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Short communication

Conductometric and indirect AAS determination of antimalarials

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Abstract

Two methods are described for the determination of amodiaquine hydrochloride, chloroquine phosphate and primaquine phosphate, based on the formation of their ion-associates with [Cd^{2+}, Co^{2+}, Mn^{2+} and Zn^{2+}] thiocyanate, ammonium reineckate and/or sodium cobaltinitrite. The molar combining ratio reveal that (1:1) (drug:reagent) ion associates are formed for all reagents except for ammonium reineckate which form (1:2) ion associates with all studied drugs. The optimum conditions for the ion-association have been studied. Conductometric method was applied for the direct determination of the suggested drugs in bulk powders, whereas indirect atomic absorption spectrometric method, depending on the measurement of the excess metal ion present in supernatant solutions after precipitation of the ion associates is used to calculate the drug concentration. Optimum concentration ranges for the determination of aminoquinoline antimalarial drugs under consideration were 0.46–12.90 and 0.155–3.87 mg using conductometric and indirect atomic absorption spectral methods, respectively. The proposed procedures have been applied successfully to the analysis of these drugs in certain formulations and the results are favourably comparable to the official methods.

Keywords: Ion associates; Conductometric titration; Atomic absorption spectra; Antimalarial determination; Dosage forms

1. Introduction

Aminoquinolines are widely prescribed therapeutic agents used as antimalarials. Due to their medicinal importance, several methods have been reported for there determination, either in pure or in dosage forms. They have been determined colorimetrically through ion-associate formation using ammonium reineckate [1] or through the formation of ternary complex with cobalt thiocyanate [2]. They have been determined titrimetry [3,4], spectrophotometry through the formation of charge-transfer complexes using tetracyanoethylene [5], 7,7,8,8-tetracyanoquinodimethane [6], chloranilic acid [7] and acid dye technique [8,9].

Amodiaquine has been determined spectrophotometrically using potassium periodate [10] or 2-benzothiazolinone [11]. Reported methods for

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primaquine include atomic absorption spectrometry [12], spectrofluorometry [13], thin layer and gas chromatography/mass spectrometry [14]. Chloroquine has been determined by ion selective electrode using tetraphenylborate [15], the acid dye technique [16], fluorometric [17] and high performance liquid chromatographic methods [18–22].

The previous methods [1–17] suffer from disadvantages such as lack selectivity and have low sensitivity, take long time for assaying, and require prior extraction. The goal of the present methods is to develop conductometric and indirect atomic absorption spectrometry (AAS) methods for the determination of amodiaquine hydrochloride (AQCl), chloroquine phosphate (CQP), and primaquine phosphate (PQP) in row materials and in some pharmaceutical preparations without interference from other constituents in formulation. The proposed methods can be used in laboratories where modern and expensive apparatus such as that required for GLC or HPLC are not available. An attempt to provide two simple, rapid and accurate methods for the quantitative determination of AQCl, CQP and PQP as row materials and in some pharmaceutical preparations with no interference from other constituents in the formulations is given. The first method is based on direct conductometric titration of the drug with Cd^{2+}, Co^{2+}, Mn^{2+} and Zn^{2+} thiocyanate, ammonium reineckate and/or sodium cobaltinitrite to form stable ion-associates. The second method depends on precipitation of the ion-associates formed, the excess metal ions present in the supernatant solutions are determined using AAS and used to calculate the concentration of the drug. Conductometric and AAS are well suited for these types of determination because of its accuracy, precision, sensitivity and free from interferences.

2. Experimental

2.1. Reagents

Double-distilled water and analytical grade reagents were used to prepare all solutions. Cadmium nitrate, cobalt sulphate, manganese chloride, zinc acetate, ammonium reineckate and sodium cobaltinitrite (Aldrich products) were used.

The aminoquinoline antimalarials studied are AQCl, CQP and PQP, all of pharmaceutical grade. Representative dosage forms are obtained from commercial sources. The purity of these drugs was checked by their official methods of analysis [4,23].

