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Amodiaquine polymeric membrane electrode

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Abstract

The construction and electrochemical response characteristics of two types of poly(vinyl chloride) (PVC) membrane sensors for the determination of amodiaquine hydrochloride (ADQ·2HCl) are described. The sensing membrane comprised an ion-pair formed between the cationic drug and sodium tetraphenyl borate (NaTPB) or potassium tetrakis(4-chlorophenyl) borate (KTCPB) in a plasticized PVC matrix. Eight PVC membrane ion-selective electrodes were fabricated and studied. Several plasticizers were studied namely, dioctyl phthalate (DOP), 2-nitrophenyl octyl ether (NPOE), dioctyl phenylphosphonate (DOPP) and bis(2-ethylhexyl)adipate (EHA). The sensors display a fast, stable and near-Nernstian response over a relative wide ADQ concentration range (3.2×10^{-6} to 2.0×10^{-2} M), with slopes comprised between 28.5 and 31.4 mV dec^{-1} in a pH range comprised between pH 3.7 and 5.5.

The assay of amodiaquine hydrochloride in pharmaceutical dosage forms using one of the proposed sensors gave average recoveries of 104.3 and 99.9 with R.S.D. of 0.3 and 0.6% for tablets (Malaritab®) and a reconstituted powder containing ADQ·2HCl, respectively. The sensor was also used for dissolution profile studies of two drug formulations. The sensor proved to have a good selectivity for ADQ·2HCl over some inorganic and organic compounds, however, berberine chloride interfered significantly. The results were validated by comparison with a spectrophotometric assay according to the USP pharmacopoeia.

Keywords: Amodiaquine; PVC; Potentiometry; *P. falciparum*; Malaria; ISE

1. Introduction

Amodiaquine, 7-chloro-4-(3-diethylaminomethyl-4-hydroxyphenylamino) quinoline, is an antimalarial drug prophylactic against malaria which is a mosquito-borne disease and one of the major killers of the world, currently causing an estimated one million deaths each year in Africa alone [1,2]. Attributed frequently to the protozoaire parasite *Plasmodium falciparum*, the most dangerous of all the malaria parasites, and transmitted by the *Anopheles mosquito*, this infection is frequently more fatal in children than in adults—producing respiratory distress, neurological problems and severe anaemia, and leading to death in 5–35% of severe infections. Malaria also poses a particular danger to pregnant women and may lead to miscarriage or low birth weight of the child. In endemic regions, the disease is recognized as serious impediment to economic and social development [3,4].

The incidence of resistance in *P. falciparum* malaria to antimalarial drugs continues to increase in large areas of the developing world and this increasing drug resistance limits the choice of efficacious chemotherapy against *P. falciparum* malaria. Amodiaquine (ADQ) was formerly used as a prophylactic agent against malaria but lost its importance due to the risk of development of agranulocytosis and hepatic disorders [5].

For those reasons, the usefulness of ADQ for treatment of malaria remained limited. However, recently, ADQ received renewed interest since its safety and efficacy have been demonstrated in several clinical trials [5–7]. Due to the vital importance of the assay of ADQ in pharmaceutical and biological fluids, several analytical methods including liquid chromatography [5,7,8–10], conductometry [11], fluorimetry [12] and spectrophotometry [13–15] have been reported for the determination of the drug in its pure and dosage forms. However, some of these methods suffer from severe interferences by various organic

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compounds and require relatively sophisticated instrumentation and reagents.

Selective potentiometric electrodes have been reported for the assay of antimalarial drugs such as chloroquine [1,16,17] and primaquine [18]. A thorough literature survey revealed that no potentiometric sensor for ADQ have been published to date. Therefore, the aim of this work was to develop polymeric ion-selective sensors for ADQ determination in pharmaceutical formulations and for the dissolution profile studies. Potentiometric membrane electrodes have been widely described for pharmaceutical analyses [19,20]. This can be explained by the good analytical performances in terms of selectivity and accuracy, low detection limit, wide concentration range, application in coloured and turbid solutions for a relatively limited financial investment.

The membrane used in these electrodes was made from liquid-plasticized PVC and was based on a water-insoluble ADQ-TPB or ADQ-TCPB ion-pair complex as ion-exchanger. Several plasticizers were investigated since their nature may significantly limit the concentration range and/or the sensitivity of the sensor.

