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Micellar acid–base potentiometric titrations of weak acidic and/or insoluble drugs

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Abstract: The effect of various surfactants [the cationics cetyl trimethyl ammonium bromide (CTAB) and cetyl pyridinium chloride (CPC), the anionic sodium dodecyl sulphate (SDS), and the nonionic polysorbate 80 (Tween 80)] on the solubility and ionization constant of some sparingly soluble weak acids of pharmaceutical interest was studied. Benzoic acid (and its 3-methyl-, 3-nitro-, and 4-*tert*-butyl-derivatives), acetylsalicylic acid, naproxen and iopanoic acid were chosen as model examples. Precise and accurate acid–base titrations in micellar systems were made feasible using a microcomputer-controlled titrator. The response curve, response time and potential drift of the glass electrode in the micellar systems were examined. The cationics CTAB and CPC were found to increase considerably the ionization constant of the weak acids (ΔpK_a ranged from −0.21 to −3.57), while the anionic SDS showed negligible effect and the nonionic Tween 80 generally decreased the ionization constants. The solubility of the acids in aqueous micellar and acidified micellar solutions was studied spectrophotometrically and it was found increased in all cases. Acetylsalicylic acid, naproxen, benzoic acid and iopanoic acid could be easily determined in raw material and some of them in pharmaceutical preparations by direct titration in CTAB-micellar system instead of using the traditional non-aqueous or back titrimetry. Precisions of 0.3–4.3% RSD and good correlation with the official tedious methods were obtained. The interference study of some excipients showed that a preliminary test should be carried out before the assay of formulations.

Keywords: *Potentiometric titrations in micellar media; ionization constants; micellar solubilization of acids; acetylsalicylic acid; naproxen; iopanoic acid.*

Introduction

Micelles are aggregates formed by amphiphiles (surfactants or surface-active agents) at above their critical micellar concentration (CMC). Micellar systems are classified in four categories, according to the type of the amphiphilic monomer, i.e. cationic, anionic, diionic and nonionic. These systems, often referred to as 'organized assemblies' or 'ordered media', exhibit some interesting properties; they can solubilize substances with low solubility, concentrate ions and molecules on and/or within the organized assemblies, modify equilibria and acid–base or redox properties, alter reaction rates and reaction mechanisms, enhance spectroscopic properties, and influence the stereo-selectivity of chemical processes. These aspects can be useful in quantitative analytical methods and separation procedures [1–3]. Reported analytical applications of micellar systems cover a variety of techniques: UV–vis spectrophotometry (especially on metal ions determination with dyes) [4, 5], fluorimetry [6], phosphorimetry [7, 8], chemiluminescence spectrometry [9–12], atomic absorption spectrometry [13], chromatography [14, 15], and kinetic analysis [16, 17].

The solubilization properties of micellar systems, in conjunction with their ability to cause a shift in the pK_a of weak acids has been exploited in a limited number of applications for potentiometric, visual and thermometric titrimetry [18–21]. It was suggested that micellar systems can be used for the titrimetric determination of sparingly soluble compounds instead of the non-aqueous titrimetry. However, due to the sluggish response of the glass electrode system in micellar solutions (uncertainty at the second and third decimal digit of pH value), the conventional way of continuous addition of titrant in potentiometric titrations was not recommended for accurate routine analysis [19, 20].

In this paper the effect of various types of micellar systems which include the cationics cetyl trimethyl ammonium bromide (CTAB)

