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Application of new membrane selective electrodes for the determination of drotaverine hydrochloride in tablets and plasma

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Abstract

The construction and electrochemical response characteristics of poly vinyl chloride (PVC) membrane sensors for the determination of drotaverine hydrochloride were described. The sensors are based on the use of the ion association complexes of drotaverine cation with sodium phosphotungestate (Dro-PTA) or ammonium reineckate (Dro-R) counter anions as ion exchange sites in the PVC matrix. The performance characteristics of these sensors, which were evaluated according to IUPAC recommendations, reveal a fast, stable and linear response for drotaverine over the concentration range 10^{-5} to 10^{-2} M with cationic slopes of 49.55 and 51.36 mV per concentration decade. The direct potentiometric determination of drotaverine hydrochloride using the proposed sensors gave average recoveries of 99.95 ± 0.71 and 100.04 ± 0.60 for Dro-PTA and Dro-R, respectively. The sensors are used for determination of drotaverine hydrochloride in tablets, in its mixture with caffeine and paracetamol and in plasma. Validation of the method shows suitability of the proposed sensors for use in the quality control assessment of drotaverine hydrochloride. The developed method was found to be simple, accurate and precise when compared with a reported HPLC method.

Keywords: Drotaverine hydrochloride; Ion selective electrodes; PVC membranes; Sodium phosphotungestate; Ammonium reineckate

1. Introduction

Drotaverine, 1-[(3,4-diethoxyphenyl)methylene]-6,7-diethoxy-1,2,3,4-tetra hydroisoquinoline, Fig. 1, is an analogue of papaverine with excellent smooth muscle relaxant properties, though more effective as antispasmodic than papaverine. It is available as HCl and theophylline-7-acetic acid salts [1].

Few methods have been reported for the determination of drotaverine HCl in pharmaceutical dosage forms and in plasma. These include spectrophotometric methods [2–4], polarographic analysis [5,6] and HPLC techniques [7–11].

The development and application of ion-selective electrodes continue to be of interest for pharmaceutical analysis because these sensors offer the advantages of simple design and operation, reasonable selectivity, fast response, low cost, wide pH working range, reasonable selectivity, broad concentration range and applicability to turbid and colored solutions [12].

In the present work, two ion selective membrane sensors were developed for drotaverine hydrochloride based on the use of the ion association complexes of drotaverine hydrochloride with phosphotungestate and ammonium reineckate. The high lipophilicity and remarkable stability of these complexes suggested their selective use as electroactive materials in PVC matrix membrane sensors for the determination of drotaverine hydrochloride in the presence of excipients and plasma without the need of preliminary extraction and separation steps. Moreover, they offer highly sensitive, selective and convenient technique for the determination of drotaverine hydrochloride in its pure and pharmaceutical preparations.

2. Experimental

2.1. Apparatus

Potentiometeric measurements were made at 25 ± 1 °C with a Hanna (Model 211) pH/mV meter. A single junction calomel reference electrode (Model HI 5412) was used in conjunction with the drug sensor. A WPA pH combined glass electrode Model CD 740 was used for pH measurements.

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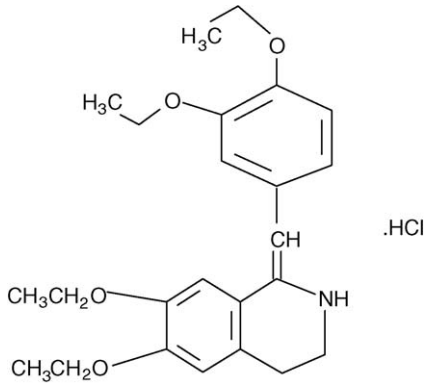

Fig. 1. Chemical structure of drotaverine hydrochloride, $C_{24}H_{32}NO_4Cl$, MW = 434.01, pK_a = 6.3 (25°).

2.2. Reagents and solvents

All chemicals were of analytical grade and bidistilled water was used. Dioctylphthalate, PVC, high molecular weight (10,000), ammonium reineckate and tungestophosphoric acid (TPA) from Sigma. Tetrahydrofuran, 99% (Lab Scan). Phosphate buffer pH 3 and 4: it was prepared by dissolving 136 g of potassium dihydrogen phosphate or 6.8 g of disodium hydrogen phosphate for pH 3 and 4, respectively, in sufficient water to produce 1000 ml buffer and pH was adjust with phosphoric acid [13].

