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Ion-pair formation of Bi(III)–iodide with some nitrogenous drugs and its application to pharmaceutical preparations

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Abstract

A systematic spectrophotometric study on the ion-pair formation of Bi(III)–iodide with amineptine hydrochloride, piribedil and trimebutine maleate is carried out. The optimal experimental conditions pH, concentration of Bi(III) nitrate, potassium iodide; and the nature and amount of organic solvent have been studied. The ion pairs are soluble in 1,2-dichloroethane and the optimum pH range is 2.0–2.8. By application of the methods of Sommer and Job involving non-equimolar solutions, the conditional stability constant (log K') of the Bi(III)–piridedil ion pair (1:1) at the optimum pH of 2.4 and an ionic strength (μ) 0.1 M, was found to be 5.436. The validity of Beer's law has been tested in the concentration range 5–50 μg ml^{-1} in the organic layer, the relative standard deviation is less than 1%. The method is applied to the determination of these drugs in tablets without interference. © 1998 Elsevier Science B.V.

Keywords: Bi(III)–iodide; Amineptine hydrochloride; Piribedil; Trimebutine maleate; Spectrophotometry; Ion pairs; Tablets

1. Introduction

Amineptine, 7 - [(10,11 - dihydrodibenzo[a,d]cyclohepten-5-yl)amino]heptanoic acid, is a potent dopaminergic antidepressant [1] characterized by a stimulant clinical effect [2,3]. Only a few chromatographic methods for its assay in biological samples have been described [4–6].

Piribedil, 2 - (4 - piperonyl - 1 - piperazinyl)pyrimidine has vasodilatory activity [7]. Methods for the analysis of piribedil or its basic metabolites in biological specimens have used gas chromatography with a nitrogen-sensitive detector [8] or combined with mass spectrometry [9] and HPLC [10].

Trimebutine, 2-dimethylamino-2-phenylbutyl 3,4,5-trimethoxybenzoate, is an antispasmodic compound used in various gastrointestinal diseases and in radiological examinations [11]. Only an HPLC method [12] has been used for the assay of trimebutine in human plasma.

Methods for the determination of the cited drugs in pharmaceutical preparations are not yet available in the literature or in pharmacopoeias.

In this paper, I propose a simple and sensitive spectrophotometric method for determining some nitrogenous drugs, based on the formation of ion-pair associates with Bi(III)–iodide complex and their extraction into 1,2-dichloroethane. The

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Table 1
Analytical data for ion pairs of nitrogenous drugs in 1,2-dichloroethane ($\lambda = 490$ nm)

Drug	Conc. range (μg ml^{-1})	Linear regression			RSD* (%)	∈ (l mol^{-1} cm^{-1})[a]
		Intercept (a)	Slope (b)	Corr. coeff. (r)		
Amineptine hydrochloride	5–40	0.001	0.0173	0.9999	0.30	6.48×10^3
Piribedil	5–40	−0.005	0.0195	0.9997	0.45	5.77×10^3
Trimebutine maleate	5–50	−0.008	0.0136	0.9998	0.40	6.71×10^3

*Relative standard deviations ($n = 6$).
[a]∈ = The apparent molar absorptivity.

proposed method has been applied to the assay of these drugs in tablets.

2. Experimental

2.1. Apparatus

A Camspec M 301 spectrophotometer with matched 1-cm quartz cells was used for absorbance measurements. A Schott Gerate CG711 pH meter with a combined glass-saturated calomel electrode was used for pH measurements.

2.2. Materials

All solutions were prepared with analytical-reagent grade chemicals and water was always doubly distilled. The studied drugs were of pharmaceutical grade.

Standard bismuth(III) solution, 0.02 M, was prepared by dissolving 0.9702 g of $Bi(NO_3)_3.5H_2O$ (Merck) in 2 ml of HNO_3 and adding distilled water to 100 ml and standardized complexometrically [13]. Potassium iodide solution, 1 M, was prepared by dissolving 16.66 g of KI (Merck) in 100 ml of water. Solutions of lower concentration were obtained by accurate dilution of these solutions with water.

The ionic strength of the final solution was kept constant at 0.1 M by adding of 1 M potassium nitrate.

2.3. Preparation of standard sample solutions

Amineptine hydrochloride stock solution, 100 μg ml^{-1}, was prepared by dissolving 10 mg of amineptine hydrochloride in 5 ml of methanol and diluting to 100 ml with water.

