[Chem. Pharm. Bull. 21(5)1042–1046(1973)] UDC 615.011.3.014

Determination of Micelle Size by the Stokes–Einstein Equation

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(Received October 30, 1972)

Using micellar diffusion coefficients calculated by means of dissolution-rate and solubility measurements, the Stokes–Einstein equation was employed to estimate the relative micelle size and the micellar weight of benzoic acid-micelle species in solutions of polysorbate 80. The necessity of considering the relative viscosity of the micellar solutions and the variance of diffusion coefficients with concentration was demonstrated. Under the experimental conditions described it does not seem justifiable to use the Stokes–Einstein equation in the determination of micellar weight and/or size.

The recent interest in the dissolution of a solute in the presence of a nonionic surface-active agent has been indicated in a review by Gibaldi and Feldman.[2] Higuchi[3] presented a diffusion layer model for the dissolution rate of a pure solid in a stirred medium containing a colloidal solubilizing agent. The model assumes that there is an equilibrium between the solid and the solution at the solid-solution interface and that the dissolution rate is controlled by the diffusion of the molecule and the solubilized solute across an effective diffusion layer of thickness, h. If the solubilization involves only a single solubilized species, the model is described by the relationship

$$R = \frac{1}{h}(D_0C_0+D_mC_m) \qquad \text{(Eq. 1)}$$

where R is the dissolution rate, D_0 is the diffusion coefficient of the molecular species in solution, C_0 is the solubility of the molecular solute, D_m is the diffusion coefficient of the micelle-solubilized species, and C_m is the increase in solubility due to solubilization, *i.e.*, $C_m=C_s-C_0$, where C_s is the concentration of the saturated solution.

The use of dissolution rates to estimate the diffusion coefficients[4,5] and the molecular weights of interacting colloids[4] has been reported. Using the reported[6] anhydrous micellar molecular weight of polyoxyethylene (23) lauryl ether and estimating the water of hydration Gibaldi, *et al.*[7] calculated the mean micellar diffusion coefficient of the solubilized species by use of the equation

$$\frac{D_0}{D_m} = \frac{(M_{\text{micelle}})^{1/3}}{(M_0)^{1/3}} \qquad \text{(Eq. 2)}$$

which is based on the Stokes–Einstein equation that predicts an inverse cube root relationship between the diffusion coefficient and the molecular weight, M.

The purpose of this report is to further explore the use of the Stokes–Einstein equation in the determination of the micelle size in various concentrations of polysorbate 80.

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[2] M. Gibaldi and S. Feldman, *J. Pharm. Sci.*, **59**, 579 (1970).
[3] W.I. Higuchi, *J. Pharm. Sci.*, **56**, 315 (1967).
[4] S. Feldman, M. Gibaldi and M. Reinhard, *J. Pharm. Sci.*, **60**, 1105 (1971).
[5] R.J. Braun and E.L. Parrott, *J. Pharm. Sci.*, **61**, 592 (1972).
[6] P. Becher and H. Arai, *J. Colloid Interface Sci.*, **27**, 634 (1968).
[7] M. Gibaldi, S. Feldman and N. Weiner, *Chem. Pharm. Bull.* (Tokyo), **18**, 715 (1970).

Experimental

Determination of Dissolution Rate——The dissolution rate of benzoic acid from nondisintegrating tablets was determined as previously reported[8] at a stirrer speed of 324 rpm in 2 liters of various concentrations of polysorbate 80[9] in which the concentration of benzoic acid was not allowed to exceed 3% of its solubility. Typical data are given in Table I. In a similar manner the dissolution rates of benzoic acid were determined in various concentrations of polysorbate 80 adjusted by a trial-and-error method to 3.53 and 6.0 cps by sucrose and methylcellulose (1500 cps), respectively. The data are given in Table II.

Determination of Diffusion Coefficients——Feldman, *et al.*[4] reported agreement of the value of the diffusion coefficient calculated by dissolution-rate and solubility data using Eq. 1 with the value determined in a diffusion cell. They stated that "caution must be exercised in use of this method if dissolution rate is not entirely diffusion controlled." Using the criterion discussed by Singh, *et al.*[10] it has been demonstrated by Braun and Parrott[5] in a plot of log R/C_s *vs.* log D_{exp} that the dissolution of benzoic acid in solutions of polysorbate 80 is diffusion controlled. Thus, the micellar diffusion coefficients were calculated by means of the dissolution-rate and solubility method, which was more expedient for the dissolution media used than the diffusion cell method.

