Rate of Solute Transport out of Emulsion Droplets in Micron Size Range

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An experimental verification of the theory for rate of external-phase-diffusion-controlled solute transport from emulsion droplets in the micron size range has been carried out. The Coulter counter was employed to follow the change in size distribution in aqueous sodium chloride solutions of dibutyl phthalate droplets with time. The rate was proportional to particle radius according to theory, and the diffusion coefficient of dibutyl phthalate calculated from data and theory agreed well with the Stokes-Einstein law predictions. The effect of the presence of a water immiscible component in the dibutyl phthalate droplet was also studied.

As PART OF the program on the behavior of dispersed systems in these laboratories the transport of solute out of emulsion droplets is under study. This problem has bearing on a number of important pharmaceutical situations. In many instances the understanding of the release rate of a drug from orally and parenterally administered emulsions may be critically dependent on a consideration of factors associated with this phenomenon. It is also important in the understanding of the physical degradation process in emulsions taking place *via* molecular diffusion (1).

This report gives the results of an experimental examination of the theory for the diffusion-controlled dissolution from small droplets. The method of study is simple and unique. It should be useful in similar studies of more complex systems.

THEORY

Recently (2, 3), the theory for the rate of diffusion-controlled dissolution and growth of small spherical particles was examined. Although the equations were aimed at and applied to dissolution and growth from solid particles, the same model may be employed here. The expression for the steady state rate, G, may be written

$$G = 4\pi a D \, \Delta C \qquad \text{(Eq. 1)}$$

Here D is the diffusion coefficient of the solute in the external phase, a is the droplet radius, and ΔC is the difference between the solute concentration at the surface but on the external phase side[1] and the solute concentration in the external phase but far away from any droplet. According to theory, Eq. 1 is in reality a limiting equation valid when hydrodynamic effects on the solute diffusion near the droplets become negligible. Thus, for large particles ($\gtrsim 50 \ \mu$) (because even small shearing in the

[1] For external phase diffusion-controlled processes, this surface concentration would be in equilibrium with the droplet and therefore would be the solubility. This means, furthermore, that no concentration gradients in the droplet and no interfacial barriers are present.

external phase may alter the concentration gradients in a region within a few particle diameters of a droplet and because sedimentation or creaming effects would be more important) Eq. 1 would not be expected to be always in quantitative agreement with experiments. However, for smaller particles ($\gtrsim 1 \ \mu$) Eq. 1 would be expected to be obeyed even under moderate amounts of agitation and shear due to gravitational forces.[2]

If the droplet is substantially one component, we may equate G to the rate of change in mass of the droplet, *i.e.*

$$G = \frac{dm}{dt} = 4\pi a^2 \rho \, \frac{da}{dt} \qquad \text{(Eq. 2)}$$

where m is the mass of the droplet, $\frac{4}{3}\pi a^3 \rho$, ρ is the density of the droplet, and t is time. Combining Eqs. 1 and 2 and integrating we obtain as before (2, 3)

$$a^2 = a_o^2 + \frac{2D\Delta C}{\rho} t \qquad \text{(Eq. 3)}$$

where ΔC is positive for growth and negative for dissolution.

It should be mentioned that Eq. 3 was recently (3, 4) incorporated into the theory for the dissolution rate of a finely divided powder. Comparison of this theory with data on micronized methylprednisolone was satisfactory. However, some deviations were observed. This suggested that a much better test of Eq. 3 would be provided by suitably selected emulsion droplets.

EXPERIMENTAL

General Considerations.—The primary aim of this work was to test Eq. 3 with emulsion droplets. It was decided to employ the Coulter counter[3] to follow the time change in the number and size distribution of an emulsion of a slightly miscible liquid in aqueous media. The instrument is uniquely able to count and size particles conveniently and rapidly in the size range of $\sim 0.5 \ \mu$ and above.

Dibutyl phthalate was selected as the oil phase because the water solubility (miscibility) of this material in water appeared to be small enough so

[2] It is assumed that interfacial turbulence, spontaneous emulsification, and gross droplet distortion effects are absent. Also it is assumed that no reactive agents are present in the external phase other than the main external phase component itself.
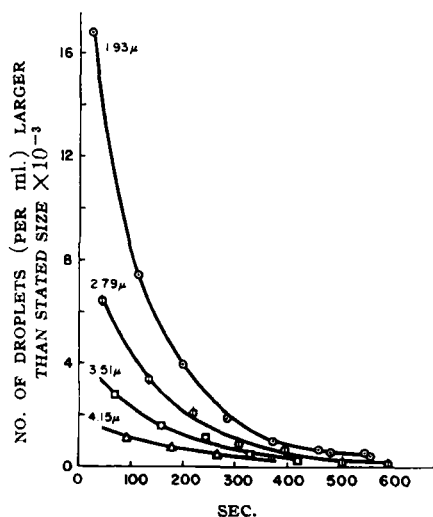[3] Coulter Industrial Sales, Chicago, Ill.

