_1)}{k\eta}$$

(Eq. 2)

where x_2 and x_1 are positions of the particle at t_2 and t_1, respectively, V is the volume of the particle, ρ and ρ' are the densities of the particle and medium, respectively, k is a shape constant for the particle size, and η is the coefficient of viscosity of the fluid.
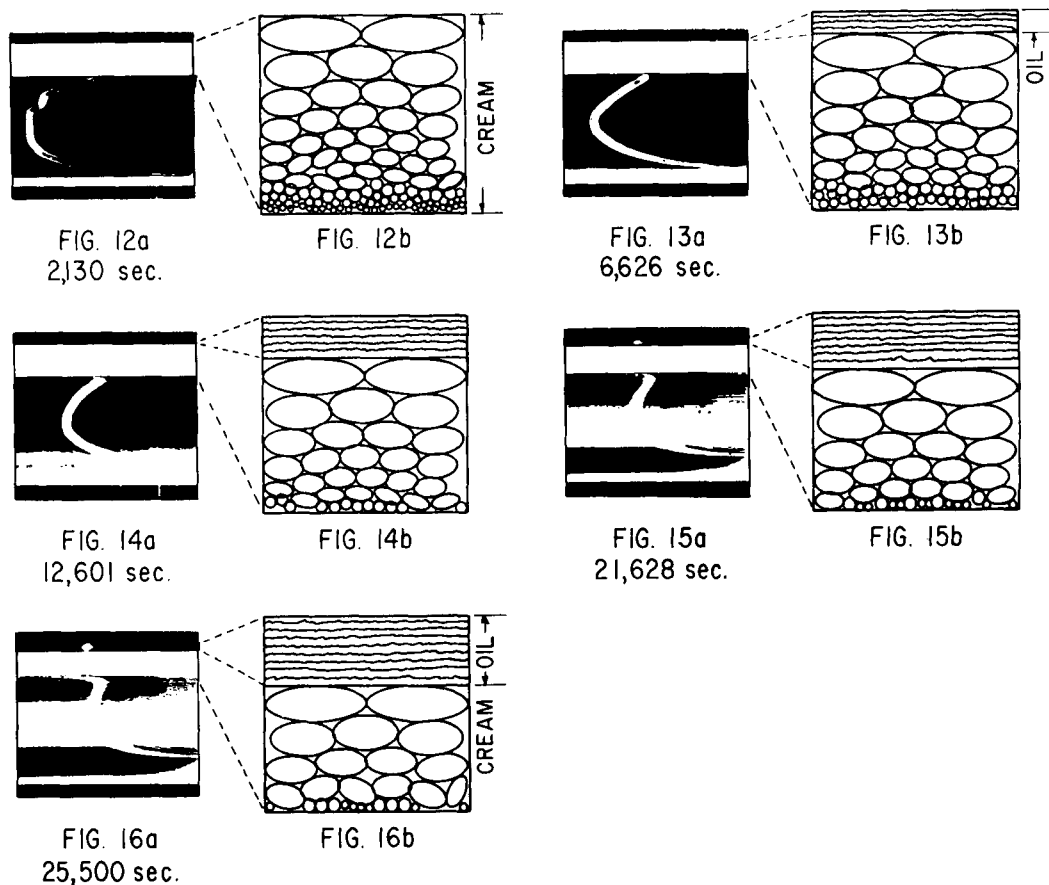
For a given material at a given temperature, the equation reduces to

$$\log x_2 = kt + \log x_1 = S(\text{r.p.m.})^2 t + \log x_1 \quad \text{(Eq. 3)}$$

where t is the time from the start of the centrifugation and S is defined as the sedimentation (or flotation) constant.

It is apparent that a plot of the logarithm of the position of a floating particle from the axis of rotation against the time of ultracentrifugation should be a straight line. Typical photographs of emulsion clearing as characterized by the appearance of a nonopaque vehicle are given as Figs. 1 through 6. The value 7.30-x cm. represents the position of the slowest floating particle from the axis of rotation. The plots of the logarithm of this value for a given r.p.m. against time are straight lines as shown by the examples in Fig. 17. These plots confirm the validity of Eqs. 2 and 3.

It also follows that plots of the slope $k = S(\text{r.p.m.})^2$ against the square of the r.p.m. should be linear and

FIG. 12a FIG. 12b
2,130 sec.

FIG. 13a FIG. 13b
6,626 sec.

FIG. 14a FIG. 14b
12,601 sec.

FIG. 15a FIG. 15b
21,628 sec.

FIG. 16a FIG. 16b
25,500 sec.

