Original Article

Electrochemical Sensor Based on Crafted Thia Polymeric Crown Ether for Determination of Carbamazepine and Ephedrine

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ABSTRACT

Background: Direct analysis methods are considered some of the best and easiest tools to quickly determine the amount of active drug in some pharmaceutical preparations. **Objectives:** In this study, an ion electrode is prepared to determine the concentration of a sample of ephedrine (Eph) and carbamazepine (CBZ) in the medicines produced by some companies directly.

Methods: CBZ and Eph drugs ion-selective electrode (ISE) based on Thia polymeric crown ether (SPCE-CZB and SPCE-Eph) as membrane carrier in polyvinyl chloride (PVC) matrix was successfully fabricated for the determination of CBZ and Eph drugs.

Results: The electrode exhibited a liner Nernstian slope response over the range of 1×10^{-1} to 1×10^{-6} M, and 1×10^{-5} to 1×10^{-1} with a slope of 28 and 33±2 mV per decade charge, respectively, by using dimethyl phthalate plasticizer and a detection limit of 1×10^{-9} M. The response time of the sensor was 10 s. The ISE showed a greater preference for CBZ and Eph over other drugs with good precision.

Conclusion: The selectivity coefficients of some drugs ranged from 1×10^{-5} to 1×10^{-1}. Meanwhile, SPCE-CZB (ISE) was successfully used as an indicator electrode for the potentiometric determination of the CBZ drug pharmaceutical formulas.

Keywords: Carbamazepine (CBZ), Ephedrine (Eph), Ion-selective electrode (ISE), Thia polymeric crown ether, Potentiometric sensor

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Introduction

The carbamazepine (CBZ), also chemically known as 5H-dibenzo azepine-5-carboxamide, is a highly lipophilic neutral tricyclic molecule with a white to off-white crystalline powder that is almost odorless and has an acid equilibrium constant (pKa of 13.9) (Alrashood, 2016). It is just marginally soluble in water, although it is soluble in alcohol and acetonitrile (Bizi & El Bachra, 2021; Kan et al., 2022). CBZ, one of the most commonly used antiepileptic medications, is used to treat psychomotor, generalized tonic-clonic and complex partial seizures (Hampton & Benjamin, 2022). With an 85% chemical bioavailability, it is commonly taken orally as a tablet or suspension (Bertoni et al., 2022). Several analytical techniques have been developed to determine CBZ and its contaminants in bulk drugs and biological fluids. The fluorescence polarization immunoassay employs Graphene nano gold electrodes and multi-walled carbon nanotubes film-coated glassy carbon was used for the determination of CBZ (Kacirova et al., 2022). Ephedrine (Eph) ([1R, 2S]-(-)-[1-methylaminoethyl) benzyl alcohol]) is a sympathomimetic drug that stimulates both α and β adrenergic receptors (Onoka et al., 2020). Eph has been determined in pharmaceutical formulations by potentiometer using a modified carbon paste electrode and adopting ISE with flow injection technique (Wahba et al., 2021). Numerous studies in this field have attempted to solve this problem by using ion-selective electrodes (ISE) based on polymers or nanomaterials; however, only a few have used the host-ghost polymer to determine the drug CBZ and Eph. Using the potentiometric method has rarely been the focus of studies. An alternative approach to address this problem involves using work-applied ionophore adsorption on CBZ and Eph surface polymers to increase sensitivity. In this study, the development of a CBZ- and Eph-selective electrode sensor based on the crafted Thia polymeric crown ether (SPCE) and its application in a pharmaceutical formulation have been investigated. Another advantage of using this method, compared to other methods, is that its application is easy and low-cost.

Materials and Methods

Study instruments and materials

All solvents, which were utilized without further purification, were purchased from Merck, namely ethanol, methanol, acetonitrile, tetrahydrofuran, polyvinyl chloride (PVC), CBZ (99%), Eph (99%), nitro phenyl octyl ether (99%), dimethyl phthalate (DMP; 99%), gelatin (99%), and glucose (99%). The pH was calculated using a Hannah HI9811-5 pH meter with a microprocessor. The Fourier-transform infrared spectroscopy spectrophotometry (FTIR), Shimadzu 8400 Series, Japan, FESEM was recorded on the FEI NOVA NANOSEM 450I, EDX BRUKER X FLASH6L10, and x-ray powder diffraction (XRD) spectra were recorded on RIGAKU (Japan).

Synthesis of ionophore (carbamazepinium and ephadrinium)

In an acidic medium, 0.1 g of SPCE was disseminated in a 1:1 (alcohol: Water) combination of 0.1 M CBZ (50 mL) and agitated for 24 h. When the mixture's color changed from yellow to green, it was washed and dried at room temperature. Eph-SPCE was prepared using the same procedure; however, the color turned pink.

Fabrication of a drug selective electrode

The selective sensors were made by combining 1.5 mg (4.9%) of ionophore (CBZ-SPCE, Eph-SPCE) with 18 mg (59.01%) of plasticizer as DMP and 11 mg (36.06%) of PVC. Afterward, 3 mL of tetrahydrofuran was added while stirring. The solution was poured into a glass casting and allowed to sit for two days so that the solvent evaporated (Sead et al., 2023). The body electrode design was produced by using a test tube Pyrex length of 10 cm, a radius of 10 mm, a submerged wire length of 10 cm, and a radius of 10 mm (1 mm). Gold was present in the form of a wire spring. Then, the ISE membrane was split in half and linked to a cover film soaked in a 1 M solution containing medication. The internal solution used to fill the electrode was a mixture of 0.1 M CBZ and gelatin (Figure 1).

