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Development of Potentiometric Sensor for Determination of Isoprenaline in Pharmaceutical Drug

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Abstract: In this study, a potentiometric ion-selective electrode (ISE) was developed for the determination of isoprenaline, a pharmaceutical active substance. For this purpose, initially, IP-PM, IP-TCA, IP-TPB, IP-REY, IP-PTA ion pairs were synthesized. The synthesized ion pairs were used as the ionophore in the structure of the electrode membrane. In order to ensure membrane optimization, PVC membrane ion selective electrodes were produced in various compositions using the synthesized ion pair and the potentiometric performance characteristics of these electrodes were investigated. It was determined that the best potentiometric performance characteristics were obtained with the PVC membrane electrode in the composition of 3.0% isoprenaline-tetrafenylborate ion pair, %64.0 nitrophenyloctylether, 32.0% polyvinylchloride and %1.0 Tetrakis (4-chlorophenyl) boron potassium compound. The linear operating range of this electrode is 5.0x 10^{-6} M - 1.0x 10^{-1} M and the slope at the 10-fold concentration change is 45.3 mV; determination limit, 5.0x10^{-6} M, pH working range, 2.6-3.6 and 5.7-7.9; response time < 5s. The electrode exhibited a reproducible potentiometric response. Isoprenaline content was determined in drug by using the isoprenaline selective electrode.

Keywords: Isoprenaline, potentiometric sensor, ion selective electrode

Farmasötik İlaçta İzoprenalin Tayini İçin Potansiyometrik Sensör Geliştirilmesi

Öz: Bu çalışmada, farmasötik etken madde olan izoprenalinin tayini için potansiyometrik iyon seçici bir elektrot (İSE) geliştirildi. Bu amaçla, ilk olarak, İP-FM, İP-TSA, İP-TPB, İP-REY, İP-FTA iyon çiftleri sentezlendi. Sentezlenen iyon çiftleri elektrot membranının yapısında iyonofor olarak kullanıldı. Membran optimizasyonunu sağlamak için sentezlenen iyon çiftleri kullanılarak çeşitli bileşimlerde PVC membran elektrotlar üretildi. Bu elektrotların potansiyometrik performans özellikleri araştırıldı. En iyi potansiyometrik performans özelliklerinin % 3.0 İzoprenalin-Tetrafenilborat iyon çifti, % 64 Nitrofeniloktileter (NPOE), % 32.0 Polivinilklorür (PVC), % 1 Potasyum tetrakis (4-klorofenil) borat (KTpClPB) bileşimine sahip membran kullanılarak elde edildi. Bu elektrodun doğrusal çalışma aralığının 5.0x 10^{-6} M-1.0x 10^{-1} M ve 10 katlık konsantrasyon değişimindeki eğimi, 45,3 mV; tayin limiti, 5.0x10^{-6} M; pH çalışma aralığı 2.6-3.6 ve 5.7-7.9; cevap zamanı < 5 sn olarak belirlendi. Elektrot oldukça tekrarlanabilir bir potansiyometrik cevap sergilemiştir. İzoprenalin içeriği, izoprenalin seçici elektrot kullanılarak ilaçta tayin edildi.

Anahtar Kelimeler: İzoprenalin, Potansiyometrik sensör, İyon seçici elektrot

1. Introduction

Isoprenaline, a catecholamine, is an important neurotransmitter and it is used in treatment of bronchitis, hypertension, cardiac obstruction, and heart attacks [1]. The excess amounts of this agent may cause heart failure and arrhythmia[2]. Therefore, it is very important to quantify this compound in clinical tests and pharmaceutical preparations and develop high-sensitive methods. In the literature, quantification of isoprenaline is performed using methods that both require expensive

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Kanberoğlu G. S., Özarslan O., *"Farmasötik İlaçta İzoprenalin Tayini İçin Potansiyometrik Sensör Geliştirilmesi"*, El-Cezerî Fen ve Mühendislik Dergisi 2020, 7 (1); 211-222.

instruments and consumables andare time-consuming such as spectrophotometry [3], flow injection analysis [4,5], chemiluminescence [6], chromatography [7], capillary electrophoresis [8] and electrochemical sensor [9]. Apart from these expensive and time-consuming methods, studies in which isoprenaline is quantified electrochemically have gained momentum in the recent years [10–14]. Among the electrochemical methods, potentiometry is one of the widely preferred methods because of its advantages such as simplicity, cheapness, providing rapid and reliable results, allowing creating miniaturized measuring systems, and not requiring specialist technicians. Studies on the development of ion-selective electrodes (ISE) and their applications started in the late 1960s[15]. Ion-selective electrodes have been used frequently in quantifications in many fields as an alternative to the aforementioned expensive quantification methods in the recent years because of their advantages such as selectivity, wide working range, low limits of quantification, high accuracy and precision, short analysis period, simple design, low cost, not damaging measured material, not requiring predissociation most of the time, and allowing for measurement in even colored and cloudy solutions.

In the literature, it is seen that selective potentiometric sensors for drug active substances is generally fabricated by using the ion-pairs of the target drug active substances as ionophore in the cunstruction of PVC membrane electrode. Numerous studies and reviews on electrodes prepared in this way are available in the literatüre [16-21]. An overview of literature indicated that there is only one work regarding the fabrication of isoprenaline-selective potentiometric electrode [22] In the mentioned study a PVC-membrane electrode were prepared based on naphthylethylenediamine-tetraphenylborate ion pair as electroactive material. Although the potentiometric performance characteristics of this electrode were satisfactory, the operating pH range was found to be quite narrow. Particularly when working in body fluids, additional buffering process is required. Since we think that the narrower pH range originated from the amine-type ion pair-forming reagent used as electroactive material, we included a new type ion pair into the PVC membrane to extend the operational pH range. Therefore, we synthesized isoprenaline-TPB ion pair and fabricated an isoprenaline-selective PVC membrane electrode based on the synthesized ion pair. The potentiometric data indicated that the operational pH range of the electrode was improved compared to the above mentioned study [22] as expected. By using the developed PVC membrane isoprenaline-selective potentiometric sensor, the quantification of isoprenaline in an isoprenaline-containing drug was successfully carried out.