2.3. Materials

2.3.1. Pure samples

Drotaverine hydrochloride, caffeine and paracetamol were kindly supplied by Alpha Chem Advanced Pharmaceutical Industries (ACAPI) Co., Cairo, Egypt. Their purity were found to be 99.72 ± 0.69, 99.63 ± 0.58 and 100.31 ± 0.47, respectively according to reported HPLC method [14].

2.3.2. Market samples

Do-spa tablets (Alexandria Co. for Pharmaceuticals, Alexanderia, Egypt); Batch No. 3135003. It was labeled to contain 40 mg drotaverine hydrochloride per tablet.

Petro tablets (ACAPI Co.); Batch No. 01101157. It was labeled to contain 40 mg drotaverine hydrochloride, 60 mg caffeine and 400 mg paracetamol per tablet.

2.4. Stock standard solutions

1. Drotaverine hydrochloride 10^{-2} M in water from which aqueous 10^{-3} to 10^{-6} M of the drug solutions were freshly prepared by accurate dilutions.
2. Drotaverine hydrochloride (10^{-6} to 10^{-2} M) in phosphate buffer pH 3 and 4.

2.5. Procedures

2.5.1. Preparation of the membranes

Two membranes namely, drotaverine-phosphotungestate and drotaverine-reineckate were prepared using a reported method [15].

2.5.2. Preparation of drotaverine-phosphotungestate membrane

Ten milliliter of 10^{-2} M drotaverine hydrochloride aqueous solution was mixed with 10 ml of a saturated aqueous solution of phosphotungestate (PTA). The resulting precipitate was filtered, washed with cold water, allowed to dry at room temperature and grounded to fine powder. Elemental analysis for carbon, hydrogen and nitrogen was carried to study the formation of the complex.

In a glass petri dish (5 cm diameter), 10 mg of the previously prepared ion association complex was mixed thoroughly with 0.35 ml of dioctylphthalate then 0.19 g of poly vinyl chloride was added (PVC). This mixture was dissolved in 5 ml tetrahydrofuran (THF), covered with a filter paper and left to stand overnight to allow slow evaporation of the solvent at room temperature, thus a master membrane with 0.1 mm thickness was formed [16,17].

2.5.3. Preparation of drotaverine-reineckate membrane

The same procedure described under Section 2.5.2 were followed using saturated aqueous solution of ammonium reineckate instead of phosphotungestate (PTA).

2.5.4. Electrode assembly

A disk of an appropriate diameter (about 8 mm) was cut from the previously prepared master membranes and cemented to the flat end of PVC tubing with THF. A mixed solution consisting of equal volumes of 10^{-2} M drotaverine hydrochloride and 10^{-2} M sodium chloride was used as an internal reference solution. Ag/AgCl coated wire (3 mm diameter) was employed as an internal reference electrode. The sensors were conditioned by soaking for 24 h in a solution of 10^{-2} M of drug and stored in the same solution when not in use.

2.5.5. Sensors calibration

The prepared electrodes were immersed in conjunction with the single junction calomel reference electrode in aqueous solutions of drotaverine hydrochloride in the range of 10^{-6} to 10^{-2} M. They were allowed to equilibrate whilst stirring and recording the emf readings within ±1 mV. The membrane sensors were washed between measurements with water. The mV–concentration profiles were plotted. The regression equations for the linear part of the curves were computed and used for subsequent determination of unknown concentrations of drotaverine hydrochloride.

2.5.6. Selectivity measurements

Potentiometry selectivity coefficients ($K^{pot}_{Dro,I}$) were evaluated according to IUPAC guidelines using the separate solutions method [16,17] in which the potential of cell compromising the membrane electrode and a reference electrode is measured with two separate solutions, A and B where A (Dro ions) and B (interfering ion) at the same activity aA = aB.