Electrochemical measurements and statistical analysis

Measurements electromotive force (EMF) were carried out using a pH meter (mV) at 25 ˚C to 0 ˚C, and the calculations were performed based on Debye–Huckel. The sensor EMF was measured at 25 ˚C using a saturated-calomel electrode single junction and gold-wire as an internal reference for drug-selective electrodes submerged in 20 mL of varying concentration ion solution investigation to identify the potential sensor with stirring. Before using it, all sensors were submerged in the main solution at 0.1 M for 24 h and then washed with deionized water. The software (Origin 2018 Pro, Digitmizer) was used to analyze the collected.

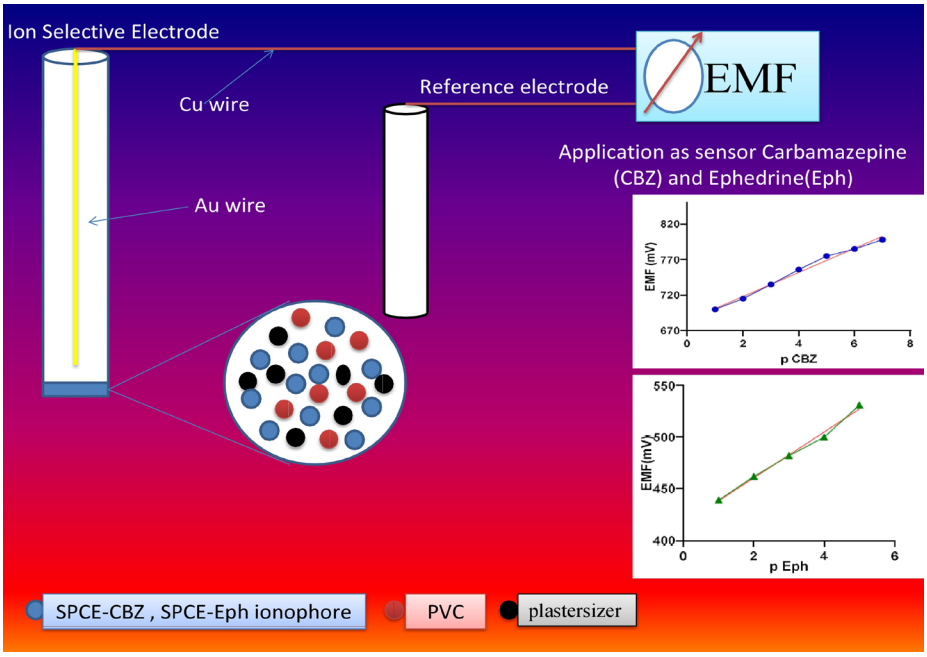


Figure 1. The fabrication of an ion selective electrode sensor design

Results

FTIR spectra of polymer SPCE and drug (CBZ, Eph)

The FTIR data from polymer SPCE and their complexes (SPCE-CBZ and SPCE-Eph) along with their probable assignments are presented in Figure 2. Important bands were observed in the spectra of the SPCE compared to CBZ and Eph, which helped detect donation sites. The FTIR spectra of similar frequencies correspond to (N_3) at 2110.12 cm^{-1} for SPCE, SPCE-CBZ, and SPCE-Eph. While the spectra of these show additional bands in 520 cm^{-1} for (SPCE), they show an additional 630 cm^{-1} in Eph in-plane ring with oop 5H in peak 920 cm^{-1} and appear ring -oop in peak 670 cm^{-1} in SPCE-CBZ (Mehrabi et al., 2023).

Studying morphology field-emission scanning electron microscopy (FESEM) and electron destructive x-ray

The study of morphology involved performing morphology FESEM analysis. Images taken from the distance between SPCE and SPCE-CBZ, SPCE-Eph revealed differences in surface aggregation and distri-