Fig. 1.—Coulter counter data showing changes in cumulative counts with time at various threshold settings when 5 μl. of the dibutyl phthalate emulsion was pipeted into 100 ml. of saline.
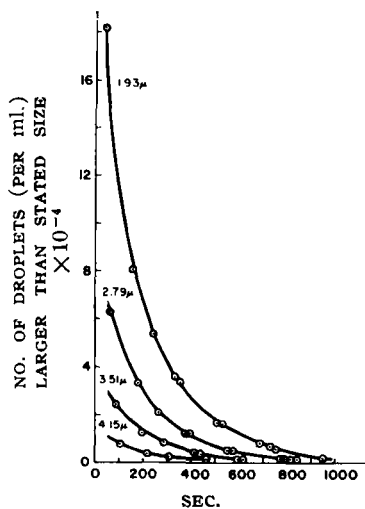

Fig. 2.—Coulter counter data showing changes in cumulative counts with time at various threshold settings when 50 μl. of the dibutyl phthalate emulsion was pipeted into 100 ml. of saline.

that dissolution would not occur too rapidly according to Eq. 3, yet large enough so that at a convenient droplet concentration the water would not become saturated (*i.e.*, $\Delta C \rightarrow o$) before an appreciable change in sizes occurred.

Procedure.—Fisher reagent grade dibutyl phthalate was distilled at 115° under reduced pressure. Approximately 1% by weight of this material in 0.10% aqueous sodium lauryl sulfate[4] was emulsified by about 10 minutes of ultrasonic irradiation generated by the Acoustica cleaning unit (model DR-125AH, 40 kc).[5] Dibutyl phthalate containing various amounts of hexadecane was also emulsified in this manner. These latter experiments were

conducted to see the effects of an immiscible second component in the oil phase.

The Coulter counter was calibrated with monodispersed polystyrene latex particles[6] as in the previous work (5, 6). The 50-μ aperture tube was used in the present studies.

From 5 to 100 μl. of the emulsion was pipeted into 100 ml. of the Abbott[7] 0.90% sodium chloride solution for injection contained in a 150-ml. beaker ready in counting position. Temperature was maintained at 25.0 ± 0.5°. Slow (~50 r.p.m.) to moderate (~300 r.p.m.) stirring of the saline
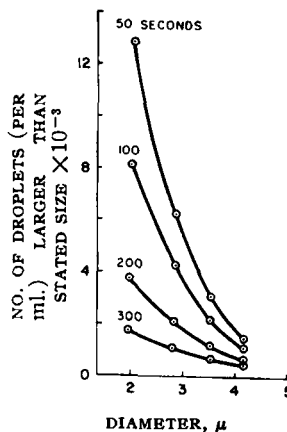

Fig. 3.—Cumulative size distribution curves constructed from the data in Fig. 1. These illustrate the dissolution of the dibutyl phthalate droplets with time.
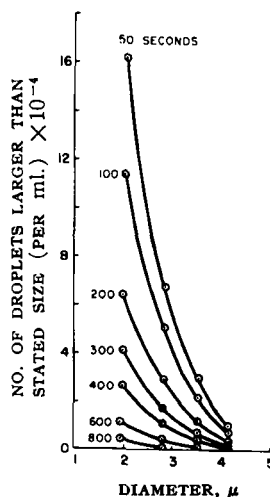

Fig. 4.—Cumulative size distribution curves constructed from data in Fig. 2 showing dissolution of the dibutyl phthalate droplets with time.

solution was provided during and after the addition of the aliquot of emulsion. This was achieved by a conventional glass stirrer (blade length 3 cm., width 0.8 cm., and at maximum pitch) positioned at a slight angle and driven from above the beaker. A timer was initiated after the addition, and both the counts per sample volume and the times were

recorded at various settings of the threshold dial. The time period for counting the usual sample volume of 0.05 ml. was about 5 seconds; the time between counts was about 25 seconds. Count rates were always sufficiently low so that coincidence errors were negligible.