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and cetyl pyridinium chloride (CPC), the anionic sodium dodecyl sulphate (SDS), and the nonionic polysorbate 80 (Tween 80) on the solubility and the ionization constant of some sparingly soluble weak acids is studied. Benzoic acid, naproxen (6-methoxy-α-methyl-2-naphthaleneacetic acid), acetylsalicylic acid and iopanoic acid (3-amino-α-ethyl-2,4,6-triiodobenzene propanoic acid) were chosen as model examples. These acids are of pharmaceutical interest and were chosen in order to examine the usefulness of micellar systems in routine pharmaceutical analysis, in which nonaqueous titrimetry is traditionally used. Some derivatives of benzoic acid (3-methyl-, 3-nitro- and 4-*tert*-butyl-) and two phenols (2-nitrophenol and 2,4-dinitrophenol) were also included in this study in order to examine any relation between structure and solubility/acidity of the acids in the presence of micelles. A microcomputer-controlled titrator, with the capability of stepwise potentiometric titrations (titrant addition after the potential has been stabilized), made feasible the performance of precise and accurate acid–base titrations in properly selected micellar systems. Finally, the applicability of direct acid–base titrations in micellar systems is shown in routine assays of aspirin and naproxen in pharmaceutical formulations (tablets). The effect of some common excipients for tablet formulation on the determinations is also presented.

Experimental

Apparatus

A microcomputer-controlled potentiometric titrator system consisting of the following commercially available units was used: (a) a multispeed burette driven by a stepper motor (Sargent-Welch S-11120-12), (b) a digital electrometer (Orion 801 pH/mV-meter) equipped with a combination glass electrode (Metrohm 9100), and (c) an eight-bit microcomputer (Amstrad CPC-6128).

Some modifications were made in order (a) to increase the display frequency of the digital pH/mV-meter, and (b) to allow the control of the burette by the microcomputer. A brief description of these modifications and the interface circuitry can be found elsewhere [17, 22].

A double-walled 50-ml beaker thermostatted at 25 ± 0.2°C with continuous magnetic stirring was used as titration cell. The glass electrode was stored in 0.01 M HCl solution when not in use.

For the solubility studies a double-beam UV–vis spectrophotometer (Hitachi 2000) was used for the determination of dissolved acids in aqueous and micellar media.

Brief description of the software. The control program was written in BASIC. This program allows: (a) a fast two-point calibration of the electrometer over the entire useful pH range, (b) the titration and the automatic location of the end-point, (c) the evaluation of the pK_a of the titrated weak acid or base, and (d) the creation of files of the titrations data in magnetic disks and hard copies of the titration curves for general archival purposes. The titration curve is displayed on the computer screen during the titration.

The addition of the titrant in constant volume increments (doses) was preferred over the variable volume increments commonly used with the commercial titrators (e.g. based on the algorithm developed by Christiansen *et al.* [23]). This titration mode was found to be less influenced by the occasionally observed sluggish response of the glass electrode, it was also the most suitable for the collection of data required for the calculation of the pK_a values of the titrated acid or base. The commonly used smoothing techniques for signals collected as equidistant points could also easily be applied. The volume of each dose is selected by the operator, and it is a compromise between the precision required and the overall duration of the titration.

The delivery of each dose of the titrant is followed by collecting a number (5–10) of consecutive readings of pH and calculation of the standard deviation (SD) regarded as a measure of the potential stability. If SD exceeds a preset value (typically 0.005 pH unit) this sequence is repeated, otherwise the mean pH value is stored and the next dose of the titrant is delivered. If the required stability cannot be achieved after a predetermined number of consecutive trials, a warning message is issued to the operator. In this case the titration may resume by either reducing the stability requirements or by manual control of the delivery of each dose.

From the stored data the first derivative of the titration curve is calculated using the Savitzky–Golay polynomial smoothing technique [24]. The maximum $(dpH/dV)_i$ is located

and the exact equivalent point is calculated by interpolation, taking in consideration this point and the two surrounding points.

Reagents

The surfactants and the weak acids were used as obtained without any further purification and deionized-distilled water was used throughout.

Surfactants. Cetyl trimethyl ammonium bromide (CTAB, crystalline, approx. 99%) and polysorbate 80 (Tween 80, syrup $M_r \approx 1300$) were obtained from Serva; cetyl pyridinium chloride (CPC, crystalline, pure) and sodium dodecyl sulphate (SDS, solid, approx. 99%) were obtained from Sigma. Stock solutions (0.10 M) of the surfactants were prepared in water. These solutions were stable for several weeks. Since crystals are formed in the CTAB stock solution at temperatures below 20°C, this solution has to be warmed up to 25°C before use. Working 0.050 M surfactant solutions in water and 0.10 M HCl were prepared.

