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Novel potentiometric methods for the estimation of bisoprolol and alverine in pharmaceutical forms and human serum

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Abstract: Two new potentiometric sensors were created for the quantification of bisoprolol fumarate and alverine citrate in bulk pharmaceutical dosage forms and human serum. Bisoprolol and alverine sensors were manufactured by combining potassium tetrakis (*p*-chlorophenyl) borate ion pairs to serve as electroactive substances, plasticized poly (vinyl chloride) matrix membranes, and *o*-nitrophenyl octyl ether. They demonstrated high responses over the concentration ranges of 1.0×10^{-6} to 1.0×10^{-2} mol L^{-1} bisoprolol and alverine with close to Nernstian cationic slopes of 52 and 56 mV $decade^{-1}$, respectively. The detection limits for bisoprolol and alverine were 2.6×10^{-6} and 1.75×10^{-6} mol L^{-1}, respectively. For both medications, the response time was instantaneous (2.0 s). The working pH ranges for bisoprolol and alverine were 4.50-8.50 and 2.00-8.80, respectively. For both sensors, the life cycle was long (3 months). The sensors were used in pharmaceutical dosage types for the assay of bisoprolol and alverine, recording average recoveries of 99.40% and 99.98% respectively and were also successfully used for estimating the two drugs in human serum with an average recovery of 99.60% for both drugs. For all multiple staged interfering materials, the reported latest potentiometric sensor methods displayed high selectivity. The current sensor obtained a high percentage recovery and an excellent relative standard deviation compared with those obtained from previously published methods.

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1 Introduction

Potentiometry is an electrochemical method widely studied by researchers due to its many advantages. Thousands of potentiometric sensors have been successfully developed and applied in diverse fields such as medicine, environmental monitoring, agriculture, industry, and pharmaceutical sciences. From a medical point of view, clinical drug research and the determination of drugs in biological samples are extremely significant. Such experiments are performed using various analytical instruments, including electrochemical sensors. With regards to many parameters, potentiometric sensors can out-perform other instruments and are therefore commonly used in research. The use of potentiometric sensors to recognize drug molecules in body fluids has shown promising results in the literature. In this research, we apply potentiometry-based sensors to biological blood serum samples for the determination of drugs and document their performance characteristics [1-5].

High blood pressure is a widespread global health issue and is one of the key causes of cardiovascular disease. Bisoprolol fumarate (BIS), ((E)-but 2enedioicacid;1-(propan-2-ylamino)-3[4-(2-propanyloxyethoxymethyl) phenoxy] propan-2-ol) (Figure 1a) is used for the treatment of hypertension. It is considered a potent drug with a long-half life that can be used once daily to reduce the need for multiple doses of antihypertensive drugs. Bisoprolol is well-tolerated, possibly because of the selectivity of its β1-adrenergic receptor. It is a useful alternative to non-selective β-blocker medications such as carvedilol and labetalol in the treatment of hypertension . It can be used alone or in conjunction with other medications to treat

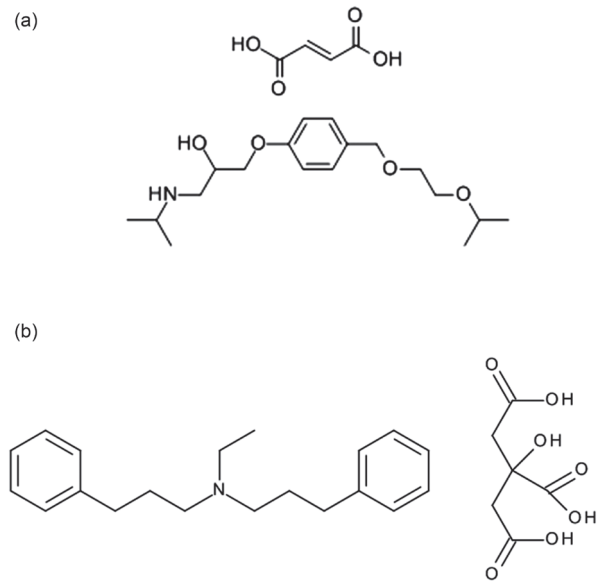

Figure 1: Chemical structure of (a) bisoprolol fumarate and (b) alverine citrate.

hypertension and can also be used in chronic obstructive pulmonary disease (COPD) due to its receptor selectivity (no β2 effect).

Pharmacodynamics and mechanisms of action are a reduction of heart rate (chronotropy) by bisoprolol, contractility (inotropy) and blood pressure alterations. Bisoprolol decreases cardiovascular mortality and all-cause mortality in patients with heart failure and reduced cardiac ejection fraction (CEF) has been documented in several clinical trials [6].

Bisoprolol's mechanisms of action in hypertension are thought to be achieved by β1 adrenoceptor antagonism, resulting in lower cardiac output. Bisoprolol is a competitive, cardio-selective β1-adrenergic antagonist that decreases cardiac workload through competitive inhibition of β1-adrenergic receptors by reducing contractility and oxygen requirements [7]. Side effects can include stomach cramps or colic.

Alverine citrate (ALV), (N-ethyl-3-phenyl-N-(3-phenylpropyl) propan-1-amine; hydroxypropane-1, 2, 3-tricarboxylic acids) (Figure 1b) is also known as Alverine.

