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Carbon Potentiometric Sensors Modified with Beta-cyclodextrin as a Carrier for the Determination of Bisoprolol Fumarate

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Beta-cyclodextrin (BCD) has been used as electroactive material for preparing carbon paste electrodes (CPEs) selective for bisoprolol fumarate (BPF). The paste incorporating BCD, graphite, and *o*-NPOE as a solvent mediator in weight percent ratio (1.4:69.6: 29.0) for electrode I. Another mode of preparation was made by mixing different ratios of graphene and graphite with BCD and *o*-NPOE or TCP as a plasticizer for electrodes II and III, respectively. The developed electrodes I, II and III show divalent Nernstian response of 28.2±0.85, 29.2±0.34 and 29.4±0.33 mV decade^{-1} over the concentration ranges 1.0x10^{-5} – 1.0x10^{-2}, 1.0x10^{-6} – 1.0x10^{-2} and 1.0x10^{-5} – 1.0x10^{-2}mol L^{-1}, respectively. The electrodes were independent on pH changes in the range 3.05-7.17 for electrode I and 3.50-7.15 for electrodes II and III, respectively. The developed electrodes show good selectivity and have been used for the quantitative determination of BPF in pure, pharmaceutical samples and biological fluids.

Keywords: Bet-cyclodextrin, bisoprolol fumarate, CPEs, potentiometric sensors, biological fluids.

1. INTRODUCTION

Bisoprolol is a cardioselective beta-blocker. Chemically is 1-(propan-2-ylamino)3-[4-(2-propan-2-yloxyethoxymethyl) phenoxy] propan-2-ol as shown in Figure (1) [1]. It is prepared in the fumarate form in order to control the hypertensive. For the analysis of bisoprolol fumarate in pharmaceutical, biological fluids and pure form, several methods have been recorded. These methods includes: spectroscopy [2-17], high-performance liquid chromatography [18-29], liquid chromatography-tandem mass spectrometry (LC-MS/ MS) technique [30-33], the cyclic voltammetry and square wave voltammetry (SWV) [34] and potentiometric determination using polyvinyl chloride (PVC) matrix membrane electrodes[35-36].Some of these methods are very expensive technique, requiring high expertise and large quantities of expensive organic solvents. Cyclic voltammetry is considered as one of

the most expensive techniques and the method used involve the preparation of carbon nanotube electrode which is very expensive and the others two potentiometric methods [35,36] involved the using of PVC matrix membrane electrodes which does not resist the mechanical stress and the internal reference solution increased the system impedance and the electrode response time. For these reasons, the beta-cyclodextrin was chosen for the determination of bisoprolol fumarate via its incorporation in the proposed selective sensors, which is available, stable, low cost, highly accurate and precise and gives good response toward the drug under investigation.

For the best of our knowledge, this is the first time that BPF was determined using CPEs modified with BCD and its potentiometric response for estimating BPF in pure, pharmaceutical samples and biological fluids was measured. The performance characteristics of the developed electrodes were examined according to IUPAC recommendations.