Weak acids. Benzoic acid, 3-methylbenzoic acid, 3-nitro-benzoic acid, 4-*tert*-butyl-benzoic acid, 2-nitrophenol, and 2,4-dinitrophenol were obtained from Merck. Acetylsalicylic acid, naproxen and iopanoic acid were obtained from local manufacturers and their purity was determined using the official methods described in the USP XXII monographs. For the solubility studies by spectrophotometric means, working solutions in the appropriate concentration range in 0.10 M HCl (0.10 M NaOH for 2,4-dinitrophenol and methanol for iopanoic acid) in the absence and in the presence of each surfactant (0.050 M) were prepared using 1000 mg l^{-1} stock solutions of each acid. The stock solutions of the acids were prepared by dissolving the appropriate amount of acid and adding the least necessary amount of NaOH to facilitate their dissolution.

NaOH standard solutions. A 0.1000 or 0.01000 M standard solution was used.

pH calibration solutions. A potassium hydrogen phthalate solution (pH 4.01 at 25°C) and a phosphate buffer solution (pH 6.86 at 25°C) were used for the calibration of the pH-meter.

Procedures

Determination of apparent ionization constants in micellar systems. A 2.5-mmol amount of each weak acid was dissolved in 500 ml volume of 0.010 M solution of each surfactant. The rapid dissolution of the acid was achieved using an ultrasonic bath. A 50.00 ml aliquot of this solution was titrated with the 0.1000 M NaOH standard solution. From the stored titration curve the equivalent volume (V_{eq}) is calculated, and all pH_i–V_i data of the titration curve, within the pH range $pH_{1/2} - 0.5$ to $pH_{1/2} + 0.5$ ($pH_{1/2}$ is the pH corresponding to the half-neutralization point), were fitted by linear least-squares regression analysis to the simplified form of the Henderson–Hasselbalch equation

$$pH_i = pK'_a + \log \left[\frac{b + [H^+] - [OH^-]}{c - b - [H^+] + [OH^-]}\right]_i \approx pK'_a + \log \frac{V_i}{V_{eq} - V_i}, \quad (1)$$

where K'_a is the apparent ionization constant ($K'_a = \alpha_{H^+}[A^-]/[HA] = K_a f_{HA}/f_{A^-}$), b is the stoichiometric concentration of the conjugate base formed from reaction between the acid HA and the titrant of V_i volume, and c is the initial concentration of acid corrected for the dilution by the titrant at each point. The intercept of this fitting is pK'_a while the slope must be unit.

Solubility studies. An excess amount of each acid, finely pulverized, was dispersed in 100 ml of each one of the following solutions: H_2O, 0.10 M HCl, 0.050 M CTAB, 0.050 M CTAB in 0.10 M HCl, 0.050 M CPC, 0.050 M CPC in 0.10 M HCl, 0.050 M SDS, 0.050 M SDS in 0.10 M HCl, 0.050 M Tween 80, and 0.050 M Tween 80 in 0.10 M HCl. The dissolution was assisted using ultrasonic bath and after 12 h at 25°C clear saturated solutions were obtained by filtration through filter paper (Whatman No. 42). The concentration of each acid in the saturated solutions was determined spectrophotometrically at the wavelength of maximum absorbance after the appropriate (extensive) dilution in the suitable medium (0.10 M NaOH for 2,4-dinitrophenol, methanol for iopanoic acid and 0.10 M HCl for the rest acids). In each case, the corresponding solvent system diluted in the same way as the measured filtrate was used to correct any absorbance of

the surfactant (especially that of CPC with a molar absorptivity of about 4.1×10^3 M^{-1} cm^{-1} at 259 nm) and as a solvent to prepare working standard solutions of each acid studied for the construction of a calibration curve.