2.2. Apparatus

The pH of solutions was measured using an Orion research model 601A/digital ionalyzer pH-meter. A YSI model 32 conductance meter with a YSI model 3417 dip type cell ($k_{cell} = 1.0$) was used. The AAS for the determination of metal ion is carried out using Hitachi atomic absorption spectrometer Z-6100 Polarized Zeeman. For AAS, Cd^{2+}, Co^{2+}, Mn^{2+}, Zn^{2+} and Cr^{3+} ions were measured at wavelengths 228.8, 240.7, 279.6, 213.9 and 357.9 nm, respectively, slit width, 0.2 nm, relative noise, 1.0; detection limit, 0.01 μg ml^{-1}; linear dynamic range, 0.01–100 μg ml^{-1}; lamp current, 5.0 mA and integration time, 3.0 s. The flame used was the acetylene–air mixture.

2.3. Preparation of sample solutions

A 10^{-3} M of each drug was prepared by dissolving the calculated weight in a 100-ml calibrated flask and completed to the mark with water.

Solutions of Cd^{2+}, Co^{2+}, Mn^{2+} and Zn^{2+} thiocyanate complexes (0.010 M) are prepared by dissolving the accurately weighed amount of the metal ion salts and potassium thiocyanate in the proper volume of bidistilled water. Also 0.10 M of ammonium reineckate and/or sodium cobaltinitrite was freshly prepared by dissolving the accurate weight of salts in 100 ml-calibrated flask with water. Working solutions of lower concentrations were prepared by appropriate dilution of the standard solutions.

2.4. Conductometric measurements

The stoichiometry of the ion-associates was elucidated by conductometric titration of $5 \times$

10^{-4} M of AQCl, CQP or PQP with 5×10^{-3} M of Cd^{2+}, Co^{2+}, Mn^{2+} or Zn^{2+} thiocyanate, ammonium reineckate or sodium cobaltinitrite. The conductance was measured subsequent to each addition of reagent solution and after thorough stirring. The conductance reading, taken after 2.0 min of each addition was corrected for dilution [24]. A graph of the corrected conductivity vs. the volume of added reagent was constructed (Fig. 1).

2.5. Preparation of ion-associates

The ion associates were prepared by mixing solutions containing 10^{-2} M of Cd^{2+}, Co^{2+}, Mn^{2+} or Zn^{2+} thiocyanate, ammonium reineckate and/or sodium cobaltinitrite, and the requisite amount of AQCl, CQP or PQP. The precipitates obtained were filtered, thoroughly washed with water, and dried at room temperature. They were subjected to elemental analysis, IR spectroscopy and determination of the metal ion content [25] (Table 1).

2.6. Effect of pH on the solubility of ion associates

The choice of a suitable pH value at which the ion associate exhibits the lowest solubility and the effect of pH on the degree of completeness of ion-associate formation were studied. The solid ion associates were added to form saturated solutions in a series of solutions of different pH values ranging from 2.0 to 11.0; the pH value was adjusted with 0.1 M HCl or 0.1 M NaOH. The solutions were shacked for 3.0–4.0 h and left to stand for 1 day to attain a stable equilibrium, then filtered in a dry beaker. The equilibrium concentration of the metal ion present in the form of soluble inorganic complex ion is measured using AAS, and hence the solubility of the precipitate is evaluated, from which the solubility products of the ion associates were calculated.

2.7. Effect of ionic strength on the solubility of ion-associates

A series of saturated solutions of the ion-associate adjusted to the optimum pH value and having different ionic strengths (0.1–1.0 M) were prepared using KCl as electrolyte. The same procedures as those described above have been followed to determine the optimum ionic strength values at which ion-associates have the lowest solubility.