Figs. 12a–16b.—Flotation of oil in a "good" oil-water emulsion, i.v. emulsion, at 52,640 r.p.m. from the "cream" of adhered oil particles. The times in seconds of ultracentrifugation are given below the appropriate *a* figures. The *b* figures are diagrammatic representations of the coalescence of particles in the "cream." The rotor reached full speed in 6 minutes.

pass through the origin as do the examples given in Fig. 18. The resultant sedimentation coefficient is $S = 12.14 \times 10^{-14}$ for rate of rotation in min.$^{-1}$ and rate of particle displacement in the cell in sec.$^{-1}$ as calculated from the slope of the line in Fig. 18.

The data plotted in Fig. 18 are given in Table I and are typical of the data obtained from both "good" and "bad" emulsions, defined as such by the stability tests previously described. Maintenance of emulsion[1] at 40° for one-half year produces a "bad" emulsion.

The observed clearing of the emulsion by ultracentrifugation does not vary with the degree of "goodness" of the emulsion. This is not wholly unexpected since an oil-in-water emulsion should posses a spectrum of oil particle sizes and, the smaller the particle, the greater its resistance to flotation by Brownian motion and charge repulsion, i.e., higher charge/mass ratio.

In general, flotation, creaming, and coalescence are not necessarily correlated with emulsion clearing as manifested by the appearance of a clear solution. It follows that a "bad" emulsion may have a sufficient population of small oil particles which impart turbidity to the solution for as long a time as "good" emulsion under the same conditions of ultracentrifugation. It also follows that the measure-

ment of the emulsion clearing rate and the sedimentation constant measures only the flotation of that population of particles which is the smallest size possible and says nothing about the population of larger particles.

The clearing of "good" emulsion[1] proceeded until a narrow band of opaque material remained at the "top" of the cell, adjacent to the air-liquid boundary, i.e., closest to the axis of rotation (see Figs. 5a and 5b). A clear liquid slowly appeared adjacent to the air-liquid boundary and in both "bad" (Figs. 7–11) and "good" (Figs. 12a–16b) emulsions replaced a portion of the area of opacity. The initial rate of clearing of the opaque band for "good" emulsion[1] accelerated with time, as can be observed by the plots of Fig. 19, curves b, c, and d.

Inspection of the sector cell after ultracentrifugation disclosed a clear aqueous solution below a semisolid froth-like band or "cream" which lay below a transparent oil. Agitation of the cell redispersed the "cream" which had the same flotation parameter for emulsion clearing as did new or fresh emulsion.

Emulsion which was characterized as "bad" on the premises of poor dispersivity, high acid titer, and toxicity did not show the long inductive period of "good" emulsion in spinning out oil from the "cream" (see Fig. 19a). Whereas the "good" emul-
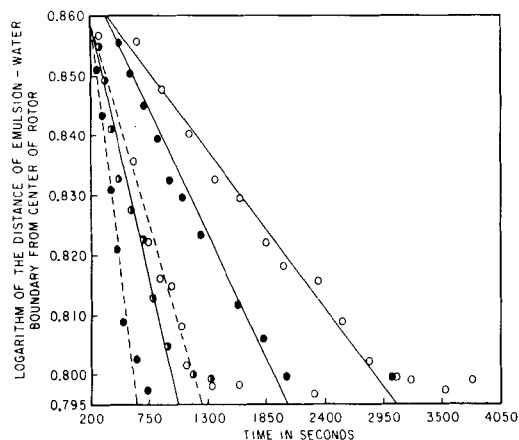
Fig. 17.—Examples of clearing of oil-water emulsion from i.v. emulsion at various centrifugal speeds. Plots of the logarithm of the distance of the emulsion-water boundary from the center of the rotor against the time of ultracentrifugation in seconds at 30°. The symbols and corresponding r.p.m. are: —⊙—, 12,590; —●—, 15,220; - -○- -, 20,410; —◑—, 24,630; - -●- -, 35,600.

sion manifested an induction period and then an acceleration of rate in spinning out oil, where such factors are an apparent function of r.p.m. or centrifugal field intensity (see Figs. 19b, c, and d), "bad" emulsion produced oil almost instantly with a first-order decay in amount of oil formed. Subsequent to this initial spin-out by "bad" emulsion the inductive and accelerated process of further oil spin-out characteristic of "good" emulsion was noted (see Fig. 19a).

