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Indirect atomic absorption spectrometric determination of pindolol, propranolol and levamisole hydrochlorides based on formation of ion-associates with ammonium reineckate and sodium cobaltinitrite

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Abstract

A new simple, accurate, precise and sensitive indirect method for the determination of pindolol HCl (1), propranolol HCl (2) and levamisole HCl (3) using atomic absorption spectrometry has been developed. The method is based on precipitation of the ion-associates formed from the reaction of (1), (2) or (3) with ammonium reineckate and/or sodium cobaltinitrite. The solubility of the solid complexes at the optimum conditions of pH and ionic strength values have been studied. Saturated solutions of each ion-associate were prepared under the optimum conditions and the metal ion content in the supernatant was determined. The method has been used for the determination of 1.14–17.07, 1.18–17.75 and 1.08–16.24 μg/ml of (1), (2) and (3), respectively, using ammonium reineckate, and 1.71–25.60, 1.77–26.62 and 1.62–24.36 μg/ml of (1), (2) and (3), respectively, using sodium cobaltinitrite. The method developed was applied for analysis of bulk drugs and some of their pharmaceutical preparations.

Keywords: Drug analysis; Atomic absorption spectrometry; Ammonium reineckate; Sodium cobaltnitrite; Pindolol; Propranolol; Levamisole

1. Introduction

Pindolol, propranolol and levamisole of hydrochlorides are very important pharmaceutical compounds. Pindolol is used as B-adrenoceptor blocking agent with intrinsic sympathomimetic activity; it also prevents hypertension, angina pectoris and certain types of arrhythmias. Propranolol is used for management of hypertension, angina pectoris, cardiac dysrhythmias, hypertrophic obstructive cardiomyopathy, anxiety and essential tremor. Levamisole is used for treatment of ascariasis, hook-worm and mixed worm infections. Therefore, we found it important to prepare new ion-associates containing these drugs and to study and elucidate their chemical structure. Also

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the work 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 the hydrochlorides of pindolol [1–12], propranolol [9–26], and levamisole [27–36]. Although atomic absorption spectrometry (AAS) is a rapid method and has very low detection limits which cannot 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 indirect method for pindolol, propranolol and levamisole hydrochlorides. This method is based on the precipitation of the ion-associates formed of these drugs with ammonium reineckate, $NH_4[Cr(NH_3)_2(SCN)_4]$, and sodium cobaltinitrite, $Na_3[Co(NO_2)_6]$. The metal ion content present in the supernatant after precipitation of the ion-associates is determined by employing AAS and is used to calculate the concentration of pindolol, propranolol and levamisole hydrochlorides.

2. Experimental

2.1. Reagents and materials

Doubly distilled water and analytical grade reagents were used to prepare all solutions. Pindolol, propranolol and levamisole hydrochlorides were obtained by Misr Company for Pharmaceutical Industries, Egypt. Ammonium reineckate and sodium cobaltinitrite were Aldrich products. The pharmaceutical preparations were obtained locally and were produced in Egypt. Standard solution of chromium and cobalt 1000 μg/ml was prepared as previously reported [37,38].

2.2. Apparatus

The pH values of solutions were measured using an Orion Research Model 601A digital pH-meter. The atomic absorption measurement for the determination of metal ion was carried out using Hitachi atomic absorption Z-6100 polarized Zeeman spectrometer. For AAS, the cobalt and chromium were measured at wavelengths 240.73 and 357.87 nm, respectively, slit width 0.2 nm, relative noise 1.0, detection limit 0.01 μg/ml, linear dynamic range 0.01–100 μg/ml, lamp current 5 mA and integration time 3 s. The flame used was the acetylene-air mixture. Conductimetric measurements were carried out using YSI model 32M conductance meter with YSI 3417 dip type cell ($K_{cell} = 1$).

2.3. Preparation of ion-associates

The solid ion-associates were prepared by mixing 0.01 mol of ammonium reineckate or sodium cobaltinitrite with the calculated amount of pindolol, propranolol or levamisole hydrochlorides. The precipitates obtained were filtered, thoroughly washed with distilled water and dried at room temperature. They were subjected to elemental microanalysis at the microanalytical center, Cairo University, infrared spectroscopy and determination of the metal ion content [39].

The stoichiometry of the ion-associates was also elucidated by conductimetric titration [40].