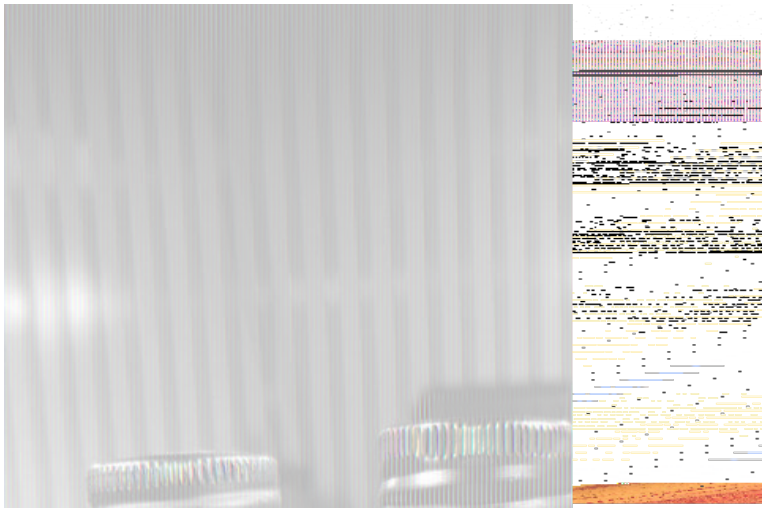
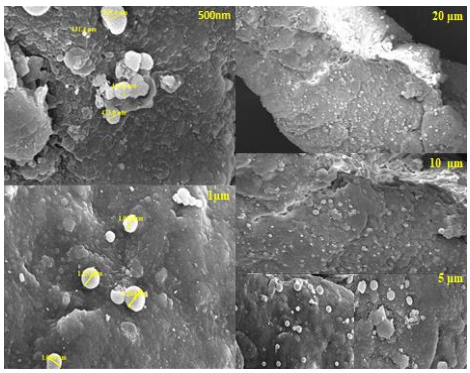
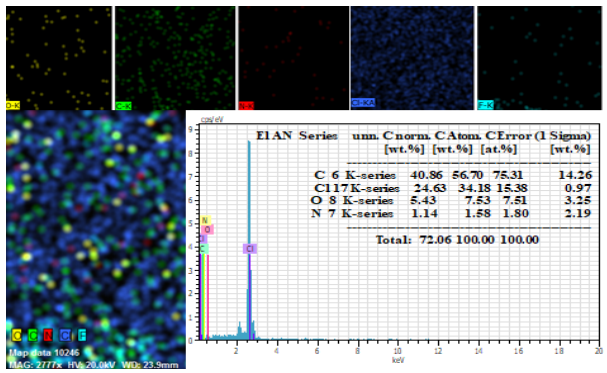


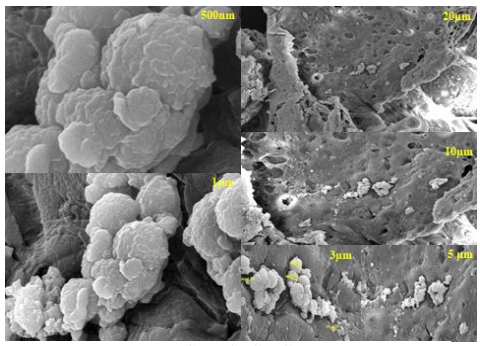
Figure 2. FTIR of polymer SPCE with interaction CBZ and Eph drug



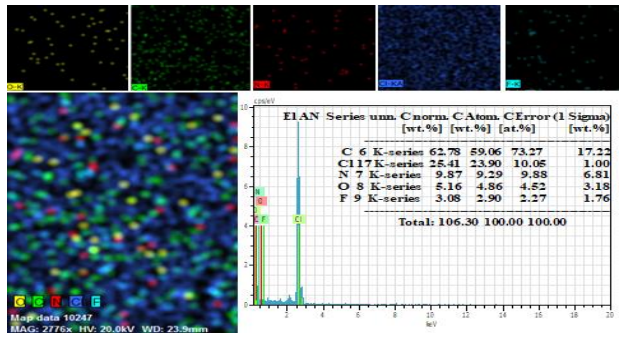
(a) FESEM SPCE



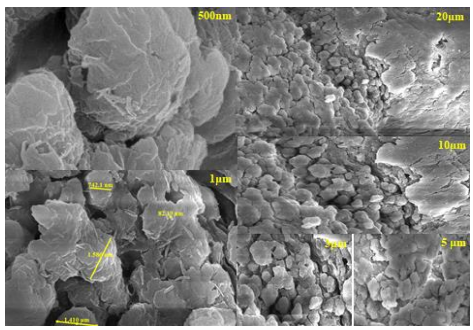
(b) EDX SPCE



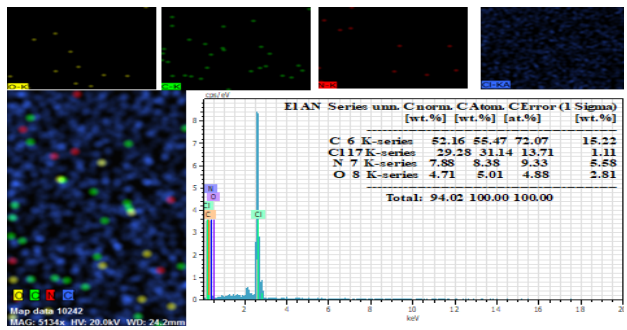
(c) FESEM SPCE-CBZ



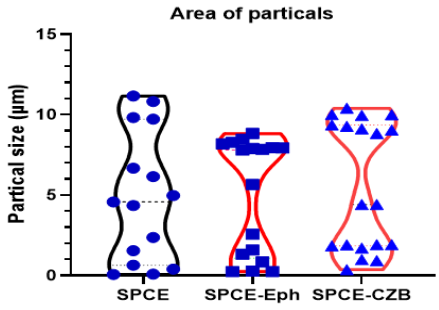
(d) EDX SPCE-CBZ



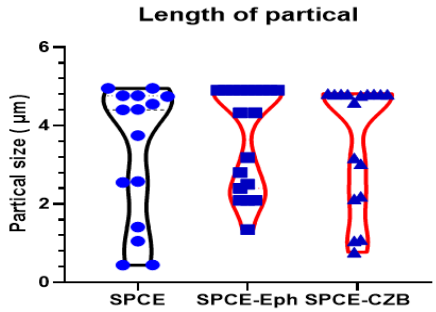
(e) FESEM SPCE-Eph



(f) EDX SPCE-Eph



(g) Histogram area of particles



(h) Histogram length of the particle

Figure 3. FESEM image of a) SPCE, c) SPCE-CBZ, e) SPCE-Eph, EDX of b) SPCE, d) SPCE-CBZ, f) SPCE-Eph, g) particle histogram area, and h) particle length histogram

