Research Article

Potentiometric Sensor for the Determination of Betaxolol Hydrochloride in Plasma and Urine

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ABSTRACT

A novel betaxolol ion-selective electrode is prepared, characterized, and used in biological fluids analysis. The electrode incorporates PVC membrane with betaxolol-tetraphenylborate (BT-TPB) ion pair complex with di-butyl phosphate (DBP) as a plasticizer. The calibration curve is linear in the range from 1.0×10^{-6} to 1.0×10^{-2} mol/L with a correlation coefficient of 0.997 and slope of 59.0 mV/decade, which is close to the Nernstian slope. Selectivity coefficients of BT related to a number of interfering cation, sugars and amino-acids were investigated. The influence of pH of the tested solutions on the formulation of the electrode is not as considerable since the electrode works correctly in the pH range 3.20-8.30. The electrode was successfully used for potentiometric determination of betaxolol hydrochloride both in pure solutions and in biological fluids.

Keywords: Betaxolol HCl; Potentiometry; Membrane electrode.

INTRODUCTION

Betaxolol, (±)-1-{4-[2-(cyclopropylmethoxy)ethyl]-phenoxy}-3-(isopropylamino)-2-propanol hydrochloride (Figure 1), is a selective β-adrenoceptor blocker used in the treatment of hypertension and glaucoma[1].

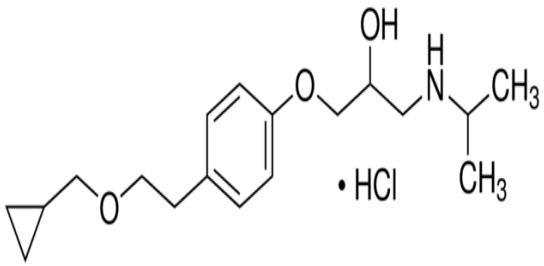

Figure 1: Chemical Structure of Betaxolol HCl

In previously published reports, the quantification of betaxolol in biological fluids by automated high-performance liquid chromatography with fluorimetric detection was described[2-4]. The concentration levels determined by these techniques are quite low but performed by highly skilled technicians at expense of laborious front end sample treatments and thus hardly suitable for screening tasks purposes. The HPLC method is sensitive despite requiring the use of organic solvents and an expensive equipment. The alternative resort to sensor technologies could be envisaged and the use of potentiometric sensors came recently into play in this context[5-7]. Potentiometric sensors offer the advantages of simple design, implementation and use additionally providing reversible and reproducible measurements at modest costs[8,9]. This paper describes a sensitive and reasonably selective poly (vinyl chloride) membrane electrode based on the use of betaxolol-tetra phenyl borate as a novel electroactive material. This electrode is satisfactorily used for the determination of betaxolol HCl as a substance in pure form and in biological fluids.

MATERIALS AND METHODS

Materials and Reagents

All chemicals were of analytical grade, and double distilled water was used throughout the experiments. Pure grade betaxolol HCl (BT), Poly (vinyl chloride) (PVC) of high relative molecular weight and tetraphenyl borate (TPB) were obtained from Sigma-Aldrich. Di-butyl phosphate (DBP) and tetrahydrofuran (THF) were obtained from (Fluka).

To investigate the selectivity of the proposed electrode towards inorganic cations, amino acids and sugars, 1.0×10^{-3} M solution of each of the following ions were prepared: Na^+, Co^{2+} and Al^{3+}. Also 1.0×10^{-3} M solution of glucose, lactose, fructose, maltose, starch, glycine, leucine, cysteine and valine were prepared.

Standard Drug Solution

Stock betaxolol hydrochloride solution (1.0×10^{-1} mol/L) was prepared daily by dissolving an appropriate amount of the drug in distilled water.

More dilute solutions were prepared by appropriate dilution using double distilled water.

Apparatus

Potentiometric measurements were carried out at 25±0.1°C on a digital pH/millivoltmeter (Jenway, Model 3510). A (WTW) packed saturated calomel electrode (SCE) was used as an external reference electrode. The electrochemical system may be represented as follows:

Ag/AgCl/internal solution/PVC membrane/test solution/ SCE (sat. KCl).

