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Potentiometric membrane sensors for the selective determination of cinnarizine in pharmaceutical preparations

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Abstract

The construction and general performance characteristics of four novel potentiometric PVC membrane sensors responsive to the cinnarizinium cation are described. These sensors are based on the use of the ion-association complexes of the cinnarizinium cation with tetraphenylborate, flavianate, reineckate and 12-molybdatophosphate counter anions as ion exchange sites in a plasticized PVC matrix. These sensors exhibit fast, stable and near-Nernstian response for the doubly charged cinnarizinium cation over the concentration range 10^{-2} to 10^{-6} M and pH 2–3. No interferences are caused by many inorganic and organic cations. Direct potentiometric determination of 4–400 $\mu g\ ml^{-1}$ cinnarizine shows an average recovery of 99.5% and a mean standard deviation of $\pm 0.5\%$. The sensors proved useful for determining cinnarizine in various dosage forms, monitoring tablet dissolution rates and testing tablet uniformity. The results compare favourably with data obtained by liquid chromatography.

Keywords: Sensors; PVC membranes; Pharmaceutical analysis; Tablet dissolution; Potentiometry; Flavianate; Tetraphenylborate; Reineckate; Phosphomolybdate

1. Introduction

Cinnarizine [1-(diphenylmethyl)-4-(3-phenyl-2-propenyl)-piperazine is effectively used in the treatment of cerebral and peripheral vascular insufficiency [1]. Although clinical experience of the use and prescription of cinnarizine goes back over a period of two decades, no pharmacopoeial method is available, so far, for its assay.

Methods available in the literature for quantification of cinnarizine involve spectrophotometry either directly [2] or after formation of coloured products by reaction with iodine [3], 2,3-dichloro-5,6-dicyano-*p*-benzoquinone [3], or dinitrobindonecarboxylic acid [4]. Non-aqueous titrimetry using perchloric acid as a titrant [5], thin-layer chromatography [6], polarography [7,8], gas chromatography [9–11] and liquid chromatography [12–14] have also been used. Some of these methods, however, suffer from severe interferences by various organic compounds [2,5,6], are not applicable for determining low drug concentrations [5] and require sophisticated instruments [7–14].

Ion selective electrodes have been increasingly used for quantitative measurement of basic and acidic drugs [15–20]. Potentiometric methods based on this technique are simple, rapid and offer enough selec-

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tivity towards the drugs in the presence of various pharmaceutical excipients [21]. This paper describes the construction, electrochemical evaluation and pharmaceutical applications of four novel potentiometric sensors for cinnarizine. These sensors incorporate the ion-association complexes of the cinnarizinium cation with tetraphenylborate, flavianate, reineckate and 12-molybdatophosphate counter anions in a plasticized PVC matrix.

2. Experimental

2.1. Equipment

The potentiometric measurements were made at 25 ± 1°C using a Metrohm pH/mV meter (Model 632). The cinnarizine 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 pH and temperature measurements were performed with an Orion Ross combination pH electrode (Model 91-02) and Metrohom automatic temperature compensator, respectively. Tablet dissolution measurements were made according to method 1 of the United States Pharmacopeia (USP) [22], using a Pharma Test (PTW 1) dissolution instrument (Hamburg, Germany). The ultraviolet measurements were carried out at 251 nm with a Perkin-Elmer Lambda 15 UV–visible spectrophotometer using 10 mm quartz cuvettes.

Liquid chromatographic measurements were made with a Waters 721 chromatograph equipped with a Waters Model 600 solvent delivery pump, a μBondapak C_{18} (250 mm × 4.6 mm i.d.) column, a universal LC injector (Model U6K), a Waters 730 data module and variable wavelength spectrometer (Lambda Max Model 481). A mobile phase consisting of methanol–acetate buffer (pH 5.2) (85:15) was used.

2.2. Reagents and materials

All reagents were of analytical grade and doubly distilled water was used throughout unless otherwise specified. Pharmaceutical grade cinnarizine powder, and cinnarizine dosage forms were supplied by El-Nasr Pharmaceutical Chemicals Co. (Egypt). Poly(vinyl chloride) (PVC), powder tetrahydrofuran (THF), sodium tetraphenylborate (NaTPB), ammonium reineckate, flavianic acid, 12-molybdophosphoric acid and dioctyl phthalate (DOP) were purchased from Aldrich (Milwaukee, WI). Methanol (HPLC grade) was obtained from BDH (Poole, UK).