Abbreviations: FESM: Field-emission scanning electron microscopy; Eph: Ephedrine; CBZ: Carbamazepine.

bution of a drug in SPCE. The sizes of particles were calculated based on the data and by using Digmizer and Prism software (Javadi et al., 2021). The FESEM showed a difference in the shape of the surface, whereas polymer SPCE showed the presence of balls on the surface of the Azide, which indicates the bonding of the Thia crown ether particles showed a change in the surface of the polymer, where a change in the morphology was observed through the interference of the CBZ and Eph molecules and their adsorption on the surface of the polymer (Figures 3a, 3c, and 3e). The images of FESEM histograms of SPCE, SPCE-CBZ, and SPCE-Eph area and length in Figures 3h and 3g showed the area size particles SPCE (11 µM), SPCE-CBZ (10 µM), and SPCE-Eph (9 µM). The length particle size histogram shows varied sizes for SPCE (0.5–5 µM), SPCE–CBZ (0.7–5 µM), and SPCE–Eph (0.6–5 µM). Electron destructive x-ray (EDX) image analysis of C, O, N, and Cl elements in ionophores demonstrated differences in weight percentage. Carbon and nitrogen percentage atoms increase by more than 100% during CBZ and Eph drug adsorption (Figures 3b, 3d, and 3f).

X-ray diffraction analysis

XRD is a technique employed to determine the structure of a molecule. Figure 4 shows the low angle of XRD between 20 and 70 in the pattern peak. The figure illustrates the diffractogram peaks for SPCE at 29.51, 24.2, 36.3, 42.1, 55, 66.9; for SPCE-CBZ at 22.8, 26.7, 31.1, 37, 42.1, 47.5, 53.1, 59.1, 66.5; in addition to SPCE-Eph at 22.8, 26.7, 31.1, 37, 42.1, 47.5, 53.1, 59.1, 66.5, along with additional peaks at 22.4, 24.8, 28.6, 30.3, and 37.7. Since determining XRD was difficult in this compound, a new approach was proposed for determining it by drawing a straight line between high and low peaks. The greatest peaks at the straight-line level were then selected for application to the Scherer equation (Equation 1) for producing a value crystalline size (D) average based on the data diffractogram as well as increasing crystalline size (D) average SPCE (0.356 nm), SPCE-CBZ (1.17 nm), and SPCE-Eph (1.17 nm) (0.78 nm) (Figure 4, Table 1).

1. $D=K\times\lambda/\beta\times\cos\Theta=0.13869/\beta\times\cos$

where, D=crystalline size; k=constant if the particles were not spherical=0.9; λ=Wavelength cu=0.1540 nm;

β=Full width at half maximum (FWHM)

Calibration curve sensor SPCE- CBZ and SPCE-Eph

The complex (SPCE-CBZ, SPCE-Eph) was used to build one electrode by utilizing one respective plasti-