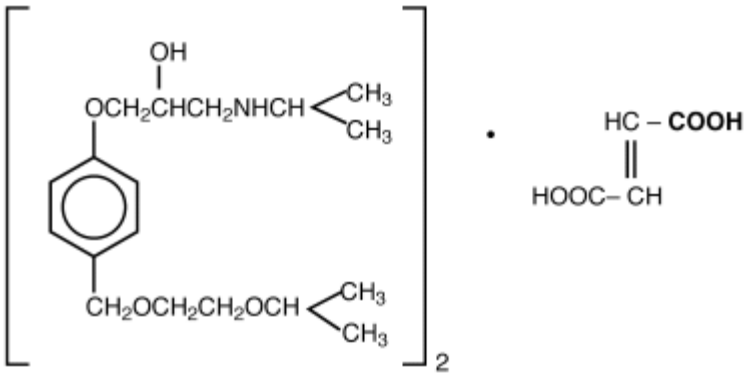


Figure 1. Chemical structure of bisoprolol fumarate

2. EXPERIMENTAL

2.1. Reagents and apparatus

Throughout the experiments, reagents of the analytical grade quality were used and also double distilled water. BPF provided by EVA PHARMA Company and pharmaceutical preparation Concor 10mg was produced by Merck SeronoCompany (each tablet contain 10mg BPF). *o*- nitrophenyl octyl ether (*o*-NPOE) was supplied from Fluka. Beta-cyclodextrin (BCD), Tricresylphosphate (TCP), graphite powder (synthetic 1–2 mm) and graphene were supplied from Aldrich. Dioctyl sebacate (DOS) and dioctyl phthalate (DOP) were supplied from BDH. Lactose, fructose, maltose, starch, sucrose, KCl, $PbCl_2$, $ZnCl_2$, $MnCl_2$, $CaCl_2$, NaCl, $NiCl_2$, $CoCl_2$ and $CdCl_2$ were used as interfering materials and they were purchased from El-Nasr Company, Egypt.

Stock BPF drug solution ($1.0x10^{-2}$ mol L^{-1}) was prepared by dissolving 0.7669 g of BPF in 100 ml double distilled water. Other diluted solutions ($1.0x10^{-3}$ -$1.0x10^{-9}$mol L^{-1}) were prepared by serial dilution from the stock BPF drug solution.

The potential measurements were performed using a digital Hanna pH/mV meter (model 8417). Ag-AgCl double-junction reference electrode (Metrohm 6.0222.100) in conjugation with different drug ion-selective electrodes was used. pH measurements were done using Jenway 3505 pH meter. The

electrode surface was scanned using an electron microscope (Quanta FEG250) SEM and energy dispersive X-ray analyzer (EDX), (National Research Center, Egypt).

2.4. Procedure

2.4.1. Carbon paste electrodes

Different mass ratios (0.56 - 6.6%) of BCD were mixed with carbon powder and (*o*-NPOE) plasticizer. The mixture was thoroughly mixed in the mortar until the mixture becomes homogenous. In the hole of the electrode body, the homogenous paste packed firmly. A new working surface was obtained by polishing the surface of the electrode using a filter paper and then rinsed carefully with double distilled water.

Another mode of preparation was used by embedding different ratios of graphene to graphite to paste composition to improve the Nernstian response.

2.4.2. Calibration of the sensors

The modified sensors in conjunction with silver-silver chloride reference electrode were immersed in beakers containing a definite aliquot part from 1.0×10^{-9} to 1×10^{-2}mol L^{-1} standard PBF drug solutions. From the low to high concentration of BPF the potential readings were recorded and were plotted as a function of -log[BPF] concentration. The sensors were washed and rinsed in bidistilled water between measurements to remove the memory effect.

2.4.4. Determination of BPF in pharmaceutical preparation and biological fluids

Tablets of concor which equivalent to 1.0×10^{-2}mol $L^{-1}$was ground to a fine powder and was dissolved in double distilled water, then the resulting solution was shaken well, filtered through filter paper and washed with double distilled water. The filtrate and washings were collected in 100 mL measuring flask. Other concentrations were prepared by serial dilution from the concentrated one. The potential of the prepared samples was measured using the proposed sensors in conjunction with a reference electrode, and the potential readings were compared to the calibration plots of the standard drug solution.

A series of human serum and urine samples were collected from different healthy donors. Aliquots samples of urine or serum were spiked with different concentration of BPF and the content was determined using the proposed potentiometric sensor.

