Anal. Bioanal. Electrochem., Vol. 7, No. 5, 2015, 569-581

Analytical & Bioanalytical Electrochemistry

www.abechem.com

Full Paper

PVC Membrane Selective Electrode for Determination of Isoproterenol based on Naphthylethylenediamine Dihydrochloride–Tetraphenyl Boranuide

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Received: 23 May 2015 / Received in revised form: 5 October 2015 / Accepted: 7 October 2015 / Published online: 31 October 2015

Abstract- A new coated–wire membrane selective electrode as a potentiometric sensor was developed for the determination of isoproterenol. Naphthylethylenediamine dihydrochloride–tetraphenyl boranuide ion–exchangers was used as an electroactive material on the membrane. The sensor displays a linear response with a slope of 56.9 mV decade^{-1} for isoproterenol in the concentration range of 1.0×10^{-2}–5.0×10^{-6} mol L^{-1}, with detection limit of 3.3×10^{-6} mol L^{-1}. The potentiometric response is independent of the pH of the solution in the pH range of 3.0 – 6.8. Selectivity coefficient data for some common inorganic cations, sugars and components of the mixed drugs were investigated and showed negligible interference. The response time of <5 s was displayed. The sensor can be used for more than 2 months without any considerable divergence in the potential. For the practical purposes, the efficiency of the method in the extraction and determination of isoproterenol for biological fluids such as urine and blood serum samples was evaluated without any special pretreatment.

Keywords- Isoproterenol, Potentiometry, Coated wire electrode, Potentiometric titration

1. INTRODUCTION

Isoproterenol or isoprenaline, (*RS*)–4–[1–hydroxy–2–(isopropylamino) ethyl]benzene–1,2–diol, is a sympathomimetic beta adrenergic agonist medication. It had been used in the treatment of allergic emergencies, status asthmatics, bronchial asthma, ventricular bradycardia, cardiac arrest, and glaucoma [1]. Nevertheless, the excess of isoproterenol causes heart failure and arrhythmias [2]. It is structurally similar to adrenaline. The isopropyl amine group in isoproterenol makes it selective for β–receptors. The free catechol hydroxy groups keep it susceptible to enzymatic metabolism [3]. Isoproterenol is a β_1– and β_2–adrenoceptor agonist, which was commonly used to treat asthma before the more widespread use of salbutamol, which has more selective effects on the airways [4]. Its route of administration is intravenous, oral, intranasal, subcutaneous, or intramuscular, depending on use. The plasma half–life for isoproterenol is approximately two hours [4]. Isoproterenol effects on the cardiovascular system (non–selective) relate to its actions on cardiac β_1 receptors and β_2 receptors on skeletal muscle arterioles. Isoproterenol has positive inotropic and chronotropic effects on the heart. In skeletal muscle arterioles it produces vasodilatation. The adverse effects of isoproterenol are also related to the drug's cardiovascular effects. Isoproterenol can produce an elevated heart rate (tachycardia), which predisposes patients to cardiac dysrhythmias [4]. It is supplied as 5 ml (0.2 mg/ml) vial. Its dosage is governed by the clinical presentation of the patient and varies greatly. A standard dose of insulin administration in diabetic coma follows: for adults, Infusion: 2–10 mcg/min titrated to increase heart rate and perfusion. For pediatric, infusion: 0.5 mcg/kg/min titrated to increased heart rate and perfusion [4]. Therefore, determination of isoproterenol is very important. A great number of various methods have been developed for the determination of isoproterenol. The determination of isoproterenol in biological fluids, where it is found in relatively low concentrations, usually requires the use of selective and of high detectable techniques.

Several procedures have been reported in literature for the analysis of isoproterenol. These methods are gas chromatography [5], high performance liquid chromatography (HPLC) – mass spectrometry [6], chemiluminescence [7–9], and electrochemical detections [10–12], spectrophotometry [13–15], voltammetry [16–18], and flow injection analysis [19]. These methods are reliable and sensitive; however they are limited by high costs originating from instrument acquisition and maintenance or time consumption in sample preparation.

Analytical methods based on potentiometric detection with ion selective electrodes (ISEs), offers several advantages such as eco-friendly, speed and ease of preparation and procedures, simple instrumentation, relatively fast response, wide dynamic range, good selectivity and non-destructive analysis [20–25]. As a result, ISEs are employed in clinical applications, environmental monitoring and process control as routine tools [26]. To the best of our knowledge, there is no report on the use of potentiometric sensor for the determination of isoproterenol. In this paper, a Pt coated–wire membrane electrode has been constructed.