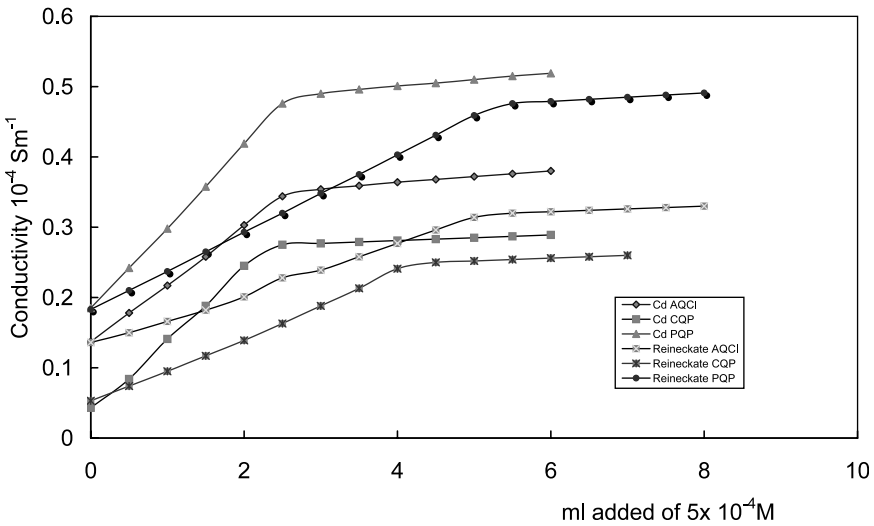

Fig. 1. Conductometric titration curve for the studied drugs using cadmium and reineckate salts.

Table 1
Elemental analysis and IR data for the drug–ion associate

Ion-associate composition	Percentage found (calculated)				IR band (cm^{-1})		
	C	H	N	M	ν_{SCN}	$\nu_{asv\ NO_2}$	$\nu_{sv\ NO_2}$
$[C_{20}H_{22}ClN_3O][Cd(SCN)_4]$	41.60 (41.14)	3.24 (3.14)	13.88 (14.00)	16.15 (16.07)	2065		
$[C_{18}H_{26}ClN_3][Cd(SCN)_4]$	40.05 (39.76)	4.02 (3.92)	14.60 (1476)	17.00 (16.94)	2070		
$[C_{18}H_{26}ClN_3][Co(SCN)_4]$	43.55 (43.24)	4.35 (4.26)	15.93 (16.05)	9.70 (9.66)	2055		
$[C_{15}H_{21}N_3O][Co(SCN)_4]$	41.70 (41.45)	3.90 (3.82)	17.70 (17.82)	10.80 (10.73)	2060		
$[C_{20}H_{22}ClN_3O][Mn(SCN)_4]$	45.00 (44.82)	3.51 (3.42)	15.17 (15.25)	8.75 (8.56)	2045		
$[C_{15}H_{21}N_3O][Mn(SCN)_4]$	41.90 (41.76)	3.93 (3.85)	17.80 (17.95)	10.10 (10.07)	2065		
$[C_{18}H_{26}ClN_3][Zn(SCN)_4]$	43.02 (42.79)	4.30 (4.21)	15.73 (15.88)	10.70 (10.60)	2075		
$[C_{20}H_{22}ClN_3O][Zn(SCN)_4]$	44.25 (44.10)	3.45 (3.37)	14.88 (15.01)	10.00 (10.02)	2050		
$[C_{15}H_{21}N_3O][Cr(NH_3)_2(SCN)_4]_2$	31.03 (30.84)	3.58 (3.45)	23.28 (23.46)	11.70 (11.62)	2040		
$[C_{20}H_{22}ClN_3O][Cr(NH_3)_2(SCN)_4]_2$	34.05 (33.91)	3.50 (3.43)	21.07 (21.19)	10.60 (10.49)	2065		
$[C_{18}H_{26}ClN_3]Na[Co(NO_2)_6]$	32.05 (31.88)	3.95 (3.84)	18.44 (18.60)	8.80 (8.71)	–	1505	1330
$[C_{20}H_{22}ClN_3O]Na[Co(NO_2)_6]$	33.81 (33.64)	3.20 (3.08)	17.40 (17.66)	8.30 (8.27)	–	1510	1335