The readily spun-out oil of "bad" emulsion had an apparent half-life in this particular sector cell of 1,200 seconds and was relatively independent of the r.p.m. values studied. However, all the emulsion was well cleared by that time for the same r.p.m. For as low as 35,600 r.p.m. the emulsion was cleared in 620 seconds. When the determined S value is used in Eq. 3, it can be calculated that the emulsion would be cleared in less than 200 seconds at 59,600 r.p.m.

It is thus apparent that the rate of coalescence to produce an oil layer, even with "bad" emulsion, was significantly slower than the rate of clearing of the oil emulsion of the smallest oil particle.

DISCUSSION

The coincidence of the apparent flotation rates of "good" and "bad" oil-in-water emulsions indicated that a population of the smallest oil particles was present in both preparations and lagged behind on ultracentrifugation. An alternative explanation is that the solutions were so concentrated that the larger oil particles "swept out" the emulsion, that is, aggregates were formed during the process of emulsion clearing that had similar clearing rates in both "good" and "bad" emulsions. This latter explanation implies that there would be no gradation in size of oil particles from bottom to top of the clearing emulsion and thus in the ultimate "cream." It also suggests that Eq. 2 would not hold, that there would be a nonlinearity early in the plots of Fig. 17 as
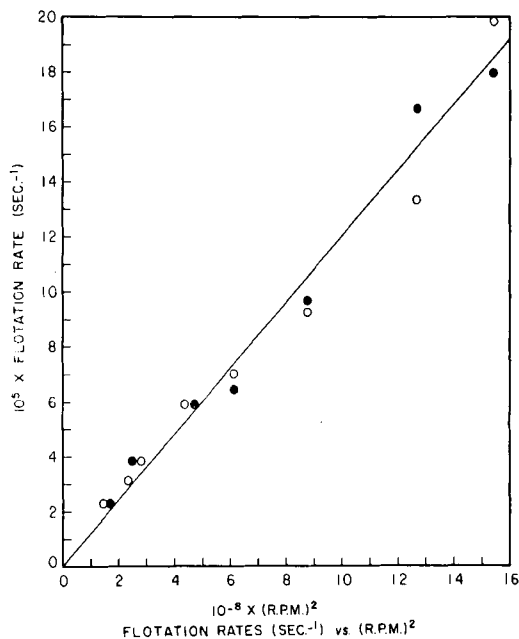

Fig. 18.—Flotation rates for the clearing of oil-water emulsion at 30° against the square of the r.p.m. The open circles are for a stable or "good" emulsion. The closed circles are for an unstable or "poor" emulsion. The flotation rates are the slopes of the plots of the logarithm of the distance of the emulsion-water boundary from the rotor center against time for each r.p.m. The apparent flotation constant from the slope of this figure is 12.14 × 10^{-14}.
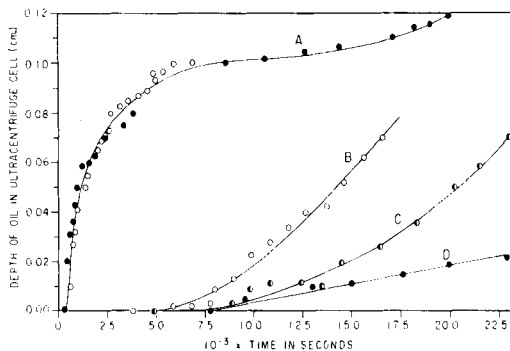

Fig. 19.—Increase of oil coalescence as a function of time for "bad", curve A, and "good", curves B, C, and D, oil-water emulsions. The symbols and ultracentrifugal r.p.m. at 30° are: ⊙, 59,780; ◐, 52,640; ●, 47,660.

aggreates were formed by "sweep-out." However, no deviation from linearity was observed in such plots until the emulsion clearing approached the meniscus or the phase boundary of the "cream."

Also, the slower the ultracentrifugal speeds, the greater would be the opportunity for particle "slippage" and thus gradation according to size. If aggregation on ultracentrifugation (before "cream" formation) was a distinct factor, the flotation rates

would not be expected to be as linear with the (r.p.m.)^2 as they were in Fig. 18.

It may also be predicted that clearing rates would be expected to change with the dilution of the oil-in-water emulsion by the continuous (water) phase if it is the aggregates rather than the smallest particles that determine emulsion clearing rates since particle stratification would be more favored under dilute conditions. Investigations are planned to evaluate these possible models.

The flotation of oil particles to the top of the cell continued until a "cream" of oil particles was formed, i.e., an adhered mass of particulate oil where the "skin" of each particle is highly resistant to the applied gravitational forces.

A model can be proposed that is consistent with the facts to explain the coalescence of the "cream."