Jenway 4330 conductivity meter was used for conductance measurements.

BT-TPB Ion-Pair Complex

The ion-pair was prepared by mixing 50 ml aliquots of 1.0 × 10^{-2} mol/L betaxolol HCl and sodium tetraphenyl borate. The resulting precipitate was filtered through G4 sintered glass crucible and washed thoroughly with deionized water, then dried at room temperature for 24 h. The ion-pair should be stored in a desiccator. Elemental analyses were carried out to study the formation BT-TPB ion-pair complex. The agreement between calculated and found values was very good confirming the postulated stoichiometry; the 1:1 (BT-TPB) molar ratio stoichiometry.

Membrane Composition

The membrane composition was studied by varying the percentages (w/w) of the ion pair, poly (vinyl chloride) PVC and plasticizer di-butyl phosphate (DBP), until the optimum composition that exhibits the best performance characteristics was obtained. The membranes were prepared by dissolving the require amount of PVC, DBP and ion-pair of total weight 0.2 gram in 5.0 cm (diameter) petri dish containing 8 ml THF. To obtain homogenous and uniform thickness, the membranes were left to dry freely in air (not less than 24 hours). Several membranes of different compositions as indicated in Table 1.

Construction of Electrode

A punched circular membrane and glued using PVC-THF paste to the end of a glass tube (17 mm in diameter). The electrode body was then filled with a mixture containing equal volumes of 1.0×10^{-3} mol/L BT and 1.0×10^{-2} mol/L NaCl (as internal reference solution) in which the Ag/AgCl reference electrode was dipped. The electrode was finally conditioned for overnight by soaking in a 1.0×10^{-3} mol/L BT solution. When not in use the sensor was kept stored in a refrigerator.

Calibration Graph

Suitable increments of standard drug solution were add to 50 ml doubly distilled water so as to cover the concentration range from 1.0 × 10^{-7}-1.0 × 10^{-1} mol/L.

In this solution the sensor and reference electrode were immersed and the *e.m.f* values were recorded after each addition. The electrode was washed with double distilled water and dried between measurements.

The electrode potential was plotted versus negative logarithmic concentration of BT, Slopes of the resulting calibration curves were calculated.

Effect of pH on the Electrode Response

The effect of pH on the potential values of the BT electrode was studied over the pH range of 1–12 at 1-pH interval. This is done by immersing the electrode in 10^{-2} and 10^{-4} mol/L BT solutions. The pH was gradually increased or decreased by adding aliquots of diluted sodium hydroxide or hydrochloric acid solutions, respectively. The potential obtained at each pH was recorded.

Conductimetric Determination of BT

A volume containing 10.0-90.0 mg of BT was transferred to a 50.0 ml volumetric flask and made up to the mark with double distilled water.

The contents of the volumetric flask were transferred to a beaker, and the conductivity cell was immersed.

Then 10^{-2} M NaTPB was added, and the conductance was measured subsequent to each addition of the reagent solution after thorough stirring.

The conductance reading after each addition was corrected for dilution[10] by means of the following equation, assuming that conductivity was a linear function of dilution:

$$\Omega_{corr} = \Omega_{obs}\left[{}^{V_1 + V_2}\!\!\diagup\!\!{}_{V_1} \right] \quad \text{eq. (1)}$$

where Ω is electrolytic conductivity, v_1 is the initial volume and v_2 is the volume of the added reagent (corr.= corrected and obs.= observed).

A graph of corrected conductivity *vs.* volume of the added titrant was constructed, and the end point was determined.

Standard Addition Method

The standard addition method[11] was applied, in which small increments of a standard BT solution 1 × 10^{-2} M were added to 50 ml aliquot samples of various drug concentrations. The change in potential reading at a constant temperature of 25˚C was recorded for each increment and used to calculate the concentration of the drug sample solution using the following equation:

$$C_x = C_s\left(\frac{V_s}{V_s + V_s}\right)\left(10^{n\left({}^{\Delta E}\!\diagup\!{}_{S}\right)} - \frac{V_x}{V_x + V_s}\right)^{-1} \quad \text{eq. (2)}$$

where C_x and V_x are the concentration and volume of the unknown, respectively, C_s and V_s are the concentration and volume of the standard, respectively, S is the slope of the calibration graph, and ΔE is the change in potential due to the addition of the standards.