2.8. General procedures

2.8.1. Conductometric procedure

Transfer suitable aliquot of a sample solution containing 0.465–12.54, 0.516–12.90 and 0.455–11.95 mg of AQCl, CQP and PQP, respectively into a 100 ml beaker, complete with water up to 50 ml, the conductivity cell immersed in and then 5×10^{-3} M of the reagent under consideration was added from a microburette. The conductance is measured subsequent to each addition of reagent solution after thorough stirring. A graph of conductivity (corrected for dilution) vs. volume of titrant added is thus constructed and the end-point determined (Fig. 1). Ten millilitres of 5×10^{-3} M Cd^{2+}, Co^{2+}, Mn^{2+} or Zn^{2+} thiocyanate and sodium cobaltinitrite is equivalent to 2.323, 2.580 and 2.277 mg of AQCl, CQP and PQP, respectively, whereas on using ammonium reineckate, it is equivalent to 1.162, 1.290 and 1.138 mg of AQCl, CQP and PQP, respectively.

2.8.2. Atomic absorption spectrometric procedure

Aliquots of sample solution containing up to 3.72, 3.87 and 3.64 mg of AQCl, CQP and PQP, respectively, are quantitatively transferred into 25 ml calibrated flask. To each flask, 1.0 ml of 0.01 M standard solution of the reagent under consideration is added and the flask is filled to the mark with the recommended buffer solution of the optimum pH and ionic strength values. The solutions are shaken well, 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 is determined using AAS. The metal ion consumed in the formation of ion associates is calculated, and the drug concentration is determined indirectly.

Each 1.0 ml of 10^{-3} M of Cd^{2+}, Co^{2+}, Mn^{2+}, Zn^{2+} thiocyanate and sodium cobaltinitrite is equivalent to 0.465, 0.516 and 0.455 mg of AQCl, CQP and PQP, respectively, whereas 0.232, 0.258 and 0.228 mg, respectively is equivalent on using ammonium reineckate.

2.9. Procedure for dosage forms

Weigh and pulverize 20 tablets or mix the contents of 20 ampoules. Transfer an amount of the powdered tablets or measure a volume of the mixed ampoules equivalent to one tablet or one ampoule. Dissolve or dilute with water in a 100 ml calibrated flask, filter if necessary, then prepare an assay solution in similar manner as (the sample solution) mentioned under the general procedures. The contents of the tablets or ampoules are calculated from the calibration graphs previously

prepared under the general procedures using the standard drugs.

3. Results and discussion

Conductometric analysis can be used for many titration procedures where ionic species are involved. As the conductance of a solution relates to the total ionic content, it can be used to follow reactions that result in a change in this quantity. Conductometry is one of the most successful yet simple analytical techniques; it can be used for the determination of the titration end-point.

3.1. Composition and structure of the ion-associates

Conductometric titrations of the inorganic complexes formed with each drug have been previously used to give insight into the stoichiometric compositions of the ion associates formed in solution, in this study, the same technique is used for quantitative purposes. Representative conductometric titration curves are shown in Fig. 1. Two straight lines are obtained intersecting at the end point, the first branch is ascending, the second one. The increase of conductance may be attributed to the hydrogen ion resulting from the dissociation of the protonated cation drug and partially to the drug cation and chloride or phosphate ions.

$$CQP + [Cd(SCN)_4]^{2-} \rightleftharpoons (CQP)[Cd(SCN)_4] + HPO_4^{2-}$$

$$PQP + Na_3[Co(NO_2)_6] \rightleftharpoons (PQP)Na[Co(NO_2)_6]$$

$$AQCl + 2NH_4[Cr(NH_3)_2(SCN)_4] \rightleftharpoons (AQ)\,[Cr(NH_3)_2(SCN)_4]_2 + 2NH_4Cl$$

After the end point, the conductivity do not change due to complete formation of the ion-associates. The measured conductance was stable for at least 1.5 h. The results of elemental analysis, metal content determination and IR of the solid ion associate, Table 1, reveal that (1:1) (drug:reagent) ion associates are formed for all reagent except for ammonium reineckate which form (1:2) ion associate with all studied drugs.

