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Polymer Membrane Electrodes for Sensitive Potentiometric Determination of β-blockers

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ABSTRACT The construction of PVC matrix-type β-blockers (sotalol, carvedilol, and betaxolol) ion selective electrodes and their use for direct potentiometry of their respective species are described. The proposed sensors are based on the complex ion associates of β-blockers with tungstophosphate (TP) and Ammonium Reineckate (Rein) ionophoris in poly vinyl chloride membrane (PVC) with Dioctylphthalate (DOP) plasticizer. The four electrodes (Beta-TP), (Sota-TP), (Carve-TP), and (Cave-Rein) show stable potential response with near Nernstian slope of 50.8, 33.7, 32.35, and 33 mv per decade, range of concentration 10–2–10–7 M β-blockers. Selectivity coefficients data obtained for 11 different organic and inorganic ions are presented. The electrodes have fast response time (30 and 40 s) and were used over wide range of pH 4.5–8.5. Validation of the method according to the quality assurance standers shows suitability of proposed sensors for use in the quality control assessment of these drugs. The results obtained for the determination of β-blockers with the proposed electrodes show average recoveries of 100.78% and a mean standard deviation of ±1.2. The nominal are obtained. The data agree well with those obtained by standard methods.

KEYWORDS Determination of β-blockers, Potentiometry, Tungstophosphate, Reineckate, Pharmaceutical analysis

INTRODUCTION

β-adrenergic blocking drugs sotalol, betaxolol, and carvedilol (Scheme 1) are chemical agents that exert their principle pharmacological and therapeutic effect by acting at peripheral sites to either enhance or reduce the activity of components of the sympathetic division on autonomic nervous system (Delagodo & Remers, 1991). β-blockers are clinically important drugs used in angina pectorals, certain arrhythmia, systematic hypertension, and other cardiovascular disorders, such as a trial fibrillation flutter, myocardial infarction, and sinus tachycardia (Andrejus, 1988). Several methods have been described for the determination of β-blocking agents including;

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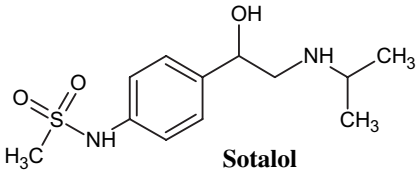
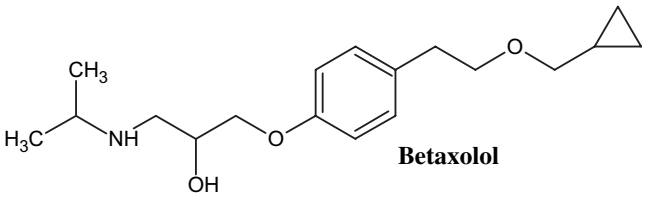
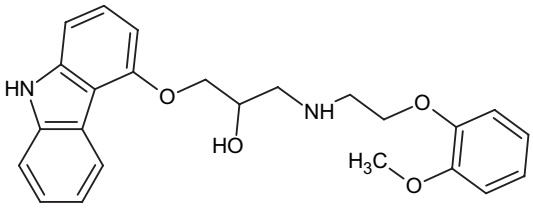


Sotalol



Betaxolol



Carvedilol

SCHEME 1 **Chemical structure of β-blocker drugs investigated.**

Spectrophotometry (Seemanta Institute of Pharmaceutical Science, 2001; Amin et al., 2002; Khalil & Rabiehi, 2000; Sanghavi & Vani, 1980), fluorometric (Prasad et al., 1997; De-Castro et al., 1998; Muvillo-Pulgarin et al., 1998), chromatographic (Tenberken et al., 2004; Wang et al., 2004), titrimetric (United States Pharmacopeia, 2005; British Pharmacopoeia, 2003), and electrochemical methods (Arranz et al., 1999; El-Maali et al., 1990).

This study described simple, direct methods for accurate and precise potentiometric methods for the determination of sotalol, betaxolol, and carvedilol β-blockers. The sensors are sensitive enough to measure a low concentration of drugs with reasonable selectivity and fast response. These electrodes incorporate the ion-association complexes of β-blockers cations with tungstophosphate (TP) and reineckate anions as electro active materials in plasticized PVC matrix membranes.

EXPERIMENTAL

Apparatus

All potentiometric measurements were made at ±25°C with an PH/mv meter. A glass combined pH electrode (Cambridge model WPA) Model CD 740 was used in pH measurements; the drug membrane electrode were used with a JenWay single junction Ag/AgCl reference electrode. For HPLC reported method Waters 486 tunable absorbance detector and Waters 600 controller, for data handling and integration, a Millennium Chromatography manger was used.