Alverine is a smooth muscle (an involuntary muscle found in the gastro-intestinal tract, uterus, etc.) relaxant. In conditions such as irritable bowel syndrome, biliary colic, diverticular disease, and different types of intestinal colic, this prevents muscle spasms that occur in the gut. Diverticular disease results from persistent habitual constipation in which the colonic wall produces small, inflamed pouches. In the case of irritable bowel syndrome, normal intestinal muscle function is lost. Symptoms such as heartburn, stomach pain and bloating, alternating constipation and diarrhea are the product of muscle spasms. Alverine is a smooth muscle relaxant. Smooth muscle is a type of muscle that is not under voluntary control; it is the muscle present in places such as the gut and uterus. [8,9]. It can also be used to alleviate dysmenorrhea.

Therefore, for BIS and ALV drug determination, it is important to establish straightforward quantitative techniques. There are many analytical methods reported for the determination of the drugs BIS and ALV besides the British pharmacopeia method which involves the potentiometric titration in non-aqueous media [10], methods that have been reported for determining bisoprolol include spectrophotometry, HPLC, voltammetry, potentiometry [11- 29], with similar methods used for alverine determination [30-33]. The aim of this research is to develop accurate, precise, sensitive, cost-effective potentiometric sensors for the quantification of bisoprolol and alverine in human serum and pharmaceutical dosage forms. Herein, the use of ion-pairs of the drugs with potassium tetrakis(*p*-chlorophenyl) borate (KT*p*-ClPB) as electroactive substances in plasticized poly (vinyl chloride) matrix membranes with *o*-nitrophenyl octyl ether, were investigated as novel bisoprolol and alverine sensors.

2 Experimental

2.1 Reagents and apparatus

Many of the reagents used were of high purity and all tests used double-distilled water. Potassium tetrakis (*p*-chlorophenyl) borate (KTp-ClPB) and *o*-nitrophenyloctyl ether (*o*-NPOE) were bought from Fluka (Buchs, Switzerland). BP Chemicals International supplied poly (vinyl chloride) (PVC) (Breon S 110/OP) (Barry, UK). Authentic samples of bisoprolol and alverine (purity 99.90%) were gathered from (SEDCO) Egypt. From local pharmaceutical stores, commercial bisoprolol (Concor® and Bisotens® 10 mg per tablet) and alverine (Alsotrin® 60 mg per capsule) were obtained. KCl, $Pb(NO_3)_2$, $CaCl_2$, NaCl, $NiCl_2$, $CoCl_2$, $CdCl_2$, $ZnCl_2$, $MnCl_2$, starch, talc, lactose, fructose, ascorbic acid, glucose, heptaminol HCl, atenolol, propranolol HCl, and amlodipine were used as interference materials and purchased from the El-Nasr Company, Egypt. Serum samples were collected from healthy donors. All biological samples were collected in accordance with the applicable laws and institutional guidelines (Profession and Ethics Legislation, Ministry of Health and Population Resolution No 238/2003). The protocol was accepted by the institutional committee of the Faculty of Science (Zagazig University, Egypt).

Potentiometric measurements were carried out using potentiometric sensors built in conjunction with the EIL-Type RJ 23 calomel reference electrode used by some instruments, such as the PTI-15 digital pH meter. For pH measurements, a glass Ag-AgCl combination electrode (Consort, 5210 B BB5) of the Consort P907 mV pH meter was used.

2.1.1 Solutions

The standard stock solutions of 1.0×10^{-2} mol L^{-1} for both drugs were freshly prepared by dissolving (0.044 g) bisoprolol fumarate and (0.473 g) alverine citrate in the least amount of double-distilled water plus 5 mL acetate buffer of pH = 4.6 to keep the drugs in protonated forms, and the volumetric flasks were made up to the 100 mL mark with double distilled water. A series of standard bisoprolol and alverine solutions covering the range from 1.0×10^{-6} to 1.0×10^{-2} mol L^{-1} were prepared by suitable dilutions.

2.2 Ion-pair preparation

Ion pair preparation was achieved by mixing a 50 mL drug solution of 1.0×10^{-2} mol L^{-1} with a 50 mL solution of 1.0×10^{-2} mol L^{-1} potassium tetrakis (*p*-chlorophenyl) borate. The precipitate was filtered, washed with double-distilled water and dried at 90°C for 30 min. The resulting powder was used in the plasticized membrane with *o*-nitrophenyl octyl ether as an electroactive material.

2.3 Sensor construction

The constituents of the membrane sensor were: the ion-pair, drug -tetrakis (*p*-chlorophenyl) borate (10.0 mg) (1.85 mass%), (PVC) (170 mg) (31.48 mass%), and *o*-nitrophenyl octyl ether (*o*-NPOE) (360 mg) (66.66 mass%). The membrane was casted and the sensor constructed as described previously [34,35]. The sensors were immersed in BIS and ALV solutions of 1.0×10^{-2} mol L^{-1} for one day prior to use and remained in the same solution while not in use. The sensors were calibrated by spiking the normal solution into a 1.0×10^{-6} mol L^{-1} solution of BIS and ALV calibrating solutions with successive liquids. Alternatively, the calibrations were carried out by immersing the sensors in 50-mL beakers containing regular 1.0×10^{-6}-1.0×10^{-2} mol L^{-1} BIS and ALV solutions of 25.0 mL aliquots from low to high concentrations. The electromotive force (EMF) was tracked and plotted against the logarithmic drug concentrations. The calibration graph was used for the subsequent measurement of the unknown drug levels.