A 1×10^{-2} M cinnarizine stock solution was prepared by dissolving 0.368 g of cinnarizine in 15 ml of ethanol, sonicated, and diluted with 1×10^{-2} M HCl to 100 ml in a standard flask. Dilute solutions (10^{-3}–10^{-6} M) were prepared by appropriate dilutions with 1×10^{-2} M HCl.

2.3. Sensors preparation and calibration

A 25 ml aliquot of 1×10^{-2} M cinnarizine solution was mixed with 50 ml of aqueous 1×10^{-2} M NaTPB, flavianic acid, ammonium reineckate or 12-molybdophosphoric acid, and continuously stirred. Each ion-pair complex was precipitated, filtered off through a G4 sintered glass crucible, washed thoroughly with distilled water, dried at room temperature and ground to a fine powder. A 10 mg portion of cinnarizine ion pair was mixed with 350 mg of DOP plasticizer and 130 mg of PVC powder and dissolved in 5 ml of tetrahydrofuran. The solution was poured into a petridish (5 cm diameter) and the solvent left to evaporate slowly at room temperature. The membrane formed was used for sensor construction as previously described [23,24]. A solution consisting of equal volumes of 2×10^{-3} M sodium chloride and 2×10^{-3} M cinnarizine hydrochloride was used as an internal reference solution in the sensor. The sensor was preconditioned by soaking overnight in a 1×10^{-3} M cinnarizine hydrochloride solution before use and stored in distilled water between measurements. The electrochemical cell used for potential measurements was: Ag/AgCl/1 $\times 10^{-3}$ M cinnarizine hydrochloride, 1×10^{-3} M NaCl||PVC membrane||test solution (pH 2.5)|Ag/AgCl double junction reference electrode. The potential readings of stirred 10^{-3}–10^{-5} M cinnarizine solutions were measured at 25 ± 1°C, and recorded after stabilization to ± 0.2 mV. A calibration graph was constructed and used for subsequent measurements of unknown cinnarizine test solutions.

2.4. Potentiometic determination of cinnarizine in pharmaceutical tablets

Ten tablets of cinnarizine were accurately weighed and powdered. A portion of the powder equivalent to one tablet of the drug (20–25 mg) was weighed, dissolved in 2 ml of ethanol and diluted with 15 ml of 1×10^{-2} M HCl. After adjustment of the pH to 2.5 ± 0.3, the solution was transferred to a 25-ml standard flask, completed to the mark with distilled water and shaken. A 1.00 ml aliquot of the solution was transferred to a 25-ml standard flask and diluted to volume with distilled water. The potential of the solution was measured using the cinnarizine sensor in conjunction with an Orion Ag/AgCl double-junction reference electrode. The potential of the stirred solution was recorded after stabilization to ± 0.2 mV and compared with the calibration graph. Alternatively, the standard addition technique [20] was used by addition of a 1.00 ml aliquot of the standard 1×10^{-2} M cinnarizine solution to 25 ml of the unknown test solution and the change in the potential was measured.

2.5. Potentiometric monitoring of cinnarizine tablet dissolution

One tablet of cinnarizine drug was placed in the basket of 16 tablet dissolution instrument and the dissolution medium (500 ml of 0.1 M HCl) was maintained at 37 ± 0.5°C. The basket was rotated at 100 rpm. After appropriate time intervals, the potential values were recorded using the cinnarizine sensor in conjunction with a double junction Ag/AgCl reference electrode and the amount of cinnarizine released was calculated from the calibration graph. For the spectrophotometric measurements, 5.0 ml aliquots of the dissolution solution were withdrawn, filtered, diluted with 0.1 M HCl and the absorbances were measured at 251 nm. A calibration graph was used for drug release calculation.

3. Results and discussion

Reineckate, flavianate, molybdatophosphate and tetraphenylborate anions were tested as ion-pair agents for the preparation of electroactive ion association complexes of cinnarizine. Sensors incorporating membranes with the composition 34.5 wt.% PVC as a plastic matrix, 63.5 wt.% dioctyl phthalate as a solvent mediator and 2 wt.% cinnarizine ion-pair were prepared and electrochemically evaluated at 25 ± 1°C using the recommendations of IUPAC [25]. The response characteristics of cinnarizine sensors based on these complexes are summarized in Table 1.

