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Indirect Atomic Absorption and Atomic Emission Spectrometric Determination of Antazoline, Hydralazine and Amiloride Hydrochlorides and Quinine Sulphate

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Abstract. Ion-association complexes of antazoline HCl [I], hydralazine HCl [II], amiloride HCl [III] and quinine sulphate [IV] with $[Co(SCN)_4]^{2-}$ and $[Co(NO_2)_6]^{3-}$ were precipitated and the excess unreacted cobalt complex was determined. A new method using atomic emission and atomic absorption spectrometry for the determination of the above drugs in pure solutions and pharmaceutical preparations is given. The drugs can be determined in the ranges 0.3–3.0, 0.19–1.96, 0.3–3.0, and 0.78–7.82 mg/25 ml solutions of I, II, III, and IV, respectively, with mean relative standard deviations of 0.65–2.03% and recovery values of 95.76–101.2% indicating high precision and accuracy.

Key words: atomic absorption, atomic emission, drug analysis, antazoline, hydralazine, amiloride, quinine, cobalt complexes.

The investigated drugs are very important pharmaceutical compounds, antazoline HCl [91-75-8] (I) has local antihistaminic and also some anticholinergic properties. It is less irritating to the tissues than most other antihistamines. Hydralazine HCl [304-20-1] (II) is used as a vasodilator in the treatment of hypertension. Amiloride HCl [17440-83-4] (III) is recommended in edema of cardiac origin, in hepatic cirrhosis with ascites and in hypertension. Quinine sulphate [6119-70-6] (IV) is used for the specific treatment of malaria. It is very effective in combination with 8-aminoquinoline for radial cure of vivax malarias. Because of these pharmaceutical properties of the investigated drugs, we found it important to prepare new ion-association complexes containing these drugs and to study and investigate their chemical composition. The work also presents a new rapid method for the determination of these drugs after transformation into the ion-associates.

Several methods have been reported for the determination of antazoline HCl [1–3], hydralazine HCl [4–6], amiloride HCl [7, 8] and quinine sulphate [9–11].

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Although, DCP-AES and AAS are rapid methods and have very low detection limits which cannot be reached by most other methods, they have not been applied yet to the determination of these drugs. The present work includes new DCP-AES and AAS methods for the determination of the investigated drugs. The methods are based on precipitating the drugs with an excess of $[Co(SCN)_4]^{2-}$ or $[Co(NO_2)_6]^{3-}$. The equilibrium concentration of the metal ion present as the soluble inorganic complex ion in the supernatant solution was determined using direct current plasma atomic emission spectrometry (DCP-AES) and atomic absorption spectrometry (AAS).

Experimental

Reagents

Doubly-distilled water and analytical grade reagents were used to prepare all solutions. Antazoline HCl, hydralazine HCl, amiloride HCl and quinine sulphate were provided by Misr Company for Pharmaceutical Industries, Egypt. Cobalt sulphate, sodium cobaltinitrite and potassium thiocyanate were supplied by Aldrich. The pharmaceutical preparations assayed were Antistine tablets (100 mg antazoline HCl/tablet), Apresoline ampoules (20 mg hydralazine HCl/ml) and Ser-Ap-Es tablets (25 mg hydralazine HCl/tablet) from Ciba, Swisspharma, Cairo, Egypt: Calazol lotion (1% antazoline HCl) from Misr Company for Pharmaceutical Industries, Cairo, Egypt; quinine sulphate tablets (200 mg quinine SO_4/tablet) from the Nile Company for pharmaceutical and Chemical Industries, Cairo, Egypt and Moduretic tablets (5 mg amiloride HCl/tablet) from El-Kahira Company for Pharmaceutical and Chemical Industries, Cairo, Egypt.

The cobalt thiocyanate complex solution was prepared by mixing solutions containing 1×10^{-3} mole of cobalt sulphate with a solution containing 4×10^{-3} mole of potassium thiocyanate. No free Co^{2+} ions could be detected in the filtrate after the addition of excess antazoline, hydralazine, amiloride or quinine indicating the absence of free unreacted Co^{2+} ions in the solution.

Apparatus

Direct-current plasma atomic emission measurements were carried out using a Beckman Spectra Span V emission spectrometer and atomic absorption measurements with a Perkin Elmer 2380- atomic absorption spectrometer. Conductometric measurements were carried out using a conductivity meter Model CM-1K (TOA Electronics Ltd., Japan). The pH of the solutions was measured using a Chemtrix type-62 digital pH-meter (USA).

Preparation of the Standard Solutions

The standard Co^{2+} solution was prepared by weighing 1.0 g of highly pure cobalt, transferring to 1-liter volumetric flask and then adding 50 ml of concentrated HNO_3. After complete dissolution, the solution was completed to the mark with distilled water. The 1000 µg Co/ml solution was stored in a plastic bottle which had been pre-soaked in dilute HNO_3. The solution was stable for approximately one year.