Reagents

All chemicals were of analytical reagent grade and double distilled water was used. Dioctylephalate (DOP) was obtained from British Drug House (Pool, England, UK). Tetrahydrofurance (THF) and ammonium reineckate (Rein) were obtained from Aldrish Chemical Company (Milwaukee, WI, USA). Stock 10^{-2} mol L^{-1} β-blockers (sotalol, carvedilol,and betaxolol) solution were prepared by dissolving 0.1374, 0.203, and 0.172 gm respectively, in 25 mL doubly distilled water.

Betaxolol was pharmaceutical grade, obtained from Alcom Company (Cairo, Egypt). Sotalol was supplied from Amoun Pharmaceutical Company (Cairo, Egypt) and carvedilol from Chemipharm Company (Cairo, Egypt).

β-blockers Ion-Pair Complex

Aliquots (10 mL) of 10^{-2} M of β-blockers (sotalol, betaxolol, and carvedilol) were individually mixed with 10 mL of 10^{-2} M TP or Rein solution. The precipitates were filtered off, washed with deionised water, dried at room temperature and ground to a fine powder. Elemental analysis infra red data revealed the formation 2:1 tungstoposphate-carvedilol, reineckate-carvedilol, TP-sotalol and TP-betaxolol. The complexes were used as electro active materials in PVC membrane electrode.

Sotalol and carvedilol behave as divalent species due to the presence of two amino groups while as betaxolol behave as monovalent due to presence of one amino group.

β-blockers-PVC Membrane Electrodes

The membranes of the electrodes were prepared as previously reported (Hassan et al., 2003) with 10 mg β-blocker ion-pair complexes, 190 mg PVC and 350 mg of DOP plasticizer in 5 mL THF. The solution was poured into a Petri dish (3.5 cm diameter) and the solvent was evaporated at room temperature. Discs were cut from the membranes for the construction of the electrodes (Hassan & Marzouk, 1994). An internal solution consisting of equal volumes of 10^{-2} M sodium chloride and 10^{-2} M β-blockers was used. The electrodes were preconditioned after preparation by soaking for at least 24 h in 10^{-2} M aqueous β-blockers (soatolol, betaxolol, and carvedilol) solutions and stored in the same solution when not in use.

The electrodes were calibrated by transferring 10 mL aliquots of 10^{-2}–10^{-7} aqueous β-blockers solution to 50 mL beaker. The pH of the solutions were adjusted to 4.5–8.5 by the addition of dilute sodium hydroxide and/or hydrochloric acid solutions. β-blockers PVC membrane electrodes in conjunction with a double junction Ag /AgCl reference electrode were immersed in the solutions.

Direct Potentiometry and Potentiometric Titration of β-blockers

A 10 mL aliquot of the drug test solution (10^{-2}–10^{-7} M) was transferred to 50 mL beaker. The β-blockers PVC membrane electrode and reference electrode were immersed in the test solution. The emf was recorded after stabilization ±0.2 mv and compared with the calibration graph. Alternatively, the slandered addition method was used by measuring the emf before and after each addition of β-blockers standard solutions.

Determination of β-blockers in Pharmaceutical Preparations

Five tablets of the drug formulations were weighted and finely powdered in a small dish. An accurately weight of the powder, equivalent to weight of 10^{-2} mol L^{-1}, was dissolved in suitable volume of double distilled water and few drops of 0.01 mol L^{-1} HCl . The solution was filtered into suitable calibrated flask. Diluted to the mark with 0.01 mol L^{-1} NaCl solution and measured as described above and the potential reading was compared with the calibrated Plot.

RESULTS AND DISCUSSION

Plasticized PVC membrane sensors incorporating β–blockers TP (Beta-TP), (Sota-TP), (Carve-TP), and (Carve–Rein) ion-pairs were prepared with suitable plasticizers and electro chemically evaluated under static and hydrodynamic modes of operation according to IUPAC recommendations (IUPAC Analytical Chemistry Division, 2000).