2.4. Analytical determination of the drugs in aqueous solutions

Aliquots (0.1–1.5 ml) of 0.001-M drug solutions were quantitatively transferred into 25-ml measuring flasks. To each flask 0.15 ml of 10^{-2} M standard solution of ammonium reineckate or sodium cobaltinitrite was added and the flask was filled to the mark with solutions of the optimum pH and ionic strength values. The solutions were shaken well and left to stand for 15 min and then filtered through Whatman P/S filter paper (12.5 cm) and the equilibrium metal ion concentration in the filtrate was determined using AAS. The metal ion consumed in the formation of ion-associates was calculated. Each 0.1 ml 10^{-2} M of ammonium reineckate is equivalent to 1.14, 1.18 and 1.08 μg pindolol, propranolol and levamisole hydrochlorides, respectively, whereas each 0.1 ml 10^{-2} M of sodium cobaltinitrite is equivalent to 3.42, 3.54 and 3.24 μg of the three drugs, respectively.

2.5. Assay of pharmaceutical preparations

For analysis of pindolol, eight tablets of Visken were ground, and 0.043–0.4 mg dissolved in water (25 ml). For analysis of propranolol, sampling was made by grinding 12, eight, ten, eight and 20 tablets, then dissolving 0.056–0.406, 0.05–0.356, 0.087–0.406, 0.053–0.39 and 0.08–0.41 mg of Inderal, Pranolol, Bedranol, Obsidian and Indicardin, respectively, in water (25 ml). In the case of levamisole ten and eight tablets were ground, and 0.043–0.387- and 0.043–0.4-mg samples of Decaris and Ketrax, respectively, were dissolved in water (25 ml). These samples were analysed in the same way as the pure solutions.

3. Results and discussion

The results of elemental analysis (Table 1) and determination of the metal content and IR spectra of the solid ion-associates show that 2:1 and 3:1 (drug:reagent) compounds are formed using ammonium reineckate and sodium cobaltinitrite, respectively. Conductometric titrations of pindolol, propranolol and levamisole hydrochlorides with the studied reagents confirm such results.

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

The hydrochlorides of pindolol, propranolol and levamisole were determined precisely and accurately under optimum conditions of pH and ionic strength using the proposed method in pure solutions and in their pharmaceutical preparations Tables 2 and 3. The results given in Table 3 reveal that for ammonium reineckate and sodium cobaltinitrite, the recoveries are in the range 98.03–101.67%, reflecting a high accuracy in addition to the high precision indicated by very low values of relative standard deviations. The pro-

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

Drug	Ion-associate composition	M.p., °C	Molar ratio	Color	Found (calculated), %			
					C	H	N	Metal
Ammonium reineckate				Red				
Pindolo	$(C_{14}H_{21}N_2O_2)[Cr(NH_3)_2(SCN)_4]$	265	1:1	Pink	38.02 (38.09)	4.72 (4.76)	19.71 (19.75)	9.16 (9.17)
Propranolol	$(C_{16}H_{22}NO_2)[Cr(NH_3)_2(SCN)_4]$	218	1:1	Pink	41.49 (41.52)	4.85 (4.84)	16.95 (16.95)	9.00 (8.99)
Levamisole	$(C_{11}H_{13}N_2S)[Cr(NH_3)_2(SCN)_4]$	248	1:1	Pink	34.42 (34.41)	3.65 (3.63)	21.40 (21.41)	9.96 (9.94)
Sodium cobaltinitrite				Yellow				
Pindolol	$(C_{14}H_{21}N_2O_2)_3[Co(NO_2)_6]$	186	3:1	Orange	46.58 (46.58)	5.83 (5.82)	15.50 (15.52)	5.45 (5.45)
Propranolol	$(C_{16}H_{22}NO_2)_3[Co(NO_2)_6]$	154	3:1	Orange	51.67 (51.65)	5.93 (5.92)	11.28 (11.30)	5.33 (5.29)
Levamisole	$(C_{11}H_{13}N_2S)_3[Co(NO_2)_6]$	194	3:1	Orange	41.68 (41.68)	4.06 (4.10)	17.63 (17.68)	6.18 (6.21)

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

Ion-associate	pH	μ	p^s	pk_{sp}
Pindololium reineckate	6.0	0.3	4.48	9.69
Pindololium cobaltinitrite	5.0	0.6	5.02	18.66
Propranololium reineckate	8.0	0.5	4.64	9.28
Propranololium cobaltinitrite	6.0	0.4	5.14	19.15
Levamisolium reineckate	7.0	0.2	4.55	9.10
Levamisolium cobaltinitrite	6.0	0.5	4.93	18.32

[a] $pk_{sp} = -\log$ solubility product; $p^s = -\log$ solubility.

posed methods are compared to those of the British Pharmacopoeia [41] for pindolol and propranolol hydrochlorides and the United States Pharmacopoeia [42] for levamisole hydrochloride. Also, the proposed method is applicable over wider concentration ranges: 1.14–17.07, 1.18–17.75 and 1.08–16.24 μg/ml of (1), (2) and (3), respectively, using ammonium reineckate and 1.71–25.60, 1.77–26.62 and 1.62–24.36 μg/ml of (1), (2) and (3), respectively, using sodium cobaltinitrite. Statistical analysis of the results using the *t*-test [43] at a 95% confidence limit was satisfactory. Comparison of the precision of the proposed method with those of the British and US Pharmacopoeia methods by the *F*-test [43] showed that it was reliable.

