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Indirect atomic absorption determination of atropine, diphenhydramine, tolazoline, and levamisole based on formation of ion-associates with potassium tetraiodometrcurate

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Abstract

Ion-associate complexes of atropine sulphate (I), diphenhydramine HCl (II), tolazoline HCl (III) and levamisole HCl (IV) with potassium tetraiodomercurate 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 metal ion-content in the supernatant was determined. The solubility products were thus calculated at different temperatures. A new accurate and precise method using atomic absorption spectrometry for the determination of the investigated drugs in pure solutions and in pharmaceutical preparations is described. The drugs can be determined by the present method in the ranges 13.6–138.8, 5.6–58, 3.6–39.6 and 4.8–48 μg/ml solutions of I–IV, respectively.

Keywords: Atomic absorption spectrometry; Potassium tetraiodomercate; Atropine; Diphenhydroamine; Tolazine; Levamisole

1. Introduction

Atropine, diphenhydramine, tolazoline and levamisole are very useful pharmaceutical compounds. These drugs have characteristic physiological function and pharmacological action. Therefore, we found that it is 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.

Several methods were previously reported for the determination of atropine [1–3], diphenhydramine [1,4–12], tolazoline [13–18] and levamisole [19–30]. Although atomic absorption spectrometry (AAS) is a rapid method and has very low detection limits which can not be reached by most of the other methods, it has not

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been applied yet to the determination of these drugs. The present work includes a new (AAS) method for the determination of the investigated drugs. It is based on precipitation of the ion-associate formed from the combination of the drug with tetraiodomercurate. The equilibrium concentration of the metal ion present in the form of soluble inorganic complex ion in a supernatant of saturated solution of the ion-associate was determined using atomic absorption spectrometry.

2. Experimental

2.1. Reagents and materials

Double-distilled water and analytical grade reagents were used to prepare all solutions. Atropine, diphenhydramine, tolazoline, and levamisole provided by Misr Company for Pharmaceutical Industries, Egypt, mercury (II) iodide, potassium iodide and mercury atomic absorption standard solution 1000 μg/ml of Hg in 10% HNO_3 (Aldrich). The pharmaceutical preparations were obtained from a local market produced in Egypt.

2.2. Apparatus

The pH of the solutions was measured using an Orion Research Model 601A digital pH-meter. The atomic absorption measurements for the determination of metal ion is carried out using Hitachi atomic absorption Z-6100 polarized Zeeman spectrometer using a hollow cathode lamp of Hg, under the following conditions; wavelength 253.7 nm, slit width 0.7 nm, relative noise 4.2, detection limit 0.28 μg/ml, linear dynamic range, 0.01–100, lamp current 5 mA, and integration time 3 s, the flame used was the acetylene-air mixture.

2.3. Preparation of ion-associates

The ion-associates were prepared by mixing solutions containing 1×10^{-3} mole of potassium tetraiodomercurate 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 elemental microanalysis for carbon, hydrogen, nitrogen and metal content (The Micronalytical Center, Cairo University).

2.4. Calibration of the AAS

Under the optimum conditions, calibration graphs were constructed using standard mercury solutions in 1 M HNO_3 (Aldrich) 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.

2.5. Analytical determination of the drugs

Aliquots (0.5–5.0 ml) of 0.001 M drug solutions were quantitatively transferred into 25 ml measuring flasks. To each flask 1.0 ml of 0.1 M standard solution of potassium tetraiodomercurate 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 metal ion concentration in the filtrate was determined using AAS. The consumed metal ion in the formation of ion-associates was calculated and the drug concentration was thus determined indirectly.

2.6. Analytical determination of drugs in pure solutions and in pharmaceutical preparations

For analysis of atropine sulphate sampling was made by mixing 14 ampoules of atropine sulphate injection, (15–130 μg) then transferred to the solution. In case of diphenhydramine sampling was made by mixing 12 capsules of broncholase then taking 8.00–52.65 μg and by transferring 3.4–12.5 ml of bronchophane syrup containing 6.0–55 μg. For analysis of tolazoline sampling was made by grinding eight tablets of sympacid then taking 4.5–36.5 μg and in case of levamisole sampling was made by grinding 12, ten and eight tablets then taking 5–46, 6.5–42 and 5.25–45.5

μg, of decaris, ketrax and bonapace tablets, respectively.

3. Results and discussion

The results of the elemental analysis (Table 1) and metal content determination of the produced solid ion-associates reveal that in all cases two drug cations formed ion-associates with one [HgI^{-2}]. The results are comparable to the previously reported results [31].

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

Atropine sulphate, diphenhydramine HCl, tolazoline HCl, and levamisole 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 the table [3] reveal that the recoveries are in the range of 100.00–101.26% reflecting high accuracy in addition to the high precision indicated by very low values of relative standard deviation.