The emf for A and B are measured values, respectively. Different interfering anions at a concentration of 1×10^{-3} M at a suitable pH were utilized and the results were obtained using the

equation

$$\log K^{\text{pot}}_{\text{A,B}} = \frac{\text{EB} - \text{EA}}{S} + \frac{1 - \text{ZA}}{\text{ZB}} \log \text{aA}$$

where $K^{\text{pot}}_{\text{A,B}}$ is the potentiometric selectivity coefficient, S the slope of the calibration plot, aA the activity of Dro and ZA and ZB are the charges on Dro and the interfering anion, respectively.

2.5.7. Application to pharmaceutical formulations

Ten tablets of each Do-spa and Petro tablets were weighed and powdered separately. An amount of the powdered tablets equivalent to 21.7 mg drotaverine hydrochloride was accurately transferred separately to a 50-ml volumetric flask and the volume was completed to the mark with phosphate buffer (pH 3 for Dro-R sensor and pH 4 for Dro-PTA sensor) to prepare a 10^{-3} M solution of drotaverine hydrochloride. The emf produced by immersing the prepared electrodes in conjunction with single junction calomel reference electrode in the prepared solutions were determined then the concentration of drotaverine hydrochloride was calculated from the regression equation of the corresponding electrode.

2.5.8. Application to plasma sample

4.5 ml of human plasma were placed into two stoppered shaking tubes, then 0.5 ml of 10^{-2} and 10^{-3} M drotaverine hydrochloride were added separately and shacked. The membrane sensor was immersed in conjunction with the single junction calomel reference electrode in these solutions. The membrane sensor was washed with water between measurements. The emf produced for each solution was measured by the two proposed electrodes then the concentration of drotaverine hydrochloride was determined from the corresponding regression equations.

3. Results and discussion

The 1980s and 1990s were characterized by enormous exploratory efforts in the theory and methodology of ion selective electrodes and their possible application to chemical problems [18]. Recently ion selective electrodes were used to solve some analytical problems such as direct determination of drugs in presence of their degradation products [15,18,19].

In the present work, two membranes belonging to the type of supported ion exchangers were fabricated with PVC as a polymer matrix.

In the proposed PVC sensors, drotaverine hydrochloride acts as a cation, which suggests the use of ion exchangers of the anionic type like sodium phosphotungestate and ammonium reineckate with their low solubility products and suitable grain size. Drotaverine hydrochloride reacted with sodium phosphotungestate and ammonium reineckate to form stable 1:1 water insoluble ion association complex.

This ratio was confirmed by elemental analysis, calculated was agreed with found one, and the Nernstian response of the suggested sensors which was about 60 mV; the typical value for monovalent drugs.

PVC acts as regular support matrix and as traps for the sensed ions, it has the advantages of chemical inertness, high tensile strength, low glass transition temperature and low cost, but its use creates a need for a plastisizer [20]. In the present investigation, dioctylphthalate was chosen as plastisizers from diesters of carboxylic acids. With PVC, the diesters of carboxylic acids were found to be the optimum plastisizers, they plasticize the membrane, dissolve the ion association complex, and adjust both permittivity of the final organic membrane and mobility of the ion exchange sites. Such adjustments influence the partition coefficient of the studied drug with subsequent effect on electrode selectivity. Other plasticizers such as nitrophenyl phenyl ether and caster oil failed in dissolving the ion association complexes and thus gave noisy responses.

Electrochemical performance characteristics of the proposed sensors were evaluated according to the IUPAC recommendation data [16]. The slopes of lines, response times (the time required for the system to reach equilibrium), detection limits, quantification limits (0.14×10^{-5} and 0.12×10^{-5} for Dro-PTA and Dro-R, respectively) and intervals of linearity over a period of 1 month for 10 different assemblies of each sensor at optimal pH are shown in Table 1. The sensors displayed constant potential readings within 2 mV from day-to-day and the calibration slopes did not change by more than 2 mV per decade over a period of 1 month for PVC sensors.

In measurements with the investigated sensors, the experimental conditions were studied to reach the optimum. The response time of the electrodes was tested for concentrations of the drug from 10^{-6} to 10^{-2} M. The measurements was characterized by a fast stable response within 20–30 s for concentrations less than 10^{-4} M and 10–20 s for concentrations more than 10^{-4} M.

