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Estimation of Diffusion Coefficients and Molecular Weights of Interacting Colloids from Dissolution-Rate Data

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Abstract □ Based on dissolution-rate theory, diffusion coefficients for the salicylamide–micelle species were calculated from dissolution and solubility data obtained in micellar solutions of sodium taurodeoxycholate and sodium taurocholate at 20°. The calculated values were in good agreement with those determined experimentally using a diffusion cell and silver membrane. By assuming that the solubilized drug does not interfere with the organization of the micelle, the Stokes–Einstein equation was employed to estimate the molecular weight of the micelle. Excellent agreement was found between values calculated from dissolution data and those determined directly by ultracentrifugation or light scattering.

Keyphrases □ Diffusion coefficients, salicylamide–micelle species—calculated from dissolution, solubility data □ Molecular weight determinations, micellar—sodium taurodeoxycholate and sodium taurocholate with salicylamide □ Bile salt solutions—diffusion coefficients, molecular weight estimations, from dissolution-rate data

Numerous methods have been proposed to measure diffusion coefficients of colloids (1–5). These methods often involve rather complex experimental procedures, and much time may be required before experimental results can be obtained.

The most common method of determining diffusion coefficients of colloids has been the use of a diffusion cell and some means to separate the drug solution from the solvent "sink." Desai *et al.* (3) utilized a sintered-glass disk to separate the two solutions. An improvement on the glass disk was reported by Singh *et al.* (4), who used a filter made of glass reinforced with epoxy. Recently, Goldberg and Higuchi (5) successfully measured diffusion coefficients utilizing a silver membrane filter. These workers found that the silver filter produced good data precision and resulted in a fairly rapid method of determining diffusion coefficients.

A number of different investigators (4, 6) confirmed that dissolution from a rotating disk conforms to the theoretical equation presented by Levich (7) for that system. Since the dependence of the dissolution rate on the diffusion coefficient is known for the rotating-disk system, one should be able to use a reversal of the usual procedure—that is, measure dissolution rate of a drug in colloidal and aqueous systems and then calculate the diffusion coefficient of the drug in the system utilizing the Levich equation. This approach could lead to an improvement over the usual methods to determine diffusion coefficients because dissolution-rate measurements are rapid and reproducible. Moreover other factors such as changes in the membrane or cell constant or the incomplete washing out of the diffusion cell would not be problems in the dissolution-rate determination.

THEORY

Levich (7) proposed a convective diffusion theory for the rate of mass transport to or from the face of a rotating disk. The equation for the dissolution rate of a solid in a medium containing a colloidal solubilizing agent according to the rotating disk theory is (4):

$$DR = 0.621\gamma^{-1/6}\omega^{1/2}(D_{\text{eff.}})^{2/3}C_T \qquad \text{(Eq. 1)}$$

where DR is the dissolution rate per unit area of dissolving solid, C_T is the total solubility of the drug in the dissolution medium, γ is the viscosity of the medium, ω is the angular velocity of the rotating disk, and $D_{\text{eff.}}$ is the effective diffusion coefficient. The

Table I—Solubility and Dissolution Rate of Salicylamide at 50 m*M* Concentration of Each Bile Salt at 20°

	Solubility, mg./ml.[a]	Dissolution Rate[b], mcg./ml./min.	Ratio[c]
Control	2.04 ± 0.08	4.36 ± 0.05	1.00
Sodium taurodeoxycholate	3.24 ± 0.14	5.51 ± 0.03	1.26
Sodium taurocholate	3.21 ± 0.14	5.77 ± 0.05	1.32
Equimolar mixture	3.24 ± 0.10	5.60 ± 0.03	1.28

[a] Mean and standard deviation of five determinations. [b] Mean and standard deviation of three determinations. [c] Ratio of dissolution rate of salicylamide in surfactant solution to that in 0.15 *M* sodium chloride.

effective diffusion coefficient is defined as:

$$D_{\text{eff.}} = \frac{DC_s + D_mC_m}{C_T} \qquad \text{(Eq. 2)}$$

where D and D_m are the diffusion coefficients of the free and colloid solubilized drug, respectively. The solubility of the drug in the absence of the colloidal solubilizing agent is denoted by C_s, and C_m is the increase in solubility of the drug due to the presence of the colloid. (Therefore, $C_T = S_s + C_m$.)

By taking the ratio of the dissolution rate of the solid in a colloidal solution to that in a noncolloidal aqueous solution, Eq. 3 results:

$$\text{ratio} = \frac{(D_{\text{eff.}})^{2/3}C_T}{D^{2/3}C_s} \qquad \text{(Eq. 3)}$$

Thus, by determining the dissolution rate of a drug with a known diffusion coefficient in a colloidal solution and pure aqueous solution, and by measuring the equilibrium solubility of the drug in each solution, it is possible by means of Eqs. 2 and 3 to calculate the colloidal diffusion coefficient of the drug molecule.