In general, the larger oil particles should be on top of the small (see Fig. 12b). The higher the oil concentration, the less probable should be a truly systematic gradation of particle size. On subjection to gravitational force the larger particles are more readily deformed than the smaller in the same manner that large balls of mercury on a table top are more deformed than small ones (8). The larger particles are thus more subject to unequal forces and the skin may be more readily ruptured so that coalescence of two larger particles may occur to form even larger ones (see Figs. 13b–16b). The strength of the "skin" would be a function of the dispersing agent concentration and the retention of maximum conditions in the vehicle for its function and stability.

In the case of "bad" emulsion, the production of higher acidity most probably by hydrolysis indicated a variation in conditions which decreased the skin-strength of the more readily deformed larger particles. The coalescence, which undoubtedly proceeded to a minor degree in the nonstressed "poor" emulsion, was thus accelerated in the "cream" where maximum close contact of oil particles was effected. Sufficient numbers of unstable large particles exist in "bad" emulsion so that after a definite amount of distortion (since the rate of coalescence is very much less than the rate of creaming) coalescence readily occurred as a function of the numbers of large unstable particles.

Subsequent to this spin-out of oil by a first-order process under gravitational stress, the phenomenon encountered in "good" emulsion becomes predominant. In this case, the skins of the larger particles had greater strength than those in "bad" emulsion. Nevertheless, they coalesced to form larger particles but a certain population had to exist before a continuous phase of oil appeared. Simultaneously, the populations of smaller particles were coalescing although at lower rates. However, since the greatest portion of the oil is distributed among the populations of small particles and since these need more time to coalesce, an acceleration in the formation of a continuous oil phase was noted only after a large induction period.

Since the force of deformation is a function of r.p.m. (see Appendix), it is to be expected that the rate of this acceleration of continuous oil phase formation would also be a function of the r.p.m.

After the ready coalescence of the relatively large, unstable, deformed particles in "bad" emulsion, only a fraction of the total oil available had been spun out. The residual small oil particles followed the same coalescing pattern of the "good" emulsion.

This model is consistent with the prediction that the stability of a rigid sphere approaching an unbounded plane is inversely proportional to the radius of the sphere, provided that electrical double layer interaction, electroviscous effects and London-van der Waals forces of attraction are negligible (9). Rigid behavior was reported to occur with high interfacial tensions, small bubble diameters (<0.1 cm.), and in the presence of surfactants, conditions which certainly exist in our oil-in-water emulsions (9, 10). In an oil/water system containing surfactants, Cockbain and McRoberts (10) have shown that the stability of oil droplets increased rapidly with decreasing diameter below 0.1 cm.

These studies and the conclusions drawn therefrom provide the necessary background for the prediction of stability of emulsions and dispersions by use of the analytical ultracentrifuge.

Knowledge of flotation parameters under the stress of a centrifugal field permits the prediction of flotation (or sedimentation) under the influence of simple gravity. The Appendix provides a detailed procedure which when applied to the emulsion[1] predicts that less than 1 cm. depth of the oil-water emulsion as initially constituted would be cleared in a year's time. It can also be safely stated that no significant coalescence of the oil particles in the initially constituted emulsion to form a continuous phase would occur during the pharmaceutical lifetime of the product.

The specific qualification considered is that the preparation is as initially constituted. Obviously, when chemical changes occur with time and result in "bad" emulsion, this is not so.

However, the effect of chemical deterioration on emulsion stability can be studied in such a manner as to expedite prediction. Ultracentrifugal characterization of thermally stressed preparations would permit evaluation of rate constants of continuous oil phase appearance as functions of gravitational stress. Measurements of sedimentation and coalescent rates as functions of enhanced temperature and time of subjection to enhanced temperature should permit prediction of emulsion stability by combining the lessons learned from accelerated thermal and ultracentrifugal stability studies.

SUMMARY

1. It is shown that the analytical ultracentrifuge is an excellent tool for the evaluation of emulsion stability.

2. The slopes of the plots of the position of the emulsion-water boundary from the center of the ultracentrifugal rotor against time are shown to be functions of the square of the r.p.m.

3. The discontinuous oil phase is cleared from the continuous phase by ultracentrifigation to form a cream, a packed particulate mass of adhered oil globules. The rate of clearing under simple gravity has been predicted for the emulsion as initially constituted. Less than 1 cm. depth

of the oil-water emulsion would be cleared in a year's time on the shelf provided that no change in chemical constitution occurred in that interval.

4. Emulsion clearing rates essentially may measure the flotation of the population of smallest particles, which exist in both "good" and "bad" emulsions, and may not permit differentiation between two such preparations.