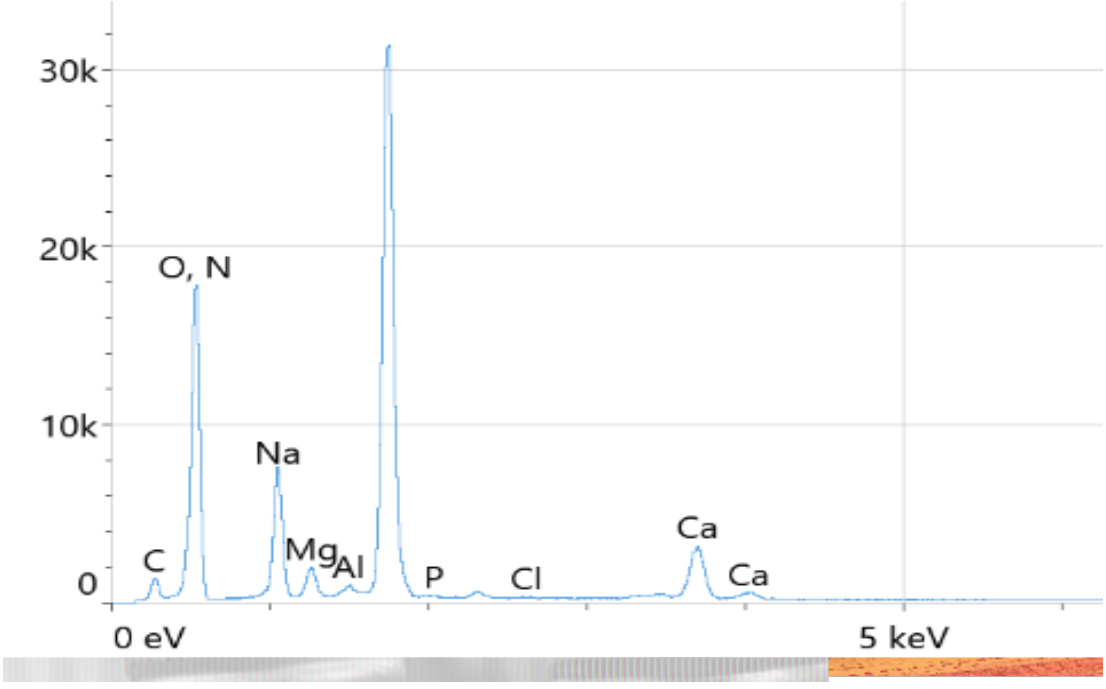


Figure 4. XRD a) Gaussian curve SPCE, b) Gaussian curve SPCE-Eph; c) Gaussian curve SPCE-CBZ; d) XRD SPCE, SPCE-CBZ and SPCE-Eph

Abbreviations: FESM: Field-emission scanning electron microscopy; Eph: Ephedrine; CBZ: Carbamazepine.

Table 1. Data of XRD SPCE, SPCE-CZB, SPCE-Eph

Peak Position 2 θ	θ	COS θ	FWHM (deg)	β=FWHM-0.25(deg)	β(radian)	Cos θ*β	K*Lambda	Grain Size(D)nm
				SPCE data				
24.24541	12.12	0.903184258	3.16504	2.91504	0.050877046	0.045951347	0.13869	3.018192269
36.39132	18.19	0.793720004	15.91976	15.66976	0.273488905	0.217073615	0.13869	0.638907682
42.09576	21.04	-0.58714531	19.51228	19.26228	0.336190207	-0.197392505	0.13869	-0.702610263
48.68861	24.34	0.704955285	23.74441	23.49441	0.41005481	0.289070306	0.13869	0.479779477
55.09617	27.54	-0.74767066	28.20089	27.95089	0.487835059	-0.364739961	0.13869	-0.380243502
60.65072	30.32	0.461982987	32.42797	32.17797	0.561611523	0.259454969	0.13869	0.534543627
66.8837	33.44	-0.43957651	37.78944	37.53944	0.655186827	-0.288004741	0.13869	-0.481554573
73.89352	36.94	0.730083739	45.39868	45.14868	0.787993119	0.575300963	0.13869	0.241073819
82.47926	41.23	-0.92147889	62.145	61.895	1.080271541	-0.995447421	0.13869	-0.139324285
							Sum D=3.208764251	
							D average=0.356529361	
				SPCE-CBZ data				
18.32118	9.16	-0.96530486	3.49366	3.24366	0.056612547	-0.054648367	0.13869	-2.537861755
23.41081	11.7	0.65170538	3.49366	3.24366	0.056612547	0.036894701	0.13869	3.759076368
55.92168	27.96	-0.95126192	28.79866	28.54866	0.498268114	-0.473983483	0.13869	-0.292605133
27.47742	13.73	0.387996628	3.49366	3.24366	0.056612547	0.021965477	0.13869	6.313998933
65.90927	32.95	0.032082357	36.89016	36.64016	0.63949143	0.020516392	0.13869	6.7599605
38.4839	19.24	0.923996209	17.21389	16.96389	0.296075734	0.273572856	0.13869	0.50695819
49.4376	24.71	0.915542693	24.22414	23.97414	0.418427678	0.383088404	0.13869	0.362031319
43.70562	21.85	-0.99044647	20.45443	20.20443	0.352633827	-0.349264929	0.13869	-0.397091115
32.63087	16.31	-0.82109376	3.49366	3.24366	0.056612547	-0.046484209	0.13869	-2.983593856
73.94484	36.97	0.74737643	45.46426	45.21426	0.789137706	0.589782922	0.13869	0.235154317
							Sum= 11.72602777	
							D average= 1.172602777	
				SPCE-Eph data				
19.70954	9.854	-0.90896907	3.45666	3.20666	0.055966775	-0.050872067	0.13869	-2.72625052
24.83164	12.41	0.988688645	3.45666	3.20666	0.055966775	0.055333715	0.13869	2.506428497
40.217	20.1	0.30682207	3.45666	3.20666	0.055966775	0.017171842	0.13869	8.076594334
36.35024	18.17	0.781059318	15.94685	15.69685	0.273961715	0.21398035	0.13869	0.648143626
41.73028	20.86	-0.43026629	19.24517	18.99517	0.331528258	-0.142645435	0.13869	-0.972270863
48.48422	24.24	0.628921391	23.59685	23.34685	0.407479402	0.256272513	0.13869	0.541181723
57.52939	28.76	-0.88216285	29.99356	29.74356	0.519123053	-0.457951072	0.13869	-0.302848947
73.53896	36.76	0.598129064	44.94576	44.69576	0.780088174	0.466593409	0.13869	0.297239518
81.43463	40.71	-0.99239717	59.07904	58.82904	1.026760444	-1.018954158	0.13869	-0.136110147
91.90282	45.95	-0.38786721	556.86307	556.61307	9.714730731	-3.768025467	0.13869	-0.036807076
							Sum D=7.895300145	
							D average=0.789530015	

Abbreviations: Eph: Ephedrine; CBZ: Carbamazepine; XRD: Electron destructive x-ray.

