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Measurement of the Distribution Parameter in Solubilized Systems. Application of the Derivative Spectrum Method to Alkylparabens Solubilized with Sodium Dodecyl Sulfate

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Solubilization of drugs with surfactants often causes changes of the absorbance and the maximum absorption wavelength. In this study, it was found that the shifts of the absorption maxima of alkylparabens depended on the concentration of the surfactant, sodium dodecyl sulfate, but not on the concentration of the drugs. The first derivative absorption spectrum was used to evaluate the wavelength shift.

The distribution parameter is defined as the ratio of the amount of the drug in the micellar phase (calculated from the absorption shift-length) divided by the amount of surfactant in the micellar phase to the amount of the drug in the bulk phase divided by the amount of surfactant in the bulk phase. This distribution parameter differs from the partition coefficient. It was found that the longer the alkyl chain length of the alkylparabens, the greater the absorption shift-length and the distribution parameter. Alkylparabens are very difficult to differentiate from each other in terms of the absorption spectra, but can easily be distinguished by using the distribution parameter. This approach may be generally useful for distinguishing drug homologs.

Keywords—first derivative absorption spectrum; critical micelle concentration; distribution parameter; micelle; wavelength shift; sodium dodecyl sulfate; alkylparaben; solubilization

Introduction

The mechanism of solubilization by surfactants can be investigated by means of measurements of the distribution of solute in the micellar phase and in the bulk phase (aqueous phase containing surfactant monomer). At the present time, some data¹⁻⁶⁾ are available on the partition coefficient, which is the concentration ratio of the drug in the micellar phase to that in the bulk phase. However, since the volume of the micelles is not known exactly, the concentration of the drug in the micellar phase can not be determined accurately, and so the partition coefficient is only approximate. The distribution parameter defined in this study differs from the partition coefficient; it is defined as the ratio of X to Y , where X is the ratio of the amount of the drug incorporated into the micellar phase to the amount of the surfactant forming micelles, and Y is the ratio of the amount of the drug dissolved in the bulk phase to the amount of the surfactant in the bulk phase.

It has been found that the absorption maximum of a drug in surfactant solution shifts at surfactant concentrations above the critical micelle concentration (cmc). We measured the shift-length (mm) of the maximum absorption wavelength by utilizing the first derivative absorption spectrum, and calculated the distribution parameter for a series of alkylparabens.

The distribution parameter increased with alkyl chain length, and yielded information about the drugs which could not readily be obtained from the absorption spectra alone.

Theory

Generally, the absorption spectrum of a drug in surfactant solution below the cmc (I)

differs from that in surfactant solution above the cmc (II).

In case I, the absorption spectrum of the drug generally coincides with that in aqueous solution, unless there are specific intermolecular interactions, e.g. charge transfer, ion pair and/or complex formation. However, in case II, micelles are formed in the surfactant solution, and a part of the drug may be incorporated into the micellar phase. The absorption spectrum of the incorporated drug is expected to show changes in both intensity and peak position, though in this study, only the wavelength shift has been examined, by making use of the first derivative absorption spectrum. The degree of the shift-length depended on the concentration of the surfactant, but not on the drug concentration. There should be a positive relation between the volume of the micelles and the amount of the drug incorporated into the micelles, and the degree of shift-length should correspond to the amount of the drug incorporated into the micelles.

When the concentration of the surfactant is infinitely high, the degree of shift-length can be assumed to be unity. Therefore, the amount of the drug in the micellar phase (A_m) is

$$A_m = A \times S \quad (1)$$

where A is the total amount of the drug in this system, and S is the degree of shift-length (0—1). The amount of surfactant forming micelles (B_m) is

$$B_m = B - B_b \quad (2)$$

where B is the total amount of the surfactant, and B_b is the amount of the surfactant in the bulk phase,⁷⁾ given by the product of the cmc and the volume of the bulk phase, which is comparable to the volume of the total solution as long as the micellar volume is very small. The ratio of the amount of the drug in the micellar phase to the amount of surfactant in the micellar phase is

$$X = A_m/B_m \quad (3)$$

Similarly, the amount of the drug in the bulk phase (A_b) is given by

$$A_b = A \times (1 - S) \quad (4)$$

The ratio of the amount of the drug in the bulk phase to the amount of the surfactant in the bulk phase is

$$Y = A_b/B_b \quad (5)$$

Thus, the distribution parameter (K_{dp}) is defined as follows,

$$K_{dp} = X/Y \quad (6)$$

Substituting Eqs. 3 and 5 into Eq. 6, the following equation can be derived,

$$K_{dp} = [S \times B_b]/[(1 - S) \times B_m] \quad (7)$$

Experimental

Materials—Methyl-*p*-hydroxybenzoate (methylparaben), ethyl-*p*-hydroxybenzoate (ethylparaben), propyl-*p*-hydroxybenzoate (propylparaben), butyl-*p*-hydroxybenzoate (butylparaben) and sodium dodecyl sulfate (SDS) were obtained from Nakarai Chemicals, Ltd., and *p*-hydroxybenzoic acid and potassium chloride (KCl) were obtained from Wako Pure Chemical Ind., Ltd. These chemicals were used as received.