The diffusion coefficient of benzoic acid at 25° in distilled water is 1.082×10^{-5} cm^2/sec.[5,11,12] In aqueous micellar solutions the mass transport of the molecular species and the solubilized species depends on the diffusion coefficients of the molecular species and of the micelle as shown in Eq. 1. As dissolution was diffusion controlled the thickness of the effective layer was evaluated by experimentally measuring the dissolution rate and solubility of benzoic acid in distilled water at 25°, and:

$$h = \frac{D_0 C_0}{R} = \frac{1.082 \times 10^{-5} \times 3.42}{127.2 \times 10^{-4}} = 0.00291\ \text{cm} \qquad \text{(Eq. 3)}$$

As it is possible that h may be influenced by hydrodynamics and vary with viscosity, it was evaluated in a similar manner for dissolution of benzoic acid in solutions of sucrose and methylcellulose. The value of h in aqueous methylcellulose solution with a viscosity of 6.0 cps was 0.00302 cm; h in aqueous sucrose solution with a viscosity of 3.53 cps was 0.0032 cm.

After determining the dissolution rate and the solubility, D_m was calculated by Eq. 1 as all terms except D_m were evaluated. For example, the D_m of benzoic acid in an aqueous 2% polysorbate 80 solution is:

$$D_m = \frac{(170.2 \times 10^{-4}) - (1.082 \times 10^{-5} \times 3.42)/29.1 \times 10^{-4}}{(6.06 - 3.42)/29.1 \times 10^{-4}}$$
$$= 0.475 \times 10^{-5}\ \text{cm}^2/\text{sec} \qquad \text{(Eq. 4)}$$

The values of D_m in various concentrations of polysorbate 80 are given in Table I. The values of D_m in various concentrations of polysorbate 80 at constant viscosity are given in Table II.

Other Parameters——All determinations were made at 25°. The densities of the solution were measured using a pycnometer. The viscosities of the solutions were measured using an Ostwald-Fenske viscometer. Solubility measurements were made as reported earlier,[13] and the data are given in Table I and Table II.

Table I. Dissolution Rate, Solubility and Calculated Micellar Diffusion Coefficient in Various Concentrations of Polysorbate 80 at 25°

Percent of polysorbate 80	C_s, mg/ml	$10^4 R$, mg/cm^2/sec	$C_s - C_o$, mg/ml	$10^5 D_m$,[a] cm^2/sec
0	3.42[b]	127.2		1.082[c]
1	4.90	158.7	1.48	0.620
2	6.06	170.2	2.64	0.475
5	10.63	198.7	7.21	0.289
10	17.90	196.4	14.48	0.139
15	26.40	162.6	22.98	0.045

a) calculated by Eq. 1, h=0.00291 cm; *b*) C_o; *c*) D_o

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8) R.J. Braun and E.L. Parrott, *J. Pharm. Sci.*, **61**, 175 (1972).
9) Tween 80 supplied by Emulsion Engineering Inc.
10) P. Singh, S.J. Desai, D.R. Flanagan, A.P. Simonelli and W.I. Higuchi, *J. Pharm. Sci.*, **57**, 959 (1968).
11) C.V. King and S.S. Brodie, *J. Amer. Chem. Soc.*, **59**, 1583 (1937).
12) C.V. King and W.H. Cathcart, *J. Amer. Chem. Soc.*, **59**, 63 (1937).
13) E.L. Parrott and V. Sharma, *J. Pharm. Sci.*, **56**, 1341 (1967).