Table 2. Characterization sensor SPCE- CBZ and SPCE-Eph

Membrane		SPCE- CBZ	SPCE- Eph
Dimethyl phthalate (mg)		18	18
PVC (mg)		11	11
Range		1×10^{-6}	1×10^{-5}
Concentration (molarity)		1×10^{-1}	1×10^{-1}
Detection limit (ppm)		0.009	0.004
pH		2-5	7-10
T/°C		5-50	5-50
Time response (s)		>10	>10
Slope Nernstian mV (per decade)		28	33
R^2		0.98	0.99
Statistical analysis	N total	6	6
	Mean±SD	777.6667±1.0328	531.3333±0.5164
	Variance	1.06667	0.26667
	Sum	4666	3188
	Coefficient of variation	0.00133	9.72E-04
	E real	0.085801	0.12594
	Recovery (%)	99.9142	99.87406

cizer (Di methyl phthalate [DMP]) their electrode curve is shown in Figures 5a and 5b. The equation of the liner range as well as their correlation coefficient, relative standard deviation, and slope are listed in Table 2. The potential response of the offered electrodes at different concentrations of CBZ and Eph presented a liner range from 1×10^{-6} to 1×10^{-1} M and 1×10^{-5} to 1×10^{-1} M with a Nernstian slope of 28 and 33 mV per decade for DMP as plasticizers, respectively. The correlation coefficient values for the three electrodes were 0.98, and the life was about 30 days for all. The electrode with DMP as a plasticizer exhibited a quite good response in comparison, as given in Table 2. Different in the characterization of the electrode the blank electrode works at (<400 mV) while optimization sensor PVC membrane ion selective electrode based on SPCE–CBZ and SPCE-Eph the calibration curve response potential between concentration CBZ and Eph drugs (1×10^{-2}) with slope Nernstian 28, 33 mV per decade charge and limit detection (1×10^{-7} to 1×10^{-6}), respectively (Figure 6) and time response less than 10 s (Rassouli et al., 2021).

Effect of pH

We prepared a solution with CBZ and Eph concentrations ranging from 0.01-0.1 M and a pH range of 2-10. Figure 5 b depicts the stability of SPCE-CBZ work in the pH range (2-7) so the sensor response was suitable with lower Ph level. Several factors can affect response as increased acidity leads to protonation CBZ molecules that improve increased interaction surface and another effect as electrode stability in acidic conditions might reduce oxidative degradation of electrode substance as a result, its integrity and performance remain intact over time. Figure 5a shows that the SPCE-Eph sensor functions in alkaline conditions at pH (7-10), the effect of deprotonated Eph molecule may occur leading to increased negative charge which can lead to enhancement electrostatic interaction and improving response sensor (Alighazi et al., 2021).

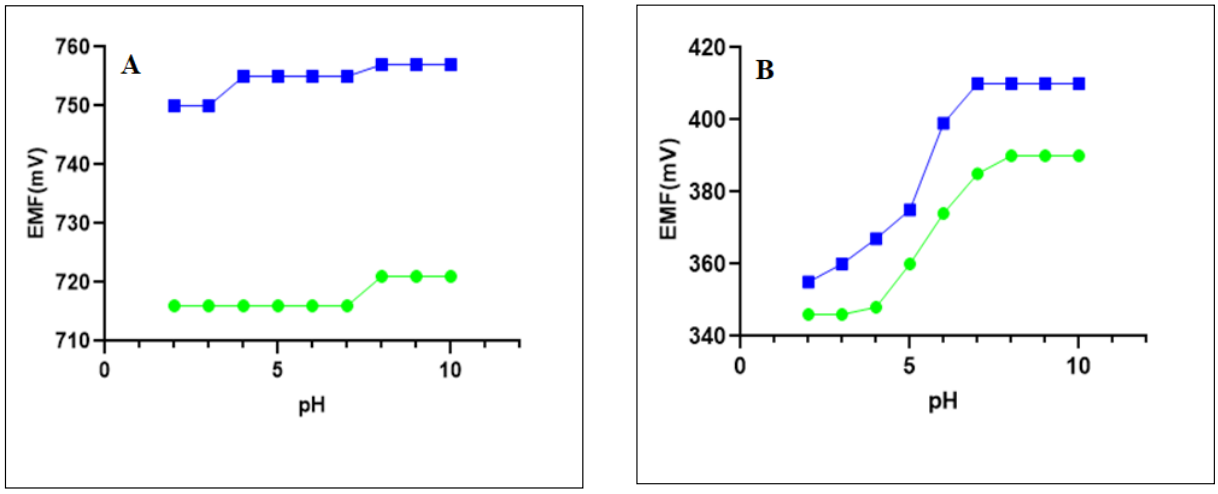


Figure 5. Effect of the pH on the sensor response

a) SPCE- CBZ, b) SPCE- Eph

●0.1 M drugs, ▪0.01 M drugs.

