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Selective Determination of Papaverine by Thermochromism after Solvent Extraction

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A new application of tetrabromophenolphthalein ethyl ester is reported for the determination of papaverine. The method is based on solvent extraction and utilization of the thermochromism of a red-colored charge transfer complex (TBPE·H·papaverine). Papaverine can be determined successfully and selectively even in the presence of quaternary ammonium salts by using the thermochromism caused by a temperature change in an organic solvent (1,2-DCE). A linear plot was obtained in the concentration range $(1—5)\times 10^{-5}$ M papaverine in the initial aqueous solution, with $\Delta A/\Delta t$ as the ordinate and the concentration as the abscissa.

Keywords——thermochromism; solvent extraction; spectrophotometry; tetrabromophenolphthalein ethyl ester; papaverine

Introduction

Tetrabromophenolphthalein ethyl ester (TBPE) shows high sensitivity to quaternary ammonium cations and amines,[2,3] but a quaternary ammonium salt complicates amine determination because the absorption spectra overlap each other. The absorbance of the amine in 1,2-dichloroethane (1,2-DCE), however, decreases nearly to zero when the temperature is increased from 25° to 60°. Thus, the quaternary ammonium cation can be determined successfully in the presence of amines.[4] On the other hand, as the rate of decrease of the absorbance with temperature change ($\Delta A/\Delta t$) is proportional to the concentration of the amine in the aqueous phase and the $\Delta A/\Delta t$ value is little affected by the presence of any quaternary ammonium cation, the amine can also be determined in the presence of quaternary ammonium salts. The tertiary amine diphenhydramine can be determined by the application of this phenomenon.[5]

This paper describes the extraction and selective spectrophotometric determination of papaverine. Papaverine gave a somewhat larger coefficient of variation and a better recovery rate than diphenhydramine.

This method shows good sensitivity and selectivity, though nonaqueous titrimetric[6] and ultraviolet (UV) spectrophotometric methods[7] have also been reported.

Experimental

Apparatus——A Hitachi 556 double-beam spectrophotometer with a temperature-controlled cell holder was used to measure absorbances at constant temperature using 1 cm quartz cells with stoppers. A Hitachi 057 X-Y recorder was used for the spectra. Constant cell temperature was maintained by circulating water through the temperature-control cell holder with a Komatsu-Yamato CTA-240 temperature-control circulator.

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[2] T. Sakai, *Bunseki Kagaku*, **24**, 135 (1975).
[3] T. Sakai and M. Tsubouchi, *Chem. Pharm. Bull.* (Tokyo), **24**, 2883 (1976).
[4] T. Sakai, *J. Pharm. Sci.*, **68**, 875 (1979).
[5] T. Sakai, N. Ishida, and S. Tsurubo, *Bunseki Kagaku*, **28**, 303 (1979).
[6] "The Japanese Pharmacopoeia," IX, Hirokawa Publishing Co., Tokyo, 1976, C-431.
[7] F.E. Kagan and L.O. Kivichenko, *Farm. Zh.*, **28**, 34 (1973) [*Chem. Abstr.*, **80**, 100245*d* (1974)].

The solvent temperature in the cell was checked by dipping the thermoelement of an Anritsu HP-4F thermometer into the solvent. A pH meter, a shaker, and a centrifuge were also used.

Reagent——Standard Papaverine Solution: A stock solution of 5×10^{-3} M papaverine was prepared by dissolving 1.8795 g of papaverine hydrochloride in distilled water and diluting to 1 liter with distilled water. The solution was used after accurate dilution.

Tetrabromophenolphthalein Ethyl Ester Solution: A 4.0×10^{-3} M solution of tetrabromophenolphthalein ethyl ester was prepared by dissolving 0.2800 g of tetrabromophenolphthalein ethyl ester potassium salt in ethanol to give 100 ml.

Buffer Solution (pH 8.5): Borate-phosphate buffer was prepared by adding 1 N NaOH to 0.3 M potassium dihydrogen phosphate containing 0.1 M sodium borate.

1,2-Dichloroethane was used as an extractant. All reagents used were of reagent grade.

Recommended Procedure——Papaverine solution, 1—5 ml (5×10^{-4} M), 2 ml of tetrabromophenolphthalein ethyl ester (4×10^{-3} M), and 10 ml of borate-phosphate buffer (pH 8.5) were pipetted into a 100-ml separator. The mixture was diluted with water to 50 ml and shaken mechanically with 10 ml of 1,2-DCE for 5 min. The organic layer was transferred into a stoppered test tube and centrifuged to remove water droplets. The absorbance (572 nm) of the organic phase was measured at 25° in the temperature-controlled cell holder against a reagent blank or water. The temperature was raised to about 60° with the cell in the holder, and the absorbance of the same phase was measured.