2. Materials and Methods

2.1. Apparatus and Chemicals

Polyvinylchloride (PVC) of high molecular weight, graphite, tetrahydrofurane (THF), potassiumtetrakis (4-chlorophenylborate) (KTpClPB), sodiumtetrafenylborate (NaTPB), ammoniumreineckate, phosphotungsticacid (PTA), Tungstosilicicacid (TCA) and 2-nitrophenyloctylether (NPOE), di-buthylphthalate (DBP), (Dioctylsebacate (DOS) plasticizersused in the preparation of the isoprenaline-selective electrode were purchased from Sigma Aldrich. The isoprenaline hydrochloride were also obtained from Sigma Aldrich. Epoxy (TP3100) and hardener (Desmadur RFE) which were used in the preparation of solid contact were obtained from Denlaks A.Ş. (Gaziantep, Turkey). Deionized-distilled water was used in the preparations of Standard and stock solutions through out all experiments. Potentiometric measurements were performed with a computer-controlled potentiometric measurement system. Gamry (USA)Ag / AgCl electrode was used as reference electrode. pH measurements were performed with OHAUS brand pH meter.

2.2. Synthesis of İsoprenaline – Tetraphenylborate (IP-TPB) Ion Pair

10^{-2} M 20 mL Sodium tetraphenylborate solution was added into 20 mL 10^{-2} M isoprenaline hydrochloride solution. 10^{-2} M 20 mL Ammonium Reineckate was added into 20 mL 10^{-2} M

isoprenaline hydrochloride solution. 10^{-2} M 20 mL Phosphotungstic acid was added into 20 mL 10^{-2} M isoprenaline hydrochloride solution. The formed precipitates were filtered and washed with deionized water 5 times, and after that, they were left to dry in dark under room conditions.

2.3. Preparation of the Electrodes

The preparation stages of the electrode were carried out similar to in literatüre [23]. The first stage consists of the preparation of the solid contact that forms the surface on which the membrane will be coated, and the second stage consists of the preparation of the membrane cocktail and coating the solid contact surface with it. The solid contact was prepared by submerging of one of the open ends of a copper wire into a mixture that contained 50% (m/m) graphite, 35% epoxy (m/m), and 15% hardener and was homogenized, and then its drying under room conditions for a period of 1 night. The PVC membranes coated over the solid contact surface had different compositions and they were prepared by solving of total membrane mass of 100 mg in 2 mL THF. The solid contact surfaces were coated by being submerged into the prepared PVC membrane cocktails for a few times and were left to dry under room conditions for at least 12 hours. After the electrode membranes dried, the electrodes were submerged into the 10^{-2} M isoprenaline solution for 12 hours and conditioned, and they were made ready for measurement. After the pH range was determined, the membranes were conditioned in 10^{-2} M isoprenaline HCl solution, which was prepared in pH 7.4 Tris buffer for 12 hours after they were dried.

3. Results and Discussion

3.1. Investigation of the Optimum Membrane Composition

In PVC membrane ion-selective electrodes, ionophore, plasticized, ionizer, and PVC ratio, and also types of plasticizers and ionizers are important factors determining the potentiometric performance characteristics of an electrode. Therefore, in order to detect the electrode that displays the best potentiometric performance characteristics, 12 different membrane compositions were prepared by changing these parameters, and the potentiometric performance characteristics (slope, the limit of quantification, linear range, and R^2 value for the calibration curve) of the electrodes that were prepared using these membranes were investigated. The composition of all electrodes was given in Table 1.

Table 1. Membrane compositions used in the prepared electrodes

Number of	Composition (mg %)				
Electrode	Ionophore	PVC	NPOE	DBF	KTpClPB
A1	3% IP-REY	32	65	-	-
A2	3% IP-PTA	32	-	65	-
A3	3% IP-PM	32	-	65	-
A4	3% IP-TPB	32	64	-	1
A5	5% IP-PTA	32	63	-	-
A6	3% IP-TPB	32	-	65	-
A7	1% IP-PTA	32	67	-	-
A8	1% IP-REY	32	-	67	-
A9	1% IP-PTA	32	66	-	1
A10	5% IP-PTA	32	-	62	1
A11	5% IP-PTA	32	62	-	1
A12	3% IP-PM	32	65	-	-

The potentiometric performance characteristics of the prepared electrodes for standard isoprenaline solutions in the concentration range of 10^{-1} M – 10^{-5} M were presented in Table 2.

Table 2. Potentiometric performance characteristics of the electrode membranes prepared using IP-TPB ion pair as ionophore

Electrode #	Potential Change (mV)	Linear Range (mol/L)	R^2	LOD (mol/L)
A1	26	$1.0x10^{-1}$ - $1.0x10^{-3}$	0.9996	$1.0x10^{-3}$
A2	49.1	$1.0x10^{-1}$ - $1.0x10^{-4}$	0.9870	$1.0x10^{-4}$
A3	50.3	$1.0x10^{-1}$ - $5.0x10^{-5}$	0.9932	$5.0x10^{-5}$
A4	53.6	$1.0x10^{-1}$ - $5.0x10^{-5}$	0.9979	$3.0x10^{-5}$
A5	50.7	$1.0x10^{-1}$ - $5.0x10^{-5}$	0.9971	$5.0x10^{-5}$
A6	49.2	$1.0x10^{-1}$ - $1.0x10^{-4}$	0.9871	$1.0x10^{-4}$
A7	50.1	$1.0x10^{-1}$ - $5.0x10^{-5}$	0.9968	$5.0x10^{-5}$
A8	53.7	$1.0x10^{-1}$ - $1.0x10^{-4}$	0.9993	$1.0x10^{-4}$
A9	49.4	$1.0x10^{-1}$ - $1.0x10^{-4}$	0.9977	$1.0x10^{-4}$
A10	60.3	$1.0x10^{-1}$ - $1.0x10^{-4}$	0.9997	$1.0x10^{-4}$
A11	57.0	$1.0x10^{-1}$ - $1.0x10^{-4}$	0.9994	$1.0x10^{-4}$
A12	48.0	$1.0x10^{-1}$ - $1.0x10^{-4}$	0.9463	$1.0x10^{-4}$

As can be seen in Table 2, the electrode A4, which had the composition of 3% IP-TPB+32% PVC+64% NPOE+1%KTpCIPB, showed the best performance. The A4 electrode has a high slope and a high R^2 value, wide linear range compared to other electrodes.