The membrane sensor is based on incorporation of naphthylethylenediamine dihydrochloride–tetraphenyl boranuide ion–exchanger in PVC matrix on a platinum wire (Pt–wire) electrode plasticized with dioctyl phthalate. The electrode is fully characterized and then used for the determination of isoproterenol in injection solution, urine, and blood serum samples. The proposed sensor has the advantages of versatility, fast response, simplicity, stability, and repeatability plus low limit of detection.

2. EXPERIMENTAL

2.1. Reagents

All reagents used for synthesis and standard solutions were of analytical grade. 2 dibutyl phthalate (DBP), poly(vinyl chloride) (PVC) of high relative molecular weight, sodium tetraphenylboranuide (NaTPB), N-(1-naphthyl)ethylenediamine, dioctylsebacate (DOS), isoproterenol, tetrahydrofuran (THF), were purchased from Sigma-Aldrich (St. Louis, MO, USA) and other drugs used as interferences were purchased from Fluka and Sigma. Phosphate buffer (sodium dihydrogen phosphate and disodium monohydrogen phosphate plus sodium hydroxide, 0.1 mol L^{-1}) solutions with pH 6.0 were used.

A 1.0×10^{-2} mol L^{-1} isoproterenol solution was prepared daily by dissolving 0.062 g isoproterenol in water in a 25 mL volumetric flask. The solution was kept in a refrigerator at 4 ^{o}C. More dilute solutions of isoproterenol were prepared by accurate dilution of the stock solution with water.

2.2. Sample pretreatment

Urine and/or human serum were taken from healthy volunteers. The sample of human serum was diluted 1:10 with methanol to participate protein of the serum. The samples of human urine and plasma were used for measurements after its centrifuged (3,000 rpm, 10 min at 25 °C) and diluted 2 times with phosphate buffer (pH 6.0). Then, the sample was spiked with a stock solution of isoproterenol to get the final concentrations of isoproterenol (between 1.0×10^{-5} and 1.0×10^{-2} mol L^{-1}) in the urine samples. The samples were spiked just before analysis

2.3. Apparatus

EMF measurements were carried out using a pH/mV meter, Corning, Model 140 (Switzerland). A double junction saturated calomel electrode was used as the reference electrode. All potentiometric measurements were carried out at 25±0.1 °C using a cell of the following type:

$$Hg/Hg_2Cl_2, KCl\ (sat'd)\ \|\ Sample\ solution\ |\ Membrane\ |\ Pt–wire$$

The readings were recorded when the potentials reached a stable and constant value (within 1.0 mV).

2.4. Electrode preparation and calibration

For preparation of ionophore, 25 mL of 1.0×10^{-4} mol L^{-1} naphthylethylenediamine solution was added to 25 mL of 1.0×10^{-4} mol L^{-1} NaTPB solution (Fig. 1). Then, white color precipitate was washed with deionized water and dried at room temperature in a desiccator. The membrane was made by the following procedure: 30.2 mg PVC plus 63.0 mg DOP and 6.8 mg of the precipitate (naphthylethylenediamine–tetraphenyl boranuide (ion–pair)) was dissolved in 3 mL of THF. 1.5 cm of a Pt–wire was dipped into the solution mixture. After coating, the membrane was dried with a stream of air. This was repeated 15–times until a thin film was formed. Then, suitable increments of standard isoproterenol solution was added to 10 mL phosphate buffer (pH 6.0) to cover the concentration range 5.0×10^{-6} to 1.0×10^{-2} mol L^{-1} isoproterenol, while the sensor and the reference electrodes were immersed. After each addition, the cell potential was recorded at 25±1 °C. The cell potentials, E_{cell}, were recorded and plotted versus -log[isoproterenol] to make the calibration graph