2. Experimental

2.1. Apparatus

Potentiometric measurements were made at $25 \pm 1\,^{\circ}C$ using a Tacussel microprocessor type II pH/mV meter (France). The amodiaquine sensors were used in conjunction with an Orion 90-02 Ag/AgCl double junction reference electrode containing 10% (w/v) potassium nitrate solution in the outer compartment.

The solutions pH and the temperature measurement were performed with a Metrohm model 744 digital pH-meter (Herisau, Switzerland) with a Metrohm combined glass electrode with built-in temperature probe.

A Shimadzu UV–vis 160 spectrophotometer (Antwerp, Belgium) was used to validate the potentiometric assays for amodiaquine tablets while the dissolution test was performed at $37 \pm 1\,^{\circ}C$ in a basket-stirrer USP 24 apparatus DISTEK type 2 with a DISTEK TCSO200C thermostat (DISTEK Inc., North Brunswick, NJ, USA) and an on-line UV–vis detector (Hewlett-Packard type 8453 spectrophotometer).

All measurements were performed in a thermostatted glass cell with constant magnetic stirring of the solution.

2.2. Reagents

All reagents were of analytical grade and used without any further purification. Deionized water was used throughout. Reagent grade amodiaquine hydrochloride powder (purity 99.9%) and sodium tetraphenylborate (NaTPB) were from ICN (Asse-Relegem, Belgium). High relative molecular weight PVC, nitrophenyl octylether (NPOE) and potassium tetrakis(4-chlorophenyl) borate (KTCPB) were from Fluka (Bornem, Belgium). Dioctyl phthalate (DOP) was from Acros (Geel, Belgium), dioctylphenyl phosphonate (DOPP), ethylhexyladipate (EHA) and tetrahydrofurane (THF) were from Aldrich (Bornem, Belgium).

ADQ tablets (Malaritab® from Alisons, Brussels and Malaridose® from Zenufa sprl, Kinshasa) were purchased from a local drug story in Kinshasa (R.D. Congo). Each tablet was labelled to contain 200 mg base form, corresponding to 241 mg of the hydrochloride form.

2.3. Membrane preparation and electrode assembly

2.3.1. Ion-pair preparation

The amodiaquine tetraphenylborate (ADQ-TPB) ion-pair was prepared by reacting 1×10^{-3} M amodiaquine hydrochloride in water with an equal volume of 2×10^{-3} M sodium tetraphenylborate solution. The mixture was filtered through a porosity-4 sintered-glass crucible. The residue was washed with cold deionized water until no chloride ion was detected into the washing solution. The yellow precipitate was dried under vacuum for 48 h, then grinded to a fine powder in a mortar. The ion-pair was blended in the PVC by sonication in the presence of the plasticizer dissolved in tetrahydrofuran (THF) in a glass made Petri dish as previously described [21]. The homogeneous cocktail was covered with a filter paper and allowed to stand overnight. A master membrane with a thickness of approximately 0.25 mm was obtained.

When using potassium tetrakis(4-chlorophenyl) borate (KTCPB), which is insoluble in water, the master membrane was prepared by dissolving KTCPB plus the plasticizer in PVC in the presence of THF. The ADQ-TCPB ion-pair was generated "in situ" at the electrode–solution interface by conditioning the assembled electrode in a 5×10^{-3} amodiaquine acetate buffer for more then 48 h. After this time conditioning, the TCPB-based membrane turned from white to yellow, indicating that the formation of the ADQ-TCPB ion-pair has occurred [1,22].

The stoichiometry of the ion-pair with tetraphenylborate and tetrakis(4-chlorophenyl) borate anions was inferred to be 2(ADQ):1(TPB or TCPB), as proved by volumetric titration and UV spectroscopy monitoring during titration. Different membrane compositions were studied by varying the percentage (w/w) and the nature of the ion-exchanger and the plasticizer.

2.3.2. Electrode construction

A 5-mm diameter disc was cut out from the prepared membrane and glued to the polished end of a plastic tube using a PVC-THF paste. The sensors were pre-conditioned by soaking into a 5×10^{-3} M ADQ acetate buffer for 1 h (ADQ-TPB) or 48 h (ADQ-TCPB) and stored in the same solution when not in use.

