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Atomic emission spectrometric determination of ephedrine, cinchonine, chlorpheniramine, atropine and diphenhydramine based on formation of ion associates with ammonium reineckate

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Abstract

Ion–associate complexes of ephedrine HCl (I), cinchonine HCl (II), chlorpheniramine maleate (III), atropine sulphate (IV) and diphenhydramine HCl (V) with ammonium reineckate were precipitated and their solubilities were studied as a function of pH, ionic strength and temperature. Saturated solutions of each ion–associate under the optimum precipitation conditions were prepared and the Cr ion content in the supernatant was determined. The solubility products were thus elucidated at different temperatures. A new accurate and precise method using direct current plasma–atomic emission spectrometry for the determination of the investigated drugs in pure solutions and in pharmaceutical preparations is described. The drugs can determined by the present method in the ranges 1.6–52,2.64–85.8,3.12–101.4,5.52–180.4 and 2.72–75.85 μg/ml solutions of I, II, III, IV and V, respectively.

Keywords: Drug analysis; Atomic emission spectrometry; Ammonium reineckate; Ephedrine; Cinchonine; Chlorpheniramine; Atropine; Diphenhydramine

1. Introduction

Ephedrine, cinchonine, chlorpheniramine, atropine and diphenhydramine are very useful pharmaceutical compounds. Therefore, we found it important to prepare new ion–associates containing these drugs and to study and elucidate their chemical structure. Also the work presents a new rapid method for the determination of these drugs after transformation into the ion associates.

Numerous alkaloids reacts with ammonium reineckate $[Cr(NH_3)_2(SCN)_4NH_4.H_20]$ under controlled conditions to give mono- and di-reineckate complex ion–associates[1–5].

Several methods were previously reported for the determination of ephedrine HCl [5–11], cinchonine HCl [5,12], chlorpheniramine maleate

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[5,11,13–20], atropine sulphate [5,12,21] and diphenhydramine HCl [5–7,11,22–27]. Although direct current plasma–atomic emission spectrometry (DCP–AES) is a rapid method and has very low detection limits, which can not be reached by most of other methods, it has not been applied yet to the determination of these drugs. The present work includes a new DCP–AES method for the determination of the investigated drugs

The method of determination was based on precipitation of the ion–associate formed from the combination of the drug with ammonium reineckate. The equilibrium concentration of the Cr ion present in the form of soluble inorganic complex ion in a supernatant of saturated solution of the ion–associate was determined using direct current plasma atomic emission spectrometry.

2. Experimental

2.1. Reagents

Double-distilled water and analytical grade reagents were used to prepare all solutions: ephedrine HCl, cinchonine HCl chlorpheniramine maleate, atropine sulphate and diphenhydramine HCl provided by Misr Company for Pharmaceutical Industries, Egypt and ammonium reineckate supplied by Aldrich were used. The pharmaceutical preparations were obtained from a local market produced in Egypt. Standard 1000-μg/ml solution of chromium was prepared as previously reported [28,29].

2.2. Apparatus

The Spectraspan V emission spectrometer from Beckman Instruments, Inc. (Fullerton, CA), was used with the standard cross-flow nebulizer and echelle grating monochromator. Instrumental specifications and typical operating conditions were followed as cited in the DCP operator's manual and the Beckman hand book. The IR absorption spectra were obtained by applying the KBr disk technique using a PYE UNICAM SP-300 infrared spectrometer. The pH of solutions was measured using an Orion Research Model 601 A digital pH-meter.

2.3. Preparation of ion–associates

The ion–associates were prepared by mixing solution containing 0.001 mol of ammonium reineckate with the calculated amount of the drugs. The precipitates obtained were filtered, thoroughly washed with distilled water and dried at room temperature. They were subjected to infrared spectroscopy and elemental micro-analysis for carbon, hydrogen, nitrogen and Cr content (The Micro-analytical Center, Cairo University).

2.4. Calibration of the DCP–AES

The DCP–AES was calibrated as previously reported [28,29]. The chromium was measured at wavelength 267.71 nm, order 84, plasma position 0.0, detection limit 0.01 ppm, linear dynamic range 0.1–1000 ppm, back ground equivalent concentration 0.4 mg, entrance slits 50×300 μm and exit slits 100×300 μm.

2.5. Analytical determination of the drugs

Aliquots (0.2–6.5 ml) of 0.001 M drug solutions were quantitatively transferred into 25 ml measuring flasks. To each flask 1.0 ml of 0.01 M standard solution of ammonium reineckate was added and the volume has been completed to the mark with the aqueous solution of the optimum pH and ionic strength values. 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 Cr ion concentration in the filtrate was determined using DCP–AES. The consumed Cr ion in the formation of ion–associates was calculated and the drug concentration was thus determined indirectly.