Potential stability of the proposed sensors over various pH ranges was also examined for 10^{-3} and 10^{-4} M of drotaverine hydrochloride. The results revealed a stable potential over pH 2–4 (phosphate buffer) for Dro-R sensor and over pH 3–5 (phosphate buffer) for Dro-PTA sensor (Fig. 2). Above pH 8, drug precipitation occurs.

Long term potential stability of the proposed sensors was fairly good as it practically unchanged over a period of 6–8 weeks.

Table 1
Response characteristics for drotaverine-phosphotungestate (Dro-PTA) and drotaverine-reineckate (Dro-R)

Parameter	Dro-PTA	Dro-R
Slope (mv/decade)	49.55	51.36
Intercept (mv)	265.9	280.16
Correlation coefficient	0.9996	0.9997
Detection limit (M)	6.8×10^{-6}	5.9×10^{-6}
Quantification limit	0.14×10^{-5}	0.12×10^{-5}
Response time (s)	30	30
Working pH range	3–5	2–4
Concentration range (M)	1×10^{-5} to 1×10^{-2}	1×10^{-5} to 1×10^{-2}
Life span (weeks)	6–8	6–8
Average recovery (%)	99.95	100.04
R.S.D.[a]	0.71	0.60

[a] Average of four determinations.

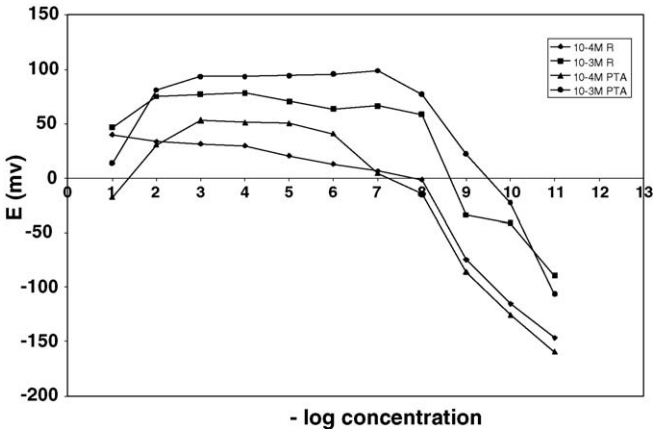

Fig. 2. Effect of pH on the response of drotaverine hydrochloride reineckate and phosphotungestate electrodes.

The potentiometric response of the two studied electrodes at the optimum pH were linear with constant slopes over a drug concentration range 10^{-5} to 10^{-2} M of drotaverine hydrochloride (Fig. 3). The accuracy and precision of the proposed membrane sensors for the quantification of blind samples of drotaverine hydrochloride was assessed by using Dro-PTA and Dro-R sensors, respectively. The results showed average recoveries of 99.95 ± 0.71 and 100.04 ± 0.60 for Dro-PTA and Dro-R, respectively. Low detection limits are one of the advantages of the investigated sensors as declared in Table 1.

The performance of the two sensors in the presence of some nitrogenous compounds such as amines, amino acids, some inorganic cation, caffeine and paracetamol were assessed by measuring and comparing the potentiometric selectivity coefficient values ($K^{pot}_{Dro,I}$). The separate solutions method [16,17] with a fixed concentration of the interferent (10^{-3}) was used for evaluation of the selectivity. The results obtained by the developed sensors, Table 2, showed reasonable selectivity for the two sensors for drotaverine hydrochloride in presence of caffeine and paractamol.

Pharmaceutical additives, diluents and ingredients commonly used in drug formulations such as lactose, sucrose, magnesium sulphate and povidone did not show any interference.