Automated titrations of pharmaceuticals. An appropriate, accurately weighed amount of the homogenized powder of raw material or solid formulation (tablets), equivalent to about 1–2 mmol of the drug was transferred in 500 ml of 0.010 M CTAB. After the complete dissolution, assisted by sonication, a 50.00 ml-aliquot of the sample solution was titrated with 0.1000 M NaOH solution as described in the software section. In the case of tablets, undissolved excipients may remain or an excipient-surfactant coagulate may settle.

Results and Discussion

Study of glass electrode characteristics in micellar systems

In order to examine the ability of the combination glass electrode to follow accurately and rapidly pH changes in micellar systems, its characteristics (response curve, response time and drift) were examined. The response curves ($E_{cell} = E' + S\log C_{H^+}$) obtained by measuring the electrode potential after the stepwise addition of microamounts of a 0.1000 M HCl solution in 0.010 M micellar solutions and in water for comparison are shown in Fig. 1. The linearity of the response curves in the C_{H^+} range 3×10^{-4}–2×10^{-3} M (nominal pH range 2.7–3.5) is excellent in all cases (r ranged from 0.99992 in CTAB to 0.999 in SDS and Tween). The differences in the values of E′ and slope S, appeared in micellar systems in comparison with water, should be attributed to the following interactions of the various types of micelles and the ions participating in the development of the electrode potential: (1) Binding of the cations of H_3O^+ and Na^+ (from the hydrated gel layer of glass electrode) by the anionic and nonionic micelles, and of the anions OH^- and Cl^- (from HCl) by the cationic micelles. (2) Effect of micelles on the junction potential of the electrode system. (3) Effect of monomers and micelles of the surfactants on the ionic strength and thus to the activity of H_3O^+ ion. (4) Effect of H_3O^+ and Cl^- ions on the CMC of each surfactant and thus to the micellar volume of the solution.

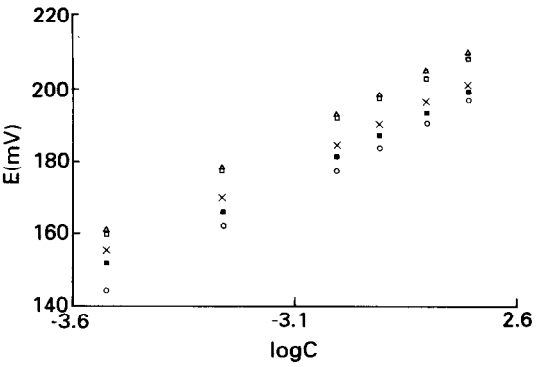

Figure 1
Response curves of the combination glass electrode in 0.010 M surfactant solutions obtained in the range of 3×10^{-4}–2×10^{-3} M HCl at 25°C. Type of surfactant and equation of response curve (±SD): (1) no surfactant (×), $E = 351.8 + 55.8\log C_{HCl}$, $r = 0.99992$; (2) CTAB (■), $E = 355.2 + 57.8\log C_{HCl}$, $r = 0.99992$; (3) CPC (○), $E = 367.6 + 63.3\log C_{HCl}$, $r = 0.9997$; (4) SDS (□), $E = 365.1 + 57.9\log C_{HCl}$, $r = 0.999$; (5) Tween (Δ), $E = 372.1 + 59.8\log C_{HCl}$, $r = 0.999$.

The response time (t_{95}) of the electrode was measured for a concentration change of 9.0×10^{-4} M HCl (caused by the rapid injection of 50 μl of 0.9 M HCl in 50.0 ml of water or 0.010 M solution of surfactant), with an initial concentration of 1×10^{-4} M HCl at 25°C and the maximum stirring rate free of vortex bubbles. Generally, the glass electrode responded faster in cationic micellar systems than in the anionic SDS and much faster than the nonionic Tween 80. The drift of the electrode was also found much less in micellar systems than in water. The static and dynamic characteristics of the glass electrode in the micellar systems are summarized in Table 1.