EXPERIMENTAL

Materials—Taurodeoxycholic acid and taurocholic acid were obtained[1] as the sodium salt (A grade) and used as such. All other chemicals were analytical reagent grade and were used without further purification.

Dissolution-Rate Determination—The dissolution rate of salicylamide from nondisintegrating tablets, prepared by compression of 600 mg. of pure drug in a Carver model B hydraulic press at 10,000 p.s.i. for 10 sec., was determined by the rotating-disk method (8). The salicylamide tablets were mounted in Plexiglas holders with the aid of paraffin, and the apparatus was attached to a Servodyne constant torque unit. A 150-ml. water-jacketed beaker, containing 50 ml. of 50 m*M* sodium taurodeoxycholate, 50 m*M* sodium taurocholate, or a 50 m*M* equimolar mixture of the two bile salts (sodium taurodeoxycholate/sodium taurocholate) in 0.15 *M* sodium chloride was maintained at 20 ± 0.1° by circulation of water through the beaker. Control dissolution-rate determinations were run in 0.15 *M* NaCl. The Plexiglas holder and tablet were rotated at 100 r.p.m. and placed in the dissolution fluid. A 1-ml. sample was withdrawn at 5-min. intervals, diluted appropriately with 0.1 *N* HCl, and read spectrophotometrically at 299 nm.

Solubility Determination—The solubility of salicylamide was determined in solutions of 50 m*M* sodium taurodeoxycholate, sodium taurocholate, or sodium taurodeoxycholate–sodium taurocholate in 0.15 *M* NaCl and in 0.15 *M* NaCl alone by adding an excess of solid salicylamide to 5 ml. of the respective solution in 10-ml. capped culture tubes. The solutions were maintained at 20 ± 0.1° and shaken for 24–48 hr. Equilibrium was established by repetitive sampling.

Diffusion-Coefficient Measurements—Diffusion coefficients were measured directly by a method similar to that described by Goldberg and Higuchi (5). The silver membrane, 47-mm. diameter, 1.2-μ pore size, was prepared according to Goldberg and Higuchi (5). At time zero, 40 ml. of the appropriate solution (50 m*M* surfactant in 0.15 *M* NaCl or 0.15 *M* NaCl alone) containing 1 mg./ml. of salicylamide was placed in the left chamber of the apparatus.

[1] Calbiochem, Los Angeles, Calif.

Table II—Effective Diffusion Coefficients and Micellar Diffusion Coefficients of Salicylamide in 50 m*M* Bile Salt Determined from Dissolution-Rate Data and Direct Experimental Measurement

	$D_{\text{eff.}}$, cm.²/sec. × 10^6 Calculated[a]	$D_{\text{eff.}}$, cm.²/sec. × 10^6 Measured	D_m, cm.²/sec. × 10^6 Calculated[b]	D_m, cm.²/sec. × 10^6 Measured
Sodium taurodeoxycholate	7.79	7.80	2.33	2.36
Sodium taurocholate	8.46	8.39	4.03	3.84
Equimolar mixture	7.97	8.00	2.82	2.90

[a] Calculated by means of Eq. 3. [b] Calculated by means of Eq. 2.

At the same time, an identical solution without drug was introduced into the right chamber. The stirring motors were started, and 1-ml. samples were withdrawn from the right chamber at appropriate intervals, diluted, and assayed spectrophotometrically for salicylamide. A volume of solution was added to the right chamber to replace that withdrawn by the sample. This was corrected for in subsequent calculations. The temperature was maintained at 21 ± 1°.

The cell was calibrated by assuming the diffusion coefficient of benzoic acid in distilled water at 21° to be 1.11 × 10^{-5} cm.²/sec. (9). The cell constant thus obtained was then used to calculate the diffusion coefficient of salicylamide in the presence and absence of 50 m*M* bile salt.

RESULTS AND DISCUSSION

The solubility of salicylamide in 50 m*M* solutions of sodium taurodeoxycholate or 50 m*M* sodium taurocholate and in a 50 m*M* solution of an equimolar mixture of the two bile salts at 20° is shown in Table I. The solubility of salicylamide in 0.15 *M* sodium chloride also appears in this table. The increased solubility of salicylamide in each of the micellar bile salt solutions was in the order of 57–59%.

The results obtained from the dissolution-rate experiments utilizing the rotating disk are also presented in Table I. The presence of the micellar bile salt solution resulted in an increase in the rate of salicylamide dissolution as compared to the rate in 0.15 *M* sodium chloride. The ratio of dissolution rate of salicylamide in bile salt solution to that of control also appears in Table I. The differences in dissolution rates between each bile salt solution were small, but each result was statistically different[2] from any other as determined by the Student t test (10). The rate of salicylamide dissolution in the various surfactant solutions decreased in the following order: sodium taurocholate > equimolar mixture > sodium taurodeoxycholate.