TABLE II. Dissolution Rate, Solubility, Calculated Micellar Diffusion Coefficient and D_o/D_m in Various Concentrations of Polysorbate 80 Maintained at Constant Viscosity at 25°

Percent of polysorbate 80	C_s mg/ml	$10^4 R$ mg/cm²/sec	$10^5 D_m$[a] cm²/sec	D_o/D_m
		6.00 cps		
0	3.70[b]	56.6	0.462[c]	1.00
1	5.00	68.1	0.266	1.737
2	6.50	75.7	0.206	2.243
3	8.00	85.2	0.201	2.298
4	9.36	92.8	0.194	2.381
5	11.50	103.7	0.182	2.538
		3.53 cps		
0	3.11[b]	17.2	0.177[d]	1.00
1	4.85	21.6	0.081	2.174
2	6.41	23.8	0.064	2.753
5	11.45	25.5	0.032	5.531
8	16.82	30.7	0.031	5.710
10	21.12	34.2	0.030	5.900

a) calculated by Eq. 1; *b)* C_o; *c)* h=0.00302 cm; *d)* h=0.0032 cm

Result and Discussion

A relationship between diffusivity and particle size is given by the Stokes–Einstein[14] equation

$$D=\frac{RT}{N}\frac{1}{6\pi\eta r} \qquad \text{(Eq. 5)}$$

where D is the diffusion coefficient in cm²/sec, R is 8.31×10^7 erg/deg./mole, T is the absolute temperature, N is Avogadro's constant, η is the viscosity in poises, and r is the radius of the particle in cm.

The parameters listed in Table III can be used to test the validity of the application of the Stokes–Einstein equation to the calculation of micelle size in high concentrations of polysorbate 80. In order to eliminate the constants and to compare size, the data were treated by taking the ratio of Eq. 5 in water to that in a given concentration of polysorbate 80. The ratio is

$$\frac{D_0}{D_m}=\frac{\eta}{\eta_0}\frac{r}{r_0}=\eta_{\text{rel}}\frac{r}{r_0} \qquad \text{(Eq. 6)}$$

where η/η_0 is the relative viscosity, η_{rel}, and r/r_0 is the relative radius or size of the micelle.

The micellar weight could be calculated by a similar treatment of the Stokes–Einstein equation in the form

$$D=\frac{RT}{6\pi\eta N}\sqrt[3]{\frac{4\pi}{3}\frac{N}{VM}} \qquad \text{(Eq. 7)}$$

The corresponding ratio would be

$$\frac{D_0}{D_m}=\eta_{\text{rel}}\left(\frac{V_m}{V_0}\right)^{1/3}\left(\frac{M_m}{M_0}\right)^{1/3} \qquad \text{(Eq. 8)}$$

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[14] A. Einstein, *Ann. Physik.*, **17**, 549 (1905).

where V_0 and M_0 are the partial specific volume and molecular weight of the solute; and V_m and M_m are the partial specific volume and the micellar weight, respectively.

The data in Table III were used to calculate the relative size of the micelle at various concentrations of polysorbate 80 by Eq. 6 and the micellar weight by Eq. 8.

TABLE III. Relative Viscosity, Cube Root of Ratio of Partial Specific Volumes, and D_0/D_m at Various Concentrations of Polysorbate 80 and the Corresponding Relative Radius and Weight of the Micelle at 25°

Percent of polysorbate 80	η_{rel}	D_0/D_m	$V_m/V_0{}^{1/3}$[a]	r/r_0[b]	M_m[c]
0	1.00			1.00	122
1	1.07	1.745	1.064	1.63	440
2	1.10	2.278	1.062	2.07	900
5	1.20	3.744	1.061	3.12	3100
10	1.28	7.784	1.057	6.08	23000
15	1.85	24.044	1.058	13.00	225000

a) Partial specific volume was based on densities and calculated by means of the equation (5): $p=p_{H_2O}+(1+Vp_{H_2O})C$.
b) Relative radius calculated by Eq. 6. c) Micellar weight calculated by Eq. 8.

In Table II the values of D_m in various concentrations of polysorbate 80 are given in the micellar solutions adjusted to a constant viscosity of 3.53 and 6.00 cps by use of sucrose and methylcellulose, respectively. Since the viscosity is maintained the same at all concentrations of polysorbate 80, $\eta_{rel}=1$ and Eq. 6 is simplified to

$$\frac{D_0}{D_m}=\frac{r}{r_0} \qquad \text{(Eq. 9)}$$

As experimentally verified in Fig. 1 with a constant viscosity the slope of the plot of D_0/D_m *versus* r/r_0 is unity. If in the solutions of unadjusted viscosity the viscosity factor is ignored, the plot of D_0/D_m *versus* r/r_0 is not linear as shown in Fig. 1; however, if the experimental data are plotted as D_0/D_m *versus* $\eta_{rel}\, r/r_0$, a straight line results. Thus, in using the ratio of diffusion coefficients in various micellar solutions to calculate the micellar weights (Eq. 2) or size (Eq. 6), the relative viscosity can not be ignored because D_0/D_m may change with changes in viscosity.