The solubility (miscibility) of dibutyl phthalate in saline was determined by pipeting 0.10, 0.20, and 0.50 ml. of dibutyl phthalate into 100 ml. of the saline and shaking vigorously for periods up to 48 hours at 25.0 ± 0.5°. Samples were removed from time to time, centrifuged, diluted 1:1 with
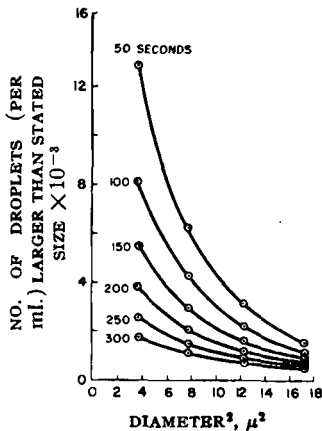
Fig. 5.—Plots of cumulative counts *vs.* diameter squared showing fit of data to the diffusion controlled theory for small droplets; 5-µl. run, obeys $a_i{}^2 = a_{io}{}^2 - 1.2 \times 10^{-10}t$.
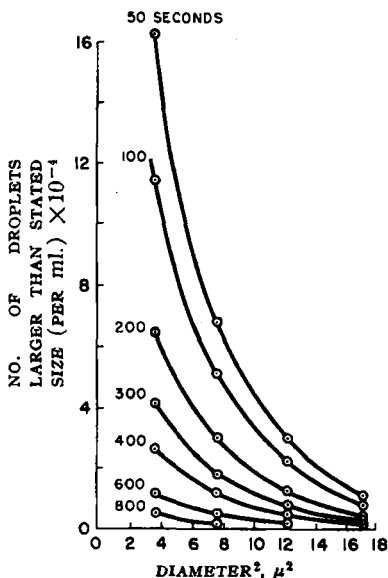
Fig. 6.—Plots of cumulative counts *vs.* diameter squared showing fit of data to theory; 50-µl. case.

ethanol and assayed at 266.5 mµ with a Beckman DU spectrophotometer. A constant value of 1.20 (± 0.10) × 10⁻⁶ Gm. per ml. was obtained for all three mixtures at sufficiently long times.

Dissolution rate runs were also carried out on dibutyl phthalate emulsions prepared in 0.10% polysorbate 20[8] solutions. These were run in both

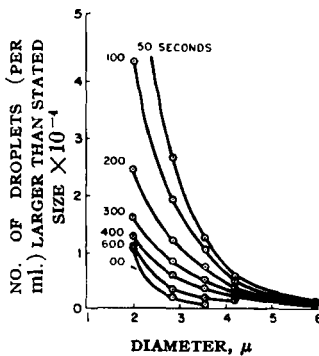[8] Marketed as Tween 20 by the Atlas Powder Co., Wilmington, Del.

Fig. 7.—Cumulative count curves showing dibutyl phthalate release from droplets initially containing 12.5% hexadecane.
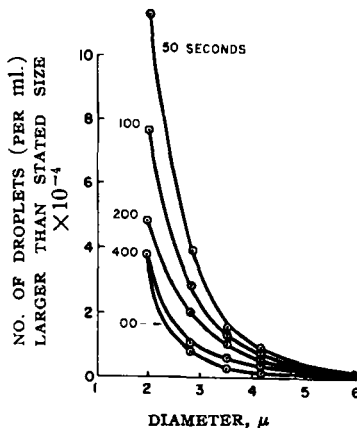
Fig. 8.—Cumulative count curves showing dibutyl phthalate release from droplets initially containing 25% hexadecane.

plain saline and in saline containing 0.1% polysorbate 20.

RESULTS AND DISCUSSION

Pure Dibutyl Phthalate Case.—Figures 1 and 2 give the Coulter counter data obtained when 5 and 50 µl., respectively, of the 1% dibutyl phthalate emulsion (0.10% sodium lauryl sulfate) were pipeted into 100 ml. of saline solution. These results were quite reproducible and independent of the stirring rate over a range of more than a factor of two.

Interpolated values from the smoothed curves in Figs. 1 and 2 were used to construct the constant time plots of the cumulative particle size distribution curves shown in Figs. 3 and 4. The background saline blank counts of 200 counts per ml. for the 1.93 µ setting, 30 counts per ml. for the 2.79 µ setting, and zero blank for the other settings were subtracted from the Figs. 1 and 2 data prior to making the Figs. 3 and 4 plots. Numerical differentiation of the $t = 50$ seconds curves in Figs. 3 and 4 shows that only about one-half of the total dibutyl phthalate can be accounted for in the sizes greater than 1.93 µ.

If Eq. 3 is applicable to the present data, it is apparent that plots of cumulative count (ordinate) *versus* the square of particle size (abscissa) should give curves that are displaced along the abscissa with time but without changes in shape. Further-
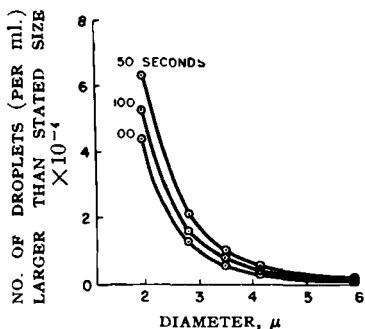
Fig. 9.—Cumulative count curves showing dibutyl phthalate release from droplets initially containing 50% hexadecane.

more, such displacements should be constant with time if ΔC is constant. In Figs. 5 and 6 the same data are plotted in this manner. In accordance with Eq. 3 it can be seen that any two points on a given curve move horizontally at the same rate. In the 5 μl. results (Fig. 5) the displacements with time are constant and obey

$$a_i^2 = a_{i_0}^2 - 1.2 \times 10^{-10}t \qquad \text{(Eq. 4)}$$

where a_{i_0} and a_i are the radii of droplet i at time $t = 0$ and $t = t$, respectively. The constancy of the time coefficient was not unexpected in this instance because ΔC was not expected to decrease by more than 5%, even when all of the droplets were dissolved.