Table 3
Determination of the Investigated drugs in pure solutions and in pharmaceutical preparations by AAS

Sample	Quantity (mg/tablet)	Taken (μg)	Mean recovery (%)	Mean RSD[a] (%)
Using $[CR(NH_3)_2(SCN)_4]-$				
Pindolol solution		1.14–17.07	101.15	0.98
Visken tablets[b]	5	1.75–16.00	101.12	0.83
Propranolol solution		1.18–17.75	98.03	1.17
Inderal tablets[c]	40	2.25–16.25	98.85	1.06
Pranolol tablets[d]	40	2.00–14.25	98.76	0.95
Bedranol tablets[e]	10	3.50–16.25	98.57	1.08
Obsidan tablets[f]	40	2.15–15.65	98.69	0.71
Indicardin tablets[g]	40	3.20–16.40	98.59	0.74
Levamisole solution		1.08–16.24	101.67	0.86
Decaris tablets[h]	40	1.75–15.50	101.36	0.83
Ketrax tablets[c]	40	1.75–16.00	101.28	1.06
Using $[Co(NO_2)_6]^{3-}$				
Pindolol solution		1.71–25.60	99.82	0.43
Visken tablets	5	1.75–16.00	99.86	0.56
Propranolol solution		1.77–26.62	100.13	0.51
Inderal tablets	40	2.25–16.25	100.08	0.48
Pranolol tablets	40	2.00–14.25	100.15	0.39
Bedranol tablets	10	3.50–16.25	100.11	0.31
Obsidan tablets	40	2.15–15.65	100.12	0.33
Indicardin tablets	40	3.20–16.40	100.06	0.67
Levamisole solution		1.62–24.36	100.06	0.48
Decaris tablets	50	1.75–15.50	100.00	0.52
Ketrax tablets	40	1.75–16.00	100.08	0.36

[a] RSD, relative standard deviation (five determinations).
[b] Sandoz.
[c] ICI.
[d] Apolab.
[e] Lagap.
[f] Germed.
[g] APM.
[h] Janssen.

Table 4
Linear regression analysis for pindolol, propranolol and levamisole using ammonium reineckate and sodium cobaltinitrite

Parameter	Ammonium reineckate			Sodium cobaltinitrite		
	Pindolol	Propranolol	Levamisole	Pindolol	Propranolol	Levamisole
Optimum concentration range (μg/ml)	1.14–17.07	1.18–17.75	1.08–16.24	1.71–25.60	1.77–26.62	1.62–24.36
Shift or intercept of the regression line[a]	0.026	0.036	0.028	0.027	0.029	0.036
Slope of regression line	0.9976	1.0026	1.0043	0.9988	0.9997	1.0026
0.9968	2.15	2.09	1.89	1.98	2.21	2.04
Range of error (%)	98.7 ± 1.3	100.0 ± 1.5	100.0 ± 1.2	99.8 ± 1.6	99.5 ± 1.3	100.0 ± 1.5

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

In pharmaceutical analysis it is important to test the selectivity toward excipients and the fillers added to the pharmaceutical preparations. Fortunately, such materials mostly do not interfere. It is clear from the results obtained for the pharmaceutical preparations (Table 3) that these excipients 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 has the advantages of simplicity, precision, higher sensitivity, accuracy and convenience. Moreover, the reproducibility of the results is superior to those obtained from other methods such as chromatography [3,4,15,17,28], spectrophotometry [9,10,30], polarography [13] and conductometry [11], where pindolol and propranolol can be determined in the range of 2–24 mg. Therefore, the method should be useful for routine analytical and quality control assays of the investigated drugs in dosage forms.

In order to establish whether the proposed method exhibits any fixed or proportional bias, a simple linear regression [44] of observed drug concentration against the theoretical values (5 points) was calculated. Student's t-test [43] (at 95% confidence level) was applied to slope of the regression line (Table 4) and showed that it did not differ significantly from the ideal value of unity. Hence, it can be concluded that there are no systematic differences between the determined and true concentrations over a wide range. The standard deviations (S.D.) can be considered satisfactory at least for the level of concentrations examined.

3.2. Conclusion

Comparing the results obtained using ammonium reineckate and sodium cobaltinitrite, the latter offers the advantage of sensitivity, greater accuracy and precision, and higher range of determination due to the formation of 3:1 (drug: cobaltinitrite) ion-associate. Both reagents are useful for quality control for hydrochlorides of pindolol, propranolol and levamisole in pure form and in pharmaceutical formulation. The proposed methods were in excellent agreement with those obtained by the official methods [41,42].

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