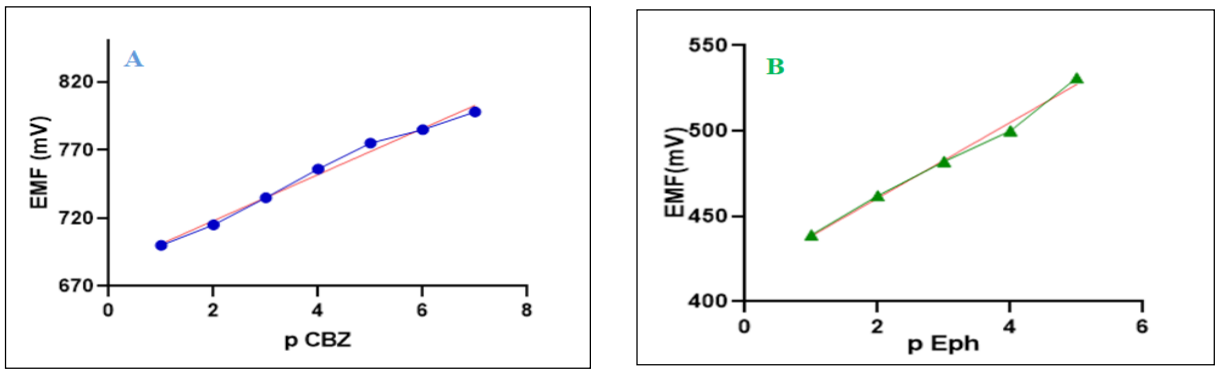


Figure 6. a) Calibration curve sensor SPCE-CBZ; b) Calibration curve sensor SPCE-Eph

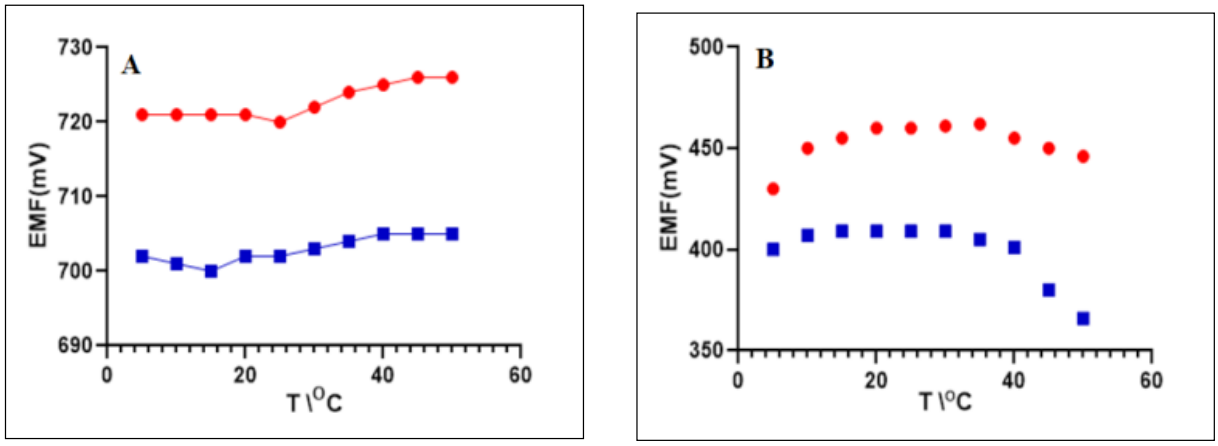


Figure 7. Effect of the temperature on the sensor response

a) SPCE-CBZ, b) SPCE-Eph

●0.01 M drugs, ▪0.1 M drugs.

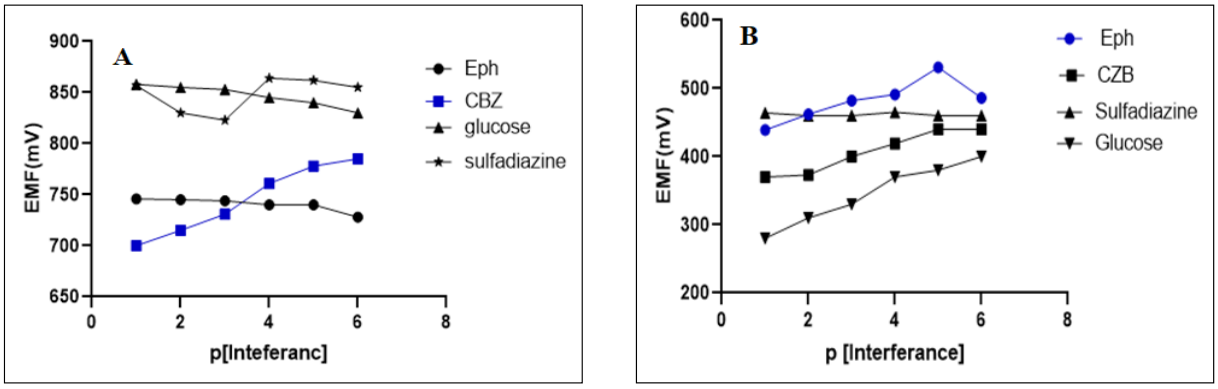


Figure 8. Interference sensor SPCE-CZB, SPCE-Eph with other substance

Effect of temperature

The effect of temperature on the ability response of the ISEs SPCE-CBZ and SPCE-Eph was investigated to determine a sensor that could be applied in the temperature influence range. Two concentrations of 0.01-0.1 M from CBZ and Eph drugs were used at temperatures between 5-50 ˚C. The response sensitivity of the sensor was represented by a graphical temperature (T/˚C) vs EMF (mV). As shown in Figure 7, different solution temperatures 5, 10, 15, 20, 25, 30, 35, 40, 45, and 50 were able to apply the sensor SPCE-CBZ without affecting the response sensitivity of 95%. Sensor SPCE-Eph was a response at a temperature between 5-35 ˚C with a sensitivity of 98%.