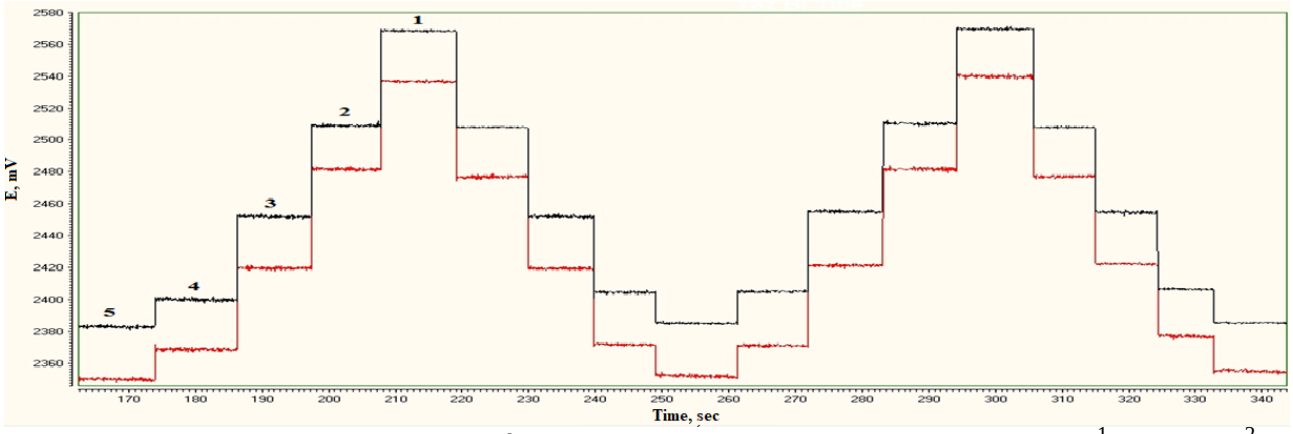

Figure 1. Potentiometric behavior of the isoprenaline-selective electrode in (1) 10^{-1} M, (2) 10^{-2} M, (3) 10^{-3} M, (4) 10^{-4} M, (5) 10^{-5} M standard isoprenaline solutions

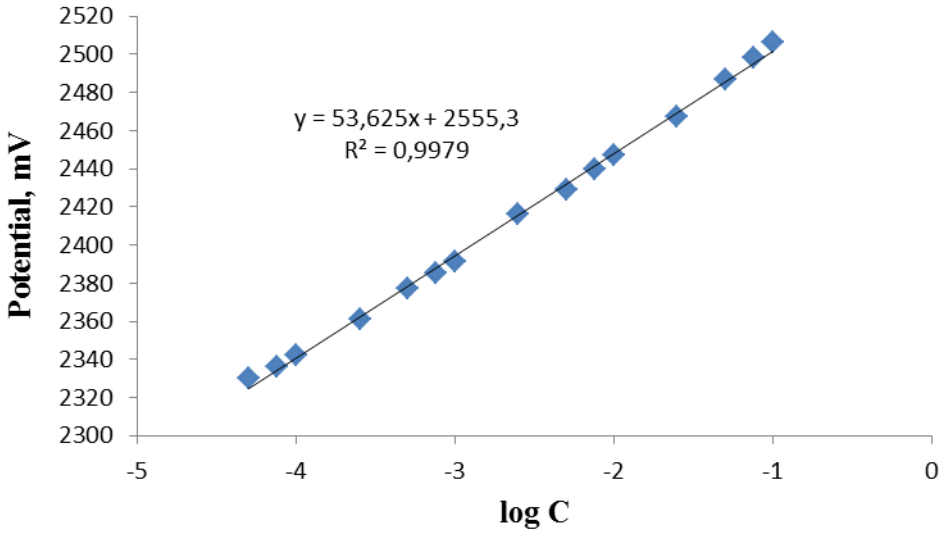

Figure 2. Calibration graph obtained from the PVC membrane isoprenaline-selective electrode in aqueous solutions

Therefore, the electrode A4 was selected as isoprenaline-selective electrode. The measurements obtained for the standard isoprenaline solutions prepared in deionized water using the electrode A4 were given in Figure 1. The obtained calibration graph was also given in Figure 2.

The repeatability values were calculated respectively as 2482.0 ±1.87,2423.2±3.03 and 2383.4±2.61 for 10^{-2}, 10^{-3} and 10^{-4} M isoprenaline solutions.

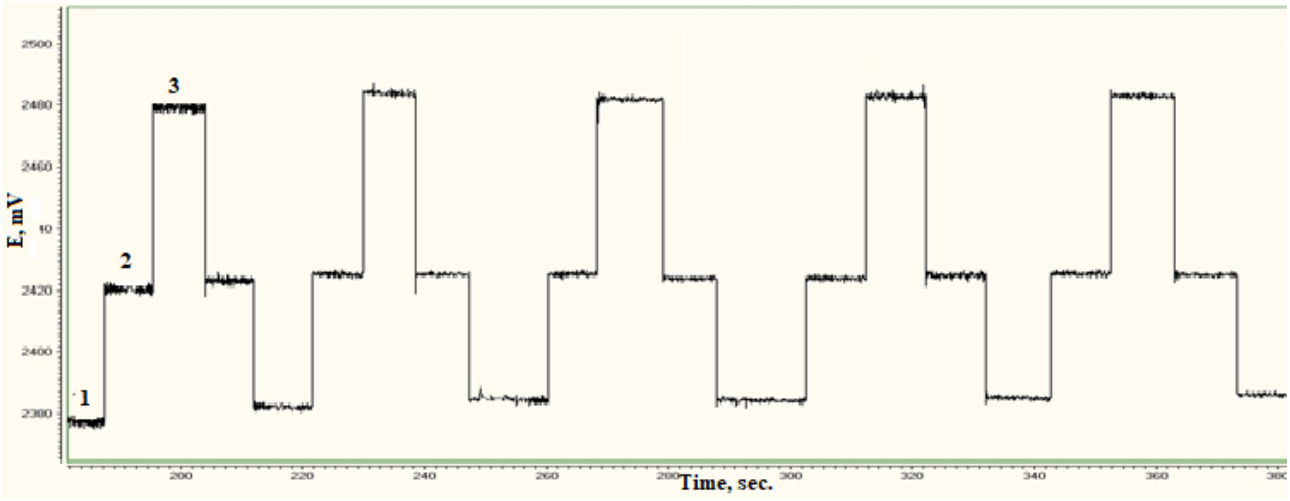

Figure 3. Repeatability measurements of the PVC membrane isoprenaline-selective electrode in the (1) 10^{-4} M, (2) 10^{-3} M and (3) 10^{-2} M isoprenaline solutions prepared in deionized water