2.3.3. Standard amodiaquine solutions

A stock solution of 0.01 M amodiaquine hydrochloride was prepared by dissolving the calculated weight of pure drug in 100 ml acetate buffer solution (for potentiometric assays) or HCl 0.12 M (for spectrophotometric assays). The working solutions (1×10^{-2} to 3.2×10^{-6} M) were prepared by serial appropriate

dilution of the stock solution while keeping the pH constant at a value 4.3 (acetate buffer 0.1 M).

2.3.4. Potentiometric measurements

Experiments were performed at 25.0 °C in a cell using a Haake FJ Circulator Thermostat (Brussels, Belgium) to control the temperature of the test solutions.

These experiments were preceded by the calibration of the electrode with several solutions of ADQ·2HCl (working solutions).

2.3.5. Application to pharmaceutical formulations

Malaritab® and Malaridose® tablets: The exact composition of the tablets was not mentioned by the manufacturer. Ten tablets were accurately weighed and crushed and mixed in a mortar. An appropriate amount was weighed, transferred to a 100 ml beaker and dissolved in about 70 ml of buffer solution by sonication during approximately 30 min without any filtration. Filtration was required for the spectrophotometric assay. The volume was completed to the mark.

A 2.5 ml aliquot of this solution was transferred to a 50 ml standard flask and diluted to the volume with the same solution.

The potential of the solution was measured using an ADQ electrode in conjunction with an Orion Ag/AgCl double junction reference electrode. The potential of the stirred solution was recorded after signal stabilization (± 1 mV min^{-1}) and the ADQ concentration was obtained by referring to a calibration plot obtained under identical experimental conditions from standard solutions of ADQ.

Reconstituted powder: One mixture was prepared with a known amount of amodiaquine chlorhydrate powder (99.9% purity) and other components such starch from rice, starch from corn, lactose and magnesium stearate. The accuracy of the potentiometric determination of ADQ in this powder was checked by evaluating the recovery.

2.3.6. ADQ tablet dissolution test

Tablet dissolution measurements were made according to method one of the US Pharmacopoeia using a basket-stirrer USP-type apparatus [23].

The dissolution media were acetate buffer 0.1 M pH 4.3 (potentiometry) and bidistilled water (spectrophotometry).

One tablet of Malaritab® or Malaridose® was placed in the basket and the dissolution medium was maintained at 37.0 ± 0.5 °C. The basket was rotated at 50 rpm and comprised the amodiaquine selective membrane electrode in conjunction with a double junction Ag/AgCl reference electrode as detection system. After an appropriate time interval (5 min) the potential values were recorded and the amount of drug released was determined from the calibration graph. For the UV–vis assay, fixed volumes of the dissolution medium were circulated, after controlled time intervals, through a UV–vis spectrophotometer and absorbance was measured at 342 nm. Determination was made by comparison with the absorbance of a standard solution of the active substance (reference substance) prepared under the same experimental conditions.

2.3.7. Effect of pH electrolyte concentration on the electrode response

The pH influence was investigated by preparing three series of ADQ solutions with different pH values ranging from 1.1 and 8.0 and recording the potential. The pH value was adjusted with 0.1 M HCl or 0.1 M NaOH. Two series of ADQ solutions adjusted to the optimum pH and having different electrolyte concentrations (0.1–1.0 M) were prepared using NaCl.

3. Results and discussion

3.1. Composition of the membrane

The operating characteristics of ISEs can be significantly modified by changing the relative proportions of the electrode membrane's component, which essentially comprised the lipophilic salt and the plasticizer.

3.1.1. Influence of plasticizer and sensing component

Amodiaquine ion-selective electrodes with different electroactive materials were investigated in order to compare their performances. Two commonly used reagents were investigated as possible counter ion for the preparation of the electroactive complex of ADQ, namely sodium tetraphenylborate (NaTPB) and potassium tetrakis(4 chlorophenyl) borate (KTCPB). The obtained ion-pairs combined with four plasticizer types, namely dioctylphtalate (DOP), nitrophenyloctyl ether (NPOE), dioctylphenyl phosphonate (DOPP) and ethylhexyl adipate (EHA) give eight combinations as shown in Table 1.