Plastic membranes papered by using a casting solution of the composition (2:34:64% w/w) ion-pair complex, PVC and DOP plasticizer, respectively, were used for constructing the sensors. Table 1 summarize the response characteristics of four different sensor, based on data collected over a period of 20 weeks for four

TABLE 1 **Response Characteristics of Some β-Blockers Tungstophosphate and Renieckate PVC Membrane Based on Sensors**

	Sensors			
Parameter	Beta-TP	Sota-TP	Carve-TP	Carve-Rein
Slope (mV per decade)	50.8	33.7	32.35	33
Intercept (mV)	400.8	269.2	230.7	233.6
Correlation coefficient (r)	0.9999	0.9998	0.9997	0.9998
LOD (mol^{-1})	2×10^{-7}	1.8×10^{-7}	1.3×10^{-6}	1.4×10^{-6}
Response time (s)	40	30	30	40
Accuracy %	100.70	101.78	99.27	101.38
Working range (PH)	4–7.5	4.5–8.5	4–8	4.5–7.5
Standard deviation	1.2	1.2	1.3	1.3

*Sensor.
(Beta-TP) : Betaxolol tungstophosphate PVCmemberane.
(Sota-TP) : Sotalol tungstophosphate PVC membrane.
(Carve-TP) : Carvedilol tungstophosphate PVC membrane.
(Carve-Rein) : Carvedilol renieckate PVC membrane.

sensors assemblies for each drug under static conditions. It was found (Fig. 1) that sensors based on (sota-TP), (carve-TP) and (carve-Rein) ion-pairs are almost identical in terms of calibrations slope and detection limit.

The three sensors exhibited Nernstian response over the range 10^{-2}–10^{-7} M β-blockers with cationic slopes of 33.7 ± 0.5, 32.3 ± 0.3 and 33 ± 0.2 mv/decade and lower limit of detection of approximately 1.8×10^{-7}, 1.3×10^{-6} and 1.4×10^{-6} M respectively. In contrast, the Betaxolol-TP (Beta-TP) sensor exhibited a near-Nernsitan slope of 50.8 ± 0.6 mv/decade over the range 2×10^{-7} M Betaxolol. The dynamic response times of the β-blockers (betaxolol, sotalol, and carvedilol) sensors were tasted for 10^{-2}–10^{-7} M test solutions. The time required for the sensors to values with in ±1 mv of the final equilibrium potential after increasing the concentration of β-blockers 10-fold was measure. The response time of the sensors for 10^{-3} M β-blockers was 30–40 s.

The useful lifetime of the electrodes was 4–5 weeks, during which the potentials were reproducible within ±2 mv and the variation of the slope did not exceed than ±2 mv/decade.

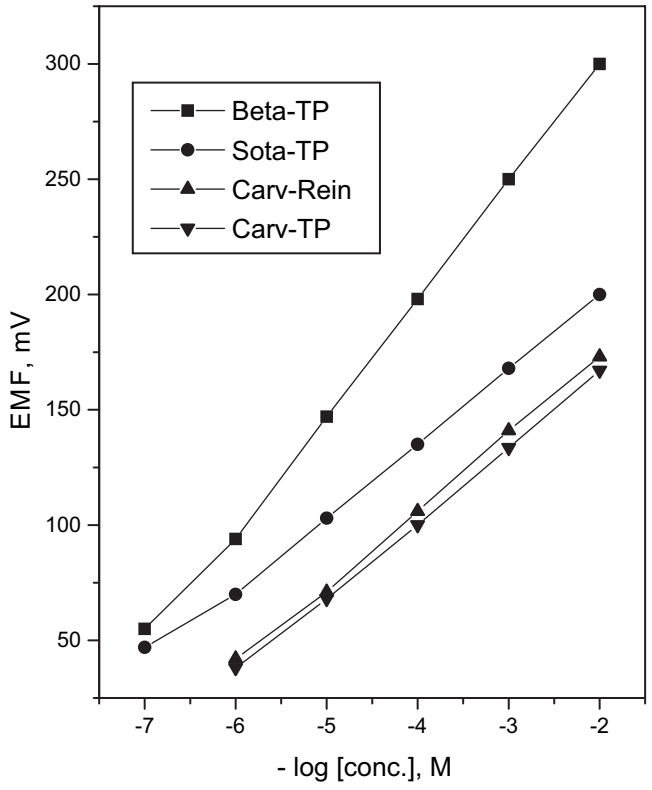


FIGURE 1 Potentiometric Response of (Beta-TP), (Sota-TP), (Carve-TP), and (Carve-Rein) PVC Membrane Sensors.

