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Measurement of the Distribution Parameter in Solubilized Systems. II. Measurement of the Distribution Parameter of Alkylparabens and Alkyl Gallates in Ionic and Nonionic Surfactant Solutions

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In a micellar solution of sodium dodecyl sulfate (SDS), it was found that the shifts of the absorption maxima of alkylparabens depended on the concentration of the surfactant, but not on the concentration of the drugs. The first derivative absorption spectrum was used to evaluate the wavelength shift, from which the distribution parameter and partition coefficient of the drug were calculated.

The method was applied to find the distribution parameters of the alkylparaben–cetyltrimethylammonium bromide (CTAB) system, the alkylparaben–polyoxyethylene (20) sorbitan monolaurate (Tween 20) system, and the alkyl gallate–CTAB system. In CTAB and Tween 20 solutions, the order of magnitude of the distribution parameter of alkylparaben was butyl- > propyl- > ethyl- > methylparaben, and that of alkyl gallate was propyl- > ethyl gallate, and these tendencies were independent of the temperature in the range from 25 to 60 °C (in the case of CTAB).

Keywords——distribution parameter; sodium dodecyl sulfate; alkylparaben; wavelength shift; critical micelle concentration; first derivative absorption spectrum method; cetyltrimethylammonium bromide; Tween 20; partition coefficient; alkyl gallate

Introduction

We previously reported[1] that the distribution parameter and partition coefficient of the alkylparaben–sodium dodecyl sulfate (SDS) system could be obtained by the first derivative absorption spectrum method. The method was based on the fact that 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. The method may be applicable to other surfactant solubilizing systems.

In this study, it was shown that the distribution parameter of alkylparabens and alkyl gallates in cationic and nonionic surfactant solutions could be obtained in the same manner. The way in which the distribution parameter values in anionic, cationic and nonionic surfactant solutions are affected by temperature was also investigated.

Experimental

Materials——Methyl *p*-hydroxybenzoate (methylparaben), ethyl *p*-hydroxybenzoate (ethylparaben), propyl *p*-hydroxybenzoate (propylparaben), butyl *p*-hydroxybenzoate (butylparaben), SDS (minimum 99%), potassium chloride (KCl) and cetyl trimethylammonium bromide (CTAB) were obtained from Nakarai Chemicals, Ltd., and polyoxyethylene (20) sorbitan monolaurate (Tween 20), 3,4,5-trihydroxybenzoic acid ethyl ester (ethyl gallate) and 3,4,5-trihydroxybenzoic acid propyl ester (propyl gallate) 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. Measurement conditions were as follows: scale expansion 20 times, scan speed 6 nm/min, derivative width ($\Delta\lambda$) 5, 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 Critical Micelle Concentration (cmc) of SDS Solution and CTAB Solution——A CD-35MII electric conductivity meter (M&S Instruments Inc.) equipped with a Tokyo Rikakikai thermostat was used for the measurement of the cmc. Two CDC-122 cells were used, and the cell constants obtained by using KCl solution were $4.96 \times 10^{-4}\,\mathrm{cm}^{-1}$ at 22 °C in SDS and $6.11 \times 10^{-4}\,\mathrm{cm}^{-1}$ at 25 °C in CTAB.

Measurement of the cmc of Tween 20 Solution——The cmc of Tween 20 solution was obtained by the surface tension method (the Wilhelmy plate method). A Kyowa Kagaku CBVP surface tensiometer A-1 equipped with a Tokyo Rikakikai thermostat and a glass plate was used. Each measurement was repeated at least four times, and plots of the absolute values (each the average of the relative values multiplied by the correction factor) were drawn by the least-squares method for each part of the biphasic plots.

Results and Discussion

Effect of Temperature on cmc

The cmc at each temperature is needed for the calculation of the distribution parameter (K_{dp}). The plot of cmc of SDS solution at different temperatures shows a curvature, in agreement with earlier work.[2,3] The values of cmc used for calculation of the distribution parameter values are 8.1 mM at 22 °C, 8.4 mM at 38 °C, 9.6 mM at 58 °C and 11.3 mM at 68 °C.

Figure 1 shows the cmc of CTAB solution at different temperatures. The curve means that micelle formation at higher temperature requires a higher surfactant concentration. The values of cmc used for calculation of the distribution parameter values are 0.99 mM at 25 °C, 1.06 mM at 35 °C, 1.22 mM at 48 °C and 1.56 mM at 60°C.