Determination of BT in Biological Fluids

5.0 mL aliquots of urine or plasma samples of a healthy person were transferred into a series of 100-mL measuring flasks. Aliquots of standard solution of BT were added so that the final concentration was in the range of 1.0×10^{-5}-1.0×10^{-2} mol/L.

The flasks were mixed well, completed to volume with biodistilled water and subjected to potentiometric determination of BT by standard addition method.

RESULTS AND DISCUSSION

PVC Membrane Composition Selection

Six different membrane compositions were investigated. They consist of 3.0, 5.0, 7.0, 9.0 and 14.0% of an ion pair.

Electrode made by using membrane consisting of 9.0% ion pair showed that the nearest performance characteristic of the Nernstian behaviour (slope 59.0 mV/decade), and the highest value of the correlation coefficient is 0.997 within the usable concentration range 1.0×10^{-6}-1.0×10^{-2} mol/L of BT.

Other membranes exhibit slopes less than 40 or about 64 mV/decade, but linearity ranges of the calibration curves are shorter and correlation coefficients are worse (0.888–0.935).

The response characteristics of BT electrode are listed in Table 2.

Response Time

The dynamic response time is an important factor with selective electrodes. For the proposed ISE, the response time were obtained from the dynamic potential response corresponding to BT concentration steps between 1×10^{-5} - 1×10^{-3} mol/L. The sequence of measurements was from low to high concentrations. The electrode exhibited a fast and dynamic response of 25 s for a period of 45 days, without significant change in the electrode parameters.

Effect of pH

A study of the potential-pH relations of membrane electrode based on BT-TPB ion pair revealed that within the pH range 3.20-8.30. The electrode potential practically independent of pH and in this range the electrode can be safely used for BT determination. The potential-pH curve for BT concentrations were constructed as shown in Figure 2.

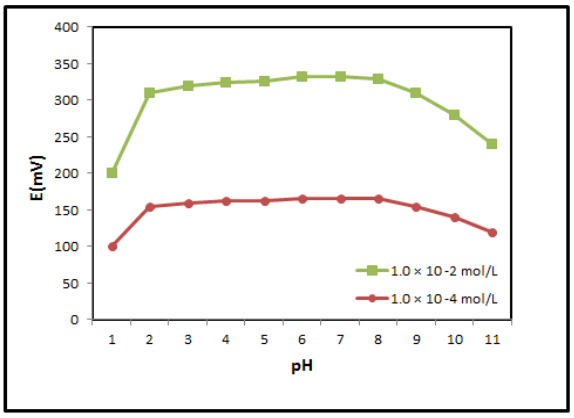

Figure 2: Effect of pH on BT Electrode Potential

Selectivity of the Electrode

The influence of various basic substances on the response of BT electrode was investigated by measuring the potentiometric interference from different kinds of sugars, inorganic cations and amino acids. The potentiometric selectivity coefficients were determined by the separate solution method[12] and calculated from the equation:

$$\log K_{i,j}^{pot.} = \frac{(E_j - E_i)}{S} \quad \text{eq. (3)}$$

where E represents the potential readings measured for the primary ion (i) and the interfering ion (j), S is the slope observed for the primary ion. The values for $K_{i,j}^{pot.}$ were calculated from the potential values measured for 1.0×10^{-3} mol/L solutions of primary and interfering ions.

The data presented in Table 3 showed that the proposed BT electrode is highly selective toward betaxolol cation.

The inorganic cations did not interfere owing to the differences in ionic size and consequently in their mobilities and permeabilites as compared with drug.

In the case of sugars, and amino acids, the high selectivity is mainly attributed to the difference in polarity and to the lipophilic nature of their molecules relative to BT cation.

Conductimetric Studies of Pure Solution of BT

Conductance measurements have been used successfully in quantitative conductimetric titration of system in which the conductance of the solution varies before and after the equivalence point.

The system under investigation showed a regular rise in conductance up to the equivalence point where a sudden change in the slope occurred.