The measurements obtained for the response time of the PVC membrane isoprenaline-selective electrode in 10^{-3} M – 10^{-4} M isoprenaline solution that was prepared in deionized water were illustrated in Figure 4. The response time (t_{95}) of the electrode was calculated as 4.5s according to the IUPAC recommendations [24].

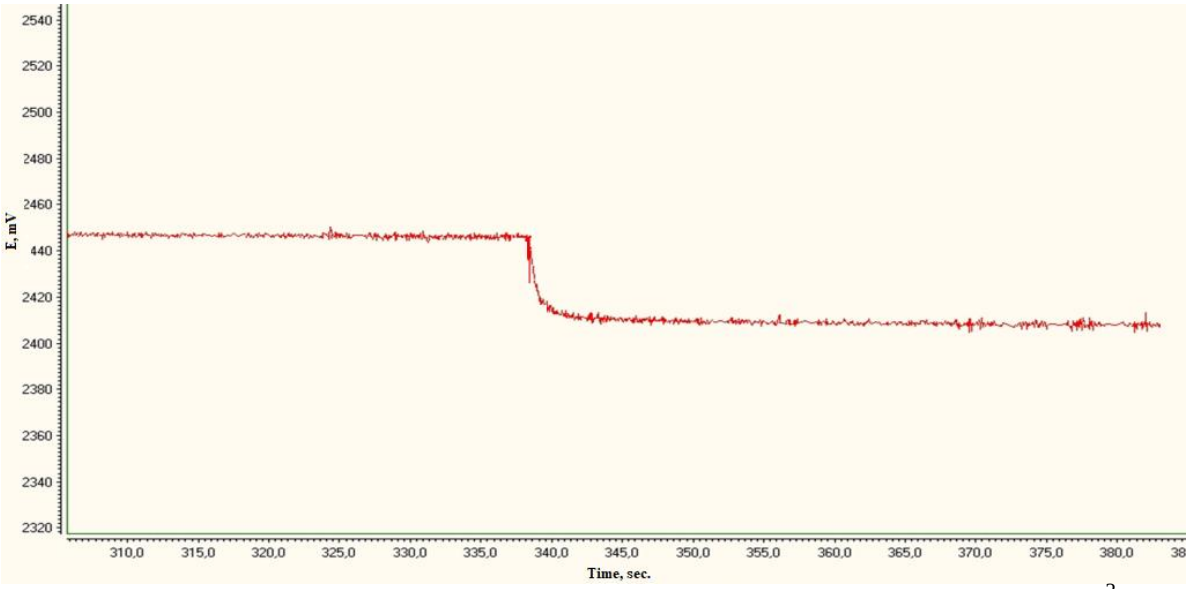

Figure 4. Response time of the PVC membrane isoprenaline-selective electrode in the 10^{-3} M – 10^{-4} M isoprenaline solution

3.2. Determining the pH Range of the Isoprenaline-Selective Electrode

To determine the pH range of the isoprenaline-selective electrode, 50 mL each of 10^{-3} M and 10^{-4} M isoprenaline and 10^{-2} M NaOH and 10^{-2} M HCl solutions were used and the pH and potential values obtained after each addition were plotted. The obtained graph was given in Figure 5.

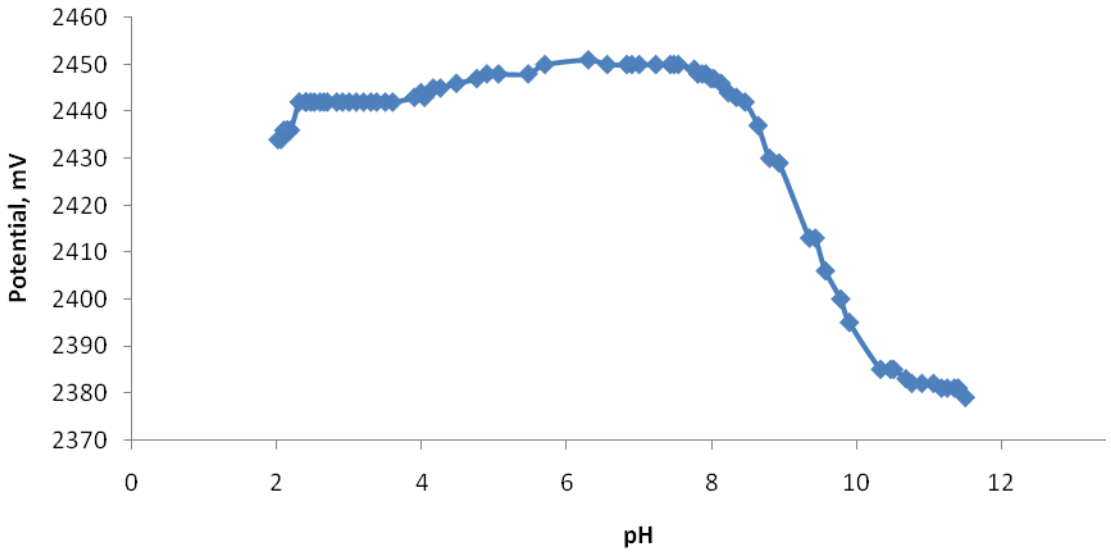

Figure 5. pH range of the isoprenaline-selective electrode

As can be seen from the graph, the potentiometric response of the electrode was not affected by hydronium ion concentration change in the pH ranges of 2.6-3.6 and pH 5.7-7.9. Compared with the above mentioned study [22], the operational pH range of the electrode was improved to allow direct operation in body fluids.