It is well known that the construction of PVC based ISEs requires the use of a plasticizer which mainly acts as a fluidizer allowing homogeneous dissolution and diffusional mobility of the ion-pair inside the membrane. The nature and/or the amount of plasticizer must be properly controlled in order to minimise electrical asymmetry of the membrane and to limit fouling of the sensor. In addition, the proper selection of the plasticizer allows one to control the value of the electrode/solution distribution ratio of the particular C^+A^- ion-pair employed as an ion-exchanger. The analytical performance of such electrode is strongly dependent on a suitable ratio of plasticizer and electroactive material. The nature of the plasticizer has a marked influence on the response slope, linear domain and also on the selectivity of PVC membrane electrodes.

In this work, the amount of polymer (poly(vinyl chloride) (PVC)) was kept constant (30%, w/w) while the ratio of the ion-exchanger (TPB or TCPB) to plasticizer (DOP, NPOE, DOPP and EHA) was varied [24]. Several membrane compositions

Table 1
Different combinations depending on the choice of ion-pairing reagent and plasticizer

Ion-pairing reagent	DOP	NPOE	DOPP	EHA
TPB	TPB-DOP	TPB-NPOE	TPB-DOPP	TPB-EHA
TCPB	TCPB-DOP	TCPB-NPOE	TCPB-DOPP	TCPB-EHA

Table 2
Ratios (%) of different components of the membrane

Composition	Ion-pair or counter ion	Polymer (PVC)	Plasticizer	Solvent (THF) (ml)
1	0.5	30	69.5	5
2	1.0	30	69.0	5
3	2.0	30	68.0	5
4	5.0	30	65.0	5
5	7.0	30	63.0	5

were investigated in which the percentage of ion-exchanger and plasticizer ranged from 0.5 to 5% and 69.5 to 65%, respectively (Table 2).

For each composition, the membranes were repeatedly prepared three times. The preparation process was highly reproducible as revealed from the low relative standard deviation values of the slopes obtained employing the prepared membranes (mean value of R.S.D. was approximately 0.4%, $n = 3$).

For all constructed electrodes, the percentage of entrapped ion-pair ranging between 1 and 2% was found to offer a better slope. This is in agreement with the literature data [19,20,25,26]. The results obtained with a 2% ion-pair content (TPB or TCPB) for four plasticizers are summarized in Table 3.

Although there are differences between linearity range and detection limit for different ion-pairs tested, they are close to the theory in terms of slope, except for sensors 6, 7 and 9. The latter contained no ion-pair. The data reported in Table 3 indicate that for all electrodes tested, a nearly Nernstian cationic response to ADQ·2HCl was obtained over approximately between two and four orders of magnitude in concentration. This fact implies that the electrode response characteristics were not significantly influenced by the type of the ion-pair except for the linear range.

Regarding the nature of the plasticizer, the best performances in terms of linear range and detection limit were obtained by using either DOP or EHA as solvent mediator. Membranes incorporating NPOE or DOPP as solvent mediator showed satisfactory slopes but lower detection limit and relatively shorter concentration range. The sensor without ion-pair gave no satisfactory slope and exhibited a long response time (defined as the time to reach a stable potential, i.e. with a fluctuation of ± 1 mV min^{-1}).

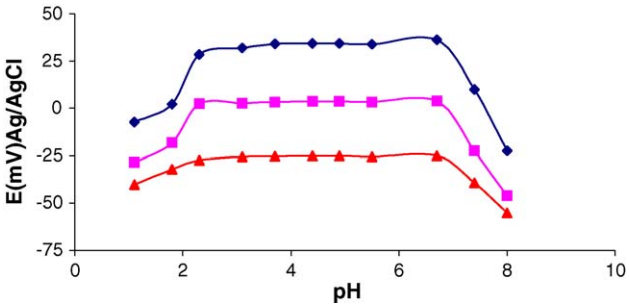

Fig. 1. Effect of pH on the response of the ADQ electrode (no. 1). amodiaquine 1×10^{-3} M (♦), amodiaquine 1×10^{-4} M (■), amodiaquine 1×10^{-5} M (▲).

Electrodes based on PVC membrane incorporating TPB or TCPB as ion-exchanger and either DOP or EHA as plasticizer were used for further investigations.