Calibration of the DCP-AES and AAS

Under the recommended conditions, calibration graphs were constructed using standard cobalt solution in 1 *M* HNO_3 by performing triplicate measurements using solutions containing 0, 10, 20, and 50 µg/ml analyte concentrations. The calibration graphs are straight lines passing through the origin.

Conductometric Measurements

The stoichiometry of the ion associates was elucidated by conductometric titration of the drugs with $[Co(SCN)_4]^{2-}$ and $[Co(NO_2)_6]^{3-}$ solutions.

Emission and Absorption Measurements

The cobalt was measured by DCP-AES at wavelength 236.37 nm, order 95, plasma position 0.0, detection limit 0.02 μg/ml, linear dynamic range 0.2–1000 μg/ml, background equivalent concentration 0.1 mg, entrance slits 50 × 300 μm and exit slits 100 × 300 μm. For AAS, the cobalt was measured at wavelength 240.7 nm, slit width 0.2 nm, relative noise 1.0, sensitivity 0.120 μg/ml and linear range 3.5 μg/ml. The instruments were equally adequate for present purposes (see below) and were used according to availability.

Determination of Solubility of the Ion Associates

The solid ion-associate was added in excess to a solution of the optimum pH and ionic strength. The solution was shaken for 4–6 h and left to stand for a week to attain equilibrium, then the saturated solution was filtered into a dry beaker (rejecting the first few ml of filtrate). The equilibrium concentration of the metal ion present in the form of soluble inorganic complex was measured using atomic spectrometry, and hence the solubility (S) of the precipitate was evaluated, from which the solubility product of the ion-associate was calculated.

Determination of the Drugs

Aliquots (1–10 ml) of 0.001 M drug solutions were quantitatively transferred into 25-ml volumetric flasks. To each flask 1.0 ml of 0.01 M standard solution of $[Co(SCN)_4]^{2-}$ or $[Co(NO_2)_6]^{3-}$ was added and the volume was completed to the mark with the aqueous solutions of the optimum pH and ionic strength (prepared from NaCl and NaOH). The solutions were shaken well and left to stand for 15 min, then filtered through Whatman P/S paper (12.5 cm) and the equilibrium metal ion concentration in the filtrate was determined using AAS or DCP-AES. The consumed metal ion in the formation of ion-associates was calculated and the drug concentration was thus determined indirectly. 1 mg Co ≡ 9.04, 5.47, 9.05 and 23.22 mg of I, II, III, and IV, respectively.

Determination of Drugs in Pharmaceutical Preparations

For analysis of antazoline HCl, sampling was done by grinding 12 tablets of Antistine and transferring 0.35–3.0 mg to a 25-ml volumetric flask or by mixing 10 bottles of Calazol lotion, then taking 4–15 ml (containing 0.4–1.5 mg). For analysis of hydralazine HCl, sampling was by taking 0.3–4.5 ml (containing 0.24–1.85 mg) of Apresoline or grinding 20 tablets of Ser-Ap-Es then transferring 0.2–1.65 mg to a 25-ml volumetric flask. In the case of amiloride HCl, sampling was by grinding 10 tablets and weighing 0.35–2.62 mg. In the case of quinine sulphate, sampling was by grinding up 10 tablets and transferring 1.0–5.5 mg to a 25-ml volumetric flask. In all cases the analysis was completed as in the general procedure.

Results and Discussion

Elemental analysis for C, H, N and Co of the solid ion-associates (Table 1) revealed that in all cases two drug cations formed ion-associates with one $[Co(SCN)_4]^{2-}$ or $[NaCo(NO_2)_6]^{2-}$ ion. These results are comparable to the results of Lemli [12].

Table 1. Elemental analysis, composition and some physical properties of the drug ion-associates

Drug	Ion-association composition	m.p. (°C)	Molar ratio	Colour	% Found (calculated)			
					C	H	N	Metal
Antazoline	$(C_{17}H_{19}N_3)_2[Co(SCN)_4]$	280	2:1	white	55.50 (55.53)	4.60 (4.66)	17.00 (17.04)	7.12 (7.17)
	$(C_{17}H_{19}N_3)_2[NaCo(NO_2)_6]$	265	2:1	yellow	45.90 (45.95)	4.28 (4.31)	18.56 (18.91)	6.60 (6.63)
Hydralazine	$(C_8H_8N_4)_2[Co(SCN)_4]$	155	2:1	white	39.30 (39.27)	2.68 (2.65)	27.29 (27.66)	9.70 (9.64)
	$(C_8H_8N_4)_2[NaCo(NO_2)_6]$	186	2:1	yellow	28.30 (28.32)	2.33 (2.37)	28.86 (28.90)	8.70 (8.68)
Amiloride	$(C_6H_8ClN_7O)_2[Co(SCN)_4]$	380	2:1	pale yellow	27.62 (26.16)	2.00 (2.19)	34.25 (34.32)	7.93 (8.02)
	$(C_6H_8ClN_7O_2)_2[NaCo(NO_2)_6]$	215	2:1	yellow	17.62 (17.63)	2.00 (1.97)	34.25 (34.27)	7.23 (7.21)
Quinine	$(C_{20}H_{24}N_2O_2)_2[Co(SCN)_4]$	194	2:1	blue	56.10 (56.22)	5.16 (5.14)	11.86 (11.92)	6.32 (6.27)
	$(C_{20}H_{24}N_2O_2)_2[NaCo(NO_2)_6]$	154	2:1	yellow	47.68 (47.72)	4.84 (4.80)	13.90 (13.91)	5.88 (5.85)