3.3. Potentiometric Performance Of The Isoprenaline-Selective Electrode in the Isoprenaline Solution in pH 7.4 Tris Buffer

The measurements made in the standard isoprenaline solutions which were prepared in pH 7.4 Tris buffer in different concentrations by the electrode. A4 that was prepared using this electrode composition were given in Figure 6.

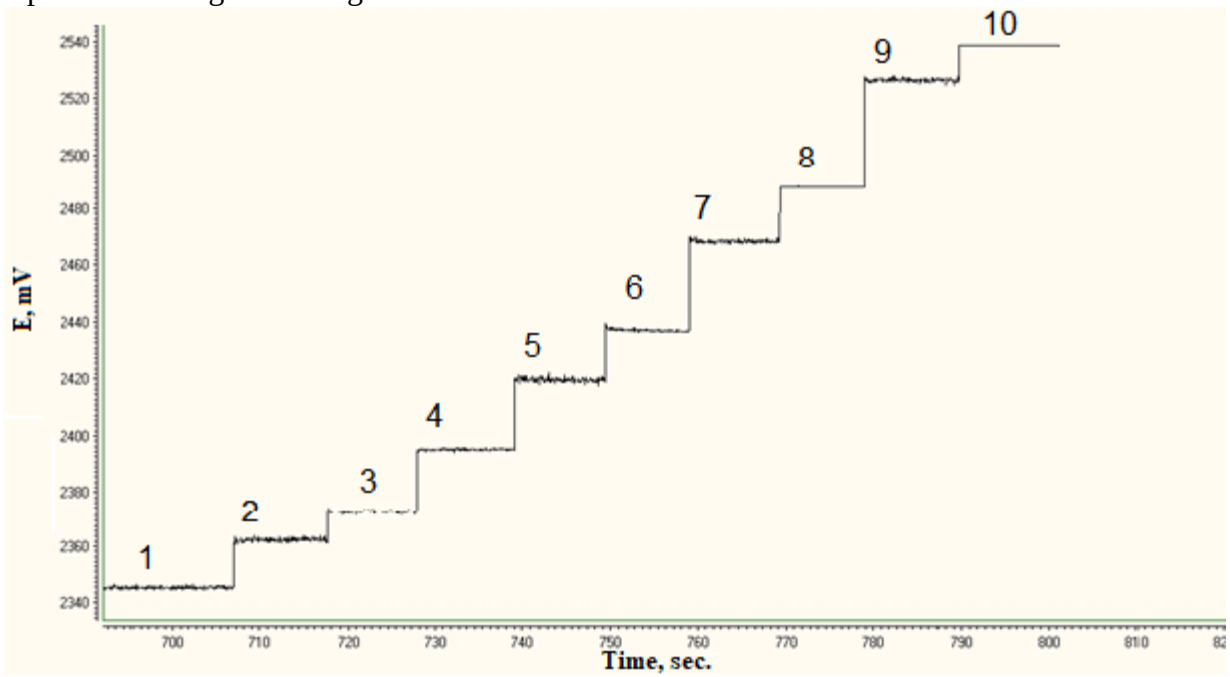

Figure 6. Potential time graph of the isoprenaline HCl standard solutions in (1) $5x10^{-6}$, (2) 10^{-5}, (3) $5x10^{-5}$, (4) 10^{-4}, (5) $5x10^{-4}$, (6) 10^{-3}, (7) $5x10^{-3}$, (8) 10^{-2}, (9) $5x10^{-2}$, (10) 10^{-1} M pH=7,4 tris buffer

3.4. Determination of Slope, Limit of Quantification and Linear Range Of The Isoprenaline-Selective Electrode in the Isoprenaline Solutions in pH 7.4 Buffer

A series of isoprenaline solutions (10^{-1} M – 10^{-6} M) prepared in pH 7.4 buffer were used to plot the calibration curve of the isoprenaline-selective electrode that was prepared using optimum membrane composition and determine its slope. The calibration graph obtained from the measurements was given in Figure 7. The electrode worked linearly in the concentration range of $1.0x10^{-1}$ - $5.0x10^{-6}$ M with a slope of 45.3 mV and its limit of quantification was determined to be $5.0x10^{-6}$ M according to IUPAC [25]. The findings indicated that the sensitivity of the calibration plot interestingly decreased compared to that of the calibration plot obtained in aqueous solutions. However the linear working range was wider than that of the previously proposed isoprenaline-selective electrode [22].

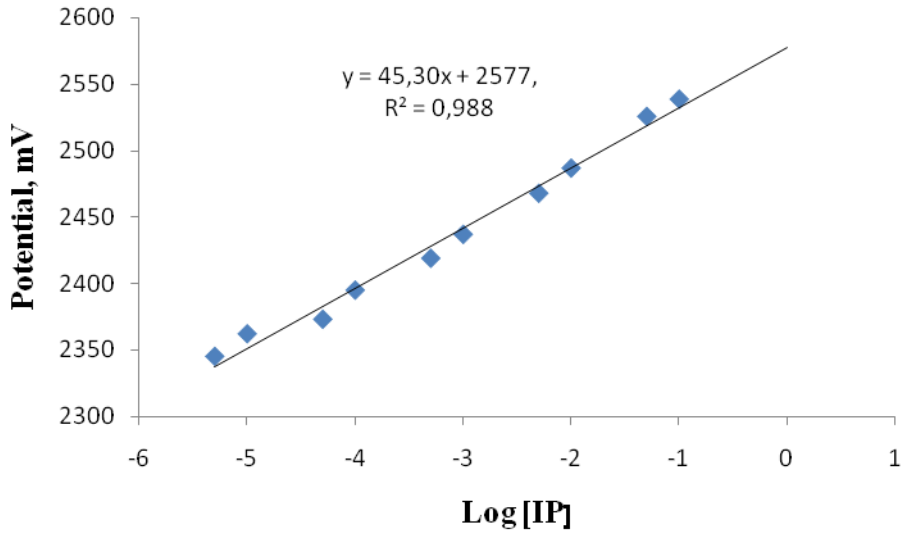

Figure 7. Calibration graph of the isoprenaline HCl standard solutions 5.0 $x10^{-6}$, $1.0x10^{-5}$, $5.0x10^{-5}$, $1.0x10^{-4}$, $5.0x10^{-4}$, $1.0x10^{-3}$, $5.0x10^{-3}$,$1.0x10^{-2}$,$5.0x10^{-2}$ and 10^{-1} M in pH=7,4 tris buffer

3.5. Determination of the Response Time of the Isoprenaline Electrode in pH 7.4 Tris Buffer

The response time in the isoprenaline solution prepared in standard 10^{-3} M and 10^{-4} M pH 7.4 Tris buffer was determined using the isoprenaline-selective electrode. The graph obtained for the response time was given in Figure 8. The response time of the electrode (t_{95}) in pH=7.4 Tris buffer was founded less than 5 seconds.