Measurement of Absorption Spectra and First Derivative Absorption Spectra—A Hitachi 557 dual-wavelength double beam spectrophotometer equipped with a Haake-F2C thermostat was used.

In this study, in order to avoid experimental errors due to differences in the concentrations of alkylparabens, the first derivative absorption spectrum was used to establish the position of the absorption maximum. Measurement

conditions were as follows: scale expansion 20 times, scan speed 36 nm/min, slit width 2 nm, scale of absorption spectra from +0.3 to -0.3. Each measurement was repeated at least four times.

Measurement of the cmc of SDS Solution—An electric conductivity meter (CD-35MII, M & S Instruments Inc.) equipped with a Tokyo Rikakikai thermostat was used for the measurement of the cmc. The temperature of measurement was 22 °C. A CDC-122 cell was used, and the cell constant obtained by using KCl solution was $4.69 \times 10^{-4} \text{ cm}^{-1}$ at 22 °C.

Results and Discussion

Figure 1 shows the effect of SDS on the absorption spectrum of butylparaben as an example. In order to measure the shift-length accurately, the first derivative absorption spectra were determined. Figures 2 and 3 illustrate the first derivative absorption spectra obtained for propylparaben and ethylparaben, and show the concentration dependence of the

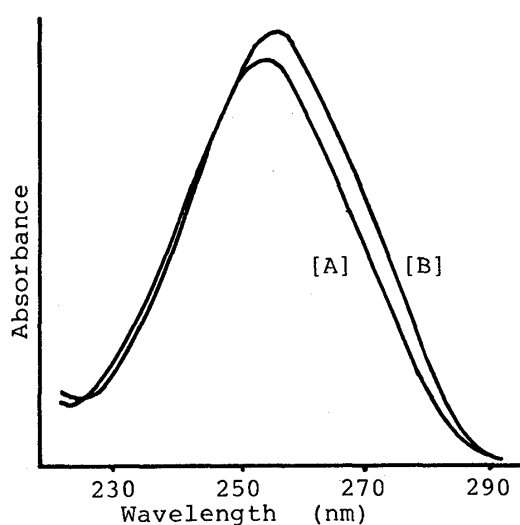


Fig. 1. Effect of SDS on the Absorption Spectrum of Butylparaben ($37.1 \mu\text{M}$)

[A], in H_2O ; [B] in 30.6 mM SDS solution.

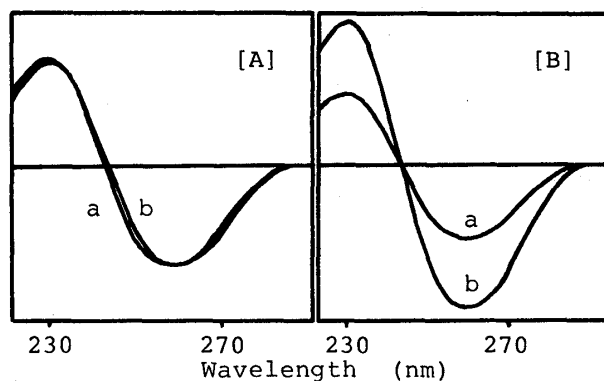


Fig. 2. First Derivative Absorption Spectrum of Propylparaben

[A] SDS: a = 0 mm, b = 30.6 mm; propylparaben: a = b = $35.0 \mu\text{M}$. [B] SDS: a = b = 22.7 mm; propylparaben: a = $23.3 \mu\text{M}$, b = $46.6 \mu\text{M}$.

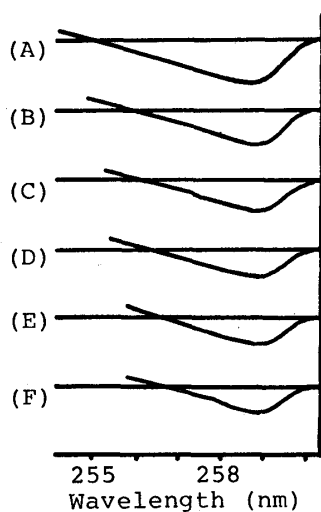


Fig. 3. First Derivative Absorption Spectra of $50.6 \mu\text{M}$ Ethylparaben

(A), in H_2O ; (B) in 13.7 mM SDS solution; (C), 18.2 mM SDS; (D), 22.8 mM SDS; (E), 27.3 mM SDS; (F) 30.3 mM SDS.