Piribedil or trimebutine maleate stock solution, was prepared by dissolving 50 mg of the drug in 5 ml of 0.5 M HCI and diluting to 100 ml with water. Other dilute solutions (100 μg ml^{-1} piribedil and 125 μg ml^{-1} trimebutine maleate) were made by diluting with water.

2.4. Recommended procedure

The mixture of 2.5 ml (2×10^{-3} M) of Bi(III) nitrate, 2 ml (0.3 M) of KI and 1 ml (1 M) of KNO_3 solutions were placed in a 75-ml separatory funnel. Two ml of the drug solution (in the concentration ranges cited in Table 1) were added and the pH adjusted to 2.4 by adding an appropriate amount of KOH or HNO_3 (0.1 M). The solution was completed to 10 ml with water, then 5 ml of 1,2-dichloroethane and 0.5 ml acetone were added and shaken for 1 min. The organic layer was filtered through a Whatman No. 41 filter paper and measured at 490 nm against a reagent blank prepared and treated similarly.

2.5. Analysis of Servector (amineptine hydrochloride) tablets

An accurately weighed amount of the powdered tablets equivalent to 100 mg of the drug was

transferred to a beaker and extracted with methanol, filtered through a filter paper and washed with methanol. The filtrate and washings were collected in a 50-ml standard flask and diluting to volume with methanol. A five-ml portion of this solution was transferred to a 100-ml standard flask and diluted to volume with water to obtain 100 μg ml^{-1} of amineptine hydrochloride, which was subjected to analysis by the recommended procedure.

2.6. Analysis of Trivastal (piribedil) and Debridat (trimebutine maleate) tablets

An accurately weighed amount of the powdered tablets equivalent to 50 mg of the drug was transferred to a beaker and extracted with 5 ml of 0.5 M HCl for 10 min and diluted with water. The mixture was filtered through a filter paper and washed with water. The filtrate and washings were collected in a 100-ml standard flask and diluted to volume with water. A volume of the later solution was diluted with water to obtain a solution equivalent to 100 μg ml^{-1} piribedil or 125 μg ml^{-1} of trimebutine maleate and then subjected to analysis by the recommended procedure.

3. Results and discussion

Bismuth(III)–iodide compounds have been used as reagents for the determination of some nitrogenous drugs [14–17]. The formation of the ion pair between the secondary or tertiary amine group of the drug and Bi(III)–iodide binary complex occurs via the protonated nitrogen atom of the drug.

On mixing aqueous solutions of Bi(III)–iodide complex and the cited drugs in an acidic medium, a reddish orange precipitate appears that is attributed to the ion pair formed in the reaction. The extraction of these ion pairs with different solvents was studied. Only low-polarity solvents, such as chloroform, dichloromethane and 1,2-dichloroethane selectively extract the ion pairs. 1,2-dichloroethane was chosen as the extraction solvent because of its higher efficiency and considerably lower extraction ability for the reagent blank. Addition of a small amount of acetone proved to be useful: the colour intensity of the analyte and the reagent blank increased with increase percentages of acetone in the aqueous phase, although the differences between them diminished. The ratio adopted in the described method was always $\leq 5\%$ (v/v) acetone–water.

The absorption spectrum of the ion pair in 1,2-dichloroethane was measured over the wavelength range 400–560 nm. The ion pair shows maximum absorbance at 490 nm (Fig. 1), which can therefore be used as the wavelength for the analytical determinations. The reagent blank at this wavelength has a low absorbance, all measurements were performed against a reagent blank.

3.1. Effect of pH

At $pH > 3$, there is a decrease in extraction yield with increasing pH, probably because of precipitation of bismuth as hydroxo-species. The absorbance at λ_{max} remains constant in the pH range 2.0–2.8. The pH of the solution at 2.4 was chosen for carrying out the procedure for the drug determination. As the shape of the absorption maximum does not vary with pH, it is as-

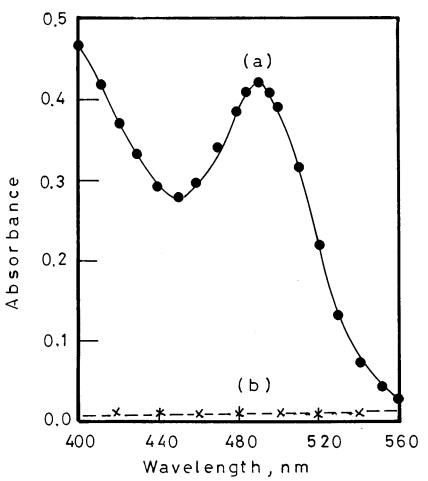

Fig. 1. (a) Absorption spectra of Bi(III)–Piriedil ion pair in 1,2-dichloroethene versus reagent blank; (b) reagent blank versus 1,2-dichloroethane, Piribedil concentration = 22 μg ml^{-1} in 1,2-dichloroethane; pH = 2.4; $\mu = 0.1$ M.