Figure 2 shows the cmc of Tween 20 (nonionic surfactant) solution at 25, 35, 45 and 55°C. The value of cmc is 0.07 g/l and is not affected by temperature.

The Distribution Parameter

In alkylparaben–CTAB, alkylparaben–Tween 20 and alkyl gallate–CTAB systems at each temperature, the absorption spectra of alkylparabens and alkyl gallates in CTAB

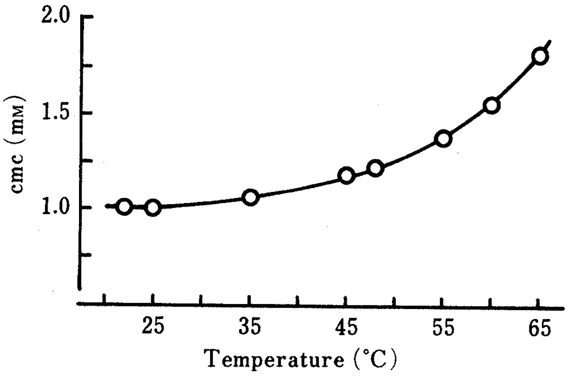

Fig. 1. Effect of Temperature on the cmc of CTAB Determined by the Electric Conductivity Method

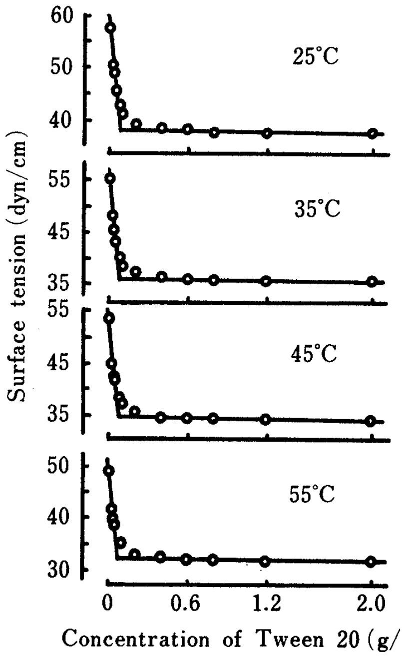

Fig. 2. Determination of cmc of Tween 20 Solution by Surface Tension Measurement

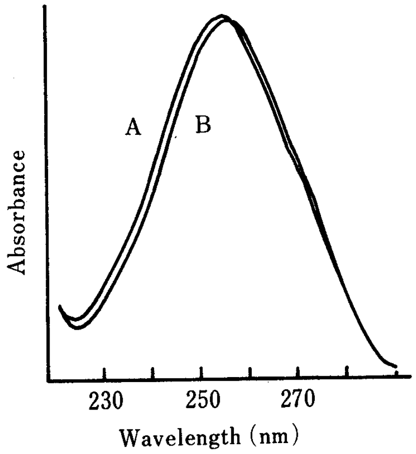

Fig. 3. Effect of Tween 20 on the Absorption Spectra of 46.6 μM Propylparaben

A, in H_2O; B, in 2.70 g/l Tween 20 solution.

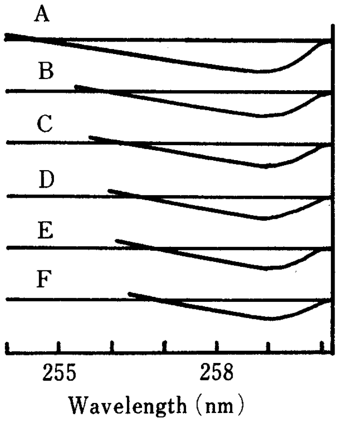

Fig. 4. First Derivative Absorption Spectra of 43.2 μM Butylparaben

A, in H_2O; B, in 0.90 g/l Tween 20 solution; C, 1.35 g/l Tween 20; D, 1.80 g/l Tween 20; E, 2.25 g/l Tween 20; F, 2.70 g/l Tween 20.