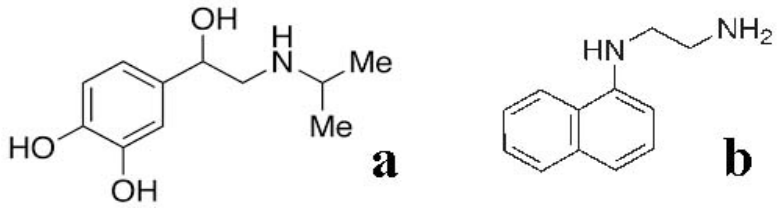

Fig. 1. Structure of a: isoproterenol and b: naphthylethylenediamine

3. RESULTS AND DISCUSSION

3.1. Influence of the membrane composition

A number of membranes incorporating with and without the ionophore and ion excluder (naphthylethylenediamine–tetraphenyl boranuide) plus the plasticizers in different compositions in PVC matrix were fabricated. Each experiment was done in three times. The response of the membrane without addition of the ionophore was not dependable. However, in the presence of the ionophore, the optimized membrane demonstrated a Nernstian response. In addition to the important role of the nature of the ion carrier in preparing membrane selective sensors, some other important features of the PVC membrane such as the amount of the ionophore, nature of solvent mediator (plasticizer), and plasticizer to PVC ratio should be considered. Thus, several membrane compositions were investigated. The behavior

of ion selective electrodes with solid state membranes depend on the composition of membrane materials used and the conditions of the membranes surface in contact with the solution in which the activity of sensed ion is monitored.

To preparation of based PVC membrane, the best ratio of plasticizer to PVC ratio is about 1.8–2.1 [20–26]. In general, the thickness and hardness of the membrane depend upon the amount of PVC used. At higher PVC content and lower PVC content, the membrane becomes too dense or mechanically weak.

It should be noted that the nature of the plasticizer influences both the permittivity of the membrane and the mobility of the ionophore, plus the dielectric constant of the membrane phase [22–24]. It was expected to plays a key role in the characteristics of the ion selective electrode. For this purpose, several solvent mediators such as DOS, DOP, and DBP were tested in the presence of different percentages of PVC, and naphthylethylenediamine–tetraphenyl boranuide. In all of the experiments here, each experiment set was done three times. The potential variations (n=3) are shown in form of standard deviation in the reported data (Table 1). To find the dynamic range of each of the electrodes, eight different concentrations of isoproterenol (from 1.0×10^{-7} to 1.0 mol L^{-1}) were tested. The potentiometric sensor based on DOP (63.0%) exhibited a better Nernstian slope (56.9±0.1 mV $decade^{-1}$) for isoproterenol over a wide concentration range of 5.0×10^{-6} to 1.0×10^{-2} mol L^{-1}, as shown in Table 1 (raw No. 1). Therefore, DOP was chosen as a plasticizer for further experiments.

Table 1. Potentiometric response of the membrane in the presence of the several solvent mediators (n=3)

No.	Composition (mass/mass, %)			Slope	Dynamic range (mol L^{-1})	R^2
	PVC	Ion pair	Plasticizer	(mV $decade^{-1}$)		
1	30.20	6.80	63.00, DOP	56.90±0.42	1.0×10^{-2}–5.0×10^{-6}	0.998
2	35.09	3.06	64.85, DOP	50.31±0.18	1.0×10^{-2}–1.0×10^{-5}	0.977
3	30.10	8.20	61.70, DOS	41.02±0.23	1.0×10^{-2}–1.0×10^{-5}	0.995
4	26.70	4.60	68.70, DOP	53.29±0.17	1.0×10^{-2}–1.0×10^{-5}	0.977
5	31.00	7.20	61.80, DBP	71.60±0.65	1.0×10^{-2}–1.0×10^{-5}	0.935
6	33.30	——	66.70, DOP	11.20±0.85	1.0×10^{-3}–1.0×10^{-5}	0.851
7	31.30	6.70	62.00, DOS	43.90±0.48	1.0×10^{-2}–5.0×10^{-6}	0.968
8	30.01	5.44	64.55, DBP	68.21±0.68	1.0×10^{-2}–1.0×10^{-5}	0.977
9	29.50	5.30	65.20, DOS	45.17±0.56	1.0×10^{-2}–1.0×10^{-5}	0.982
10	30.00	4.60	65.40, DOP	54.91±0.34	1.0×10^{-2}–1.0×10^{-5}	0.997

3.2. Influence of pH

The effect of pH on the electrode potential was investigated by recording the potential values of the drug–selective electrode in 1.0×10^{-3} mol L^{-1} isoproterenol. The pH of the solution was altered by adding very small amounts of concentrated hydrochloride acid and sodium hydroxide solutions (Fig. 2).