From these studies it is concluded that the cationic CTAB micellar system is the most suitable for pH monitoring using the glass

Table 1
Response time and potential drift characteristics of the glass electrode in micellar systems

Micellar system*	t_{95}† (s)	ΔE‡ (mV)	Drift (mV min^{-1})§
CPC	9	54.2	0.07
CTAB	10	71.3	0.10
SDS	10	52.9	0.13
Tween 80	13	55.3	0.07
(H_2O)	18	58.3	0.31

*0.010 M.
†For $\Delta C = 9 \times 10^{-4}$ M at an initial HCl concentration $C_0 = 1 \times 10^{-4}$ M.
‡Potential jump at infinitive time.
§For a period of 5 min in 0.01 M succinate buffer pH 5.4.

electrode, followed by the anionic SDS and the cationic CPC. Problems caused by the sluggish response were considerably alleviated by the selected titration mode. Albeit the poor electrode characteristics in some of the micellar systems, the saturation of the micelles with the acid species and the formation of a buffer system during titration, improves considerably the characteristics of the electrodes. Therefore, all the micellar systems were used in the following study of the effect of micelles on the ionization of weak organic acids.

Study of the effect of micelles on the ionization of the acids

The results obtained from the titrations of the various weak acids in the four micellar systems are summarized in Table 2. Their ionization constants in water, K_a^w, given for comparison, were obtained from various bibliographic sources. In all cases shown, the plot of pH_i vs $\log [V_i/(V_{eq} - V_i)]$ in the range of ± 0.5 pH unit around the pH at half-neutralization point was linear (r ranged from 0.99 to 0.999). The slope ranged from 0.89 to 0.99, showing a general validity of the simplified form of equation (1). The within-run standard deviation (SD) of the intercept of the plot of equation (1) ranged from 0.001 to 0.007. The between-run standard deviation of pK_a^m found for benzoic acid was 0.3 (three titration experiments). The time required for a typical titration experiment of a 0.25 mmol of acid with 0.1000 M NaOH was about 10 min because of the imposed strict pH stability criterion.

From the results shown in Table 2 the following conclusions can be obtained:

(1) In all cases the cationic micelles cause an increase of ionization (negative ΔpK_a) resulting in a more abrupt pH change in the equivalence region. This is in accordance with the theory that the anionic species of the acid are bound to the cationic micelles by electrostatic forces shifting the equilibrium $HA \rightleftharpoons A^- + H^+$ to the right. The two cationic micellar systems behave identically, albeit the CPC shows a greater effect in the cases of 2-nitrophenol and naproxen. It is noticeable the drastic effect on the ionization of 4-*tert*-butyl-benzoic acid of both cationic micelles. No general correlation was observed between ΔpK_a caused by the cationic surfactants, and the lipophilicity of the organic acids.

(2) The anionic SDS had a rather negligible effect on the ionization. The noticeable decrease of ionization shown in the case of naproxen may be attributed to the increased binding of the undissociated acid to the SDS micelles.

(3) The nonionic Tween 80 generally decreased the ionization due to the increased binding of the undissociated species of the acids to the micelles. This effect was greater in the case of iopanoic acid, the undissociated species of which seems to bind strongly with the micelles. A noticeable exception was observed in the case of 4-*tert*-butyl-benzoic acid.

Berezin and co-workers [26, 27] derived the following equation to describe the influence of micelles on ionization constant:

$$K_a^m = K_a^w \frac{1 + K_{A^-} C_m}{1 + K_{HA} C_m}, \qquad (2)$$

Table 2
Effect of micellar systems on the experimental ionization constants of the weak acids*

Acid	pK_a^w	ΔpK_a†			
		CTAB	CPC	SDS	Tween
Benzoic	4.20	−0.56	−0.46	−0.19	+0.40
3-Methyl-benzoic	4.27	−0.67	−0.63	NSD	+0.75
3-Nitro-benzoic	3.47	−0.38	−0.26	NSD	+1.55
4-*tert*-butyl-benzoic	6.90‡	−3.41	−3.57	NF	−1.05
2-Nitro-phenol	7.04	−1.44	−2.37	+0.16	+0.39
Acetyl-salicylic	3.82	−0.21	−0.23	−0.14	+0.15
Naproxen	4.15	−0.08	−0.25	+1.02	+1.66
Iopanoic	4.80	−0.91	−0.74	NF	+2.08