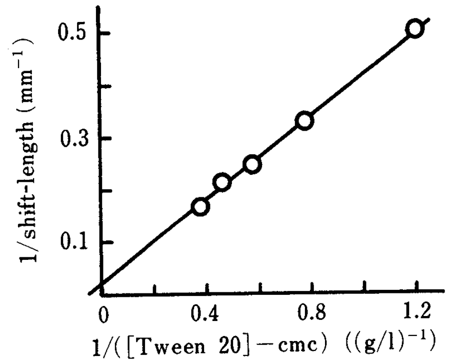

Fig. 5. Double-Reciprocal Plots of ([Tween 20]−cmc) against Shift-Length of Propylparaben

Propylparaben = 46.6 μM

solution or of alkylparabens in Tween 20 solution shift in both the maximum absorption wavelength and the absorbance as compared with the absorption spectra in aqueous solution (Fig. 3).

These results were similar to those in the alkylparaben–SDS system. In this study, the first derivative absorption spectrum was used to evaluate the wavelength shift (Fig. 4).

The distribution parameter values were obtained from the degree of shift-length at infinite concentration of surfactant and the following equation,

$$K_{dp} = (\text{cmc} \times S)/\{(1-S) \times B_m\} \qquad (1)$$

where S is the degree of shift-length (0—1), and B_m is the amount of surfactant forming micelles.[1] A double-reciprocal plot of the reciprocal of the shift-length on the ordinate against the reciprocal of ([surfactant]−cmc) on the abscissa,[4] was used to obtain the value of the shift-length at infinite concentration of surfactant (Fig. 5).

The value of the intercept on the ordinate is $1/(\alpha \times [P]_t)$, and the slope is cmc/$(\alpha \times K_{dp-a} \times [P]_t)$, where α is the proportional constant, and $[P]_t$ is the total concentration of alkylparaben (or alkyl gallate) in this system. The distribution parameter (K_{dp-a}) is the average of the values obtained at different surfactant concentrations. Furthermore, K_{dp-a} values at different temperatures were also obtained in each surfactant solution. These results are shown in Figs. 6—9.

In SDS and CTAB solutions, it was found that the distribution parameter values increased with increasing alkyl chain length of the alkylparabens, and the order of magnitude is butyl- > propyl- > ethyl- > methylparaben (see Figs. 6, 7 and 9). This order was not af-

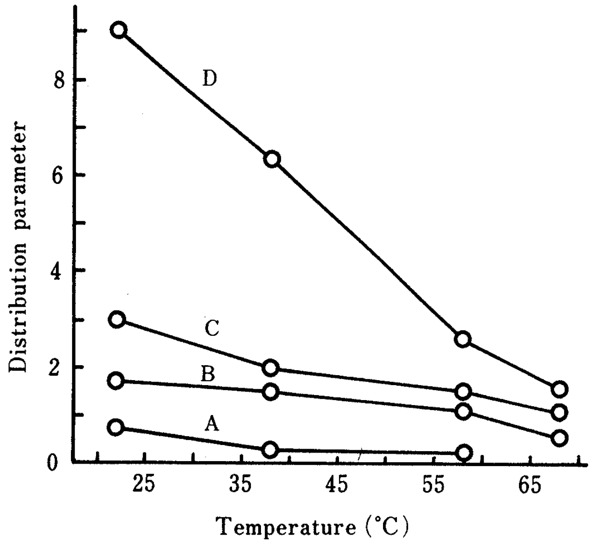

Fig. 6. Temperature Dependence of Distribution Parameter Values of Alkylparabens in SDS Solution

A, methylparaben (55.2 μM); B, ethylparaben (50.6 μM); C, propylparaben (46.6 μM); D, butylparaben (43.2 μM).

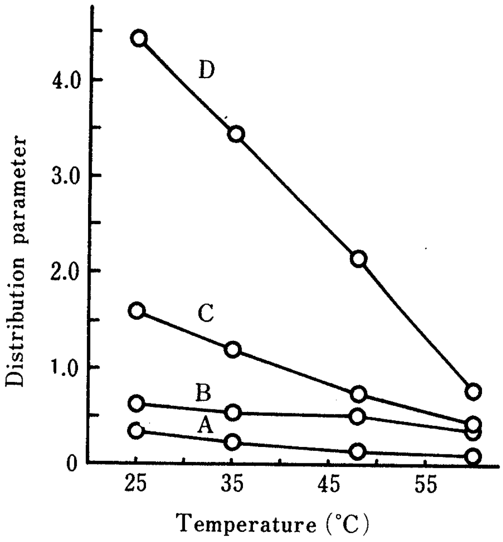

Fig. 7. Temperature Dependence of Distribution Parameter Values of Alkylparabens in CTAB Solution

A, methylparaben (78.9 μM); B, ethylparaben (60.2 μM); C, propylparaben (55.5 μM); D, butylparaben (51.5 μM).