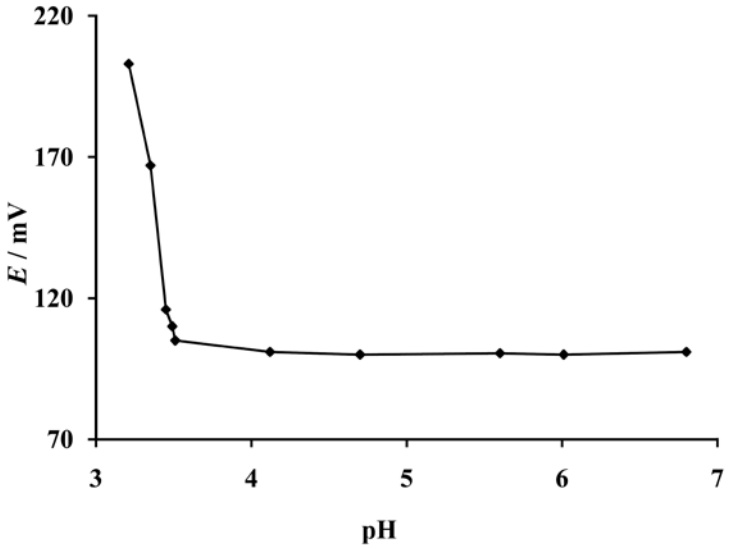

Fig. 2. Influence of pH on the response of the membrane (1.0×10^{-3} mol L^{-1} isoproterenol)

The results showed that the potential responses remained constant over the pH ranges of 3.2–6.8. With more acidic conditions, isoproterenol may be protonated, then deactivated. On the other hand, in basic solution, hydroxide ion may react with isoproterenol to produce neutral species (precipitate), which could not extract into the membrane. Thus, phosphate buffer (pH 6.0) was selected.

3.3. Response characteristics of the electrode for isoproterenol

Isoproterenol with its one ring and aliphatic part could be characterized as a lipophile compound. On the other hand, naphthylethylenediamine dihydrochloride–tetraphenyl boranuideas an ionophore has also the same characteristic. In addition, naphthylethylenediamine has amino group in the structure that can interacts with isoproterenol (has amino group too). Therefore, it seems that isoproterenol has a good interaction with the membrane to make a signal.

The response time is an important factor for any ion selective electrode. Thus, in the case of all electrodes, the average response time required for the electrode to reach a signal response within ±1 mV of final equilibrium value after successive plunging in a series of solutions each having a 10–fold difference in their concentration was measured. The response

time was recorded at different concentrations of isoproterenol in the sample solution [20]. The potentiometric response of the sensor was recorded by changing the solution from lower (5.0×10^{-6} mol L^{-1} isoproterenol) to higher (1.0×10^{-2} mol L^{-1} isoproterenol) concentrations (Fig. 3). The response time of the sensor was found to be less than 5 s at various concentrations of the test solution.

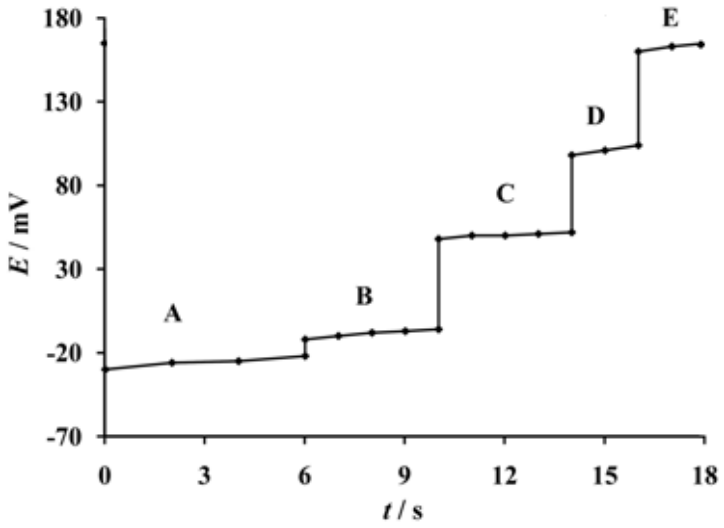

Fig. 3. Response time of the electrode; A) 5.0×10^{-6}, B) 1.0×10^{-5}, C) 1.0×10^{-4}, D) 1.0×10^{-3}, and E) 1.0×10^{-2} mol L^{-1} isoproterenol

The reproducibility of the calibration parameters were studied by drawing the calibration curve with different membranes (n=3) and with one membrane on different days (n=3). The standard deviation of ±0.42 mV per decade was obtained for the slope with the same membrane but the standard deviation of ±0.51 mV per decade was obtained with different membranes.