Potentiometric selectivity coefficients were calculated using the separate solution method [36,37], where the potential of the drug sensor and the reference electrode cell are calculated using two separate drug and interfering material solutions with the same activity (1.0×10^{-2} mol L^{-1}). The measurement of the potentiometric selectivity coefficient values is based on the equation:

$$\log\left(K^{pot}_{drug,B}\right)=\frac{(E_B-E_{drug})}{S}+\left(1-\frac{Z_{drug}}{Z_B}\right)\log a_{drug} \quad (1)$$

where E_{drug} – the measured potential values of BIS and ALV, E_B – measured potential value of the interferent, S – the slope of the calibration plot in mV decade^{-1}, a_{drug} – the activity of the drug, Z_{drug} and Z_B – the charges of the drug and the interferent, respectively.

2.4 Potentiometric estimation of BIS and ALV in pharmaceutical formulations

Bisoprolol was calculated by taking the equal weight of one tablet of both Concor® (10 mg/tablet) and Bisotens® (10 mg/tablet) and then dissolving them in an adequate volume of double-distilled water. The solution was filtered, a 5 mL acetate buffer was applied to the filtrate, and the 100 mL volumetric flask was then made up to the mark with double-distilled water. In order to assess alverine in Alsotrin® (60.0 mg per capsule), 8 hard gelatin capsules were taken and dissolved in a 100 mL volumetric flask, 5 mL of buffer solution was added and then double-distilled water was added to the mark. The calibration graph method and the standard addition technique were used to evaluate the substance, the latter based on measuring the potential of a definite volume of the unknown sample before and after applying 2.0 mL of the standard solution to the analyte solution, then calculating the unknown concentration.

2.5 Estimation of BIS and ALV in human serum

5 mL of blood from healthy donors containing doses of Concor® (10 mg/tablet) or Alsotrin® (60.0 mg per capsule) was collected in covered test tubes and these tubes were left for approximately 30 min at room temperature to permit the coagulation of the sample. The clot was extracted using centrifugation for approximately 10 min

at 1,000-2,000 g [38]. Human serum was transferred by a Pasteur pipette into a sterile polypropylene tube after the centrifugation stage had finished. The samples were stored at 2-8°C. The standard addition technique was applied for assaying the drugs at room temperature.

3 Results and discussion

In potentiometric sensor methods (potassium tetrakis (*p*-chlorophenyl) borate (KT*p*-ClPB) as a newer ion exchange used for the determination of bisoprolol fumarate or alverine citrate. In our study, drug-tetrakis (*p*-chlorophenyl) borate ion-pairs have been used as electroactive substances in plasticized (PVC) matrix membranes. The membranes were manufactured using casting solutions with the components listed previously. Referring to IUPAC [36], the electrochemical potentiometric sensor was measured, showing that it exhibited near-Nernstian responses over the concentration ranges of 1.0×10^{-6}-1.0×10^{-2} mol L^{-1} of drugs with 52 and 56 mV/decade cationic slopes for BIS and ALV, respectively (Figure 2, Table 1).

The detection limits were 2.6×10^{-6} and 1.75×10^{-6} mol L^{-1} for BIS and ALV respectively. These values were calculated in conjunction with IUPAC guidelines [27]. A minimum square review of the data gathered over 13 weeks revealed the following relationships:

$$E\ (mV) = 52 \log [BIS]-255 \quad (2)$$

$$E\ (mV) = 56 \log [ALV]-262 \quad (3)$$

3.1 Response time

Response time is the time required for the sensor to reach a stable reading. Over the measurement duration, the current potentiometric sensors reported stable potential readings within 1.0 mV, and the calibration slope did not differ by more than 1.0 mV $decade^{-1}$ over the lifetime of the current sensors. The response time values for the two sensors were 2.0 s for the initial 1.0×10^{-2} mol L^{-1} concentration. The duration of useful life of the sensors was 13 weeks.

3.2 Influence of pH

In Table 2, two separate solutions of concentrations 1.0×10^{-2} and 1.0×10^{-3} mol L^{-1} of BIS and ALV were used to illustrate the effect of pH on the sensors. In order to study the acidic pH range, dilute hydrochloric acid solution was added, and dilute sodium hydroxide solution was used to study the alkaline pH range. The potential readings for 1.0×10^{-2} mol L^{-1} were fairly constant over the pH range of 4.5-8.5 and 2.0-8.8 for BIS and ALV, respectively, and the readings for 1.0×10^{-3} mol L^{-1} of the drugs were fairly constant over the pH range of 5.5-8.5 and 5.7-7 for BIS and ALV, according to the pH potential graphs (Figures 3 and 4). These drugs were fully soluble, dissociated and sensed as singularly charged ions within these ranges. In a more alkaline medium, the potential of both sensors decreased due to the interference of OH^- ions where the drugs started to precipitate. In a more acidic medium, the potential of BIS increased, probably due to the interference of H^+ ions.