* At 25°C in the presence of 0.010 M surfactant ($n = 3$).
† $\Delta pK_a = pK_a^m - pK_a^w$; NSD: not significant difference ($\Delta pK_a < 2$ SD); NF: not feasible due to low solubility of the acid in the surfactant.
‡ Ref. 25.

where K_{A^-} and K_{HA} are the binding constants of the anion and acid species, respectively, to the micelles and C_m is above the CMC concentration of the surfactant. These binding constants are defined as: $K_{A^-} = [1 - ([A^-]_m/[A^-]_w)]\bar{V}$ and $K_{HA} = [1 - ([HA]_m/[HA]_w)]\bar{V}$, where $\bar{V}$ is the molar volume of the surfactant. The ionization increases when $K_{A^-} > K_{HA}$, a situation appeared in the case of the cationic micelles. Figure 2 shows the effect of the concentration of CTAB on the K_a^m of benzoic acid. By applying a non-linear least-squares fitting of the experimental data to equation (2) values of 1.06 ($\pm$0.12) $\times 10^3$ M^{-1} and 0.118 ($\pm$0.034) $\times 10^3$ M^{-1} ($r = 0.991$) were calculated for K_{A^-} and K_{HA}, respectively.

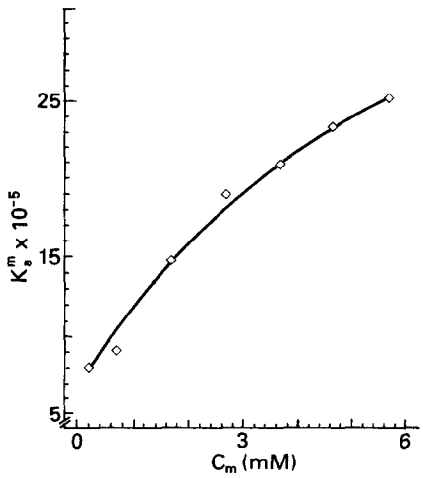

Figure 2
Effect of the micellar concentration of CTAB (C_{CTAB} – CMC_{CTAB}) on the ionization constant of benzoic acid at 25°C.

Study of micellar solubilization of the acids

The UV-spectroscopic characteristics (λ_{max} and molar absorptivity, ϵ) of each organic acid were determined experimentally in 0.10 M HCl solutions (0.10 M NaOH for 2,4-dinitrophenol and methanol for iopanoic acid) in order to maintain the acid in only one form (Table 3). Because of the extensive dilution of the measured filtrate these characteristics remained practically unchanged in the presence of the various surfactants.

The enhanced solubility of the organic acids in micellar solutions is generally attributed to: (a) the distribution of the undissociated species of the organic acids in the micellar pseudophase and (b) their apparent increased ionization. In order to differentiate the effect of these two processes the solubilities (S, in g l^{-1}) were determined in water (S_w), in micellar solutions (S_m), and in acidified water (S_{w,H^+}), and in acidified micellar solutions (S_{m,H^+}). The S_{m,H^+} values are indicative of the solubility enhancement due to the distribution in the micellar pseudophase, while in S_m values the

Table 3
Effect of micellar systems on the solubility (g l^{-1}) of the acids* and spectroscopic characteristics of the acids found in the solubility study