5. Highly unstable particles that are readily spun out of the "cream" on ultracentrifugation exist in "bad" emulsion but not in "good" emulsion. This initial spin-out of a continuous oil phase for "bad" emulsion decays with time and only accounts for a fraction of the total. The residual follows the same pattern as the spin-out of continuous oil phase in "good" emulsion.

6. "Good" emulsion demonstrates an induction period at high r.p.m. values before a continuous oil phase can be observed and may indicate a "yield" value. Subsequently, the rate of coalescence accelerates and the acceleration rate is a function of the r.p.m. and may be considered a measure of the toughness of particle "skin."

7. A consistent model for these phenomena is the more ready flotation of large oil particles so that the "cream" is a grading of large to small oil particles from top to bottom. Unstable large particles immediately coalesce as a function of their number. Stable particles coalesce to form larger ones. The larger they are, the more readily are they deformed under centrifugal stress. However, a critical number of such large ones is necessary before coalescence and the spin-out of oil in "good" emulsion.

APPENDIX

The force, F, on a particle in a gravitational field is

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

where V = volume of particle, ρ and ρ' are the densities of the particle and medium, respectively, and a is the acceleration due to the field (7). When steady state conditions are reached, there is a constant particle velocity, v, and the gravitational force equals that applied to the particle by Stokes law so that

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

where k is a shape constant and η is the coefficient of viscosity of the fluid medium (7).

Equation 2 may be solved for velocity, v, and in a centrifuge of a given r.p.m. where $2\pi x$ is the distance traveled by a particle in one rotation at a distance, x, from the axis of rotation where the acceleration is $a = u^2/x$ and u = r.p.m. $2\pi x$ is the velocity of the particle, then

$$v = dx/dt = V(\rho - \rho')\,4\pi^2\,\text{(r.p.m.)}^2\,x/k\eta \quad \text{(Eq. 3a)}$$

$$= K4\pi^2(\text{r.p.m.})^2 x \qquad \text{(Eq. 3b)}$$

$$= S(\text{r.p.m.})^2 x \qquad \text{(Eq. 3c)}$$

where t is in minutes.

If the initial distance of the particle is x_1 from the axis of rotation at $t_1 = 0$, and the distance at time $t_2 = t_c$ is x_2, then Eq. 3a, 3b, and 3c may be integrated between these limits and

$$\ln x_2/x_1 = S(\text{r.p.m.})^2 t_c \qquad \text{(Eq. 4a)}$$

$$= K4\pi^2(\text{r.p.m.})^2 t_c \qquad \text{(Eq. 4b)}$$

Under gravity, $a = g$ in Eq. 2 and

$$v = dx/dt = V(\rho - \rho')g/k\eta \qquad \text{(Eq. 5a)}$$

$$= Kg \qquad \text{(Eq. 5b)}$$

which integrates between the limits $t_1 = 0$ and $t_2 = t_g$ for x_1 and x_2 to

$$x_2 - x_1 = Kgt_g \qquad \text{(Eq. 6)}$$

The ratio of the time necessary for the particle to fall a distance $l = x_2 - x_1$ under true gravity to the time under ultracentrifugation where d is the original distance of the particle from the axis of rotation of the ultracentrifuge can be derived from Eqs. 4 and 6 and is

$$t_g/t_c = 4\pi^2\,(\text{r.p.m.})^2/g\,\ln\,(l/d + 1) \quad \text{(Eq. 7)}$$

Since $g = 980$ cm./sec.$^2 = 3.53 \times 10^6$ cm./min.^{2}, Eq. 7 may be converted to an expression in logarithms to the base ten

$$t_g/t_c = 4.856 \times 10^{-6}l(\text{r.p.m.})^2/\log(l/d + 1) \quad \text{(Eq. 8)}$$

This relation is derived for sedimentation; for flotation the sign is reversed.

For the set of flotation studies plotted in Fig. 17 the time interval, t_c, between the ordinate values of 0.8500 (log 7.08 cm.) and 0.8000 (log 6.31 cm.) corresponds to the flotation of a particle of $l = 0.77$ cm. with a $d = 7.08$ cm. initial distance from the axis of rotation of the ultracentrifuge. Based on r.p.m. values ranging from 12,590 to 35,600 and the respective t_c values the time, t_g, for the emulsion clearing of 0.77 cm. of emulsion[1] on the shelf under gravity alone as calculated from Eq. 8 averages 311 days. The range of calculation of t_g was 271 to 376 days.

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