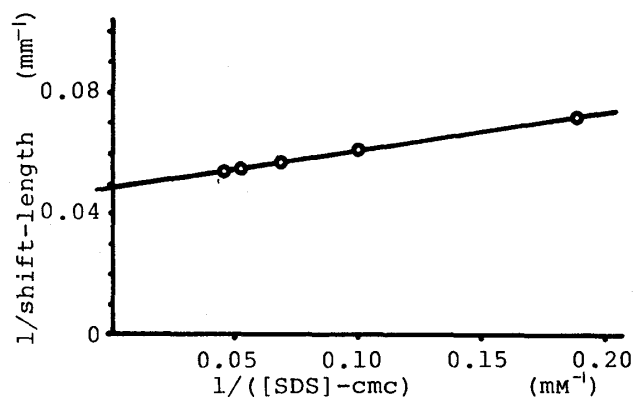


Fig. 4. Double Reciprocal Plots of $([\text{SDS}]-\text{cmc})$ against Shift-Length of Propylparaben (Propylparaben = $46.6 \mu\text{M}$)

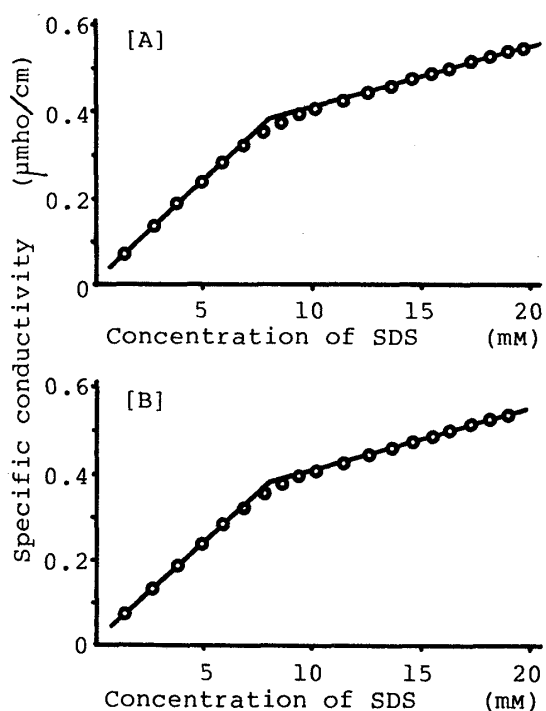


Fig. 5. Determination of cmc of SDS Solution by Electric Conductivity Measurement

Titration was performed at 22 °C by adding increasing amounts (8–20 ml) of a 35.4 mM stock solution of SDS to 200 ml of H₂O [A] or 128.8 μM methylparaben [B].

TABLE I. Distribution Parameter Values of Alkylparabens

	SDS concentration (mM)				
	13.7	18.2	22.8	27.3	30.3
Methyl- <i>p</i> -hydroxybenzoate	0.72	0.63	0.77	0.73	0.73
Ethyl- <i>p</i> -hydroxybenzoate	1.4	1.7	1.7	1.8	1.6
Propyl- <i>p</i> -hydroxybenzoate	3.0	2.9	2.8	3.1	3.0
Butyl- <i>p</i> -hydroxybenzoate	9.5	11.7	8.8	8.3	10.9

spectra. The value of the shift-length at infinite concentration of SDS was obtained by extrapolation of a plot of the reciprocal of the shift-length on the ordinate against the reciprocal of $([\text{SDS}] - \text{cmc})$ on the abscissa, as shown in Fig. 4. The degree of shift was assumed to be unity at infinite SDS concentration. The term $([\text{SDS}] - \text{cmc})$ is used since this is the concentration of SDS actually available for micelle formation. Stilbs⁸⁾ assumed that all of the surfactant in the solution contributed to form micelles, but this is a reasonable approximation only when the concentration of surfactant is very large.

Goto *et al.*^{9,10)} reported that the cmc of SDS solution tended to decrease on addition of alkylparabens. However, in this study, the very low concentrations of alkylparabens used had little influence on the cmc of SDS. For example, the cmc of SDS solution was 8.1 mM at 22 °C, and dissolving 55.2 μM methylparaben in the solution did not affect that value (Fig. 5). As for the other alkylparabens, the molar concentrations used were smaller than that of methylparaben (ethylparaben 50.6 μM, propylparaben 46.6 μM and butylparaben 43.2 μM), and should have a negligible effect on the cmc of SDS. By using this value of cmc, the distribution parameters of alkylparabens were calculated from Eq. 7, and the results are shown in Table I.