2.6. Analytical determination of drugs in pharmaceutical preparations

For analysis of ephedrine HCl sampling was made by grinding (12 tablets) of Asmolin and

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

Drug	Ion–associate composition	m.p. (°C)	Molar ratio	Colour	% Found (calculated)			
					C	H	N	Cr
Ephedrine	$(C_{10}H_{16}NO)$ $[Cr(NH_3)_2$ $(SCN)_4]$	128	1:1	Red	34.64 (34.69)	4.55 (4.57)	20.37 (20.23)	10.52 (10.73)
Cinchonine	$(C_{19}H_{23}N_2O)$ $[Cr(NH_3)_2$ $(SCN)_4]$	198	1:1	Pink	44.80 (45.00)	5.01 (4.80)	18.10 (18.25)	8.20 (8.50)
Chlorpheni-ramine	$(C_{16}H_{20}ClN_2)$ $[Cr(NH_3)_2$ $(SCN)_4]$	150	1:1	Pink	40.45 (40.43)	4.46 (4.41)	18.96 (18.86)	8.51 (8.70)
Atropine	$(C_{17}H_{24}NO_3)$ $[Cr(NH_3)_2$ $(SCN)_4]$	153	1:1	Pink	41.08 (41.40)	5.00 (4 90)	16.20 (16.10)	8.20 (8.55)
Diphenhy-dramine	$(C_{17}H_{22}NO)$ $[Cr(NH_3)_2$ $(SCN)_4]$	188	1:1	Pink	43.96 (43.91)	4.96 (4.91)	17.27 (17.06)	8.70 (9 00)

taking 3.2–42 μg/ml, by taking 4–42 ml of Coldal Syrup (2.56–48 μg) and grinding (20 tablets)of Asmacid then transferring 2–50 μg. In case of cinchonine HCl sampling was made by taking 5–25 ml of cinchonine HCl Syrup (3.45–78.4 μg). For analysis of chlorpheniramine maleate sampling was made by taking 3.5–24 m1 (4.62–96.52 μg) of Allergyl Syrup, by taking 1.5–28 ml (3.85–88.62 μg) of Rinosin, by mixing eight capsules of Coldact then transferring 4.25–74.16 μg and by grinding (20 tablets) of Nova-C-m then taking 5.45–100.50 μg. For analysis of Atropine sulphate sampling was made by mixing 16 ampoules of Atropine sulphate injection, (7.35–168.32 μg) were transferred to the solution and in case of Diphenhydramine HCl sampling was made by mixing nine capsules of Broncholase then taking 3.35–70.85 μg and by transferring 3.5–16.5 ml of Bronchophane Syrup containing (4.25–68.12 μg).

3. Results and discussion

The results of elemental analysis (Table 1), Cr content determination and IR of the produced solid ion–associates reveal that in all cases one drug cation forms ion–associate with one $[Cr(NH_3)_2(SCN)_4]^-$. These results are comparable to previously reported results [28,29].

The IR spectrum of ammonium reineckate illustrates the presence of a strong absorption band at 2110 cm^{-1} indicating NCS and a medium absorption band at 1400 cm^{-1} which is evidence for the presence of NH_4^+ group. The IR spectra of ion associate complexes show the absence of NH_4^+ and a slight shift for the thiocyanate group from 2110 to 2080–2060 cm^{-1}. This may be due to the formation of an ion–associate complex, which is also confirmed by the absence of the band at 1400 cm^{-1} indicating the removal of the NH_4^+ group.

3.1. Analytical determination of drugs in pure solutions and in pharmaceutical preparation

Ephedrine HCl, cinchonine HCl, chlorpheniramine maleate, atropine sulphate and diphenhydramine HCl were determined precisely and accurately in pure solutions at their optimum conditions of pH and ionic strength values (Table 2) and in the above mentioned pharmaceutical preparations using the present method.

The results given in Table 3 reveal that the recoveries are in the range of 100.00–101.25% reflecting high accuracy in addition to the high precision indicated by very low values of relative SD.

Table 2
Solubility and solubility product values of the ion associates at their optimum conditions of pH and ionic strength (I) values at 25°C[a]

Ion–associate	PH	I molal	PS	pK_{sp}
Ephedrinium reineckate	5.0	0.6	4.21	8.42
Cinchoninium reineckate	6.0	0.4	4.87	9.74
Chlorpheniraminium reineckate	4.0	0.5	4.57	9.14
Atropinium reineckate	7.0	0.3	4.63	9.27
Diphenhydraminium reineckate	6.0	0.2	4.26	8.53

[a] pS, $= -\log$ solubility; pK_{sp}, $= -\log$ solubility product.

Generally, the present method is as good as that reported in the United State Pharmacopia method [30] better than used by El Shahat [5] where (100–1000 ppm) of ephedrine, cinchonine, chlorpheniramine, atropine and diphenhydramine were determined, the method used by Xin [14] in which 3–21 μg/ml of chlorpheniramine can be determined and the methods used by Medvedovskii [23], Selinger [25] and Martinez [26] where diphenhydrarnine can be determined in the range of 2–5 mg, 1–100 mg/ml and 50–230 ppm, respectively. While in the present method (1.6–52, 2.64–85.8,3.12–101.4,5.52–180.4 and 2.72–75.85 μg/ml) solutions of I, II, III, IV and V were determined, respectively which means that this method is applicable over a wider concentration range than those of the above comparable methods.