It can be seen that the cinnarizine flavianate membrane sensor shows a good performance in terms of detection limit, calibration slope and response time. The sensor displays a slope of 30.5 ± 0.3 mV per decade change in concentration and a linear response over the concentration range 1×10^{-2}–1×10^{-6} M cinnarizine. Membranes incorporating cinnarizine tetraphenylborate, cinnarizine reineckate and cinnarizine molybdatophosphate sensors show calibration slopes of 38.2 ± 0.2, 27.1 ± 0.2 and 28.3 ± 0.3 mV per decade and lower limits of detection in the ranges of 8.1×10^{-6}, 5.1×10^{-5} and 6.2×10^{-6} M, respectively. The calibration slopes of the four

Table 1
Response characteristics for the cinnarizine PVC membrane sensors

Parameter	TPB	Flavianate	Reineckate	Molybdophosphate
Slope (mV log C^{-1}) [a]	38.2 ± 0.2	30.5 ± 0.3	27.1 ± 0.2	28.3 ± 0.3
Intercept (mV)	277.1 ± 0.4	210.2 ± 0.5	240.4 ± 0.6	170.3 ± 0.6
Correlation coefficient r ($n = 6$)	0.987	0.998	0.979	0.989
Response time for 10^{-3} M (s)	35 ± 2	30 ± 2	55 ± 2	60 ± 2
Lower limit of detection (M)	8.1×10^{-6}	1.1×10^{-6}	5.1×10^{-5}	6.2×10^{-6}
Working pH range	2.0–2.8	2.0–3.1	2.2–3.1	2.2–3.3

[a] Mean ± S.D. ($n = 5$).

Table 2
Potentiometric selectivity coefficients ($K^{Pot}_{C,B}$) for the cinnarizine PVC membrane sensors

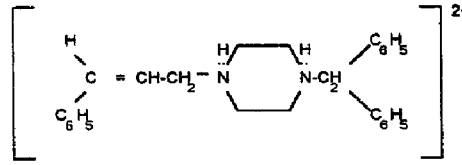
Interferent, B	$K^{Pot}_{C,B}$			
	TPB	Flavianate	Reineckate	Molybdophosphate
Dimethylamine	3.1×10^{-3}	3.7×10^{-3}	1.1×10^{-2}	4.4×10^{-3}
Glycine	4.7×10^{-4}	2.4×10^{-4}	5.9×10^{-3}	3.9×10^{-3}
Urea	7.2×10^{-3}	4.1×10^{-3}	8.4×10^{-3}	3.6×10^{-3}
Piperazine	1.3×10^{-2}	8.8×10^{-3}	2.7×10^{-2}	4.5×10^{-2}
Mg^{2+}	1.9×10^{-3}	2.6×10^{-4}	4.6×10^{-3}	3.1×10^{-3}
Ca^{2+}	2.7×10^{-3}	5.8×10^{-4}	5.3×10^{-3}	2.7×10^{-3}
K^{+}	8.6×10^{-3}	3.6×10^{-4}	7.7×10^{-3}	5.5×10^{-3}
Citric acid	5.4×10^{-3}	5.1×10^{-3}	6.5×10^{-2}	4.4×10^{-2}

cinnarizine sensors over the linear response ranges are stable within ± 0.5 mV log [cinnarizine]$^{-1}$ for at least 8 weeks.

The time required for the cinnarizine flavianate and cinnarizine tetraphenylborate membrane sensors to reach values within ± 1 mV of the final equilibrium potential after immersion in cinnarizine solutions, each having a 10-fold difference in concentration, varies from 20 s for $\geq 10^{-3}$ M cinnarizine to 40 s for $\leq 10^{-4}$ M cinnarizine. Cinnarizine reineckate and cinnarizine molybdatophosphate membrane sensors had a slightly longer response time. The four membrane sensors exhibit a day-to-day reproducibility of better than 0.6 mV for 10^{-2}–10^{-5} M cinnarizine solutions. All subsequent measurements were made with the four membrane sensors for comparison. Ageing of the sensors for up to 8 weeks has no significant effect on their performance (Table 2).

3.1. Effects of pH and other compounds

Since cinnarizine is soluble only in strongly acidic media and precipitates from aqueous solutions of pH ≥ 4, all potentiometric measurements were carried out below pH 4. A study of the potential-pH curves of cinnarizine membrane sensors reveals potential stability within ± 0.2 mV over the pH range 2–3, where the predominant species is the diprotonated cinnarizinium cation:



The influence of various basic substances on the response of cinnarizine sensors was investigated by measuring the potentiometric interference from many organic and inorganic cations. Diluents and excipients normally used in drug formulations (e.g., lactose, glucose, mannitol, sugar, corn starch, magnesium stearate, hydroxypropyl cellulose and poly(eth-