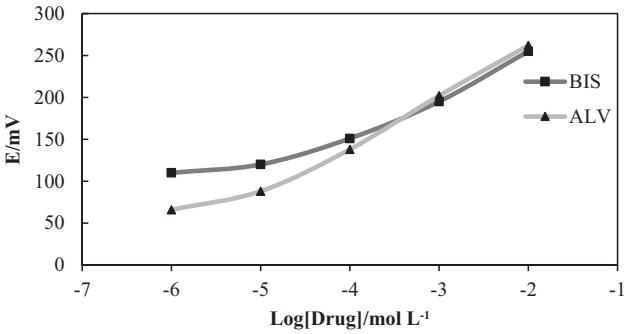

Figure 2: Potentiometric response of the BIS and ALV sensors.

Table 1: Response characteristics of BIS and ALV sensors

Parameters	BIS_{Sensor}	ALV_{Sensor}
Slope (mV $decade^{-1}$)	52	56
Intercept (mV)	255	262
Correlation coefficient (r^2)	0.998	0.989
Lower limit of linear range (mol L^{-1})	2.6×10^{-5}	2.3×10^{-5}
Lower limit of detection (mol L^{-1})	2.6×10^{-6}	1.75×10^{-6}
Working pH range of BIS sensor for 1.0×10^{-2} mol L^{-1}	4.5-8.5	2.0-8.8
Working pH range of ALV sensor for 1.0×10^{-3} mol L^{-1}	5.5-8.5	5.7-7
Response time (s) for 1.0×10^{-2} mol L^{-1}	2.0	2.0
Life span (weeks)	13	13

Table 2: The pH range for two different concentrations of both drugs

Drug	Concentration	pH range
BIS	1.0×10^{-2}	4.5-8.5
	1.0×10^{-3}	5.5-8.5
ALV	1.0×10^{-2}	2.0-8.8
	1.0×10^{-3}	5.7-7

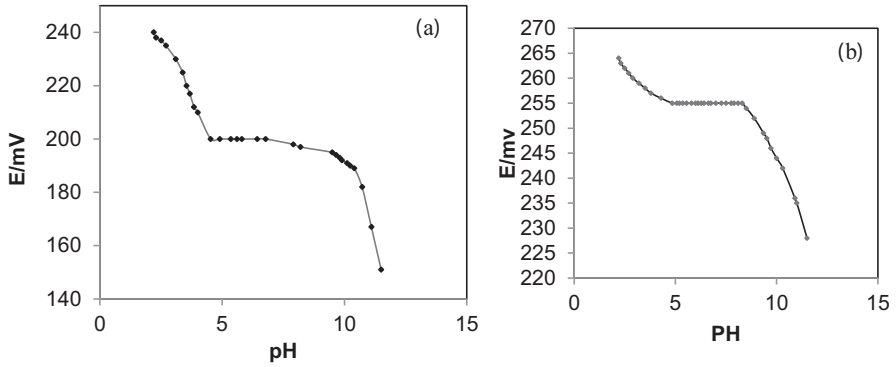

Figure 3: pH-potential profile of the BIS sensor for (a) 1.0×10^{-2} mol L^{-1} BIS and (b) 1.0×10^{-3} mol L^{-1} BIS.

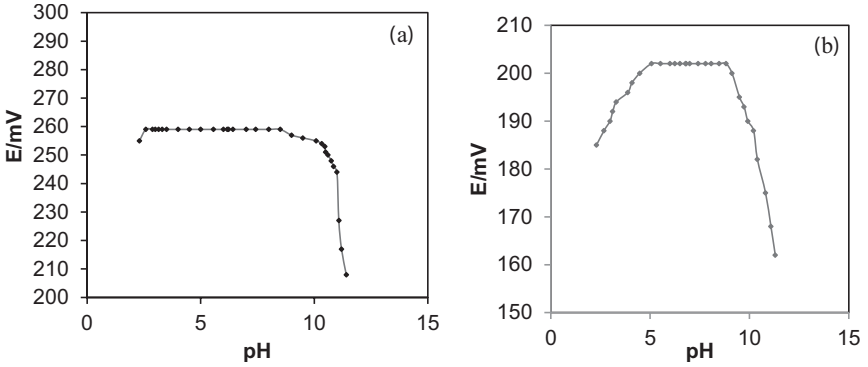

Figure 4: pH-potential profile of the ALV sensor for (a) 1.0×10^{-2} mol L^{-1} ALV and (b) 1.0×10^{-3} mol L^{-1} ALV.

3.3 Effect of the interferences

By using certain inorganic cations and cationic drugs as interfering products, the sensors were tested for selectivity. The selectivity coefficients $\left(K^{pot}_{drug,B}\right)$ [39,40] were evaluated to show the degree of interference, using a different solution method. The key dependent factor for the selectivity of ion-exchanger complexes-based membrane sensors [41] is the lipophilicity of the interfering ion and also its movements inside the membrane. We reported that the proposed sensor has a high selectivity towards BIS and ALV drugs and no interference from the studied inorganic cations, carbohydrates or structural analogs, and can therefore be used in concentrations equal to or less than that of the drugs for the determination of BIS and ALV drugs in the presence of these interfering species (Table 3).