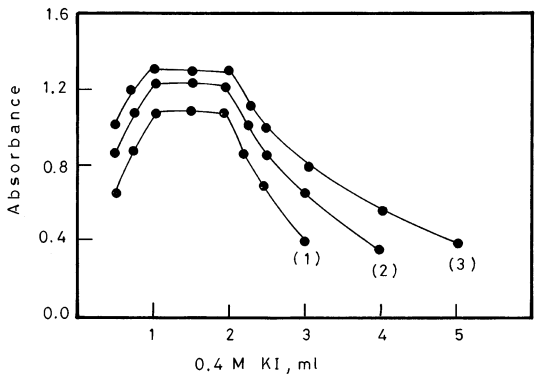

Fig. 2. Effect of KI concentration on ion-pair formation in 1,2-dichloroehtane (5 ml). (1) Piribedil; (2) Amineptine; (3) Trimebutine. $[Drug]_{aq} = 10^{-4}$ M; $[Bi(III)]_{aq} = 5 \times 10^{-4}$ M; volume of aqueous solution = 10 ml; pH 2.4; $\mu = 0.1$ M; $\lambda = 490$ nm.

sumed that in this pH range only one type of ion pair is formed. The use of a suitable buffer solution was avoided because the presence of any foreign ion could interfere with the ion-pair formation, then 0.1 M of KOH or HNO_3 was used to adjust the pH of the solution.

The effect of ionic strength (in the range 0.05–0.50 M) was found to be negligible and 0.1 M was chosen to carry out the procedure.

3.2. Optimum conditions for drug determination

Fig. 2 shows the influence of the iodide concentration on the ion-pair extraction at a constant concentration of bismuth. At the Bi concentration used, 5×10^{-4} M, the iodide concentration of 0.04–0.08 M in the aqueous phase (10 ml), was required to obtain the maximum absorbance values, then 0.06 M KI was chosen. As can be seen in Fig. 3, the ion pair was optimally extracted at a Bi concentration of 5×10^{-4} M, above which the extraction efficiency slightly decreased.

Using Dragendorf reagent solutions should be avoided because of the liberation of iodine after a short time, which interferes with the determination of the drug.

The more favourable sequence addition is bismuth(III)–KI–drug for the highest colour intensity.

The formation of the ion pairs was rapid and the absorbance readings of the 1,2-dichloroethane extracts of the associates were constant as soon as after 10 min and were stable for at least 2 h. Shaking times ranging from 0.5 to 5.0 min did not produce any change in colour intensity, and so an 1 min shaking time was selected. Consequently, the yield of a single extraction with 5 ml of 1,2-dichloroethane in optimal conditions with an organic: aqueous phase of 1:2 is practically 100%. Acetone was considered to be an ideal diluent for the extraction process, as it increases the extraction efficiency. The intensity of ion-pair extraction was stable at temperature range 20–40°C then, room temperature, 25 ± 0.5°C. was used.

3.3. Stoichiometry of the ion pair

The composition of the Bi(III)–piribedil ion pair (as example), by applying Job's method of continuous variations. The concentration of aqueous piribedil and Bi(III) nitrate solutions was 2×10^{-3} M. Nine solutions were prepared containing piribedil and Bi(III) nitrate in various molar ratios so that their volume always amounted to 2 ml with addition of 2 ml (0.3 M) KI and 1 ml (1M) KNO_3 solutions. After adjusting the pH to 2.4, the mixture was completed to 10 ml with water. The extraction was performed