3.2. Optimization of variables for AAS

The facts that, the investigated drugs form insoluble ion associates with the studied reagents initiate the probability of their use in quantitative determination. Investigations were carried out to establish the most favourable conditions to achieve complete precipitation, high stability and low solubility of the ion associates formed. The influence of each of the following variables on the reaction was tested.

3.2.1. Effect of pH

The choice of a suitable pH value at which the ion associate exhibits the lowest solubility is of prime importance in the use of such compounds in quantitative analysis. To determine this pH value, the solubilities and the solubility products of the ion associates are determined at room temperature (25 ± 1 °C) in solutions of varying pH values. From the obtained results, it is observed that increasing the pH value of the medium in the range from 4.0 to 7.0 decreases the solubility of the ion associate until a certain pH (Table 2) above which the solubility starts to increase. This can be explained by considering the solubility equilibrium of the ion associate, e.g.:

$$(AQ)[Zn(SCN)_4] \rightleftharpoons AQ_2 + [Zn(SCN_4)]^{2-}$$

In acid medium, the hydrogen ion may react with the complex anion, $[Zn(SCN)_4]^{2-}$, while in basic medium the hydroxyl ion may react with the amodiaquinium ion leading to the formation of the free base or the metal thiocyanate complexes. However, it is to be noted that the effect of pH is rather weak and the present method can be applied safely over a wide range of pH values.

3.2.2. Effect of ionic strength

The choice of a suitable ionic strength (μ) value at which the ion associate exhibits the lowest solubility is also of prime importance in the used of such ion associates in quantitative analysis. The solubility and solubility product values of the ion associates at different μ values (0.1–1.0) have been

Table 2
Characteristics of the conductometric and indirect atomic absorption spectrometric methods