The influence of the concentration of the internal reference solution on the potential response of the ADQ-selective sensor was studied using electrode no. 1. The ADQ·2HCl concentration was varied from 1×10^{-6} to 1×10^{-2} M. It was found that the variation of the concentration of the internal reference solution does not cause any significant difference in the electrode response. A 1×10^{-3} M concentration of the internal reference solution was selected for further assays. The optimum conditioning time for the membrane sensors in a 5×10^{-3} M ADQ (pH 4.3; [NaCl] = 0.1) was 1 h or more then 48 h for ADQ-TPB and ADQ-TCPB membranes, respectively. The electrodes were rinsed with water and stored in air between measurements.

3.2. Influence of pH and effect of electrolyte concentration

This study was performed with electrodes no. 1 and 5. Fig. 1 illustrates a typical potential/pH trend using electrode no. 1, for a 1×10^{-3}, 1×10^{-4} and 1×10^{-5} M ADQ solutions. As seen, the electrode response was found to be independent on the pH range from 3.7 to 5.5.

At higher pH values, the potential decreased due to the gradual increase in the concentration of the unprotonated ADQ resulting in the precipitation of ADQ base, while at low pH, a triprotonated ADQ species [ADQ·H_3^{3+}] was probably formed. The base and the triprotonated ADQ were presumably

Table 3
The influence of the nature of the pairing agent and plasticizer on the characteristics of the electrodes

No.	Ion-pairing reagent	Plasticizer	slope^n (mV dec^{-1})	Coefficient of determination	Linear range	Limit of detection (LOD)	Response time
1	TPB	DOP	−31.4	0.9999	1×10^{-2}–3.2×10^{-6}	1.2×10^{-6}	<30 s
2	TPB	NPOE	−29.5	0.9998	1×10^{-2}–8.0×10^{-5}	3.2×10^{-5}	<30 s
3	TPB	DOPP	−29.4	0.9998	1×10^{-2}–4.0×10^{-4}	1.2×10^{-4}	<30 s
4	TPB	EHA	−29.8	0.9998	1×10^{-2}–1.6×10^{-5}	9.0×10^{-6}	<20 s
5	TCPB	DOP	−29.3	0.9996	1×10^{-2}–1.6×10^{-5}	1.1×10^{-5}	<30 s
6	TCPB	NPOE	−28.5	0.9996	1×10^{-2}–4.0×10^{-4}	1.2×10^{-4}	<30 s
7	TCPB	DOPP	−28.6	0.9997	1×10^{-2}–4.0×10^{-4}	1.9×10^{-4}	<30 s
8	TCPB	EHA	−29.5	0.9998	1×10^{-2}–8.0×10^{-5}	2.3×10^{-5}	<20 s
9	–	DOP	−16.5	0.9982	1×10^{-2}–4.0×10^{-4}	2.5×10^{-4}	>3 min

Acetate buffer pH 4.3, n = mean of three determinations.

Table 4
Selectivity coefficients for the amodiaquine electrode acetate buffer pH 4.4 and NaCl 0.2 M

Interfering species (0.001 M)	Electrode no. 1		Electrode no. 5	
	$\log K_{ij}^{pot}$	K_{ij}^{pot}	$\log K_{ij}^{pot}$	K_{ij}^{pot}
Berberine	5.1		5.1	
Imipramine	4.3		4.3	
Promazine	4.2		4.2	
Quinidine	1.7		1.7	
Quinine	0.9	15.8	0.9	15.2
Chloroquine	−0.5	0.24	−0.5	0.25
Caffeine	−2.7	0.0021	−2.7	0.0019
Sulphanilamide	−3.0	0.0016	−3.1	0.0012

$\log K_{ij}^{pot}$: separate solutions method; K_{ij}^{pot}: mixed solutions method. The selectivity for the first four molecules was obtained by the separate solution method.

not detected by the electrode. Such pH–mV profile was also observed for some electrodes based on other compositions.

The choice of a suitable ionic strength value at which the membrane electrode exhibits the best response is also of prime importance in quantitative analyses. The potential values of the membrane electrode at different electrolyte concentrations (0.02–1.0 M NaCl) have been determined at the pH 4.3. It was found that the electrode followed a Nernstian behaviour for NaCl concentrations comprised between 0.1 and 0.7 M.

3.3. Selectivity of the electrodes

The selectivity of an ion-pair based membrane electrode depends on the physico-chemical characteristics of the ion-exchange process at the membrane–sample solution interface, on the mobility of the respective ions in the membrane, and on the hydrophobic interactions between the primary ion and the organic membrane [24].