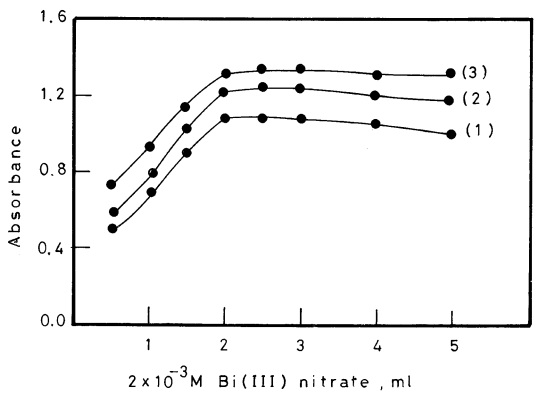

Fig. 3. Effect of Bi(III) nitrate concentration on ion-pair formation in 1,2-dichloroethane (5 ml). (1) Piribedil; (2) Amineptine; (3) Trimebutine. $[Drug]_{aq} = 10^{-4}$ M; $[KI]_{aq} =$ 0.06 M; volume of aqueous solution = 10 ml; pH = 2.4; $\mu =$ 0.1 M; $\lambda = 490$ nm.

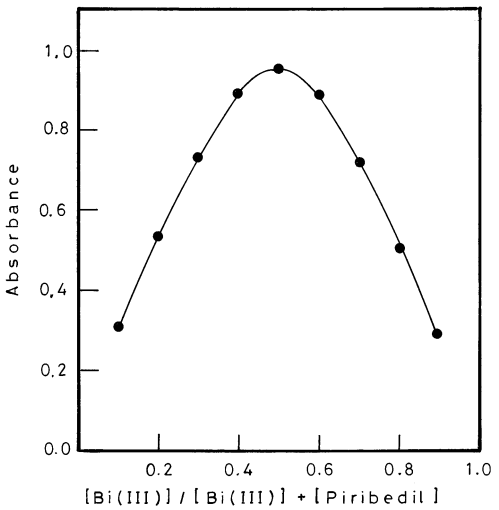

Fig. 4. Job's curve of equimolar solutions for Bi(III)–Piribedil ion-pair in 1,2-dichloroethane. [Bi(III)] + [Piribedil] = 4×10^{-4} M; pH = 2.4; $\mu = 0.1$ M; $\lambda = 490$ nm.

with 10 ml of 1,2-dichloroethane and the absorbance was measured at 490 nm. The plot reaches maximum value at a mole fraction $X_{max} = 0.5$ (Fig. 4), which indicates the formation of 1:1 ion pair.

3.4. Relative stability of the ion pair

The relative stability constant of the Bi(III)–piribedil ion pair has been determined by applying the method of Sommer et al. [18], on the basis of results obtained by Job's method for the composition of the ion pair and also by the application of Job's method of non-equimolar solutions [19] (Table 2). By Job's method of non-equimolar solutions, the curves for a five- and ten-fold excess of reagent were obtained (Fig. 5).

The conditional stability constant was then calculated in the following way:

$$K' = \frac{(P-1)(1-2X_{max})}{C_{piribedil}[(1+P)X_{max}-1]^2}$$

where $P = 5$ or 10, X_{max} is projection of the peak maximum divided by the total volume of 1,2-dichloroethane used for extraction in each case (10 ml). The values obtained by the two different methods are in good agreement.

Table 2
Conditional stability constant of the Bi(III)–piribedil ion pair

Sommer's method[a]				
log K'	log K'_{min}	log K'_{max}	SD*	RSD (%)
5.377	5.276	5.485	0.08	1.49

Job's method of non-equimolar solutions[a]			
[Bi(III)]	P	X_{max}	log K'
1.65×10^{-3}	5	0.195	5.408
1.65×10^{-3}	10	0.125	5.464
			Mean : 5.436

*$n = 5$
[a]Conditions: pH = 2.4; $\mu = 0.1$ M; temperature = 25 ± 0.5°C.

3.5. Effect of foreign ions and materials

No interferences (< 2% is considered non-interferent) were observed in the determination of the studied drugs in the presence of the common excipients of the tablets (e.g. talc, magnesium stearate, starch, lactose, glucose and sucrose).