By comparing Eq. 4 with Eq. 3 we obtain $D = (0.60 \times 10^{-10} \rho)/\Delta C$. Since $\rho = 1.04$ for dibutyl phthalate and $\Delta C = 1.20 \times 10^{-5}$ Gm. per ml., we obtain $D = 5.2 \times 10^{-6}$ cm.^{2} sec.$^{-1}$ Now from the Stokes-Einstein relation we have

$$D = \frac{kT}{6\pi v s} \qquad \text{(Eq. 5)}$$

where k is the Boltzmann constant, T is absolute temperature, v is the viscosity, and s is the hydrodynamic radius of the dibutyl phthalate molecule. For the present case $T = 298.2°K$, $k = 1.38 \times 10^{-16}$ ergs deg.$^{-1}$ molecule^{-1}, $v = 0.0091$ poise, and $s = 4.7 \times 10^{-8}$ cm. The value for s was estimated from the equation $^4/_3\pi s^3 \rho = M/N$, where M is the molecular weight of dibutyl phthalate and N is Avogadro's number. Thus we obtained from Eq. 5 $D = 5.1 \times 10^{-6}$ cm.^{2} sec.$^{-1}$ which agrees well with the above value calculated from the rate experiment and Eq. 3.

The 50-μl. runs (Fig. 6) did not show a constant dissolution rate. Comparison of Figs. 5 and 6 show that between 50 and 100 seconds the rate of dissolution in the 50-μl. run was about 70% of the 5-μl. run value. Then the rate steadily decreased to about 50% of the 5-μl. run value. It is noteworthy that even though ΔC varied in the 50-μl. run, the dependence on a was consistent with Eq. 3.

Essentially identical results were obtained with emulsions of dibutyl phthalate prepared using 0.10% polysorbate 20 as the emulsifying agent. This was expected as the amount of surfactant in either case was very small in the saline dissolution media,

i.e., about $5 \times 10^{-5}\%$. Solubility determinations indicated no increases in solubility with this amount of surfactant in the saline.

A few runs were made with 0.10% polysorbate 20 in the saline dissolution media. Dissolution rates were greater by about a factor of about two than those rates found in pure saline. Attempts were made to measure the solubility of dibutyl phthalate in these polysorbate solutions, but constant results were not obtained. Solution concentrations generally continued to increase slowly with time. Concentrations as great as 25 to 50 times greater than the solubility in pure saline were observed, yet the dissolution rates were only a factor of two or so greater. This would be consistent with Eq. 3 only if it can be assumed that the diffusion coefficients involved are much smaller than the above values for pure saline. This is reasonable (7) if the diffusing species are primarily large swollen micelles of dibutyl phthalate in polysorbate 20. After the centrifugation step in the solubility measurements of dibutyl phthalate in 0.10% polysorbate 20 it was observed that the supernatant liquid possessed a bluish tint when viewed in indirect light, suggesting the presence of colloidal species. More definitive work is planned on the effect of colloids on transport rates.

Other Cases.—Results of runs with dibutyl phthalate containing various amounts of hexadecane are given in Figs. 7–9. In all of these cases dissolution begins at about the same rate as the pure dibutyl phthalate emulsion droplets. However, the rates slow up and stop when nearly all of the dibutyl phthalate is released from the droplets, leaving behind mostly pure hexadecane. It can be seen (particularly from Figs. 7 and 8) that the smaller emulsion droplets tend to reach the final state more rapidly than the larger droplets. In experiments where 100 μl. or more of the emulsion was added to the saline solution, this situation resulted in a "rebound" phenomenon, *i.e.,* the small particles gave up more than their equilibrium share at early times, but regained their overlosses at later times. This was apparently not significant in the experiments with 50 μl. of emulsion because the solution buildup of dibutyl phthalate was not very great.

To explain these results quantitatively with dibutyl phthalate containing hexadecane it would be necessary to know (*a*) the distribution coefficient of dibutyl phthalate for the hexadecane-water pair and (*b*) the partial molal (or specific) volumes for dibutyl phthalate in dibutyl phthalate-hexadecane solutions. This information may be incorporated into Eqs. 1 and 2 to give an expression analogous to Eq. 3.

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