Acid	λ_{max} (nm) / $\epsilon(\times 10^3)(M^{-1}\ cm^{-1})$	$S_w/S_{w,H^+}$	$S_m/S_{m,H^+}$ CTAB	CPC	Tween	SDS
Benzoic	230†	3.4	9.7	10.6	10.6	6.2
	7.3	3.1	5.9	9.2	11.4	6.1
3-Methyl-benzoic	234†	0.89	2.4	4.8	4.2	2.6
	10.0	0.68	1.9	2.5	3.6	1.6
3-Nitro-benzoic	262†	3.4	7.0	13.8	11.5	5.6
	4.6	3.1	6.4	8.6	11.2	4.6
4-*tert*-butyl-benzoic	241†	0.034	1.41	2.3	2.1	0.75
	21.8	0.021	2.7	1.8	1.9	0.62
2,4-Dinitro-phenol	256‡	0.47	1.21	3.2	1.9	0.90
	4.8	0.30	1.30	5.0	1.64	0.41
Acetyl-salicylic	228†	4.0	9.0	9.0	7.6	7.1
	6.6	3.9	8.1	7.5	8.1	5.8
Naproxen	332†	0.046	3.2	3.2	1.7	0.99
	1.6	0.031	3.0	3.0	1.4	0.63
Iopanoic	230§	<0.0001	5.2	6.0	7.1	0.22
	39.5	NM	4.0	5.3	5.2	0.44

*At 25°C in the presence of 0.050 M surfactant; average of three measurements on a single saturation experiment. Between-run precision, tested for 4-*tert*-butyl-benzoic acid, was 5% ($n = 3$). NM: not measurable.
†In 0.10 M HCl, ‡in 0.10 M NaOH, §in methanol.

effect of micelles on the ionization of the acid is encountered. The solubilities (g l^{-1}) found are shown in Table 3.

The most pronounced increase in solubility was noticed in the cases of iopanoic acid and 4-*tert*-butyl-benzoic acid. The most pronounced increase was caused by the cationic CTAB and the least one by the anionic SDS. In the case of iopanoic acid the S_m/S_w was greater than 5×10^4 (in CTAB), 6×10^4 (in CPC), 7×10^4 (in Tween) and 0.2×10^4 (in SDS). The applicability of a micellar titration can be predicted by inspection of the solubility S_m.

The solubilization effect for simple (one species) compound has been described by the equation [26]:

$$S_m/S_w = 1 + K\,C_m, \qquad (3)$$

which is valid for C_m close to CMC. Figure 3 shows the effect of micellar concentration of CTAB on the solubility ratios of 4-*tert*-butyl-benzoic acid. For CTAB concentrations close to its CMC the experimental data gave the equations $S_{m,H^+}/S_{w,H^+} = 1.33 + 6.58\ (\pm 0.17) \times 10^3\ C_m$ ($r = 0.998$) and $S_m/S_w = 6.3 + 3.17\ (\pm 0.29) \times 10^3\ C_m$ ($r = 0.996$).

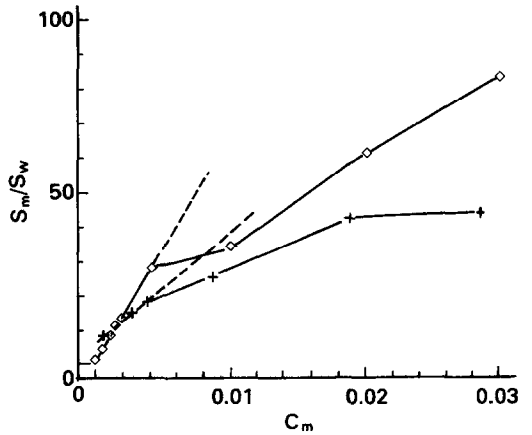

Figure 3
Solubilization effect of micellar concentration of CTAB on 4-*tert*-butyl-benzoic acid in (a) acidified (0.10 M HCl) (◇) and (b) aqueous solutions at 25°C (+).

This solubility study revealed the following:

(1) The solubility of the organic acids increased in all micellar systems. CPC in most cases is a more efficient solubilizing agent than the widely used CTAB. The non-ionic Tween, although not affecting the apparent ionization of the acids, showed a considerable solubilizing effect. The anionic SDS showed in general the weakest solubilizing effect.

(2) The S_{m,H^+} values were generally less than S_m values. In several cases, such as for 4-*tert*-butyl-benzoic acid, the $S_{m,H^+}/S_{w,H^+}$ ratio was greater than S_m/S_w ratio. This may be attributed to the decrease of the CMC of the surfactant consequently increasing of the micellar concentration. For example, the CMC of CTAB was found 1.3×10^{-3} M and 1×10^{-6} M in aqueous and 0.1 M HCl, respectively.