By light-scattering technique Paul Becher[15] determined the micelle weight of polysorbate 80 to be 98000. Considering hydration (4.7 moles of water per ethylene oxygen) the apparent micellar weight of polysorbate 80 is approximately 100000. Using Eq. 2 to calculate the mean D_m:

$$\frac{1.082\times10^{-5}\times(122)^{1/3}}{(100000)^{1/3}}=0.116\times10^{-5}\ \text{cm}^2/\text{sec}$$

As shown in Fig. 2 the experimentally evaluated D_m is concentration dependent and varies considerably; therefore, a single value or mean D_m should not be used in the calculation of micelle size.

Whether the micelle size is calculated in terms of a relative radius or a micellar weight, as shown in Table III, it appears as if the micelle is increased in size as the concentration of the solubilizing agent is increased. In view of the generally accepted concept that the linearity of a solubilization curve is a result of an increase in the number of micelles as the concentration of solubilizing agent is increased, this does not seem acceptable. Thus within the design of this report the use of the Stokes–Einstein equation as described is questionable. The application of the Stokes–Einstein equation is restricted because it was derived on the assumptions that diffusivity is constant (in fact, the diffusivity is concentration dependent),

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15) Personal communication. ICI America Inc., Wilmington, Delaware 19899.

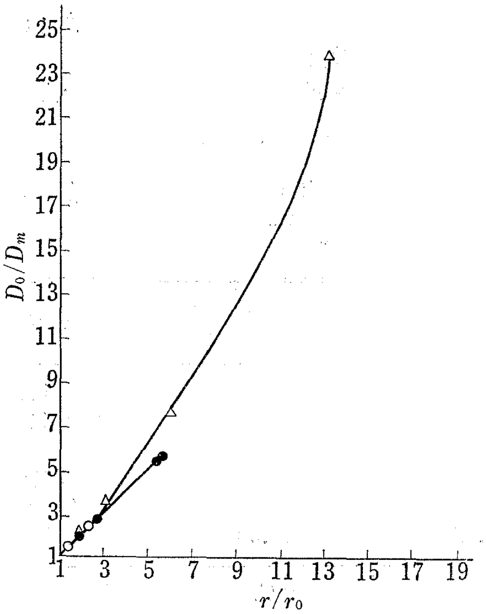

Fig. 1. Relationship of the Ratio of Diffusion Coefficients to Relative Size of Micelle

key: ●, η=3.53 cps; ○, η=6 cps; and △, unadjusted viscosity

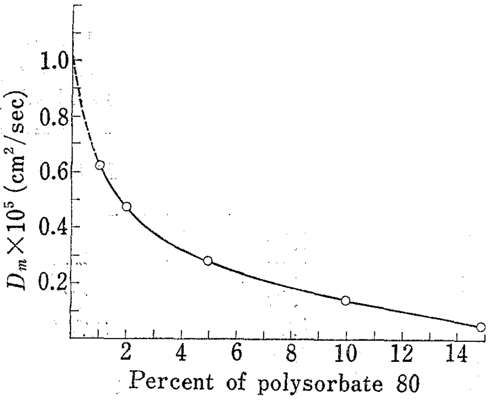

Fig. 2. Variation of Diffusivity with Concentration

and the shape of the particle is spherical (in high concentrations of solubilizing agent the shape is probably not spherical). In support of the use of the Stokes–Einstein relationship to calculate micelle size, it should be mentioned that there is the possibility that C_m, the concentration of the solubilized benzoic acid at the surface of the solid, is smaller than the calculated $C_s - C_0$. This would occur if the value of C_s obtained at solubilization equilibrium were smaller because the supply of polysorbate 80 micelles to the surface were restricted by diffusion of the empty micelles from the bulk solution.

Abstracted in part from a dissertation submitted by Robert J. Braun to the Graduate College, University of Iowa, in partial fulfillment of Doctor of Philosophy degree requirements.