EFFECT OF PH

Potential stabilities of the sensors over pH ranges were also examined for 10^{-2} and 10^{-3} M β-blockers (Fig. 2 a–d). The results show that for all electrodes the positional were stable and practically unaffected by pH change over the working pH range almost 4.5–8.5. At pHs higher than 8, β-blockers base precipitates in the aqueous test solution. At pH higher than 8, β-blockers base precipitates in the aqueous test solution.

EFFECT OF TEMPERATURE

The response characteristics of the β-blockers sensors were examined at temperatures ranging 25–55°C using 10^{-2} 10^{-6} M β-blockers test solutions. The isothermal coefficient of the sensor ($dE_\circ/dG$) according to the relation:

$$E\circ = T_{25} + (dE\circ/dG)\,(T - 25)$$

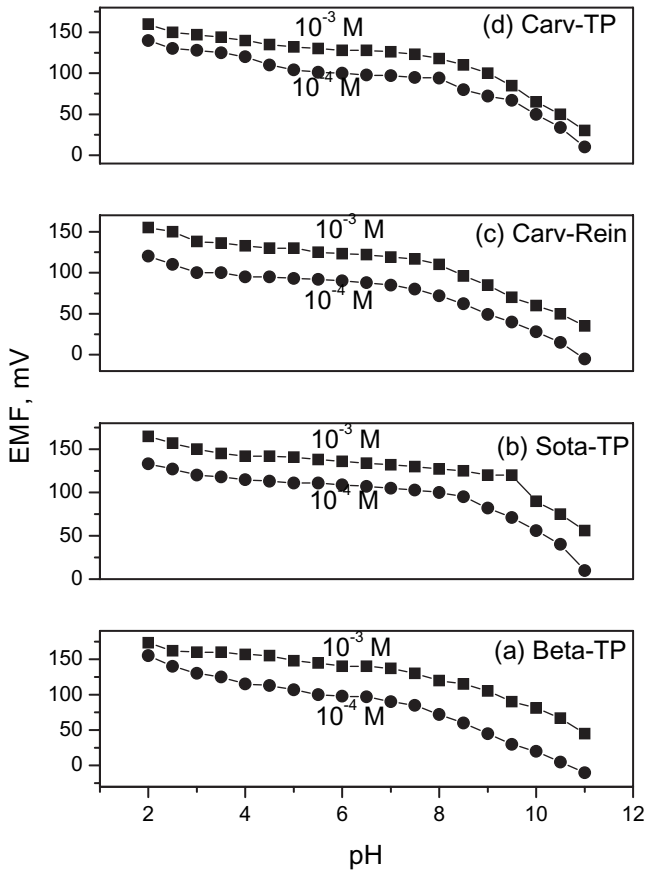


FIGURE 2 Effect of pH on the Response of (a, Beta-TP), (b, Sota-TP), (c, Carve-Rein), and (d, Carve-TP), PVC (DOP) Membrane Sensor for 10^{-3} M and10^{-4} Solutions Respectively.

was 1.5 mv (Hassan et al., 1999) . This fairly low isothermal coefficient value of the sensor within the experimental temperature range revealed a reasonable thermodynamic ionic exchange process at the membrane/drug solution interface and good mechanical and thermal stability up to 50°C.

SELECTIVITY

The influence of 11 different inorganic and organic cations, amines, amides, and pharmaceutical excipients was investigated on the electrode response. Potentiometric selectivity ($K_{D,J}^{pot}$) of TP, and reineckate β-blockers membrane-based sensors were determined using the separate solutions method [c, d], with 1×10^{-3} M aqueous solutions of β-blockers and the foreign compounds. The results obtained (Table 2) show that the proposed PVC matrix membrane electrodes were generally not susceptible to interference from many foreign basic compounds, and electrodes were generally not susceptible to interference from many foreign basic compounds, and electrodes displayed reasonable selectivity for β-blockers. Excipents and diluents normally used in drug formulations (e.g. lactose, glucose, cellulose) at levels as high as 400 fold, excess had no effect on the electrode systems.

DETERMINATION OF β-BLOCKERS

Standard β-blockers solutions (10^{-2}–10^{-7} M) were prepared, each in four replicates, and determined by direct potentiometry. The results obtained (Table 3) showed recoveries of 100.7, 99.3, 101.4, and 101.8% and mean standard deviation of 1.2, 1.1, 1.7% with TP and reineckate-based electrodes, respectively. These data are in good agreement and compared fairly well with data obtained with HPLC standard method USP 28 NF 18–2005 (United States Pharmacopeia, 2005).