The selectivity of the ADQ drug membrane electrode is related to the free energy of transfer of the ADQ drug cation between aqueous and organic phases The response of the electrode towards different substances has been checked and the selectivity coefficient K_{ij}^{pot} was used to evaluate the degree of interference. The values of selectivity coefficient was obtained using either separate solution or mixed solution methods [27–29].

Pharmaceutical dosage forms may be associated with flavouring agents, diluents and excipients, such as maltose, sucrose, glucose, lactose, starch, propylene glycol, magnesium stearate and hydroxypropyl cellulose. These substances were found to give no interference at the sensor tested. Other molecules were investigated because having either similar structure or an amine group. Caffeine and sulphanilamide gave no interference. Chloroquine and quinine interfered slightly while imipramine, promethazine and alkaloids, such as berberine cause serious interference (Table 4). This is expected for sensor based on ion-pairing agents where larger lipophilic species are efficiently extracted into the membrane, hence the origin of the interfering phenomenon. The interference from these lipophilic amines has been observed for both TPB and TCPB ion-pairing.

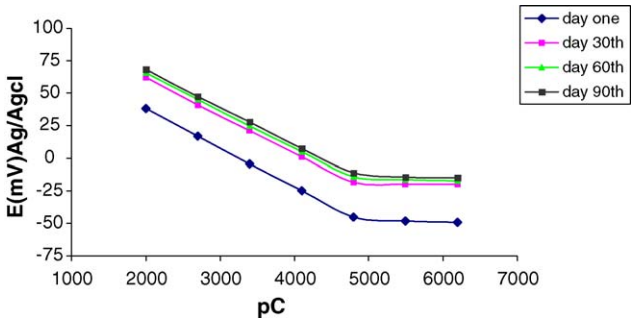

Fig. 2. Calibration of the amodiaquine electrode (no. 5) as a function of time.

However, this is of no deterrent to the use of these electrodes in the analysis of pharmaceutical preparations as these compounds are unlikely to be present together with ADQ.

3.4. Lifetime, reproducibility and response time

The electrode lifetime was investigated by performing the calibration curve and periodically testing a standard solution (6.4×10^{-7}–1×10^{-2} M, ADQ·2HCl) and calculating the response slope (Fig. 2). It was observed that the investigated electrode (no. 5) exhibited good stability in terms of slope in the linear domain of concentration and the electrode can be used continuously for about 3 months without considerable decrease in its slope value.

The reproducibility of the potential measurement for a 1×10^{-4} M standard ADQ·2HCl solution for five measurement cycles gave a R.S.D. of 1.7%.

The time required for all constructed sensors to reach values within ±1 mV of the final equilibrium potential after immersion in ADQ solutions varies from 15 s for ADQ concentrations between 8×10^{-5} and 1×10^{-2} M and 45 s for lower ADQ concentrations.

3.5. Analytical applications

The ADQ membrane electrode (no. 5) was used for the determination of ADQ in tablets and in the reconstituted powder. No sample treatment other than dilution in buffer solution was required.

The applicability of the ADQ membrane sensors to the determination of the drug in the dosage forms was firstly checked by studying the recovery of an accurate amount of pure ADQ·2HCl in a reconstituted powder samples. The recovery obtained from five measurements was found to be 99.9% with a R.S.D. of 0.6%. The sensor was subsequently used for the assay of the pharmaceuticals (Malaritab® and Malaridose®). Buffer solutions of ADQ from tablets containing 0.1–0.3 mg ml^{-1} were prepared and analysed by direct potentiometry. The displayed potentials were compared with the corresponding calibration graphs constructed the same day to assess the accuracy and reproducibility. The obtained results for Malaritab® gave a recovery of 104.3% (R.S.D. = 0.3%, $n = 4$) and 104.7% (R.S.D. = 0.5%, $n = 4$) by potentiometry and spectrophotometry, respectively. The results for Malaridose® gave a recovery of 97.7% (R.S.D. = 0.9%, $n = 5$)