Table 3: Potentiometric selectivity coefficients $\left(K^{pot}_{drug,B}\right)$ of BIS and ALV sensors

Interfering material	SSM $\left(K^{pot}_{BF,B}\right)$	PMP $\left(K^{pot}_{BF,B}\right)$	SSM $\left(K^{pot}_{ALV,B}\right)$	PMP $\left(K^{pot}_{ALV,B}\right)$
Cd^{2+}	2.45×10^{-8}	–	2.8×10^{-4}	–
Zn^{2+}	4.02×10^{-9}	–	2.00×10^{-4}	–
K^{+}	3.33×10^{-8}	–	4.54×10^{-4}	–
Ca^{2+}	1.99×10^{-8}	–	3.015×10^{-4}	–
Na^{+}	1.65×10^{-6}	–	6.83×10^{-4}	–
Pb^{2+}	4.40×10^{-9}	–	5.01×10^{-4}	–
Ni^{2+}	4.76×10^{-9}	–	3.20×10^{-4}	–
Mn^{2+}	1.12×10^{-7}	–	–	3.1×10^{-4}
Co^{2+}	4.30×10^{-7}	–	–	3.9×10^{-4}
Starch	–	2.30×10^{-7}	–	2.5×10^{-4}
Talc	–	3.54×10^{-5}	–	1.45×10^{-4}
Lactose	–	1.65×10^{-6}	–	1.44×10^{-4}
Sucrose fructose	–	1.02×10^{-6}	–	1.6×10^{-4}
Ascorbic acid	–	1.85×10^{-6}	–	5.4×10^{-4}
Maltose glucose	–	3.93×10^{-6}	–	6.5×10^{-6}
Heptaminol HCl	–	1.44×10^{-7}	–	1.65×10^{-6}
Atenolol	–	1.25×10^{-6}	–	1.50×10^{-6}
Propranolol HCl	–	1.30×10^{-7}	–	1.02×10^{-6}
Amlodipine	–	1.63×10^{-6}	–	3.3×10^{-6}

3.4 Method validation

The validation parameters such as precision, specificity, accuracy, and the limit of detection (LOD) were studied for the proposed electrodes. The lower limit of the detection

value is known to be the concentration of drugs at the point of intersection of the extrapolated linear regions of the calibration curve. The value obtained indicates that low drug concentrations can be identified by the proposed sensor (Table 1). The LOQ is the point of the linear range at which the Nernstian process begins. The LOQ is considered by some scholars to be the lowest point to make useful determinations.

3.4.1 Accuracy and precision

Through preparing solutions containing three different amounts of pure drugs and their dosage types, the consistency of the current process was apparent. Accuracy was estimated by testing solutions on five replicates on the same day and was also evaluated over five days. From the data in Tables 4 and 5, The accuracy demonstrated by the

Table 4: Assessment of pure form Concor® tablets, Bisotens® tablets, and blood serum intra- and inter-day consistency and accuracy of the proposed process

Drug	Taken (mg mL^{-1})	Inter-day			Intra-day		
		Found (mg mL^{-1})	Recovery (%)	RSD (%)	Found (mg mL^{-1})	Recovery (%)	RSD (%)
Pure form	0.7669	0.7764	101.2	0.82	0.7569	98.69	1.30
	0.0766	0.0764	99.74	0.82	0.0756	98.69	1.30
	0.0076	0.0076	100.0	0.99	0.0076	100.0	1.10
Concor®	0.7669	0.7599	99.09	0.23	0.7618	99.33	0.13
	0.0766	0.0759	99.09	0.65	0.0761	99.35	0.77
	0.0076	0.0075	98.68	0.53	0.0076	100.0	0.66
Bisotens®	0.7669	0.7723	100.70	0.20	0.7713	100.6	0.24
	0.0766	0.0761	99.35	1.33	0.0764	99.73	0.99
	0.0076	0.0077	101.3	0.65	0.0076	100.0	0.66
Blood serum	0.7669	0.7643	99.66	0.17	0.7649	99.74	0.26
	0.0766	0.0758	98.96	1.21	0.0763	99.61	1.13
	0.0076	0.0076	100.0	0.65	0.0075	98.68	0.53
Reported method	0.7669	0.7779	101.4	1.08			
	0.0766	0.0772	100.8	1.0			

Table 5: Evaluation of the proposed method in pure type ALV, Alsotrin® capsule, and blood serum intra- and inter-day consistency and accuracy of the proposed method

Drug	Taken (mg mL^{-1})	Inter-day			Intra-day		
		Found (mg mL^{-1})	Recovery (%)	RSD (%)	Found (mg mL^{-1})	Recovery (%)	RSD (%)
Pure form	1.18	1.20	101.2	0.68	1.2	100.00	0.85
	1.8	1.186	100.6	0.46	1.85	100.55	1.31
	2.3	2.15	98.2	1.76	2.19	98.7	0.50
Alsotrin®	1.18	1.12	99.09	0.23	0.998	96.33	1.73
	1.8	1.75	99.09	0.65	1.79	99.35	0.35
	2.3	2.20	98.68	0.53	2.39	101.25	0.26
Blood serum	1.18	1.08	98.66	1.32	1.10	99.74	0.66
	1.8	1.68	98.96	1.10	1.89	100.83	1.13
	2.3	2.3	100.0	0.65	2.19	98.68	0.53
Reported method	1.18	1.20	101.4	0.62			
	1.8	1.85	100.8	0.56			

relative standard deviation (RSD) values and the precision demonstrated by comparing and finding them so close between the proposed method and reported methods. The data referred to in Table 3 showed the effective use of the proposed sensors in the production of highly reliable BIS and ALV products, as shown by the recovery percentage.