In pharmaceutical analysis it is important to test the selectivity toward excepients and the fillers added to the pharmaceutical preparation fortunately, such materials mostly do not interfere. 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 (20 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 re-

Table 1
Element 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	M
Atropine	$(C_{17}H_{24}NO_3)_2(HgI_4)$	167	2:1	White	31.65 (31.67)	3.70 (3.72)	2.19 (2.17)	15.60 (15.57)
Diphenhydramine	$(C_{17}H_{22}NO)_2(HgI_4)$	192	2:1	White	33.45 (33.43)	3.59 (3.60)	2.28 (2.29)	16.43 (16.44)
Tolazoline	$(C_{11}H_{13}N_2S)_2(HgI_4)$	178	2:1	Pale-yellow	23.30 (23.29)	2.55 (2.52)	5.46 (5.43)	19.50 (19.47)
Levamisole	$(C_{10}H_{13}N_3)_2(HgI_4)$	262	2:1	White	23.59 (23.61)	2.33 (2.32)	5.01 (5.00)	17.95 (17.93)

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	pKsp
Atropine-tetraiodomercurate	4.0	0.5	4.96	14.27
Diphenhydramine-tetraiodomercurate	6.0	0.2	4.85	13.96
Tolazoline-tetraiodomercurate	3.0	0.4	5.22	15.06
Levamisole-tetraiodomercurate	5.0	0.7	5.61	16.32

[a] PS: log solubility; and PKsp: log solubility product.

Table 3
Analytical determination of the investigated drugs in pure solutions and in pharmaceutical preparations by AAS

Sample	Taken (μg)	Mean recovery (%)	Mean Rel-error (ppm)	Mean RSD (%)[a]
Atropine solution	13.60–138.80	100.00	0.00	0.63
Atropine sulphate injection (1%)[b]	15.00–130.00	101.50	+1.25	0.64
Diphenhydramine solution	5.60–58.00	101.50	+1.05	0.86
Broncholase (50 mg/capsule)[c]	8.00–52.00	101.22	+1.22	0.93
Bronchophan syrup (15 mg/5 ml)[d]	6.00–55.00	101.26	+1.26	0.78
Tolazoline solution	3.60–36.60	100.12	0.12	1.33
Sympacid tablets (20 mg/tablet)[b]	4.50–36.50	101.12	+1.15	0.85
Levamisole solution	4.80-48.00	101.06	+1.06	1.46
Decaris tablets (50 mg/tablet)[e]	5.00–46.00	101.13	+1.13	0.88
Ketrax tablets (40 mg/tablet)[f]	6.50–42.00	101.09	+1.09	0.76
Bonapace tablets (50 mg/tablet)[g]	5.25–45.50	101.06	+1.06	0.12

[a] RSD: relative standard deviation (five determinations).
[b] Chemical Industries Development, Giza, Egypt.
[c] The Memphis Chemical Company, Cairo, A.R.E.
[d] Egyptian Int. Pharmaceutical Industries Co., A.R.E.
[e] Janseen Co.
[f] I.C.Ico.
[g] Dott. Bonapace Co.

Table 4
Linear regression analysis for atropine, diphenhydramine, tolazoline and levamisole using potassium tetraiodomercurate

Parameters	Atrophine	Diphenhydramine	Tolazoline	Levamisole
Optimum concentration range (μg/ml)	13.6–138.8	5.6–58	3.6–39.6	4.8–48
Shift or intercept of the regression line[a]	0.025	0.036	0.028	0.032
Slope of regression line	0.9973	0.9958	1.0042	0.9997
Student's (2.310)[b]	2.12	2.26	2.06	1.96
Range of error (%)	100.0 ± 1.3	100.0 ± 1.5	99.6 ± 1.4	98.8 ± 1.6

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

sults are superior to those obtained from other methods such as the United State Pharmacopia method [32], better than that used by El-Shahat [1] where 100–1000 mg/ml of atropine and diphenylhydramine were determined, the method used by Mahrous in which 2–10 mg/ml of tolazo-line can be determined and the methods used by Liang [22] and Laredortiz [25] where levamisole can be determined up to 40 mg/100 ml and in the range of 5–40 mg/ml, respectively. In the present method (13.6–138.8, 5.6–58, 3.6–39.6 and 4.8 mg/ml) solution of I–IV were determined, respectively, which means that this method is applicable over a wider concentration range than those of the above comparable methods. Therefore, the method should be useful for routine analytical and quality control assay of the investigated drugs in dosage forms.

In order to establish whether the proposed method exhibits any fixed or proportional bias, a simple regression [34] of observed drug concentration against the theoretical values (five points) was calculated. Student's t-test [33] (at 95% confidence level) was applied to slope the regression line (Table 4) and showed that it didn't differ 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 standard deviations (S.D.) can be considered satisfactory at least for the level of concentrations examined.

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