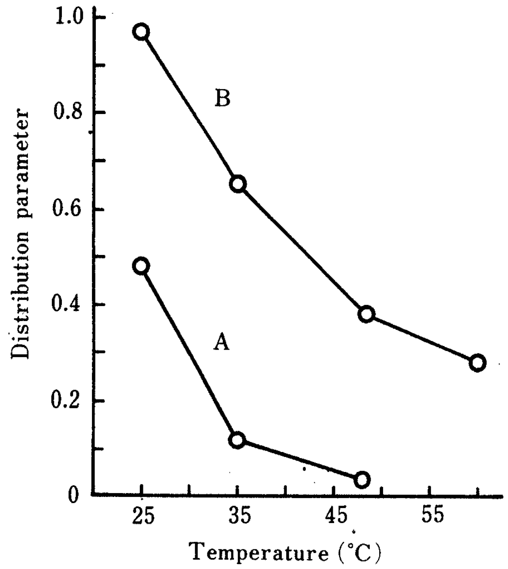

Fig. 8. Temperature Dependence of Distribution Parameter Values of Alkyl Gallate in CTAB Solution

A, ethyl gallate (201.8 μM); B, propyl gallate (188.5 μM).

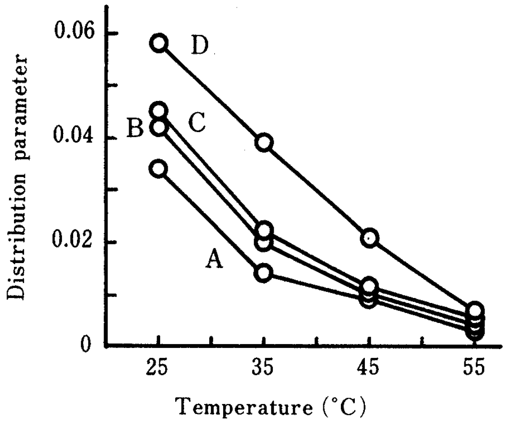

Fig. 9. Temperature Dependence of Distribution Parameter Values of Alkylparabens in Tween 20 Solution

A, methylparaben (55.2 μM); B, ethylparaben (50.6 μM); C, propylparaben (46.6 μM); D, butylparaben (43.2 μM).

fected by temperature in the range of 22 to 68 °C for SDS, and a similar result was obtained with CTAB.

In the case of the alkyl gallate–CTAB system, Fig. 8 shows that the order of magnitude of the distribution parameter values is propyl- > ethyl gallate, and again this is not affected by temperature.

When the alkyl chain length is longer (*i. e.*, the hydrophobic moiety is longer), the drug can be incorporated more easily into the micellar phase, and the distribution parameter is thus

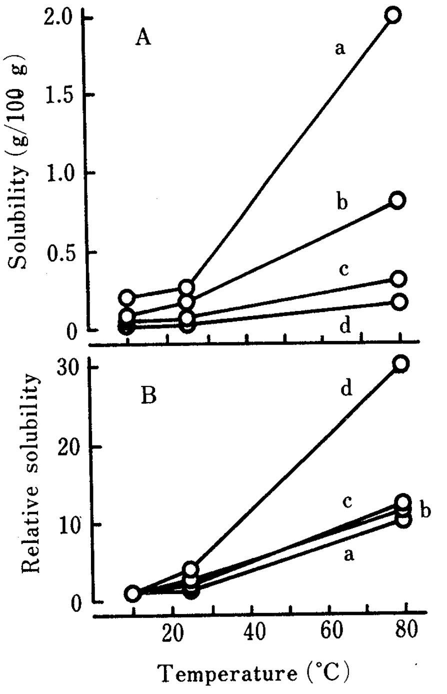

Fig. 10. Solubility (A) and Relative Solubility (Normalized to the Solubility at 10 °C, (B)) of Alkylparabens in Aqueous Solution

a, methylparaben; b, ethylparaben; c, propylparaben; d, butylparaben.

expected to become larger.