3.5 Analytical applications by standard addition method

These sensors have been used successfully to measure the active ingredients in Concor® (10 mg per tablet), Bisotens® (10 mg per tablet) and Alsotrin® (60 mg per capsule), with recoveries of 99.40 ± 0.54%, 99.67 ± 0.20% and 99.42 ± 0.15%, respectively, where n = 5 (Table 6) using the standard addition technique. The results revealed that the precision was ±0.53 and the accuracy was 99.50%. Repeatability CV_w was 0.90% and the between-day-variability CV_b was 1.2%. The statistical analysis of Student's *t*-value at 95% confidence limit showed that the calculated values were less than the theoretical ones. This proves that the prepared sensors can be developed for drug analysis.

Furthermore, Concor® (10 mg per tablet) and Alsotrin® (60 mg per capsule) drugs were successfully estimated in the human serum by using the standard addition technique for two samples of both drugs and the average recoveries were 99.96 ± 0.81% and 98.40 ± 0.69% for BIS and ALV samples, respectively (Table 7).

Table 6: Estimation of BIS and ALV in pharmaceutical preparations with standard addition and calibration graph methods

Sample	Recovery[a] ± RSD%	
Drug name and source	Potentiometric methods	
	Standard addition technique	Calibration graph method
Pure ALV	-	99.9 9 ± 0.64
Alsotrin (DBK Pharma, Egypt)	99.92 ± 0.15	99.98 ± 0.50
Pure BIS	-	99.98 ± 0.34
Concor®(Merck, Egypt)	99.40 ± 0.54	99.88 ± 0.58
Bisotens® (Antibiotice Iasi, Egypt)	99.67 ± 0.20	99.53 ± 0.50

[a] Average of five measurements.

3.6 Comparison study

A comparison of the output characteristics of the proposed sensor was made with methods previously used for BIS and ALV determination. The data in Tables 8 and 9 indicate the superiority of the proposed MIP-based sensor over the other methods as the proposed sensor gave the widest concentration range, relatively lower limit of detection, and lower RSD values than any of the other methods. The RSD and the percentage recovery values reflect the effective use of the proposed sensors for highly precise and accurate drug determination. This is one of the greatest benefits of imprinting technology; the suggested sensors have no interferences and have a high drug selectivity.

Table 7: Estimation of BIS and ALV in human serum by applying standard addition technique

Sample	Recovery[a] ± RSD%
Concor® (Sample 1)	99.98 ± 0. 83
Concor® (Sample 2)	99.95 ± 0. 79
Alsotrin® (Sample 1)	98.97 ± 0.84
Alsotrin® (Sample 2)	99.83 ± 0. 55

[a] Average of four measurements.

Table 8: Comparison between the proposed sensor and previous methods for BIS

Ref.	Slope	Concentration range (mol L^{-1})	RSD (%)	Recovery (%)	LOD (mol L^{-1})	LOQ (mol L^{-1})
Proposed BIS	56	from 1.0×10^{-6} to 1.0×10^{-2}	0.10-1.15	98.50-101.6	1.8×10^{-6}	2.6×10^{-5}
[12]	28.20	from 1.0×10^{-5} to 1.0×10^{-2}	0.30-1.11	98.50-101.3	1.00×10^{-5}	3.33×10^{-5}
[11]	–	from 1.0×10^{-5} to 1.0×10^{-4}	1.92	97.0-103.0	8.27×10^{-7}	2.75×10^{-6}
[8]	5.4161	from 5.2×10^{-5} to 2.1×10^{-4}	0.77	99.08-100.85	5.20×10^{-6}	8.60×10^{-7}
[7]	0.035	from 6.5×10^{-6} to 3.3×10^{-5}	1.19	105.0 ± 1.3	2.86×10^{-7}	8.60×10^{-7}
[9]	–	from 2.6×10^{-6} to 7.8×10^{-6}	0.99-1.3	96.7-98.8	–	–
[6]	0.112	from 2.6×10^{-6} to 1.6×10^{-5}	0.408-1.0674	99.49-101.50	0.04753	0.1584
[14]	–	from 1.0×10^{-6} to 1.0×10^{-5}	<3	–	9.8×10^{-8}	-
[10]	–	from 1.0×10^{-6} to 1.0×10^{-4}	0.66	98.5-102.7	1.69×10^{-6}	5.19×10^{-6}

Table 9: Comparison between the proposed sensor and previous methods for ALV

Ref.	Slope	Concentration range (mol L^{-1})	RSD (%)	Recovery (%)	LOD (mol L^{-1})	LOQ (mol L^{-1})
Proposed ALV	56	from 1.0×10^{-6} to 1.0×10^{-2}	0.15-0.98	99.8-101.5	1.75×10^{-6}	2.3×10^{-5}
[25]	0.02641	from 20 to 100	0.58-0.79	99.02-99.85	1.37	4.16
[26]	53.56	from 1.99×10^{-5} to 1.00×10^{-2}	0.09-0.59	99.02-99.85	4.36×10^{-6}	1.33×10^{-5}
[27]	35.0	from 1.0×10^{-5} to 1.0×10^{-2}	1.11-2.55	94.50-98.3	1.00×10^{-5}	3.33×10^{-5}
[28]	0.4794	from 0.53 to 5.2	1.34-1.46	98.23-99.8	0.640	1.94