It was confirmed that the wavelength of the absorption maximum determined from the first derivative absorption spectrum is not dependent on the concentration of alkylparaben (see Fig. 2).

It was found that the degree of shift-length and the distribution parameter increased with increasing alkyl chain length of the alkylparabens. This may be explained by assuming that the alkylparaben is more easily incorporated into the micelle when the alkyl group (lipophilic moiety) is larger. Since methylparaben, ethylparaben, propylparaben and butylparaben in aqueous solution have the same wavelength of absorption maximum (253 nm), it is impossible to discriminate them from the absorption spectra alone, but the distribution parameters in SDS solution are quite different: methylparaben 0.63—0.77, ethylparaben 1.4—1.8, propylparaben 2.8—3.1, and butylparaben 8.3—11.7.

Many methods are available for determining partition coefficients, such as the ultrafiltration method,¹¹⁾ the partial molar volumes method,¹²⁾ the calorimetric method,¹³⁾ the gel filtration method,^{4,14)} the fluorescence method,^{15,16)} the gas chromatographic method,³⁾ the tracer method,¹⁷⁾ *etc.* Further, the partition coefficients of anesthetics between aqueous and SDS micellar phases were measured by the Krafft-point depression method.⁵⁾ Gonzalez *et al.*⁶⁾ reported the mole fraction method, which does not require knowledge of the aggregation number of micelles, and obtained the partition coefficient from the mole fraction of each component. In a dilute solution of surfactant, the value obtained by their method agreed with the value of the partition coefficient obtained from the concentration ratio, but the two values did not agree at high concentrations of surfactant; this is because the system is more complex than is assumed in their approach (*e.g.*, the mole fraction of the solute and the presence of monodispersed surfactant are not considered).

As mentioned in the introduction, partition coefficients are not exact because the micellar volume can not be determined exactly, and the partition coefficient is the ratio of the concentration of the drug in the micellar phase to that in the bulk phase, *i.e.*,

$$K_{pc} = C_m / C_b \quad (8)$$

where K_{pc} is the partition coefficient of the drug between the micellar phase and the bulk phase, and C_m and C_b are the concentrations of the drug in the micellar phase and in the bulk phase, respectively. The total volume of the surfactant solution (V) is

$$V = V_m + V_b \quad (9)$$

where V_m is the volume of the micellar phase and V_b is the volume of the bulk phase in which the monodispersed surfactant can be distributed. Transforming Eq. 8 yields

$$K_{pc} = (A_m / V_m) / (A_b / V_b) \quad (10)$$

Substituting Eqs. 6 and 9 into Eq. 10, the following equation for the partition coefficient can be derived

$$K_{pc} = K_{dp} \times (B_m / B_b) \times [(V - V_m) / V_m] \quad (11)$$

The values of the partition coefficients obtained from the data in Table I and Eq. 11 are shown in Table II. The partition coefficients obtained by the gel filtration method for methylparaben,

TABLE II. K_{pc} Values Calculated by Means of Eq. 11

	SDS concentration (mM)				
	13.7	18.2	22.8	27.3	30.3
Methyl- <i>p</i> -hydroxybenzoate	266	230	283	267	267
Ethyl- <i>p</i> -hydroxybenzoate	508	625	628	664	593
Propyl- <i>p</i> -hydroxybenzoate	1094	1074	1043	1148	1091
Butyl- <i>p</i> -hydroxybenzoate	3503	4318	3242	3054	3978

ethylparaben and butylparaben between the micellar phase and the bulk phase in SDS solution were 1300—3000, 3800—8200 and 21000—63000 at 27 °C, respectively.¹⁰⁾ On the other hand, the partition coefficients of methylparaben, ethylparaben, butylparaben obtained from Eq. 11 using the distribution parameter in SDS solution were much smaller (Table II). For example, a K_{pc} value of 266 for methylparaben was obtained based on the following values: $K_{dp}=0.722$, $B_m=5.6$ mM, $B_b=8.1$ mM, $V=1000$ ml and $V_m=1.873$ ml, which was calculated by using a value of 0.862 ml/g of SDS, the micellar volume of the core and the Stern layer at 23 °C.¹⁸⁾ The discrepancy might be explained in terms of the concentration difference between the two systems, *i.e.* they used higher concentrations of alkylparabens which probably affected the cmc of SDS solution, while we used lower concentrations which had a negligible effect on the cmc.

In conclusion, the proposed method can provide information about solute distribution between micellar and aqueous phases in a solubilized system, simply by measuring the first derivative absorption spectra at several SDS concentration levels. This method is rapid and convenient, and does not require a large amount of drug.

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