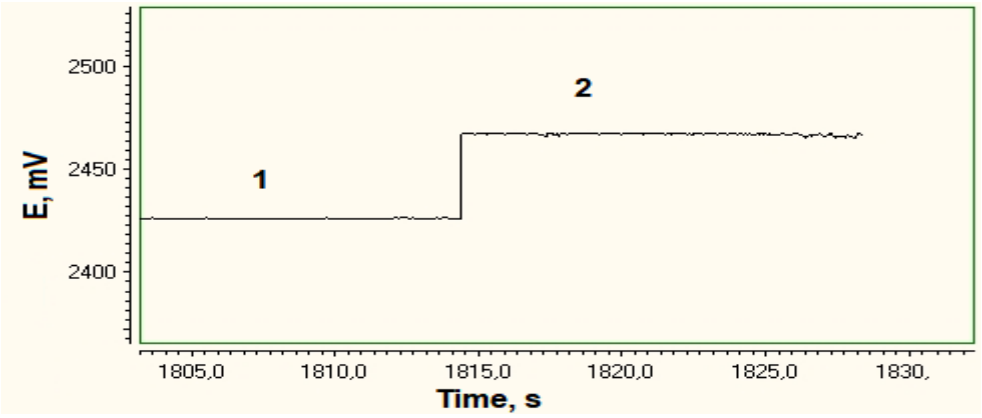

Figure 8. Response time of the isoprenaline-selective electrode in (1) 10^{-4} M and (2) 10^{-3} M isoprenaline solutions

Response time of the isoprenaline-selective electrode in 10^{-4} M and 10^{-3} M isoprenaline solutions was founded less than 5 seconds.

3.6. Determination of the Repeatability of the Isoprenaline-Selective Electrode in pH 7.4 Tris Buffer

In order to determine the repeatability of the isoprenaline-selective electrode, the measurements were made in the standard 10^{-3} M and 10^{-4} M isoprenaline solutions prepared in pH 7.4 Tris buffer consecutively and the repeatability was determined in this way. The obtained measurements of the potential displayed that the repeatability was good and they were given in Figure 9. The obtained mean and standard deviation values were given in Table 3.

Table 3. Repeatability of isoprenaline HCl standard solutions in 10^{-2} M, 10^{-3} M, and 10^{-4} M pH=7.4 buffer with the isoprenaline-selective electrode

Concentration, (M)	Potential(mV)							X±STD
10^{-2}	2489	2490	2489	2488	24888	2489	2489	2488.8±0.7
10^{-3}	2438	2438	2438	2438	2438	2438	2438	2438 ± 0
10^{-4}	2396	2396	2396	2396	2396	2396	2396	2396 ± 0

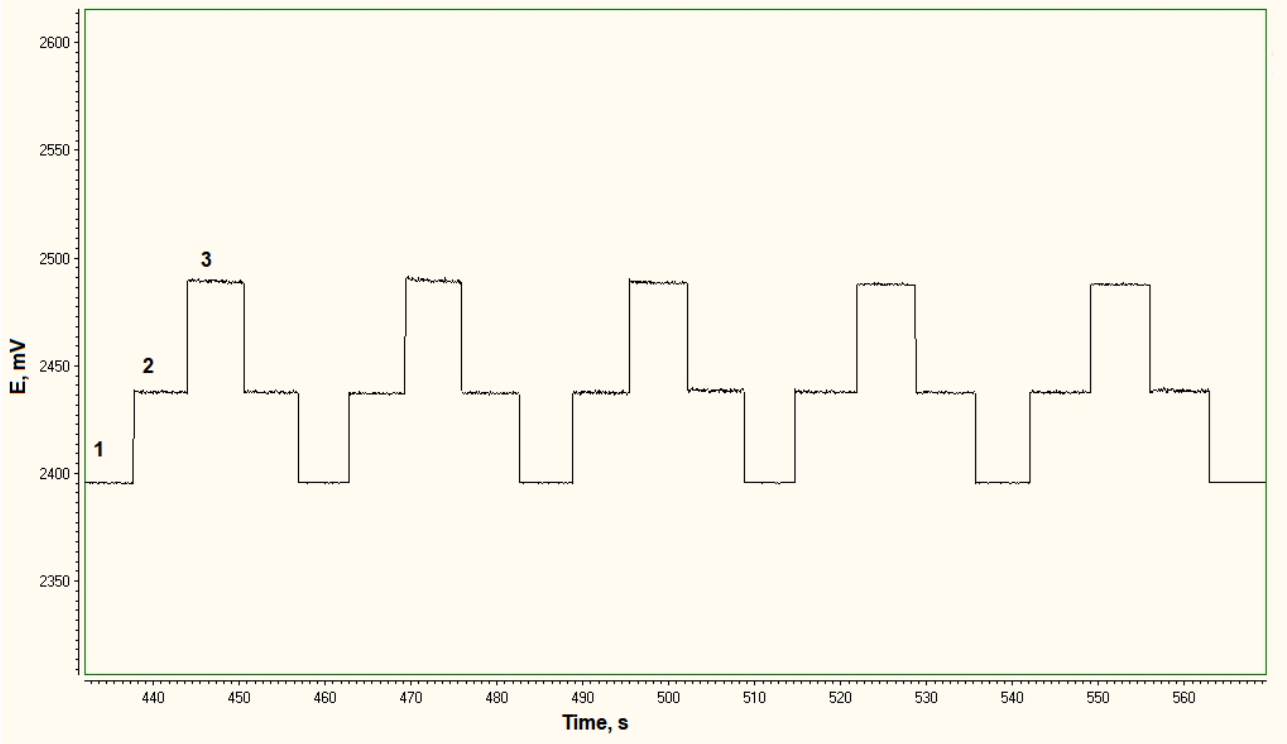

Figure 9. Repeatability of (1) 10^{-4} M, (2) 10^{-3} M and (3) 10^{-2} M, isoprenaline HCl standard solutions with the isoprenaline-selective electrode