Ion-associate	pH	μ	M.R	P_s	pK_{s_p}	Determinaton range (mg)	Conductometric				t-Test[b]	Determination range (mg)	Indirect atomic absorption spectrometry				
							Regression line[a]						Regression line [a]				
							a	b	r	RSD			a	b	r	RSD	t-test[b]
Cd–AQC	6.5	0.6	1:1	3.35	11.23	0.47–9.77	0.008	0.017	0.9982	1.44	1.23	0.186–2.97	0.005	0.011	0.9996	0.85	1.15
Cd–CQP	6.0	0.5	1:1	3.15	9.91	0.52–11.35	−0.009	0.021	0.9988	1.13	1.05	0.206–2.58	0.006	0.013	0.9998	0.96	1.22
Cd–PQP	6.0	0.5	1:1	2.10	9.59	0.46–10.65	−0.011	0.024	0.9985	1.25	1.17	0.182–2.28	−0.004	0.016	0.9992	1.00	1.30
Co–AQC	6.0	0.4	1:1	3.59	12.92	0.93–10.23	0.012	0.022	0.9994	1.32	1.29	0.155–3.25	−0.004	0.015	0.9990	0.78	1.08
Co–CQP	6.5	0.6	1:1	3.37	11.37	0.52–11.66	−0.007	0.015	0.9998	1.53	1.48	0.188–3.35	−0.006	0.017	0.9995	0.98	1.35
Co–PQP	5.5	0.7	1:1	3.28	10.75	0.46–10.74	0.010	0.019	0.9995	1.36	1.51	0.202–2.96	0.004	0.014	0.9996	0.88	1.20
Mn–AQC	4.5	0.5	1:1	3.26	10.65	0.47–9.30	0.015	0.026	0.9988	1.46	1.78	0.169–3.02	0.007	0.020	0.9994	0.90	1.38
Mn–CQP	6.0	0.6	1:1	3.09	9.53	0.52–11.15	−0.010	0.017	0.9990	1.20	1.42	0.206–3.10	−0.005	0.013	0.9998	1.07	1.40
Mn–PQP	5.5	5	1:1	3.04	9.25	0.91–10.92	0.009	0.018	0.9993	1.28	1.17	0.166–3.19	0.003	0.010	0.9998	0.97	1.35
Zn–AQC	6.0	0.7	1:1	3.16	10.00	0.47–10.70	0.013	0.020	0.9992	1.35	1.20	0.232–2.79	−0.007	0.015	0.9992	0.80	1.10
Zn–CQP	7.0	0.6	1:1	3.00	9.02	0.77–10.83	−0.016	0.019	0.9996	1.41	1.35	0.260–2.58	0.008	0.013	0.9995	0.99	1.36
Zn–PQP	5.0	0.7	1:1	2.97	8.82	0.46–10.01	−0.011	0.015	0.9998	1.57	1.64	0.230–2.28	0.005	0.011	0.9998	0.79	1.00
Rein–AQC	6.5	0.5	1:2	3.64	12.03	0.47–8.60	−0.015	0.027	0.9989	1.28	1.08	0.133–2.79	−0.008	0.017	0.9996	0.71	0.97
Rein–CQP	6.0	0.7	1:2	3.41	9.96	0.52–9.03	0.009	0.018	0.9997	1.34	1.26	0.229–2.97	0.006	0.014	0.9990	0.76	1.08
Rein–PQP	7.0	0.6	1:2	3.34	9.28	0.46–8.20	0.015	0.023	0.9990	1.48	1.40	0.182–2.73	0.004	0.015	0.9994	0.85	1.17
Nitrite–AQC	6.0	0.5	1:1	3.77	14.22	0.47–12.54	−0.008	0.018	0.9994	1.37	1.62	0.186–3.72	−0.003	0.012	0.9999	0.95	1.24
Nitrite–CQP	5.5	0.4	1:1	3.51	13.36	0.52–12.90	0.006	0.014	0.9999	1.30	1.47	0.206–3.87	−0.006	0.016	0.9996	0.87	1.33
Nitrite–PQP	6.5	0.6	1:1	3.45	11.89	0.46–11.95	0.011	0.020	0.9995	1.26	1.44	0.202–3.64	0.007	0.017	0.9992	1.03	1.40

[a] Average of six determinations.
[b] Theoretical value for t-test at 95% confidence limit for five degrees of freedom was 2.57.

determined at the optimum pH values. It was found that increasing the μ values of the medium up to 0.7 decreases the solubility of the ion associates, probably due to the salting out effect, until the optimum m value is reached (Table 2). Then the solubility increases again due to complexation reaction between the base cations and the concentrated KCl in the medium leading to precipitation of the drug, and hence the concentration of the metal ion increases and so increases in the calculated solubility values.

The values of the solubility and solubility product at the optimum conditions of pH and ionic strength (μ) are given in Table 2. The results indicate that the present ion associates are so sparingly soluble that AQCl, CQP or PQP can be determined accurately and precisely by the indirect method through precipitation of their ion associates with Cd^{2+}, Co^{2+}, Mn^{2+} and Zn^{2+} thiocyanate complexes, ammonium reineckate and sodium cobltinitrite reagents. The measurements were stable for at least one day indicating high stability. Therefore, the proposed method can be used as stability-indicating method.

3.3. Analytical data

The results given in Table 2 show the characteristics of the proposed conductometric and atomic absorption spectrometric methods. These include range of determination for each drug with each reagent, with their standard deviations. In order to establish whether the proposed methods exhibit any fixed or proportional bias, a simple linear regression [26] of observed drug concentration against the theoretical value (six points) was calculated (Table 2). The RSD% of slope and intercept were found in the range 0.027–0.053 and 0.016–0.039%, respectively, indicating high reproducibility of the proposed methods. Student's t-test (at 95% confidence level) was applied to the slope of the regression line (Table 2) 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 (0.041–0.074) can be considered satisfactory, at least for the level of concentration examined.