In pharmaceutical analysis it is important to test the selectivity toward excepients and the fillers added to the pharmaceutical preparations. Fortunately, such materials mostly do not interfere.

Table 3
Analytical determination of the investigated drugs in pure solutions and in pharmaceutical preparations by DCP–AES

Sample	Taken (μg)	Mean recovery (%)	Meam relative error (pph)	Mean RSD (%)[a]
Ephedrine solution	1.60–52.00	100.00	0.00	0.83
Asmolin tablets[b]	3.20–42.00	100.30	+0.30	0.26
Coldal Syrup[c]	2.56–48.00	101.25	+1.25	1.22
Asmacid tablets[c]	2.00–50.00	100.43	+0.43	1.16
Cinchonine solution	2.64–85.80	100.00	0.00	1.13
Cinchonine HCl injection[c]	3.45–78.40	100.12	+0.12	1.43
Chlorpheniramine solution	3.12–101.40	100.12	+0.12	1.33
Allergyl Syrup[d]	4.62–96.52	101.00	+1.00	1.12
Rinosin[e]	3.85–88.62	101.00	+1.00	1.64
Coldact[f]	4.25–74.16	101.06	+0.06	1.28
Nova-C-m[g]	5.45–100.50	101.22	+1.22	1.36
Atropine solution	5.52–180.44	100.00	0.00	1.16
Atropine sulphate injection[c]	7.35–168.32	101.05	+1.05	0.78
Diphenhydrannine solution	2.72–75.85	100.00	0.00	1.20
Broncholase[f]	3.35–70.85	100.12	+0.12	1.42
Bronchophane Syrup[b]	4.25–68.12	101.06	+1.06	1.28

[a] RSD, five determinations
[b] Egyptian Int. Pharmaceutical Industries Co., Egypt.
[c] Chemical Industries Development, Giza, Egypt.
[d] Arab Drug Company, Egypt.
[e] Pharco Pharmacuticals Co., Alexandria, Egypt.
[f] The Memphis Chemical Company, Cairo, Egypt.
[g] The Nile Co. for Pharmaceutical and Chemical Industries, Cairo, Egypt.

Table 4
Linear regression analysis for ephedrine cinchonine. chlorpheniramine, atropine and diphenhydramine using ammonium reineckate

Parameters	Ephedrine	Cinchonine	Chorpheni-ramine	Atropine	Diphenhydramine
Optimum concentration range (Mg/ml)	1.6–52	2.64–85.8	3.12–101.4	5.52–180.4	2.72–75.85
Shift or intercept of the regression line[a]	0.028	0.033	0.029	0.025	0.027
Slope of regression line	0.9985	1.0036	1.0042	0.9987	0.9972
Student's t (2.310)[b]	1.96	2.13	1.95	2.19	2.05
Range of error (%)	99.8 ± 1.3	100.0 ± 1.3	100.0 ± 1.2	99.8 ± 1.5	100.0 ± 1.4

[a] Observed vs. theoretical.
[b] Tabulated 95% confidence limit (for slope).

This is clear from the results obtained for the pharmaceutical preparations (Table 3) that these excepients do not interfere. Although the present method is more time consuming (22 min) in comparison to other methods such as (15 min for HPLC), it exhibits the advantages of simplicity, precision, higher sensitivity, accuracy and convenience. Moreover, the reproducibility of the results is superior to those obtained from other methods. Therefore, the method should be useful for routine analytical and quality control assay of the investigated drugs in dosage forms.

3.2. Statistical treatment of data

F-Test [31] has been applied to check the agreement between precision of methods for determination of ephedrine (I), cinchonine (II), chlorpheniramine (III), atropine (IV) and diphenhydramine (V) using ammonium reineckate as analytical reagent. A series of replicate analysis, (five determinations) applying, the proposed method has standard deviation values amounting 0.83, 1.13 1.16 and 1.20 for I, II, III, IV and V, respectively. Thus, by comparing I with all drugs the F-values are 1.85, 2.56, 1.95 and 2.09, respectively, in case of comparing II with III, IV and V the F-values are 1.38, 1.05 and 1.13. Also by comparing III with IV and V the F-values are 1.31 and 1.23, respectively.

Knowing that the critical value for F at the 5% level [31] (four degrees of freedom in the numerator and in the denominator) is 6.39, it is evident that on the basis of probability, the ratio for such a pairing of variances can be expected to exceed 6.39 once in 20 times. Since the observed difference in standard deviations in all cases is far less than 6.39, it is clear that the null hypothesis is confirmed and we conclude that the analyses in this test at least exhibited comparable precision.

In order to establish whether the proposed method exhibits any fixed or proportional bias, a simple linear regression [29] of observed drug concentration against the theoretical values (five points) was calculated. Student's t-test [31] (at 95% confidence level) was applied to slope of the regression line (Table 4) and showed that it did not differs significantly from the ideal value of unity. Hence, it can be concluded that there are no systematic differences between the determined and true concentration over a wide range. The SDs can be considered satisfactory at least for the level of concentrations examined.

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