3.7. Determination of the Selectivity of the Isoprenaline-Selective Electrode

In order to determine the effects of some common alkali metals, alkaline earth metals, heavy metals, and some organic molecules on the response of the isoprenaline-selective electrode, selectivity coefficients for these types were calculated using the separate solution method [26]. In calculating the selectivity coefficients, isoprenaline concentrations corresponding to the potential values read in 10^{-2}M solutions ofinterfering ions were detected by using calibration curve. The obtained isoprenaline concentration value and 10^{-2} M concentration value of interfering ion were placed in the selectivity coefficient equation and selectivity coefficient was determined for each interfering ion. The calculated selectivity coefficients were given in Table 4.

Table 4. Selectivity coefficients of the isoprenaline-selective electrode that were calculated using separate solution method for some types

Ions	$K^{pot}_{A,B}$	$-\log K^{pot}_{A,B}$
Ni^{2+}	$1.81x10^{-3}$	2.74
Ba^{2+}	$2.39x10^{-3}$	2.62
NH_4^+	$1.24x10^{-1}$	0.91
Mg^{2+}	$7.94x10^{-4}$	3.10
Na^+	$1.98x10^{-2}$	1.70
K^+	$8.99x10^{-3}$	1.05
Ca^{2+}	$2.64x10^{-4}$	3.58
Fructose	$3.98x10^{-3}$	2.40
Maltose	$8.70x10^{-4}$	3.06

When the selectivity coefficients were examined, it was seen that the electrode was highly selective for the measured types. Selectivity of isoprenaline was given Figure 10.

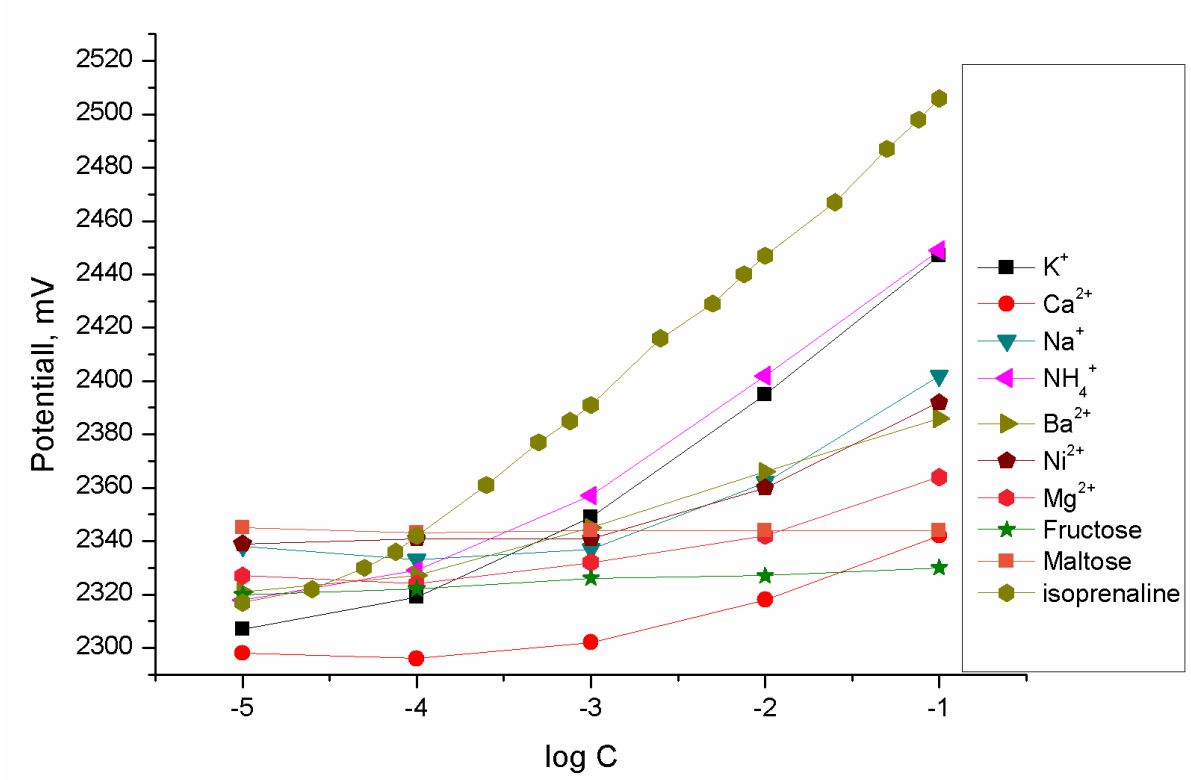

Figure 10. Selectivity of the IP-selective electrode for the other ions and molecules

3.8. Determination of the Lifetime of the Isoprenaline-Selective Electrode

In order to determine the lifetime of the isoprenaline-selective electrode, in the concentration range of 10^{-1} M – 10^{-5} M where the electrode worked linearly, the isoprenaline electrode was conditioned in 10^{-2} M isoprenaline solution for half an hour before each measurement and additional measurementswere conducted in certain days. Then, in consequence of these measurements, the slope values obtained from the calibration curves were plotted in the potential versus time graph, and inthis way, the graph in Figure 11 was obtained.

When the graph in Figure 11 is examined, it is seen that decreases occurred in the slope of the electrode and the stability in the slope of the electrode was lost at the end of the 15th day. Therefore, the lifetime of the electrode is approximately 15 days.