3. RESULTS AND DISCUSSION

3.1. Effect of ElectrodeComposition

One of the most important factors affects the response of the electrode is the amount of modifier in the paste, so six paste compositions were prepared by varying the weight percent of the beta-

cyclodextrin from 0.56 - 6.6%. From the data listed in Table (1) it is clear that the electrode I with composition mass percent ratio of (1.4 BCD: 69.6 graphite: 29.0 *o*-NPOE) gives the best Nernestian slop of 28.2±0.85 mVdecade^{-1}. While the other electrodes containing a high concentration of BCD not achieve the divalent Nernestian slope due to over-saturation occurs in the network hindering the complexation process leading to unsatisfactory measurements. To improve the performance of the electrode I, another mode of preparation was used by embedding different amounts of graphene to graphite powder keeping the total weight percent 69.6%. Several electrodes with different amounts of graphite: graphene were prepared and their response were examined by plotting their emf reading versus -log[BPF] and the electrodes response characteristics are presented in Table (2). The electrode II embedded with 69.6% graphene and plasticized with *o*-NPOE show the best performance not only increase the working concentration range from 1.0 x 10^{-5}– 1.0 x 10^{-2} mol L^{-1} to be 1.0 x 10^{-6}– 1.0 x 10^{-2} mol L^{-1} but also gives better Nernestian slope (29.2±0.34 mVdecade^{-1}) than electrode I which may be attributed to the higher surface area of graphene and the excellent electrical conductivity at room temperature, where electrons move through it faster than through graphite [37]. The chemical structure and polarity of the plasticizer used have an important role in the selectivity, the mobility of the ion exchanger and response range of ion-selective electrodes (ISEs) [38], so the effect of plasticizer was studied. Low vapor pressure, high molecular weight, high lipophilicity, and high capacity to dissolve all the components of the sensor are the most important plasticizer properties. In order to examine the effects of plasticizer on the performance of electrode I and II, these electrodes were prepared with a different plasticizer such as TCP, DOS, DBP and DOP, and their potentiometric response compared with those plasticized with *o*-NPOE. From the data listed in Table (3) it is clear that the electrodes plasticized with *o*-NPOE(electrode I)show the best Nernstain slope and wider working concentration range and this can be attributed to its relatively high molecular weight and high dielectric constant (ε=24). Also, electrode III which embedded with 69.6%graphene and plasticized with TCP (ε=20) shows divalent Nernestian slope (29.4±0.33 mV decade^{-1} over concentration range 1.0 x 10^{-5} to 1 x 10^{-2} mol L^{-1}) so that it was chosen to be one of the electrodes which are selective for BPF. From the above study, the electrodes I, II, and III were chosen as BPF selective sensors and used to complete the subsequent study.

3.2. Surface characterization

The morphology and paste composition of the proposed electrodes were examined using SEM and EDX as shown in Figures (2-4). The electrode surface before immersion in BPF drug solution showed that the cavity of BCD was empty as clear in Figures (2a, 3a, 4a), which was blocked after soaking the same sensors in drug solution due to the formation of stable host-guest inclusion as shown in Figures (2b,3b,4b) this suggestion was confirmed by the appearance of a new peak of nitrogen in EDX as representative peak for the presence of BPF in the paste. The percent of nitrogen for the electrode II which embedded by graphene and plasticized by *o*-NPOE is higher than the others as shown in Figures (2b and 3b) and this reflects the high surface area of the graphene [37] and the important role of plasticizer in the mobility of BPF into the paste which leads to increasing the sensitivity of the modifier (BCD) to the drug under investigation.

Table 1. Effect of paste composition on the performance of the proposed CPEs.

BCD content % w/w	**Graphite % w/w**	***o*-NPOE % w/w**	**Concentration range (mol L^{-1})**	**Slope± SD, mV decade $^{-1}$**	**r^2 (n=5)**
0.56	70.22	29.22	$1.0x10^{-5}$ – $1.0x10^{-2}$	20.90±0.08	0.998
1.40 (ElectrodeI)	69.60	29.00	$1.0x10^{-5}$ – $1.0x10^{-2}$	28.20±0.05	0.999
2.75	68.65	28.60	$1.0x10^{-5}$ – $1.0x10^{-2}$	24.10±0.07	0.995
4.06	67.76	28.18	$1.0x10^{-5}$ – $1.0x10^{-2}$	23.00±0.10	1.000
5.35	66.85	27.80	$1.0x10^{-5}$ – $1.0x10^{-2}$	22.40±0.09	0.999
6.60	65.96	27.44	$1.0x10^{-5}$ – $1.0x10^{-2}$	19.10±0.10	0.999

Table 2. Effect of graphene doping on the response of electrode I.