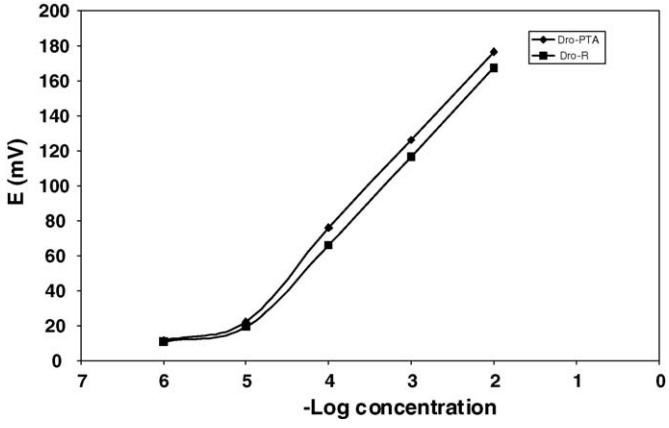

Fig. 3. Profile of the potential in mV to the −log concentration of drotaverine hydrochloride reineckate and phosphotungestate electrodes.

Table 2
Potentiometric selectivity coefficients ($K^{pot}_{Dro,I}$) for the two proposed electrodes

Interferent	Selectivity coefficient	
	Dro-PTA	Dro-R
Caffeine	8.04×10^{-3}	9.71×10^{-4}
Paracetamol	7.40×10^{-3}	7.29×10^{-4}
Povidone	7.46×10^{-3}	1.11×10^{-3}
Na^+	6.22×10^{-3}	6.18×10^{-4}
K^+	6.38×10^{-3}	6.44×10^{-4}
NH_4^+	5.78×10^{-3}	5.38×10^{-4}
Mg^{2+}	5.81×10^{-3}	5.94×10^{-4}
Ca^{2+}	7.19×10^{-3}	5.30×10^{-4}
Lactose	6.90×10^{-3}	4.72×10^{-4}
Sucrose	4.65×10^{-3}	4.75×10^{-4}
Urea	4.73×10^{-3}	4.46×10^{-4}
L-Phenyl alanine	4.95×10^{-3}	5.21×10^{-4}

Table 3
Determination of drotaverine hydrochloride in spiked human plasma by the proposed electrodes

Concentration (M)	Recovery %[a] of drotaverine hydrochloride	
	Dro-PTA	Dro-R
1×10^{-3}	100.21 ± 0.52	99.64 ± 0.47
1×10^{-4}	100.51 ± 0.48	100.16 ± 0.39

[a] Average of three determinations.

Thus, analysis was carried out without prior treatment or extraction. Dro-PTA and Dro-R were successfully used for the determination of drotaverine hydrochloride in Do-spa tablets with average recoveries of 100.09 ± 0.42 and 100.22 ± 0.79 for Dro-PTA and Dro-R, respectively, and in Petro tablets with average recoveries of 99.59 ± 0.62 and 101.13 ± 0.50 for Dro-PTA and Dro-R, respectively.

On application to the biological fluids, it has been found that the two electrodes gave stable results as revealed by high precision and accuracy of recoveries of the spiked plasma samples (Table 3).

Statistical evaluation of the results of analysis of pure drotaverine hydrochloride by the proposed electrodes and the manufacturer HPLC method [14] showed that there is no significant difference between the proposed and reported method in terms of accuracy and precision (Table 4).

Table 4
Statistical analysis of the results obtained by the proposed method and the reported HPLC methods [13] for the analysis of drotaverine hydrochloride

Parameter	Dro-PTA	Dro-R	Reported HPLC method [13]
Mean	99.95	100.04	99.72
R.S.D.	0.71	0.60	0.69
N	4	4	5
Variance	0.504	0.360	0.476
Student's *t* (2.365)[a]	0.491	0.731	–
F test	1.059 (6.59)[a]	1.322 (9.12)[a]	–

[a] The values between parenthesis are the corresponding theoretical values of *t* and *F* at the 95% confidence level.

4. Conclusion

Dro-PTa and Dro-R electroded are sufficiently simple and selective for the quantitative determination of drotaverine hydrochloride at a wide concentration range (10^{-5} to 10^{-2}) in pure, pharmaceutical formulations, in the presence of caffeine and paracetamol and in plasma.

The use of the proposed sensors offers the advantages of fast response, elimination of drug pretreatment or separation steps, low detection limit and direct determination of drugs in turbid and colored solutions. They can therefore be used for routine analysis of the drugs in quality control laboratories.

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