The limit of detection for the sensor was calculated from the intersection of the two extrapolated segments of the calibration curve, as recommended by IUPAC, and determined as 3.3×10^{-6} mol L^{-1} isoproterenol.

The electrode was used over a period of 2 months without any significant change on the membrane potential (Table 2). The slope of the electrode (56.90 mV per decade) did not change considerably during 45 days. After this period, a slight change was observed in the slope. The type of ionophore and plasticizer used as well as the number of times the electrode applied in determination affect the lifetime of the ion selective electrodes. After 2 months, the aging of the PVC matrices and the ionophore as well as the plasticizer might cause the electrode response to deteriorate [27].

Table 2. Response of the sensor during 60 days

Time (day)	Slope (mV decade^{-1})	Dynamic range (mol L^{-1})
1	56.90±0.10	5.0×10^{-6}–1.0×10^{-2}
6	56.80±0.10	5.0×10^{-6}–1.0×10^{-2}
16	56.70±0.20	5.0×10^{-6}–1.0×10^{-2}
27	56.60±0.30	5.0×10^{-6}–1.0×10^{-2}
45	56.50±0.40	5.0×10^{-6}–1.0×10^{-2}
60	55.90±0.10	5.0×10^{-6}–1.0×10^{-2}

Fig. 4 shows the calibration graph obtained for isoproterenol studied. As can be seen, the electrode exhibited a near–Nernstian response for isoproterenol within the concentration range of 1.0×10^{-2} to 5.0×10^{-6} mol L^{-1} and a slope of 56.90±0.10 mV per decade.

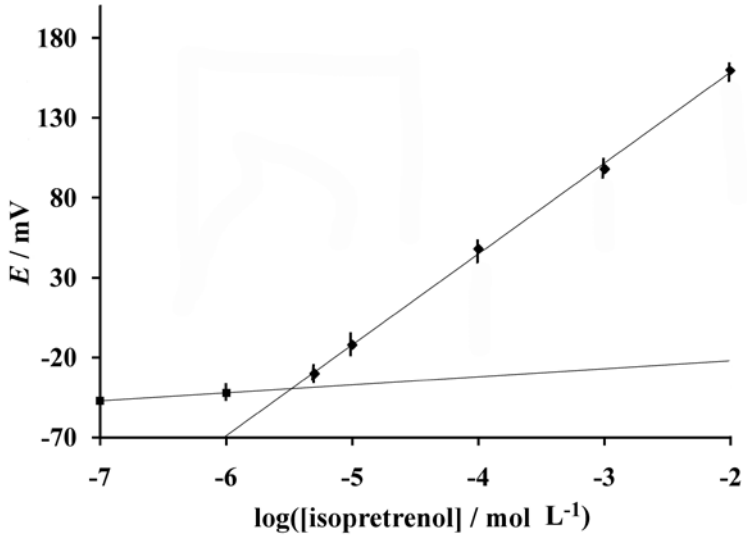

Fig. 4. Calibration graph of the membrane for isoproterenol under the optimum conditions (n=3)

3.4. Selectivity study

The influence of potential interfering substances on the response behavior of sensors described in terms of selectivity coefficients, $k_{I,J}^{POT}$. In this work, the selectivity coefficient for isoproterenol with respect to a kind of potential interfering substances were measured by separation solution method (SSM) with a fixed concentration of interference compounds at 1.0×10^{-3} mol L^{-1} isoproterenol. Then, the selectivity coefficients were evaluated from the following equation, when $a_A=a_B$ [28]:

$$log k_{I,J}^{POT} = \{(E_J - E_I)\, Z_A F/(RT.ln10)\} + (1 - Z_I/Z_J)\, log a_I \quad (1)$$

where a_I is the activity (here concentration of isoproterenol, mol L^{-1}), Z_I and Z_J are the charges of isoproterenol and interfering species, *S* is the slope of calibration graph (mV concentration^{-1}), E_I and E_J are the potential readings observed after 5 s of exposing the sensor to the same concentration of isoproterenol solution and interfering substances solution, alternatively [28].