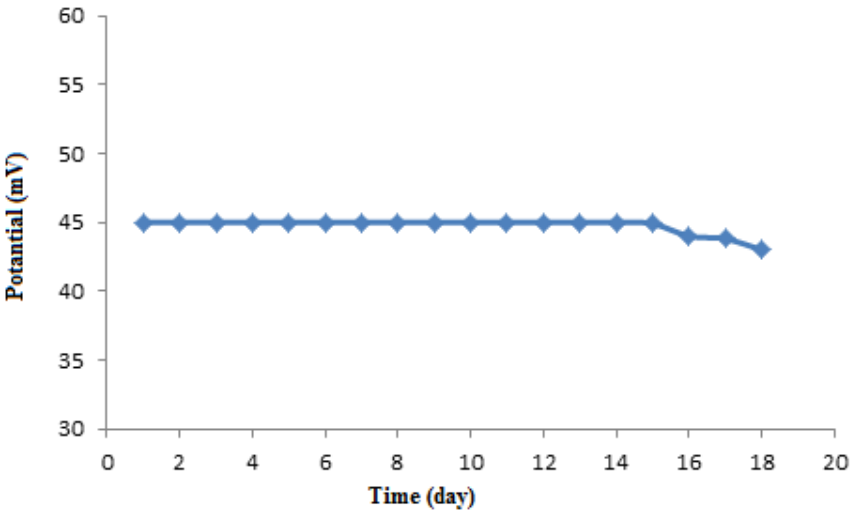

Figure 11. Lifetime of the isoprenaline-selective electrode

3.9. Analytical Application of the Isoprenaline-Selective Electrode

1 mL isoprenaline ampoule was added into 9.5 mL pH=7.4 Tris buffer. The amount of active substance in the isoprenaline-containing drug was determined. Also, quantification was carried out for the wastewater using the standard addition method.

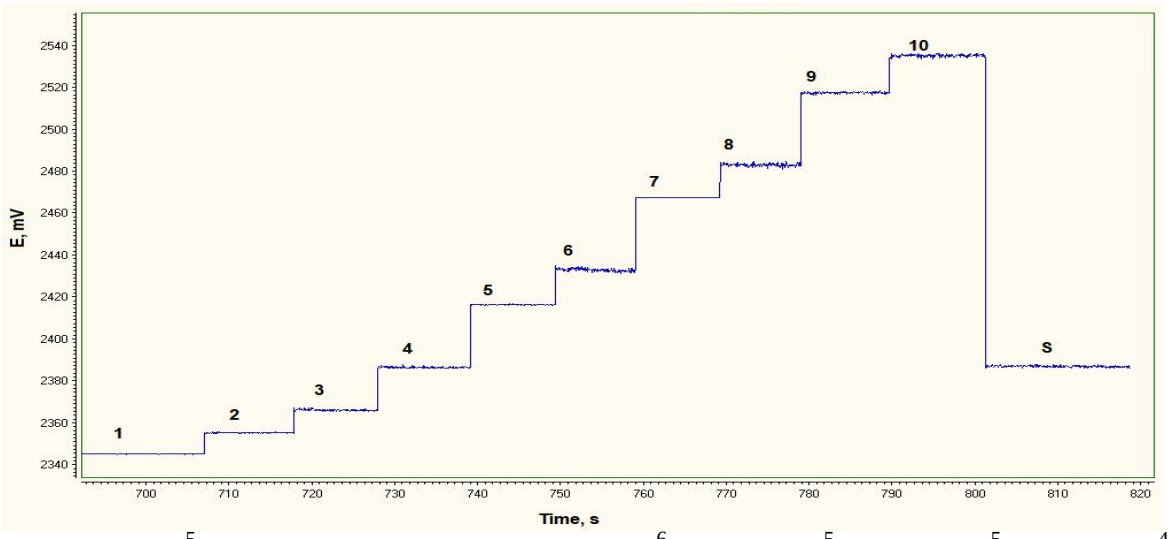

Figure 12. $8.0x10^{-5}$ M drug sample (S) and (1) 5.0 $x10^{-6}$, (2) $1.0x10^{-5}$, (3) $5.0x10^{-5}$, (4) $1.0x10^{-4}$, (5) 5.0x10-4, (6) $1.0x10^{-3}$, (7) $5.0x10^{-3}$, (8) $1.0x10^{-2}$, (9) $5.0x10^{-2}$ and (10) 10^{-1} Isoprenaline HCl standard solutions

Table 5. Application of the isoprenaline-selective electrode in the sample that contained isoprenaline HCl in ampoule form (n=5)

The sample that contained Isoprenaline HCl	The amount on the label (mg/mL)	The actual amount (mg/mL)	% Efficiency
Isuprel	0.2	0.202	101.2±0.2

4. Conclusion

Among the PVC membrane isoprenaline-selective potentiometric electrodes that were prepared using different ion pairs of isoprenaline, when the potentiometric characteristics of the electrode

that was prepared using IP-TPB ion pair was examined. A novel PVC membrane isoprenaline-selective electrode based on isoprenaline-tetraphenylborate ion pair as electroactive substance were prepared. The optimum membrane composition of the developed electrode was determined to be 3% Iso-TPB, 32% PVC, 64% NPOE, and 1% ionic additive. It was determined that the electrode displayed a highly selective potentiometric response to isoprenaline compared tothe commonly foundchemical species. The developed electrode exhibited a wider operational pH range and linear concentration range allowing for the quantification of isoprenaline directly, accurately, precisely in a reliable way in the complex matrix environments, especially in body fluids without buffering process. The response time of the electrode is less than 5 sec and allows for the rapid quantification of isoprenaline. When the electrode we developed is compared with the potentiometric isoprenaline-selective electrode [22] existing in the literature, it is seen that the linear range of the electrode we developed is wider. Its pH range allows for its application in biological fluids. It can be used without any change in the slope within the linear range of the electrode for 15 days. The developed electrode was successfully employed in studies conducted to determine the amount of isoprenaline in the ampoule drug, which is known to contain 0.2-mg/mL isoprenaline as the label amount.

As the developed electrode has advantages such as simplicity in preparation, low-cost, providing rapid, sensitive, and highly selective measurements, a wide linear range, and low limit of quantification, it has the potential to be used as an alternative to complex, more expensive, and time-consuming measurement techniques. Especially its shorter response time offers the potential to be used as a detector in automatic systems such as flow injection analysis.

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