4 Conclusion

New, sensitive, and simple potentiometric sensors have been developed for the determination of bisoprolol and alverine drugs. The approach had the merits of low cost, high precision, quick response time (2.0 s), and the methods for 1.0×10^{-2} bisoprolol and alverine also performed in a broad pH range of 4.50-8.50 and 2.00-8.80. In the presence of a wide range of interfering species, there was a high selectivity of the proposed sensors for BIS and ALV drugs and no interference from the studied inorganic cations, carbohydrates, and structural analogs, meaning that the sensor can be used for the determination of BIS and ALV drugs in concentrations of these species equal to or less than that of the drugs. LOD and LOQ values show the fitness of the new technique compared to existing methods. Direct quantification of bisoprolol and alverine in prescription dosage forms and human serum achieved high precision and recovery of up to 99.60%. The alverine sensor was novel and the first to be implemented, and the bisoprolol sensor was an alternative to the previously mentioned potentiometric sensors.

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Data availability statement: The Excel file has been used to support the data findings of current study. The results are available from the corresponding author upon request.

References

[1] Özbek O, Berkel C, Isildak Ö. Applications of potentiometric sensors for the determination of drug molecules in biological samples. Crit Rev Anal Chem 2020;4:1-12.

[2] Isildak Ö, Özbek O. Silver(I)-selective PVC membrane potentiometric sensor based on 5,10,15,20-tetra(4-pyridyl)-21H, 23H-porphine and potentiometric applications. J Chem Sci. 2020;132(1):29.

[3] Özbek O, Isildak Ö, Berkel C. The use of porphyrins in potentiometric sensors as ionophores. J Incl Phenom Macrocycl Chem. 2020;98:1-9.

[4] Isildak Ö, Özbek O, Gürdere MB. Development of chromium(III)-selective potentiometric sensor by using synthesized pyrazole derivative as an ionophore in PVC matrix and its applications. J Anal Test. 2020;4(4):273-80.

[5] Isildak Ö, Deligönül N, Özbek O. A novel silver(I)-selective PVC membrane sensor and its potentiometric applications. Turk J Chem. 2019;43(4):1149-58.

[6] Metra M, Nodari S, Bordonali T, Milani P, Lombardi C, Bugatti S, et al. Bisoprolol in the treatment of chronic heart failure: from pathophysiology to clinical pharmacology and trial results. Ther Clin Risk Manag. 2007;3(4):569-78.

[7] Tucker WD, Kariyanna PT. Selective B1 blockers. Stat Pearls Publishing. 2019.

[8] Coelho AM, Jacob L, Fioramonti J, Bueno L. Rectal antinociceptive properties of alverine citrate are linked to antagonism at the 5-HT1A receptor subtype. J Pharm Pharmacol. 2001;53(10):1419-26.

[9] Hayase M, Hashitani H, Suzuki H, Kohri K, Brading AF. Evolving mechanisms of action of alverine citrate on phasic smooth muscles. Br J Pharmacol. 2007;152:1228-38.

[10] British Pharmacopoeia, Vol. 11. London: HM Stationery Office, X, p.I – 305 and I – 126. 2007.

[11] Bhusnure OG, Dongare RB, Gholve SB, ajmane R, Munde AB, Giram PS. Spectrophotometric method developed for the estimation of bisoprolol fumarate. Int J Pharm Biol Sci. 2018;8:338-41.

[12] Mohammed SA, Adam ME, Shantier SW. Development and validation of UV spectrophotometric method for determination of bisoprolol fumarate in bulk and pharmaceutical dosage forms. Mediterr J Chem. 2017;6:196-9.

[13] Abdelmonem AA, Ragab GH, Hashem HA, Bahgat EA. Spectrofluorimetric and spectrophotometric determination of Irbesartan and Bisoprolol hemifumarate independently in their tablets. J Pharm Biosci UK. 2016;4:43-52.

[14] Sahu R. Synthesis, antibacterial and anticancer activities of some novel imidazoles. Indian J Pharm Sci. 2006;68:764-7.

[15] Mahu SC, Spac AF, Ciobanu C, Hancianu M, Agoroae Li, Butnaru E. High performance liquid chromatography (HPLC) was developed and validated for the determination of bisoprolol fumarate in tablets. Revista De Chimie. 2016;67:414-7.

[16] Mykhalkiv M, Logoyda L, Polyauk O, Zarivna N, Soroka Y, Ryabokon S, et al. *Hplc as an assay method for the investigation of conditions of bisoprolol extraction by organic solvents.* Int J Green Pharm. 2018;12:276-9.

[17] Goyal RN, Tyagi A, Bachheti N, Bishnoi S. Voltammetric determination of bisoprolol fumarate in pharmaceutical formulations and urine using single-wall carbon nanotubes modified glassy carbon electrode. Electrochim Acta. 2008;53:2802-8.

[18] Frag EY, Mohamed ME, El-Boraey HA, EL-Sanafery SS. Investigation of hydrogen release rate from electrodes of nickel-cadmium batteries at their thermal decomposition. Int J Electrochem Sci. 2019;14:6603-16.