The influence of some ions on the determination of the nitrogenous drugs was tested. The ions of Al(III), Ca(II), Mg(II) and Zn(II) did not

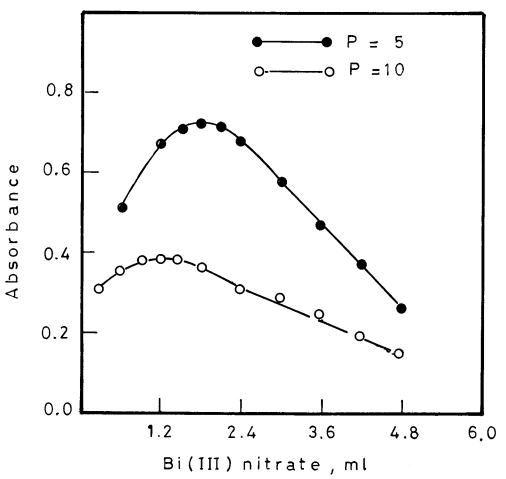

Fig. 5. Job's curve of non-equimolar solutions for Bi(III)–Piribedil ion pair in 1,2-dichloroethane, [Bi(III)] = 1.65×10^{-3} M, pH = 2.4; $\mu = 0.1$ M; $\lambda = 490$ nm.

Table 3
Precision and accuracy in the determination of pure drug

Drug	μg ml^{-1} (1,2-dichloroethane)			Confidence limits ($P = 0.05$; $n = 5$)
	Added	Found ± SD*	RSD (%)	
Amineptine hydrochloride	10	10.06 ± 0.06	0.60	10.06 ± 0.07
	20	20.10 ± 0.09	0.45	20.10 ± 0.11
	30	29.90 ± 0.07	0.23	29.90 ± 0.09
	40	39.89 ± 0.10	0.25	39.89 ± 0.12
	Mean		0.38	
Piribedil	10	10.10 ± 0.04	0.39	10.10 ± 0.05
	20	19.90 ± 0.08	0.40	19.90 ± 0.10
	30	30.05 ± 0.11	0.37	30.05 ± 0.14
	40	39.87 ± 0.09	0.23	39.87 ± 0.11
	Mean		0.35	
Trimebutine maleate	10	9.94 ± 0.07	0.70	9.94 ± 0.09
	20	20.05 ± 0.11	0.54	20.05 ± 0.14
	30	30.10 ± 0.08	0.27	30.10 ± 0.10
	40	39.95 ± 0.13	0.33	39.95 ± 0.13
	Mean		0.46	

*Average of five determinations

interfere, because they did not react with iodide to form a corresponding complex anion, but Cu(II), Hg(II), Cd(II), Pb(II), Fe(III), Ag(I), phosphates, oxalates, citrates and tartrates interfered.

3.6. Analytical data

Under the experimental conditions described for drug determination, standard calibration curves for amineptine hydrochloride, piribedil and trimebutine maleate were constructed by plotting absorbance versus concentration. Conformity with Beer's law was evident in the concentration range of the final dilution (organic layer) cited in Table 1. The molar absorptivity and the regression line equation for each drug are tabulated in Table 1. The correlation coefficients were between 0.9997–0.9999 indicating good linearity.

Table 4
Determination of the cited drugs in commercial tablets

Tablet preparation	Label claim	Taken (μg)	% Found ± SD (n = 5)	Standard analytical error
Servector[a] (amineptine hydrochloride)	100 mg	50	100.7 ± 0.46	0.204
		100	100.5 ± 0.52	0.231
		200	99.9 ± 0.39	0.175
Trivastal[a] (piribedil)	20 mg	50	101.1 ± 0.36	0.159
		100	100.3 ± 0.43	0.192
		200	99.8 ± 0.45	0.202
Debridat[b] (trimebutine maleate)	100 mg	50	99.9 ± 0.51	0.228
		100	100.1 ± 0.40	0.179
		200	99.7 ± 0.63	0.283

[a]Servector and Trivastal tablets (Servier Egypt Industries Limited, under Licence of Les Laboratories Servier, France).
[b]Debridat tablets (Roussel, Egypt).

The precision of the method was determined using four different drug concentrations which were prepared and analyzed in quintuplicate. The standard deviations (Table 3) can be considered satisfactory, at least for the level of concentrations examined.

3.7. Application to pharmaceutical preparations

The proposed method was applied to analysis of commercial tablets of amineptine hydrochloride (Servector), piribedil (Trivastal) and trimebutine maleate (Debridat). The results are presented in Table 4.

The proposed method is simple, rapid and accurate, and can therefore be applied to the determination of some nitrogenous drugs alone and in pharmaceutical preparations without fear of interferences caused by the excipients expected to be present in tablets.

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