Table 2. Solubility and solubility product of the ion-associates at their optimum conditions of pH and ionic strength (μ) values at 25 °C

Ion-associate	pH	μ	pS	pK_{sp}
Antazolinium cobalt thiocyanate	8.0	0.3	3.81	10.83
Antazolinium cobaltinitrite	6.0	0.4	2.63	7.29
Hydralazinium cobalt thiocyanate	8.0	0.5	3.19	8.97
Hydralazinium cobaltinitrite	6.0	0.5	2.64	7.33
Amiloridium cobalt thiocyanate	8.0	0.7	5.37	15.52
Amiloridium cobaltinitrite	6.0	0.4	2.94	8.21
Quininium cobalt thiocyanate	4.0	0.4	3.84	10.92
Quininium cobaltinitrite	6.0	0.4	2.83	7.89

pS = −log solubility
pK_{sp} = −log solubility product.

Conductometric titrations of the investigated drugs with $[Co(SCN)_4]^{2-}$ and $[NaCo(NO_2)_6]^{2-}$ were performed to give an insight into the stoichiometric compositions of the ion-associates formed in solutions. With all ion-associates, the characteristic curve-breaks are observed at a cation/anion molecular ratio of about 2, confirming the formation of 2:1 (drug:X^{2-}) ion-associates. The results obtained coincide with the elemental analysis of the precipitated ion-associates. The optimum pH and ionic strength values (Table 2) have been elucidated by determining the solubility of the ion-associates in NaCl–NaOH solutions of different pH values and ionic strengths. The best were those exhibiting lowest solubility values.

Determination of Drugs in Pure Solutions and Pharmaceutical Preparations

Antazoline HCl, hydralazine HCl, amiloride HCl and quinine sulphate were determined precisely and accurately in aqueous solutions at their optimum conditions of pH and ionic strength (Table 2) and in the above-mentioned pharmaceutical preparations using the present method.

The results given in Table 3 reveal that recoveries were in the range 96.9–101.2% when using $[Co(SCN)_4]^{2-}$ and in the range 95.8–97.6% when using $[NaCo(NO_2)_6]^{2-}$, reflecting the high accuracy in addition to the high precision indicated by the very low values of the relative standard deviation. However, it is worth mentioning that the thiocyanate complexes gave lower RSDs in almost all cases. Statistical treatment (F-test [13]) of the results proved that there was no advantage of one reagent over the other. AES and AAS gave very similar performance characteristics.

Generally, the present method is as good as those reported in the United States Pharmacopia [14]. In the present method, 0.3–3, 0.19–1.96, 0.3–3.0 and 0.78–7.82 mg/25 ml solutions of I, II, III and IV were determined, respectively, which means that this method is applicable over wider concentration ranges than previously reported methods.

Table 3. Determination of the investigated drugs in pure solutions and in pharmaceutical preparations

Sample	Taken[a] (mg)	Mean[b] recovery (%)	Mean RSD (%)
Using $[Co(SCN)_4]^{2-}$			
Antazoline solution*	0.30–3.00	98.8	0.8
Antistine tablets	0.35–3.00	98.6	1.2
Calazol lotion	0.40–1.50	98.4	0.7
Hydralazine solution*	0.19–1.96	96.9	0.9
Apresoline ampoules	0.24–1.85	97.0	1.2
Ser-Ap-Es tablets	0.20–1.65	97.1	2.0
Amiloride solution**	0.30–3.00	101.2	0.6
Moduretic tablets	0.35–2.62	101.1	1.0
Quinine solution*	0.78–7.82	98.6	1.2
Quinine sulphate tablets	1.00–5.50	101.0	1.6
Using $[Co(NO_2)_6]^{3-}$			
Antazoline solution*	0.30–3.00	98.8	1.2
Antistine tablets	0.35–3.00	98.9	1.2
Calazol lotion	0.40–1.50	98.5	0.8
Hydralazine solution*	0.19–1.96	96.7	1.2
Apresoline ampoules	0.24–1.85	96.2	1.1
Ser-Ap-Es tablets	0.20–1.65	95.8	0.9
Amiloride solution**	0.30–3.00	97.6	1.1
Moduretic tablets	0.35–2.62	97.4	1.5
Quinine solution*	0.78–7.82	96.8	1.3
Quinine sulphate tablets	1.00–5.50	96.9	1.3

* By AAS.

** By DCP-AES.

[a] Calculated by reference to independent analysis according to the standard USP method.

[b] Five determinations at each of six levels.

Although the present method is more time-consuming than some other methods, it exhibits fair sensitivity and accuracy. Moreover, the reproducibility of the results is superior to that obtained from other methods.

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