On the other hand, it was found that the distribution parameter values of butylparaben–SDS system became smaller with rising temperature, and the same tendency was observed in the propylparaben–, ethylparaben– and methylparaben–SDS systems. Similar results were obtained in the alkylparaben–CTAB system and the alkyl gallate–CTAB system. In the case of an ionic surfactant such as SDS or CTAB, as the surfactant molecule is small, molecular movement in the surfactant solution is activated by an increase of temperature, and it becomes more difficult to maintain a stable aggregation state (micelles) than at lower temperature. Since a higher concentration of surfactant is needed to maintain the aggregation state, the cmc become larger as the temperature increases. Therefore, ([surfactant] − cmc) become smaller if the total surfactant concentration is kept constant. Moreover, S becomes smaller and $(1-S)$ larger. According to the experimental results, the rate of decrease of S (proportional to the amount of alkylparaben incorporated into the micellar phase) is larger than the rate of decrease of micellar volume (proportional to ([surfactant] − cmc)). Further, the rate of increase of the value of cmc is smaller than that of $(1-S)$. Therefore, the denominator of the Eq. 1 becomes large when the temperature increases, and the distribution parameter values become small.

On the other hand, the distribution parameter values of the alkylparaben–Tween 20 system showed smaller values with longer alkyl chains, and this tendency was the same at different temperatures. Furthermore, the distribution parameter values in the butylparaben–Tween 20 system became smaller with higher temperature, and this tendency was the same as in the propylparaben, ethylparaben and methylparaben with Tween 20 systems. However, this tendency is not considered to be caused by the change of cmc of Tween 20 solution because the value of cmc is not affected by temperature. Therefore, we propose the following explanation. Figure 10A shows the solubility of alkylparabens in aqueous solution at different temperatures, cited from Takano.[5] Figure 10B shows the relative solubility at 25 and 80 °C when the solubility value at 10°C is assumed to be unity. The solubility of methylparaben is the largest and that of butylparaben is the smallest from Fig. 10A. However, the relative solubility of butylparaben is the largest and that of methylparaben is the smallest at 80 °C from Fig. 10B. The distribution parameter values at higher temperature are smaller. This may

Table I. K_{pc} Values Calculated by Eq. 2

	SDS	CTAB		SDS	CTAB
Methyl *p*-hydroxybenzoate	260	885	Butyl *p*-hydroxybenzoate	3294	12225
Ethyl *p*-hydroxybenzoate	629	1687	Ethyl gallate	—	1328
Propyl *p*-hydroxybenzoate	1088	4398	Propyl gallate	—	2683

be caused by the differences in the relative solubility of alkylparabens in aqueous solution at different temperatures. The relative solubility of butylparaben in aqueous solution at 80°C is about 30 times larger than that at 10°C, but that of methylparaben is about 10 times larger.

Similarly, in the alkylparaben–Tween 20 system, the relative solubilities of alkylparabens differ at each temperature, 25, 35, 45 and 55 °C. The distribution parameter values of alkylparabens become small bacause the solubilities of alkylparabens in aqueous solution increase at higher temperature. The butylparaben–Tween 20 system shows the greatest relative solubility changes with temperature, and it has the greatest variation ratio of the distribution parameter value, as shown in Fig. 9.

In the case of –SDS and –CTAB solution, it can be deduced that the phenomena described above will also occur, but in the cases of these surfactant solutions, the cmc dependency on temperature is greater than that of the relative solubility in water.

The Partition Coefficient

The partition coefficient values (K_{pc}) of the alkylparaben–SDS system at 22 °C, and the alkylparaben–CTAB system and alkyl gallate–CTAB system at 25 °C were calculated from the following equation,[1]

$$K_{pc}=\{K_{dp-a}\times B_m\times(V-V_m)\}/(\mathrm{cmc}\times V_m) \qquad (2)$$

where V is the total volume of the surfactant solution and V_m is the volume of the micellar phase. The micellar volume of the core and the Stern layer is 0.862 ml/g of SDS at 23 °C[6] and is 0.999 ml/g of CTAB at 28 °C.[7] Table I shows the values of K_{pc}, which were calculated from these micellar volume values and the surfactant concentrations (6 levels) used in this experiment. Though the temperatures of the CTAB solution system and SDS are not the same (that of the CTAB system is higher by 3 °C), the CTAB micellar phase tends to incorporate alkylparaben more effectively than SDS as the partition coefficient values of alkylparaben in the CTAB micellar solution are 2.7—4.1 times as large as those in the SDS micellar solution.

In conclusion, the first derivative absorption spectrum method can be utilized for measurement of the distribution parameter and the partition coefficient in ionic and nonionic surfactant solutions, and may be applicable to many drugs which show UV/VIS absorption and wavelength shift.

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