In addition, since the electrode shows a non–Nernstian response for some of the interfering compounds, therefore, maximum limiting values of the potentiometric selectivity coefficients ($k_{I,J}^{POT}$) were calculated by modified separate solution method (MSSM) [29] from the potential measurements at the highest activity of the interfering compounds (1.0 mol L^{-1}). In this method, calibration curves are obtained for primary and interfering ions and values of E^0_I and E^0_J are determined by extrapolating the response functions to 1.0 mol L^{-1} activities according to the following equation:

$$k_{I,J}^{POT} = \{\alpha_I/(\alpha_J)^{zI/zJ}\}.\ \exp\{(E_J - E_I)(Z_I F)/RT\} = \exp\{(E^0_J - E^0_I)(Z_I F)/RT\} \quad (2)$$

One of the problems in SSM is that $k_{I,J}^{POT}$ was originally introduced with the empirical Nicolsky–Eisenman equation, which is known to be incorrect when two ions of different charges significantly contribute to the EMF response of the electrode [30].

Table 3. Potentiometric selectivity coefficient of various interfering substance

Interfering substance	$\log k_{I,J}^{POT}$ (SSM)	$\log k_{I,J}^{POT}$ (MSSM)	Interfering substance	$\log k_{I,J}^{POT}$ (SSM)	$\log k_{I,J}^{POT}$ (MSSM)
Co(II)	–4.74	–4.52	IO_4^-	–5.22	–5.19
NO_3^-	–1.57	–1.74	K(I)	–2.79	–2.75
Cr(III)	–4.50	–4.44	Glucose	–4.25	–4.24
Mg(II)	–3.49	–3.71	Fructose	–4.32	–4.49
Ca(II)	–1.25	–1.38	Diphenhydramine	–2.33	–2.11
Ni(II)	–5.59	–5.79	Captopril	–8.15	–8.26
Cd(II)	–3.84	–4.43	Amiloride	–7.32	–7.55
Fe(III)	–1.90	–2.21	Uric acid	–2.49	–2.31
Zn(II)	–3.19	–3.15	Ciprofloxacin	–2.55	–2.53
Mn(II)	–9.89	–9.97	Fluoxetine	–4.27	–4.35
CO_3^{-2}	–4.61	–4.68	Fe(II)	–2.46	–2.42
Cl^-	–4.35	–4.30	Desipramine	–2.56	–2.61
NH_4^+	–2.74	–2.51	Dibucaine	–2.13	–2.11

Therefore, the MSSM can be used to get selectivity coefficients that are near to the thermodynamically concepts. The results of the selectivity coefficients for the potentiometric sensor are summarized in Table 3. From the results given in Table 4, it is obvious the proposed sensor is highly selective to isoproterenol with respect to a variety of the other substances.

3.5. Analytical applications

In order to evaluate the applicability of the proposed sensor for the determination of isoproterenol in real samples, determining isoproterenol in injection solution, plasma, and urine samples tested its utility. The proposed membrane sensor was found to work well under laboratory conditions. Each sample was analyzed in triplicate by standard addition, using the sensor. The changes in potential were recorded for each increment and used to calculate the concentration of isoproterenol in the sample solutions. For the analyte (unknown concentration) in the sample, we can write:

$$E_1=K+S/n\times logC_X \quad (3)$$

After addition of known volume of the standard (known concentration) isoproterenol solution to the known volume of the unknown sample, we can write:

$$E_2=K+S/n\times log\{(C_XV_{X+}C_SV_S)/(V_S+V_X)\} \quad (4)$$

Where K is a constant, S/n is the slope of the calibration curve, n is the charge of the analyte, V_x and C_x are the volume and concentration of the unknown sample, respectively, C_s and V_s are the concentration and volume of the standard solution, respectively. Therefore, $\Delta E=E_2-E_1$ can be calculated as:

$$\Delta E=S/n\times log[\{(C_XV_{X+}C_SV_S)/(V_S+V_X)\}/(C_X/1)] \quad (5)$$

By rearrangement of Eq. (5), we have

$$C_X=C_SV_S/\{(V_S+V_X)10^{n(\Delta E/S)}-V_X\} \quad (6)$$

Where ΔE is the change in the potential due to the addition of the standard solution, and S is the slope of the calibration graph (Table 4).

The recovery ratio indicates that the determination of isoproterenol using the sensor is effective and can be applied for their detection in real samples.