The results of the drug determination (**Table 4**) showed that good recoveries and low standard deviations were obtained.

The optimum concentration ranges for BT determination were 12.0–80.5 mg with mean recovery value of 99, at which sharp inflections and stable conductance readings were obtained.

Analytical Applications

The investigated electrode was shown to be useful in the potentiometric determination of the amount of BT in pure solution, spiked urine and plasma by direct potentiometry using the standard addition method.

The recovery and the relative standard deviation values are summarized in Table 5 and 6.

The standard deviations were found to be ≤ 1.5, indicating reasonable repeatability and reproducibility of the selected method.

The results of the pure solutions were compared (Tables 5) with the reference method[13] at 95% confidence level.

The results are in good agreement with those obtained from the reference method. Student's *t* test and *F* test were applied[14]. The results showed that the calculated *t*- and *F* values did not exceed the theoretical values.

Table 1: Composition of Different BT-TPB Membranes and Slopes of the Corresponding Calibration Graphs.

Membrane	Composition % (w/w)			Slope mV/decade	RSD* (%)
	Ion Pair	PVC	DBP		
a	3.0	48.5	48.5	40.56	1.88
b	5.0	47.5	47.5	64.0	0.56
c	7.0	46.5	46.5	49.22	0.18
d	9.0	45.5	45.5	59. 0	0.13
e	14.0	43.0	43.0	63.23	0.78

*Relative standard deviation (three determinations)

Table 2: Critical Response Characteristics of BT-TPB-PVC Membrane Electrode

Parameter	Value
Slope/mV decade	59.0
Linearity range/mol/L	1.0×10^{-6} - 1.0×10^{-2}
Correlation coefficient	0.997
Working pH range.	3.20-8.30
Response time/s	25
Life time/day	45

Table 3: Selectivity coefficients $K_{i,j}^{pot.}$ for the proposed electrode at 25.0°C

Interfering Species j	$K_{i,j}^{pot.}$	Interfering Species j	$K_{i,j}^{pot.}$
Na^+	3.4×10^{-4}	Valine	8.2×10^{-4}
Co^{2+}	7.5×10^{-3}	Lactose	5.4×10^{-2}
Al^{3+}	1.3×10^{-4}	Fructose	9.4×10^{-3}
Glycine	6.6×10^{-3}	Glucose	6.4×10^{-2}
Leucine	3.0×10^{-3}	Maltose	1.2×10^{-2}
Cysteine	7.1×10^{-2}	Starch	8.8×10^{-4}

Table 4: Conductimetric Determination of Betaxolol HCl in Pure Solution

Taken (mg)	Recovery (%)	R.S.D. (%)
12.00	99.90	**0.16**
24.50	99.61	**0.23**
30.75	99.42	**0.37**
50.42	98.91	**0.55**
60.33	99.98	**0.11**
70.45	99.52	**0.31**
80.50	**99.13**	**0.46**

Table 5: Determination of betaxolol hydrochloride in pure solutions applying the standard addition method.

Taken (mol/L)	Recovery (%)	Reported Method [13]
1.0×10^{-5}	105.0	99.78 ± 0.356
1.0×10^{-4}	98.8	
1.0×10^{-3}	101.5	
1.0×10^{-2}	99.9	

Mean	101.30	
Recovery ± SD[a] (%)	101.30 ± 1.29	
F-value (6.39)[c]	3.91	
Student *t* test (2.571)[c]	0.268	

[a]Mean ± standard deviation of six determinations.

[b]Theoretical values of t- and F-tests at 95% confidence level and five degrees of freedom.

Table 6: Determination of betaxolol hydrochloride in spiked plasma and urine samples applying the standard addition method.

Spiked Plasma			**Spiked Urine**	
Taken (mol/L)	Recovery (%)	RSD*	Recovery (%)	RSD*
1.0×10^{-5}	100.80	0.72	98.90	0.52
1.0×10^{-4}	97.63	2.44	100.04	0.37
1.0×10^{-3}	99.18	1.12	99.44	0.81
1.0×10^{-2}	99.95	1.04	101.11	0.15
Average recovery	99.39		99.87	

***** RSD (three determination)

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