Results and Discussion

Extraction Conditions

In the absence of papaverine, TBPE molecules (yellow color) were extracted into 1,2-DCE, while in its presence a reddish compound was formed. The absorption maximum was at 572 nm, the apparent molar absorptivity being 3.8×10^3 mol^{-1} cm^{-1} l. TBPE showed maximum and constant absorbance as a 1.6×10^{-4} M aqueous solution. Extraction was carried out at pH 8.5. Shaking for 5 min was sufficient to complete the extraction.

Thermochromism of the Ion Associate and Charge Transfer Complex with TBPE

The absorption spectra of the TBPE$^-$-R_4N ion associate (R_4N: berberine, benzalkonium, sparteine) and the TBPE·H·papaverine complex in 1,2-DCE were examined at various temperatures. It was found that the absorption spectra of the ion associates were scarcely affected by temperature. The slight decrease in absorbance with rise in temperature was due to the expansion of 1,2-DCE. On the other hand, the TBPE·H·papaverine complex (red color) in 1,2-DCE was greatly influenced by temperature. When the temperature was increased, the absorbance at 572 nm decreased and the absorbance at 410 nm increased.

This is summarized in Chart 1.

Table I. $\Delta A/\Delta t$ Value for Each Concentration of Papaverine

Conc. of papaverine $\times10^{-5}$ M	Absorbance at 25°	Absorbance at 59°	$\Delta A/\Delta t$, $\times10^{-3}$ $\Delta t=34°$
1	0.220	0.064	4.59
2	0.374	0.087	8.44
3	0.539	0.112	12.56
4	0.707	0.144	16.56
5	0.893	0.190	20.68

Ref.: water.

$$\underset{\text{(red)}}{\text{TBPE}\cdot\text{H}\cdot\text{papaverine}} \underset{\text{cool}}{\overset{\text{warm}}{\rightleftharpoons}} \underset{\text{(yellow)}}{\text{TBPE}\cdot\text{H}} + \text{papaverine}$$

Chart 1

Calibration Curve

A linear plot was obtained in the concentration range $(1-5)\times10^{-5}$ M papaverine in the initial aqueous solution, with $\Delta A/\Delta t$ as the ordinate and the concentration of papaverine as the abscissa. Δt is the difference in temperature between 25° and the elevated temperature. ΔA is the difference in absorbance between 25° and the elevated temperature. $\Delta A/\Delta t$ for 2×10^{-5} M papaverine was 8.44×10^{-3}, and the coefficient of variation was 0.5% (diphenhydramine, 1.5%[5]). The ion associate of papaverine is very stable. Table I shows $\Delta A/\Delta t$ values for various concentrations of papaverine.

Effect of Quaternary Ammonium Salts in the Determination of Papaverine

The effect of quaternary ammonium salts (berberine and sparteine) was examined using both the ordinary TBPE method and the thermochromism method, and the results are shown in Table II. It is clear that sparteine and berberine interfere strongly with the TBPE method (Recovery I in the table). In addition the recovery obtained by the thermochromism method is better than that by the TBPE method, because the $\Delta A/\Delta t$ value for a mixture of papaverine and any salt depends on papaverine alone. However, the effect of quaternary ammonium salts on the $\Delta A/\Delta t$ value of the mixture differs with different amines. For example, the magnitude of the effect decreases in the order ephedrine, dibucaine, diphenhydramine and papaverine, and so papaverine has the best recovery.

TABLE II. Effect of Salts in the Determination of Papaverine

Conc. of papaverin, M	Added		Absorbance at 25°	Recovery(I) at 25°, %	$\Delta A/\Delta t$, $\times10^{-3}$	Recovery by this method, %
	R_4N	Conc., M				
1×10^{-5}	Spar.	5×10^{-7}	0.288	130	4.62	101
		1×10^{-6}	0.372	169	4.53	99
2×10^{-5}	Spar.	2.5×10^{-7}	0.414	111	8.56	101
		5×10^{-7}	0.451	121	8.50	101
	Ber.	5×10^{-7}	0.440	118	8.26	98
		1×10^{-6}	0.555	148	8.35	99
4×10^{-5}	Spar.	2.5×10^{-7}	0.725	103	16.38	99
		5×10^{-7}	0.767	108	16.29	98
	Ber.	2.5×10^{-7}	0.724	102	16.18	98

Spar.: sparteine. Ber.: berberine.
Sparteine, though it is not a quaternary ammonium salt, gives a blue color with TBPE in 1,2-DCE.
$\Delta t=34°$.

Analysis of Practical Samples

Samples containing papaverine (7.52 mg) and methylscopolamine (0.797 mg) were analyzed by the proposed method. Methylscopolamine showed some interference at 25° (recovery, 150%), but this could be suppressed by the application of the thermochromism technique. The result obtained was 7.60 mg papaverine and the recovery was 101%. The present thermochromism method thus appears to be more selective and sensitive than other methods of determining papaverine.

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