The results of the diffusion-coefficient measurements appear in Table II. The diffusion coefficient of salicylamide in 0.15 *M* sodium chloride was found to be 11 × 10^{-6} cm.²/sec. This value was used in all subsequent calculations. Included in this table are the effective diffusion coefficients ($D_{\text{eff.}}$) determined experimentally and the $D_{\text{eff.}}$ calculated from the dissolution-rate data by means of Eq. 3. The micellar coefficient (D_m) of salicylamide in 50 m*M* of the various bile salt solutions was calculated by means of Eq. 2 from both the diffusion-coefficient measurement data and the dissolution-rate data (Table II). As can be seen from the data, the agreement between the two methods of analysis is quite good. However, caution must be exercised in the use of this method if the dissolution rate is not entirely diffusion controlled.

It was previously shown that the Stokes–Einstein relationship gives a good estimation of the micellar molecular weight of the drug–micelle complex based upon the diffusion coefficient (6). According to the Stokes–Einstein relationship, the diffusion coefficient of a solute may be calculated by means of the following equation (11):

$$D = \frac{RT}{6\pi\eta N} \cdot \sqrt[3]{\frac{4\pi N}{3\bar{M}\bar{v}}} \qquad \text{(Eq. 4)}$$

[2] $p < 0.05$.

Table III—Micellar Molecular Weight of Each Bile Salt Determined from Literature Data and Calculated Using Eq. 5 from Dissolution-Rate Data and Measured Diffusion-Coefficient Data

	—Micellar Molecular Weight—		
	Dissolution-Rate Data	Diffusion Coefficient Data	Literature[a]
Sodium taurodeoxycholate	14,148	13,306	12,500
Sodium taurocholate	2,662	3,072	2,689
Equimolar mixture	7,848	7,189	7,945

[a] From *Reference 15.*

where R is the molar gas constant, T is the absolute temperature, η is the viscosity of the solvent, N is Avogadro's number, M is the molecular weight, and $\bar{v}$ is the partial specific volume. Equation 4 predicts an inverse cube-root relationship between the diffusion coefficient and molecular weight. Therefore, estimation of micellar molecular weight can be made by means of the following relationship:

$$(M)^{1/3}\text{micelle-drug} = \frac{(M)^{1/3}\text{drug} \cdot D}{D_m} \qquad \text{(Eq. 5)}$$

The calculations were made for each bile salt solution studied from both diffusion and dissolution data (Table III). Several studies in the literature report the micellar molecular weights of a number of bile salts (12–15). Carey and Small (16) presented a detailed study of the micellar properties of sodium taurocholate and sodium taurodeoxycholate. By using the molecular weight of each individual bile salt and the rounded-off aggregation number at 20° and 0.15 M sodium chloride concentration, it was possible to calculate the molecular weight of each bile salt micelle. An estimation of the molecular weight of the mixed micelle of the equimolar mixtures of the bile salts was obtained by multiplying the aggregation number by the mean of the bile salt molecular weights. Since the molecular weights of each bile salt are similar, little error should be involved in this estimation. The molecular weight contributed by the moles of salicylamide solubilized by each mole of bile salt was then subtracted from the experimentally measured values of micellar weights to obtain the molecular weight of micelle (Table III). As can be seen in Table III, the agreement between the literature values and those calculated from Eq. 5 is excellent.

The cube-root relationship may only be used for an estimate of colloid molecular weight under those conditions where the interaction between the colloid and the drug molecule does not interfere with the organization of the colloid. If this is the case, one can determine the molecular weight of the colloid independent of the drug molecule, which is being used strictly as a probe.

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Aminotetrahydrofuranol Derivatives

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Abstract □ Some esters of 4-dimethylamino-3-tetrahydrofuranol are reported along with a methyl and benzyl quaternary ammonium salt. Compound VI possessed about one-fifth the anticholinergic activity of atropine sulfate.

Keyphrases □ 4-Dimethylamino-3-tetrahydrofuranol, esters—synthesis as possible anticholinergic agents, pharmacological evaluation □ Aminotetrahydrofuranol derivatives—synthesis, pharmacological screening as possible anticholinergic agents □ Anticholinergic agents, potential—synthesis of aminotetrahydrofuranol derivatives, pharmacological evaluation

The ethanolamine moiety is a prominent feature of most cholinergic and anticholinergic agents. The goal of this investigation was to determine whether tetrahydrofuran analogs containing a sterically restricted ethanolamine moiety would possess a greater specificity of biological activity.

Generally, 4-dimethylamino-3-tetrahydrofuranol was prepared from dimethylamine and 4-chloro-3-tetra-