The detection and quantification limits were calculated from the standard deviation of a series of 13 blank measurement for each procedure. The limit of detection ($K = 3.0$) and of quantification ($K = 10$) were established according to IUPAC definitions [27]. The results obtained were found to be 0.14 and 0.45 using conductometric method, whereas using indirect AAS were 0.037 and 0.13, respectively. The precision of conductometric and atomic absorption spectrometric methods was determined by analysing seven samples, each containing 8.0 and 2.0 mg of each drug applying the two methods, respectively. The relative standard deviations are found in the range 0.67–0.94% on using different reagent under consideration.

Comparison of the results obtained by the proposed methods using cobalt thiocyanate with those obtained by Hassan et al. [2] using cobalt and thiocyanate to form ternary complexes and measuring the nitrobenzene extracted complex by spectrophotometric and AAS. The results showed a wider range of determination, higher accuracy and precision and less time consumption with the methods proposed here.

The proposed methods using ammonium reineckate are simpler, less time consuming, wider range of determination and more sensitive than the extraction colorimetric procedure using the same reagent [1]. Although, the official methods [4,23] required less time for completion, the proposed methods showed more accurate and precise results in addition to a wider range of determinations.

It can be concluded that the proposed methods are accurate and precise. However, the expected higher sensitivity of the AAS-method can allow the determination of drugs in low concentrations.

3.4. Interferences

Several pharmaceutical dosage forms are associated with flavouring agents, diluents and excipients, such as maltose, sucrose, glucose, lactose, starch, citric acid, benzoic acid, sodium bicarbonate, and magnesium stearate. In preliminary experiments, these compounds were tested with the reagents under consideration and found not to

Table 3
Determination of aminoquinoline salts in pharmaceutical preparations

Preparation	Taken mg	Recovery[a](%)													
		Conductometric						Indirect atomic absorption spectrometry							
		Cd^{2+}	Co^{2+}	Mn^{2+}	Zn^{2+}	Cr^{3+}	Nitrite	Taken mg	Cd^{2+}	Co^{2+}	Mn^{2+}	Zn^{2+}	Cr^{3+}	Nitrite	Official
Amodiaquine HCl tablets (200 mg/tablet)	3.00	99.33	98.33	101.00	98.67	100.67	99.33	0.6	99.17	99.33	100.83	100.67	99.00	101.00	101.20
	6.00	100.83	99.17	100.83	100.67	99.00	100.50	1.2	99.17	100.83	100.83	100.33	100.83	98.33	98.60
	9.00	101.11	100.78	99.67	100.56	100.67	99.44	1.8	100.56	100.67	100.56	98.89	101.11	101.11	98.00
	Mean	100.42	99.43	100.50	99.97	100.11	99.76	Mean	99.63	100.28	100.74	99.96	100.31	100.15	99.27
	S.D.	0.52	0.47	0.54	0.32	0.37	0.46	S.D.	0.45	0.37	0.52	0.43	0.56	0.39	0.63
	$t(2.57)$[b]	1.81	1.69	1.75	1.28	1.44	1.53	$t(2.57)$[b]	1.63	1.48	1.77	0.96	1.52	1.47	
	$F(5.05)$[b]	1.47	1.80	1.36	3.88	2.90	1.88	$F(5.05)$[b]	1.96	2.90	2.51	2.15	1.27	2.61	
Dagrinol ampoules (250 mg CQP/amp)	2.50	99.20	99.60	100.40	100.80	99.20	99.60	0.7	98.57	100.86	100.57	99.71	100.29	100.43	101.50
	5.00	101.00	100.80	98.80	99.60	101.20	101.20	1.4	100.86	100.21	99.71	99.57	99.29	99.43	98.50
	7.50	102.67	99.33	100.67	101.33	99.33	101.07	2.1	100.48	99.05	100.95	101.43	101.19	99.05	98.20
	Mean	100.96	99.91	99.96	100.58	99.91	100.62	Mean	99.97	100.04	100.41	100.24	100.26	99.64	99.40
	S.D.	0.71	0.39	0.51	0.55	0.41	0.48	S.D.	0.52	0.55	0.57	0.43	0.46	0.67	0.78
	$t(2.57)$[b]	1.92	1.50	1.25	1.78	1.53	1.67	$t(2.57)$[b]	1.46	1.18	1.88	1.71	1.77	1.94	
	$F(5.05)$[b]	1.21	4.00	2.34	2.01	3.62	2.64	$F(5.05)$[b]	2.88	2.01	1.87	3.29	2.88	1.36	
Primaquine phosphate tablets (200 mg/tab)	2.75	100.73	98.91	100.36	99.27	100.73	101.09	0.8	99.38	100.50	100.88	99.00	99.25	100.38	99.20
	5.50	99.64	100.73	100.73	101.00	99.27	101.00	1.6	101.25	99.38	100.94	98.75	100.63	99.06	98.50
	8.00	99.63	100.63	99.00	101.00	100.50	99.00	2.4	99.58	100.63	99.17	100.83	100.63	99.58	100.50
	Mean	100.00	100.09	100.03	100.42	100.17	100.36	Mean	100.07	100.17	100.33	99.53	100.17	99.67	99.40
	S.D.	0.58	0.47	0.63	0.52	0.44	0.63	S.D.	0.49	0.61	0.58	0.66	0.45	0.48	0.86
	$t(2.57)$[b]	1.11	1.27	1.22	1.67	1.55	1.83	$t(2.57)$[b]	1.38	1.65	1.79	1.87	1.70	1.72	
	$F(5.05)$[b]	1.63	3.35	1.86	2.74	3.82	1.86	$F(5.05)$[b]	3.08	1.99	2.20	1.70	3.65	3.21	