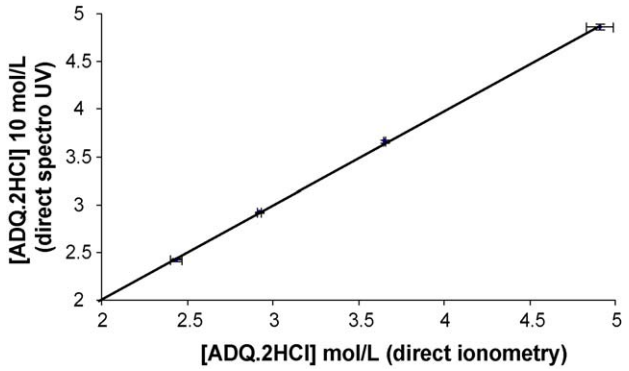

Fig. 3. Comparison of the results obtained by ionometric analysis using ADQ membrane electrode and spectrophotometric method for ADQ Malaritab® tablets.

and 98.6% (R.S.D. = 0.5%, $n = 5$) by potentiometry and spectrophotometry, respectively.

In Fig. 3 are compared the results of the analyses performed by potentiometry and by spectrophotometry for different sample concentrations (quadruplicate) for ADQ Malaritab® tablets. Linear regression between the potentiometry with the ADQ-selective membrane electrode in the case of ADQ tablets and spectrophotometric method gave a slope and intercept very close to unity and zero, respectively.

Taking into account these results and the Student test applied, no significant difference between the two methods was observed ($\alpha = 0.05$ at $p = 0.95$), which indicated the absence of systematic errors.

3.6. Dissolution test

This test is required for pharmaceuticals to simulate the release of the drug in gastric fluid. The assay was performed according to the USP XXIV recommended procedure. A dissolution profile of the studied ADQ tablets is illustrated in Fig. 4. Potentiometry and spectrophotometry data showed a similar profile. In agreement with the USP requirements, both methods allowed to demonstrate that more than 75% of the total amount

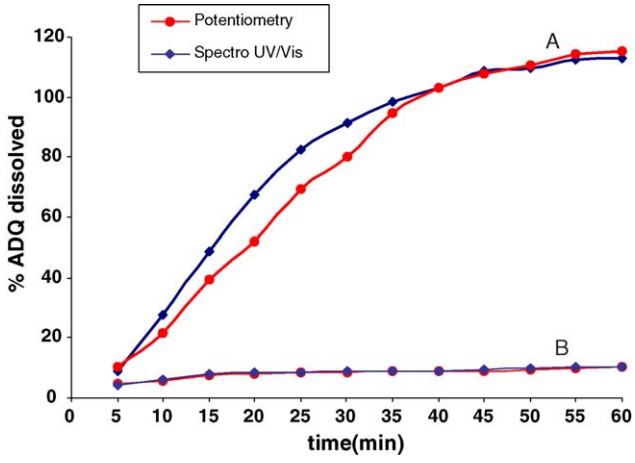

Fig. 4. Dissolution profile of Malaritab® (A) and Malaridose® (B) tablets (mean of three determinations).

of ADQ in Malaritab® tablets was released after 30 min [23]. However, for Malaridose® tablets, less than 11% of ADQ was released within the time period required. The latter unfortunate behaviour can likely be related to non-adequate manufacturing procedures leading to poor galenic formulation.

4. Conclusion

Experimental comparison of two ion-pair complexes of ADQ for use as electroactive material and several plasticizers in potentiometric sensors, revealed that in most cases, the ADQ membrane sensor displayed good analytical performance characteristics. The developed electrodes responded to the diprotonated form of ADQ in the pH range comprised between 3.7 and 5.5. Best performances were obtained with electrodes based on TPB or TCPB and DOP as ion-pairing reagent and plasticizer, respectively.

The potentiometric detection allowed no filtration and no dilution requirements (in contrast to spectroscopy) since it was not perturbed by turbidity and since it offered a good linear dynamic range. Interestingly, the determined content in the two drug formulations studied was in agreement with the declared content of ADQ·2HCl, but the dissolution profile was unsatisfactory for one of the drug formulation. Such a problem was already pointed out by several authors for number of antimalarial drugs available in countries affected by malaria and needless to say that such dissolution pattern have dramatic implications on the reduced therapeutic effectiveness and on the development of drug resistance [30,31]. The attractive characteristics of the presently developed sensor may be of particular help for countries with no or little drug regulatory infrastructure as an aid to check for amodiaquine tablets content and dissolution profile and to improve locally produced drug formulations.

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