[19] Zil'berg RA, Yarkaeva YA, Sidel'nikov AV, Maistrenko VN, Kraikin VA, Gileva NG. Voltammetric determination of bisoprolol on a glassy carbon electrode modified by poly(arylene phthalide). J Anal Chem. 2016;71:926-31.

[20] Rajesh SJ, Balaji RM, Jagdish VB. UV Spectrophotometric method have been developed and validated for determination of bisoprolol fumarate. *Int J* Univers Sci Technol. 2018;4:8-12.

[21] Preeti SB, Saurabh BG. spectrophotometric technique for simultaneous determination of bisoprolol fumarate and hydrochlorothiazide. Pharm Methods. 2017;8:40-3.

[22] Alina DG, Andreea M, Vasile D. Vis spectrophotometric method was developed for the assay of bisoprolol in pharmaceutical preparations using bromocresol green in hydrochloric acidic medium. Farmacia. 2012;60:634-7.

[23] Sevgi TU, Elif K. spectrophotometric determination, of bisoprolol. Opt Spectrosc. 2012;112:864-6.

[24] Bozal B, Gumustas M, Dogan-Topal B, Uslu B, Ozkan SA. Voltammetry, chromatographic, and spectrophotometric methods were developed for the simultaneous determination of bisoprolol fumarate and hydrochlorothiazide. J AOAC Int. 2013;96:42-5.

[25] Mohammed S, Ali E, Salah E, Hassan E. RP-HPLC method was developed for the determination of hydrochlorothiazide and bisoprolol fumarate in their combined pharmaceutical formulations. Int J Pharm Pharm Sci. 2018;3:236-40.

[26] Kondratova Y, Logoyda L, Voloshko Y, Megied A, Korobko D, Soroka Y. RP-HPLC method was developed and validated for the determination of bisoprolol fumarate in bulk and pharmaceutical dosage form. Int J App Pharm. 2017;9:54-8

[27] Gabriela P, Corneliu O, Aurel V. liquid chromatography-tandem mass spectrometry method has been developed and validated for the determination of bisoprolol in human plasma samples. Rom Biotechnol Lett. 2010;15:140-2.

[28] Hassan S, Abou-Sekkina MM, El-Ries MA, Wasse lA. Polymeric matrix membrane sensors for sensitive potentiometric determination of some β-blockers in pharmaceutical preparations. J Pharma Biomedical Anal. 2003;32:175-80

[29] Ramadan NK, Zaazaa HE. Membrane electrodes for determination of some beta-blocker drugs. J AOAC Int. 2007;7:90-8.

[30] Vijayalakshmi R, Naga YM, Dhanaraju D. Colorimetric methods for the estimation of alverine citrate (ALV), tapentadol (TAP) using bromophenol blue (BPB) reagent. Pharm Lett. 2016; 8:145-48.

[31] Khalil MM, Issa YM, Zayed SIM, Ali FQ. New potentiometric membrane sensors for determination of alverine citrate in pharmaceutical compounds and biological fluids. Int J Adv Res. 2014;2:1096-109.

[32] Dhiraj MR, Keyur RP, Hiren NM, Arvind GJ, Pranav SS, Mallika S. High performance liquid chromatography-tandem mass spectrometry method was developed and validated for the quantification of alverine (ALV) and its active metabolite parahydroxyalverine (PHA), in human plasma. J Pharma Anal. 2016;8:21-4.

[33] Amin AS, Mabrouk EM, Hassan G, Hendawy AM, Ahmed S. Voltammetric method for rapid determination of ALV has been developed. J Basic Env Sci. 2018;5:149-51.

[34] Craggs A, Moody GJ, Thomas JDR. Construction and laboratory experimental. J Chem Educ.1974;51:541-44

[35] Sebaiy MM, Elmosallamy MAF, Elhenaweec MM, Alshuwailib MK. Poly (vinyl chloride) matrix membrane sensors for the quantification of olopatadine and oxeladine in pharmaceutical preparations and human plasma. Microchem J. 2019;147: 170-5.

[36] IUPAC, Analytical Chemistry Division, Commission on Electronalytical Chemistry. Potentiometric selectivity coefficients of ISEs. Pure Appl Chem. 2000;72:1851-82

[37] Elmosallamy MAF, Saber AL. Recognition and quantification of some monoamines neurotransmitters. Electroanalysis. 2016;28:2500-5.

[38] Guder WG. Git Verlag. 3rd ed. 2003. p. 28-30.

[39] IUPAC, Analytical Chemistry Division, Commission on Electronalytical Chemistry. Recommendation for nomenclature of ISEs. Pure Appl Chem. 1994;66:2527-30.

[40] Elmosallamy MAF. Novel sensors for batch and flow injection analysis of histamine based on crown ether. Electroanalysis. 2012;24:1226-30.

[41] Cosofert VV, Buck RP. Phenothiazine drug poly (vinyl chloride) matrix membrane electrodes and their use in pharmaceutical analysis. Analyst. 1984;109:1321-5.

[42] Mohamed GG, El-Dien FN, Frag EY, Mohamed ME. In situ modified screen printed and carbon paste ion selective electrodes for potentiometric determination of naphazoline hydrochloride in its formulation. J Pharm Anal. 2013;3:367-75.