In addition, the potentiometric sensor was successfully applied as an indicator electrode in the potentiometric titration of isoproterenol hydrochloride solution with sodium tetraphenyl boranuide solution.

Table 4. Recovery of isoproterenol in urine, human plasma, and injection solution

Sample	Added (M)	Found (mol L^{-1})	Recovery(%)
Urine	——	<Limit of detection	——
Urine	1.00×10^{-5}	$1.01(\pm0.05)\times10^{-5}$	101.0
Urine	1.00×10^{-2}	$0.99(\pm0.05)\times10^{-2}$	99.0
Plasma	——	<Limit of detection	——
Plasma	1.00×10^{-2}	$0.98(\pm0.06)\times10^{-2}$	98.0
Plasma	2.00×10^{-5}	$1.97(\pm0.04)\times10^{-5}$	98.5
Injection solution[a]	——	$4.01(\pm0.03)\times10^{-4}$	99.5
Injection solution[b]	——	$4.00(\pm0.04)\times10^{-5}$	99.2
Injection solution	——	$1.41(\pm0.02)\times10^{-3}$	100.5

± Show the standard deviation for 3 replicates analysis
a:1.0 mL of isoproterenol injection solution (0.1 mg mL^{-1})
b:1.0 mL of isoproterenol injection ampoule (0.1 mg mL^{-1}) diluted with 9.0 ml water

Potentiometric titration is a technique that the voltage across the analyte, typically an electrolyte solution is measured. To do this, two electrodes are used, an indicator electrode (potentiometric sensor) and a standard reference electrode. The voltage is recorded at intervals as the titrant is added.

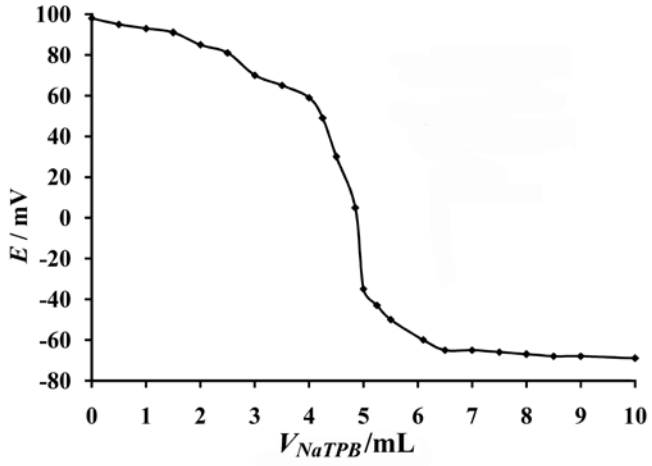

Fig. 5. Potentiometric titration of isoproterenol hydrochloride solution with NaTPB solution. Typical results for the titration of a 50.0 mL 1.0×10^{-3} mol L^{-1} isoproterenol hydrochloride solution with 1.0×10^{-2} mol L^{-1} NaTPB

A graph of voltage against volume added can be drawn and the end point of the reaction is half way between the jumps in voltage. This technique have been used for fast analysis of wide concentration ranges of analytes with potentiometric sensors those have fast response. As determination of isoproterenol hydrochloride base on the reaction with sodium tetraphenyl

boranuide, potentiometric titration method was used with the proposed electrode. Typical results for the titration of a 50.0 mL 1.0×10^{-3} mol L^{-1} isoproterenol hydrochloride solution with 1.0×10^{-2} mol L^{-1} sodium tetraphenyl boranuide is shown in Fig. 5.

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4. CONCLUSION

A membrane with a 1:2 (w/w%) dioctyl phthalate to PVC ratio, doped with 6.8% (*w*/*w*) naphthylethylenediamine dihydrochloride–sodium tetraphenyl boranuide, performed well in the development of a potentiometric sensor for the determination of isoproterenol. Meanwhile, it also has many advantages such as selectivity, simplicity, and long lifetime. The characters make us believe that this sensor will be used widely. The electrode is very easy to prepare and to use. These characteristics and the typical applications presented in this paper show that the sensor suitable for measuring isoproterenol content in real samples without any significant interaction from concomitant substances. The proposed sensor works well under laboratory condition.

Acknowledgements

The authors express their appreciation to Isfahan University of Technology Research Councils and Center of Excellence in Sensors and Green Chemistry for financial support of this work.

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