Interference ion selective electrode

Selectivity K pot. is an important study parameter interference indicating the sensor's ability to distinguish other substances. In this study, the selected organic elements such as glucose, sulfadiazine, CBZ, and Eph drugs were used in interaction with each other to verify electrode responses and distinguish them. The potentiometric selectivity coefficient was examined by adopting the separated solution method based on the Nikolsky-Eisenman equation. From Figure 8, Nernstian slope interference for SPCE-CBZ, and SPCE-Eph electrodes were calculated Nernstian value ISE response with other interference appeared Nernstian slope more than in an interference substance. The selectivity coefficient K value is less than 1 so the sensor SPCE-CBZ and SPCE-Eph selectivity toward drugs CBZ and Eph (Haputhanthri & Perera, 2021).

Determination of drug CBZ in some company samples

The proposed sensor of SPCE-CBZ has been used to analyze CBZ drugs in some companies, such as the Novartis Turkish-Egyptian Sabhan sample. The obtained results were compared to those produced after adopting the extraction method, as a reference method, and then were used for determining the new sensor (Shamohamadi et al., 2021) . The results obtained are presented in Table 3. There was no significant difference between the determination results of the proposed sensor and those of the reference method (at a confidence level of 93%). The proposed methodology showed great promise for the accurate and rapid determination of the samples.

Table 3. CBZ levels (mg) in some company samples by proposing methods and extraction method

Drug Amount Taken		A (mg)	B (mg)	RSD A	RSD B
*	200	190	193	99	99
**	200	189	191	97	98
***	200	191	190	96	97
****	200	192	189	99	95

*(Tegretol) Novartis (Swiss) company, dose form=tablet; **Tegretol Novartis (Turkish) company, dose form = tablet; ***Tegral CID (Egypt) company, dose form = tablet; ****Carbamazpin SABH (Iran) company, dose form = tablet.

Notes: A = Extraction method; B = Electrochemistry ISE SPCE-CBZ method.

Discussion

In this study, selective ion sensors based on polymeric Thia crown ether (SPCE) were effectively produced inside a PVC matrix for the detection of CBZ and Eph concentrations in pharmaceutical samples. The study found a linear sensitivity response with a Nernstian slope of 28±2 mV/decade for CBZ and 33±2 mV/decade for Eph. The detection limit for CBZ was 1×10^{-9} M. and for Eph was 1×10^{-6} M. The reaction time was rapid, less than 10 s, demonstrating the sensor's ability to take rapid and reliable measurements. Our findings outperform several earlier studies that employed selective sensors based on polymers or nanomaterials without attaining comparable sensitivity. For example, Alrashood, 2016 experienced trouble identifying CBZ using conventional approaches, but our sensor provided an accurate and timely response. Furthermore, several previous studies that relied on similar methodologies produced less accurate results and slower responsiveness than the current strategy based on the Thia crown polymer. The high sensitivity and fast response of the sensor are attributed to the strong interactions between the SPCE and the CBZ and Eph molecules, where the chemical structure of the ether contributed to the improved adsorption of the molecules on the polymer surface. FESEM showed a significant improvement in the distribution of molecules on the surface compared to other sensors, which led to the enhanced sensitivity of the sensor. XRD analyses also showed an increase in the crystal size. This sensor may be utilized in pharmaceutical applications to rapidly and accurately assess CBZ and Eph levels. These characteristics make the sensor an excellent alternative for applications in pharmaceuticals that require rapid and low-cost drug analysis. Despite the sensor's wide acceptance, several limitations must be addressed. For example, the sensor's 30-day lifespan may be unsuitable for some long-term applications. Future research might focus on enhancing the materials used to render the sensor more durable and long-lasting. In addition, the sensor's suitability for different types of pharmaceuticals or biological substances might be investigated.

Conclusion

In this study, the ISEs (SPCE-CZB and SPCE-Eph) were effectively designed for the direct and precise measurement of CZB and Eph concentrations in pharmaceutical formulations. These electrodes exhibited a linear Nernstian response throughout extensive concentration ranges and displayed exceptional selectivity and sensitivity, with detection limits as low as 1×10^{-9} M for CBZ and 1×10^{-4} for Eph. The ISEs demonstrated rapid response times and high precision in measurements, rendering them dependable for real-time pharmaceutical quality control. Moreover, the ISE SPCE-CZB demonstrated efficacy as an indicator electrode for the potentiometric assessment of CZB in pharmaceutical formulations. The developed ISEs are a promising, user-friendly, and efficient analytical instrument for the direct quantification of these medicines in pharmaceutical formulations.

Ethical Considerations

Compliance with ethical guidelines

The research did not involve any ethical considerations.

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Authors' contributions

All authors contributed equally to the conception and design of the study, data collection and analysis, interpretation of the results, and drafting of the manuscript. Each author approved the final version of the manuscript for submission.

Conflict of interest

The authors declared no conflict of interest.

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