[a] Average of six determinations.
[b] Theoretical values for five degrees of freedom and 95% confidence limits.

form an ion associate and therefore do not interfere in the determination of the studied drugs. Moreover, the degradation products of AQCl, CQP and PQP do not interfere in their determinations.

3.5. Analytical applications

Table 3 summarizes the results of the application of both conductometric and atomic absorption spectrometric methods to determine amodiaquine HCl, chloroquine phosphate and primaquine phosphate in some pharmaceutical formulations. The accuracy and reproducibility with respect to the official method (based on spectrophotometric determination of AQCl at 342 nm [23] and non-aqueous titration using 0.1 M perchloric acid for CQP and PQP [4]) were assessed by calculation of Student's t-test and F-value, respectively. Mean values recorded in Table 3, show the absence of any systematic error and no significant difference between the methods compared.

4. Conclusion

Two methods for the determination of AQD, CQP and PQP using direct conductometric titration and indirect atomic absorption spectrometric techniques are reported. The methods are based on the formation of ion associates between these drugs and [Cd^{2+}, Co^{2+}, Mn^{2+} and/or Zn^{2+} thiocyanate], ammonium reineckate and sodium cobaltinitrite. The proposed methods have the advantages over other spectrophotometric and chromatographic methods with respect to simplicity, stability, reproducibility, rapidity, accuracy and precision. Although, the spectrophotometric method for the determination of the studied drugs with Co^{2+} and thiocyanate as ternary complex [2] requires 30 min for extraction and measurements, the proposed methods are simpler, less time consuming and more sensitive. Moreover, using ammonium reineckate as a reagent for determination has the advantage over a previously method [1], of a wider range of determination, higher sensitivity, free from interferences and less time consumption. Also the proposed methods were compared with the official ones [4,23], indicating the absence of any systematic error and no significant difference between the compared methods. Although, the official methods [4,23] required less time for completion, the proposed methods showed more accurate, reproducible, precise results and wider range of determinations, in addition to stability indicating method especially indirect AAS method. The proposed methods are suitable for the determination of the studied drugs in dosage forms without interferences from excipients such as starch and glucose or from common degradation products suggesting applications in bulk drug and in dosage forms analysis.

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