(3) The most pronounced solubilization effect (in both aqueous and acidified solutions) was noticed in the cases of iopanoic acid, 4-*tert*-butyl-benzoic acid and naproxen, probably attributed to their higher lipophilic character. Generally, no correlation was observed between the solubility ratio S_m/S_w and ΔpK_a (Table 2) or the lipophilicity of the organic acids. The latter was expressed in terms of the logarithm of the partition ratio in the decanol–water system, log P.

Automated titrations of pharmaceuticals

The usefulness of the proposed stepwise potentiometric micellar titrations of weak and sparingly soluble organic acids in routine pharmaceutical analysis was evaluated by analysing raw material and commercial formulations of acetylsalicylic acid, naproxen and iopanoic acid. The obtained analytical results are summarized in Table 4. As shown precisions in the range of 0.3–4.3% RSD and good comparison with the tedious official methods have been obtained. Although CTAB was not the most efficient solubilizing agent in all the cases of the acids, it was selected as a general surfactant for titrations because of the better precisions obtained.

In order to examine the effect of some common excipients used in the formulation of tablets, recovery experiments were carried out using synthetic mixed solutions of acetylsalicylic acid with various excipients in 0.010 M CTAB. The results are shown in Table 5. No interference was found in the cases of sorbitol, lactose, cellulose acetate hydrogen phthalate and sucrose. In the presence of magnesium stearate, starch and acacia at relatively high concentrations, a precipitate is formed which interferes at varying degree with the determination.

The solubilization of the drugs along with the increase of their ionization, make the

Table 4
Application of micellar titrations for the determination of drugs in raw materials and commercial formulations

	Nominal content	Proposed method	Official method*	*t*-test†
Acetylsalicylic acid				
Raw material (% w/w ± SD)	100	100.4 ± 0.3 (n = 3)	100‡	—
Aspirin tablets (mg tablet^{-1} ± SD)	500	497 ± 2 (n = 3)	489 ± 6 (n = 3)	2.27
Naproxen				
Raw material (% w/w ± SD)	100	98 ± 2 (n = 3)	100.9 ± 0.2 (n = 3)	2.00
Naprosyn tablets (mg tablet^{-1} ± SD)	250	254 ± 11 (n = 3)	240 ± 3 (n = 3)	2.13
Benzoic acid				
Raw material (% w/w ± SD)	100	99.5 ± 0.5 (n = 3)	100‡	—
Iopanoic acid				
Raw material (% w/w ± SD)	100	99.6 ± 1.5 (n = 3)	100‡	—

*Potentiometric acid–base back titration for acetylsalicylic acid raw material and UV spectrophotometry after column chromatography separation for aspirin tablets (USP XXI); potentiometric titration in 75% methanol for naproxen raw material and UV spectrophotometry for naprosyn tablets (USP XXI); titration with NaOH in alcohol for benzoic acid (USP XXII); titration of iodide with $AgNO_3$ after refluxing with powdered zinc for iopanoic acid (USP XXII).
†t theoretical, for 95% confidence interval, is 2.78 for 4 degrees of freedom.
‡Determination performed by the manufacturer.

Table 5
Effect of excipients on the micellar titration of acetylsalicylic acid (0.72 g l^{-1})

Excipient	Excipient–drug ratio (m/m)	Recovery (%)
Sorbitol	2.5	100
Lactose	2.5	102
Sucrose	2.5	99
Cellulose acetate hydrogen phthalate	2.5	100
Saccharin sodium	2.5	98
Magnesium stearate*	2.5	91
Starch*	2.5	66
	0.5	97

*Precipitation occurs.

cationic micellar systems a preferable medium for titrations of acidic drugs in raw material instead of non-aqueous media. In order to apply the micellar titrimetric method for assays in formulations, a preliminary interference test by the excipients at the concentrations used in the formulation is necessary.

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