Table 3
Determination of cinnarizine in some pharmaceutical preparations using cinnarizine PVC membrane sensors

Drug (trade name and source)	Nominal cinnarizine (mg tablet^{-1})	Cinnarizine recovery (%) [a]				
		TPB	Flavianate	Reineckate.	Molybdophosphate	LC [b]
Stugron (Glaxo)	25	99.4 ± 0.5	99.2 ± 0.4	98.1 ± 0.6	98.5 ± 0.6	99.1 ± 0.7
Cerebal (Alex. Pharm. Co.)	25	99.1 ± 0.5	99.1 ± 0.6	98.4 ± 0.4	98.9 ± 0.6	99.7 ± 0.5
Siuval (Cid Pharm. Co.)	25	99.2 ± 0.6	99.5 ± 0.5	98.1 ± 0.4	99.2 ± 0.5	98.9 ± 0.6
Sureptil (Memphis/Delgland)	20	98.1 ± 0.5	98.5 ± 0.6	97.8 ± 0.6	97.3 ± 0.3	97.6 ± 0.5
Cinnarizine (El-Nasr Pharm. Co.)	25	99.4 ± 0.4	98.9 ± 0.5	98.5 ± 0.5	98.9 ± 0.6	98.1 ± 0.5

[a] Average of 5 measurements $\pm$ S.D.
[b] Liquid chromatography.

ylene glycol)) did not show any interference. When 5 mg of cinnarizine was spiked with 100 mg of any of these excipients, cinnarizine was recovered almost quantitatively (99.5 ± 0.4%, mean standard deviation 0.7%, $n = 5$).

3.2. Determination of cinnarizine

The results obtained by direct potentiometric measurement of standard cinnarizine solutions (4 μg ml^{-1}–0.4 mg ml^{-1}, each in five replicates) show an average recovery of 99.5% and a mean standard deviation of ±0.4%. Similar results are obtained using the standard addition spiking technique [20]. Cinnarizine in some dosage forms was similarly determined. An average recovery of 98.7% of nominal and a mean standard deviation ($n = 5$) of 0.5% were obtained. These results compare favorably well with data obtained using liquid chromatography. The results (Table 3) are highly precise and are in good agreement, i.e., within < ±1.0%.

3.3. Cinnarizine tablet dissolution

Cinnarizine sensors were used for determining tablet content uniformity and dissolution profile. The content uniformity test indicates 96–103% of the label amount and a standard deviation of < 4.2% ($n = 10$). Dissolution tests at 100 rpm in 500 ml of 0.1 M HCl (stimulated gastric fluid) were also made using both the cinnarizine flavianate sensor and spectrophotometric measurement at 251 nm. With the potentiometic method, the potential values were continuously recorded at 1-min time intervals and compared with a calibration graph. For the UV spectrophotometric assay, fixed volumes of the dissolution medium were withdrawn, diluted with 0.1 M HCl, measured at 251 ± 2 nm and compared with a calibration graph. Fig. 1 shows the dissolution profiles of cinnarizine tablet using both measurement techniques. The results obtained by spectrophotometry and potentiometry are almost identical. The use of the potentiometric sensor, however, has the advantage of in situ monitoring.

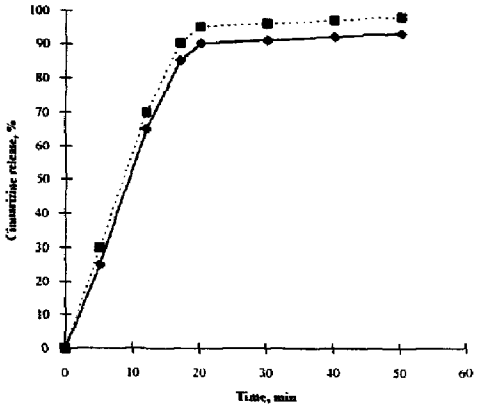


Fig. 1. Dissolution profiles of 25 mg cinnarizine tablet obtained by: (---) potentiometric; and (—) spectrophotometric measurements.

4. Conclusion

Experimental comparison of several ion-pair complexes of cinnarizine for use as electroactive materials in potentiometric sensors, reveals that the cinnarizine–flavianate PVC membrane sensor displays the best performance characteristics. In general the cinnarizine sensors described in this work are sufficiently simple and specific for quantitative determination of cinnarizine concentrations at a level as low as 4 μg ml^{-1} in pure powders and in dosage forms. The use of the proposed sensors offers the advantages of fast response, elimination of drug pretreatment or separation steps, low cost and possible interfacing with computerized and automated systems.

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