The determination of measurements and range of determination under statistical control. An F-test revealed that there was significant difference between the means and variances of the two sets of results. Validation of the proposed potentiometric methods for determining β-blockers drugs (sotalol, betaxolol, and carvedilol) were made by measuring the range, lower limit of detection (LOD), accuracy (recovery), repeatability (CV_W), linearity, and sensitivity (slope).

The data in Table 1 render the proposed potentiometric methods applicable for quality control of drug formulations.

CONCLUSIONS

The proposed potentiometric methods described in this work offer many advantages over the other methods in terms of low limit detection 10^{-7} M with an accuracy of 100.7%, wide range of concentration assay 10^{-2}–10^{-7} M and wide PH working range (4.5–8.5). The sensors offer other advantages of fast response, reasonable selectivity, elimination of drug pretreatment or separation steps and low cost compared to HPLC methods. The advantages offered by the present methods suggest their use for the routine analysis of β-blockers (sotalol, betaxolol, carvedilol) in pharmaceutical preparation.

TABLE 2 **Potentiometric selectivity coefficient ($K^{POT}_{D,I}$) of β-blockers tungstophosphate and Ranickatte PVC membrane based sensors.**

	$K_{D.I}^{POT}$			
Interferent ,I	Carv-Renik	Carv-TP	Sota-TP	Beta-TP
Sodium Chloride	3.50×10^{-4}	2.67×10^{-5}	2.38×10^{-4}	1.56×10^{-4}
Potasium Chloride	3.63×10^{-4}	2.49×10^{-5}	2.56×10^{-4}	1.96×10^{-4}
Magnesium Chloride	3.26×10^{-4}	2.86×10^{-5}	2.22×10^{-4}	2.35×10^{-4}
Ammonium Chloride	3.04×10^{-4}	3.07×10^{-5}	2.1×10^{-4}	1.87×10^{-4}
p.Amino benzoic acid	3.89×10^{-4}	2.16×10^{-5}	2.22×10^{-4}	2.46×10^{-4}
p.Amino Phenol	3.86×10^{-4}	2.76×10^{-5}	2.38×10^{-4}	1.85×10^{-4}
Urea	3.26×10^{-4}	3.3×10^{-5}	2.56×10^{-4}	2.14×10^{-4}
Lactose	2.64×10^{-4}	3.25×10^{-5}	2.38×10^{-4}	2.05×10^{-4}
Glucose	2.44×10^{-4}	2.91×10^{-5}	1.93×10^{-4}	2.09×10^{-4}
Benzalkonim chloride	2.83×10^{-4}	2.97×10^{-5}	2.95×10^{-4}	2.57×10^{-4}
Di-sod.EDETA	3.50×10^{-4}	2.63×10^{-5}	3.16×10^{-4}	2.69×10^{-4}

TABLE 3 **Potentiometric Determination of β-blockers in Some Pharmaceutical Preparations Using β-blockers Tungstophosphate & Renieckate PVC Membrane Based on Sensors**

Sensor	Trade name & source	Nominal content (mg/tab)	Recovery (%)* potentiometry	Recovery (%)* **HPLC reported method USP 28 NF 18- 2005
Betaxolol-tungstophosphate	Betoptic solution ® (Alcon)	5.6 mg/mL	100.7 (±1.2)	99.25 (±0.7)
Carvedilol- tungstophosphate	Dilatrend tab ® (chemipharm)	25 mg/tab	99.27 (±1.1)	100. (±0.9)
Carvedilol-Ranieckatte	Dilatrend tab ® (chemipharm)	25 mg/tab	101.38 (±1.5)	100.1 (±1.2)
Sotalol-tungstophosphate	Betacore tab ® (Amoun)	80 mg/tab	101.78 (±1.7)	101 (±1.4)

*average of four measurements.

**HPLC determination of betaxolol hydrochloride by using ammonium phosphate buffer pH 6, acetonitrile and methanol (35:35:30) on silica column C18 (4.6 × 250 nm I.D. 5 μm) at λ 273 nm, for sotalol hydrochloride used phosphate buffer pH 3 and acetonitrile (9:1) silica column C18 (4.6 × 250 nm I.D. 5 μm) at λ 238 nm, and for carvedilol at λ 240 nm at C18 column and mobile phase consists of 1.77 gm potassium dihydrogen phosphate in water R and dilute to 650 mL adjust pH to 2 with phosphoric acid R and 350 mL of acetonitrile R.

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