Graphite, %w/w	**Graphene %w/w**	**BCD %w/w**	***o*-NPOE %w/w**	**Concentration range (mol L^{-1})**	**Slope (mV $decade^{-1}$)**	**r^2 (n=5)**
55.70	13.90	1.40	29.00	$1.0x10^{-6}$ – $1.0x10^{-2}$	14.70	0.999
41.72	27.88	1.40	29.00	$1.0x10^{-6}$ – $1.0x10^{-2}$	17.80	0.993
27.82	41.78	1.40	29.00	$1.0x10^{-6}$ – $1.0x10^{-2}$	21.40	0.996
13.89	55.71	1.40	29.00	$1.0x10^{-6}$ – $1.0x10^{-2}$	26.20	0.999
0.00 (ElectrodeII)	69.6	1.40	29.00	$1.0x10^{-6}$ – $1.0x10^{-2}$	29.40	0.999

Table 3. Effect of plasticizer type on the response of electrodes I and II.

Plasticizer	**Concentration range (mol L^{-1})**		**Slop (mV/decade)**		**r^2 (n=5)**	
	Electrode I	**Electrode II**	**Electrode I**	**Electrode II**	**Electrode I**	**Electrode II**
***o*-NOPE**	$1.0x10^{-5}$ – $1.0x10^{-2}$	$1.0x10^{-6}$ – $1.0x10^{-2}$	28.20	29.40	0.999	0.999
TCP	$1.0x10^{-5}$ – $1.0x10^{-2}$	$1.0x10^{-5}$ – $1.0x10^{-2}$	26.10	29.20	0.999	0.999
DOP	$1.0x10^{-4}$ – $1.0x10^{-2}$	$1.0x10^{-4}$ – $1.0x10^{-2}$	27.34	28.10	0.996	0.995
DOS	$1.0x10^{-4}$ – $1.0x10^{-2}$	$1.0x10^{-4}$ – $1.0x10^{-2}$	27.20	27.7	0.998	0.998
DBP	$1.0x10^{-4}$ – $1.0x10^{-2}$	$1.0x10^{-4}$ – $1.0x10^{-2}$	26.00	27.00	0.998	0.999

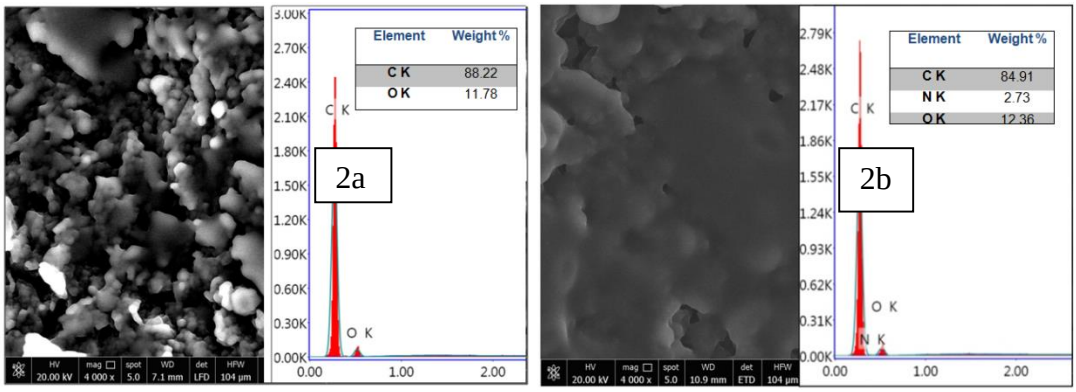


Figure 2. SEM image for the sensor I surface (a) before and (b) after soaking in 1.0×10^{-3}mol L^{-1} BPF with EDX analysis showing weight % of different elements present in the paste of sensors.

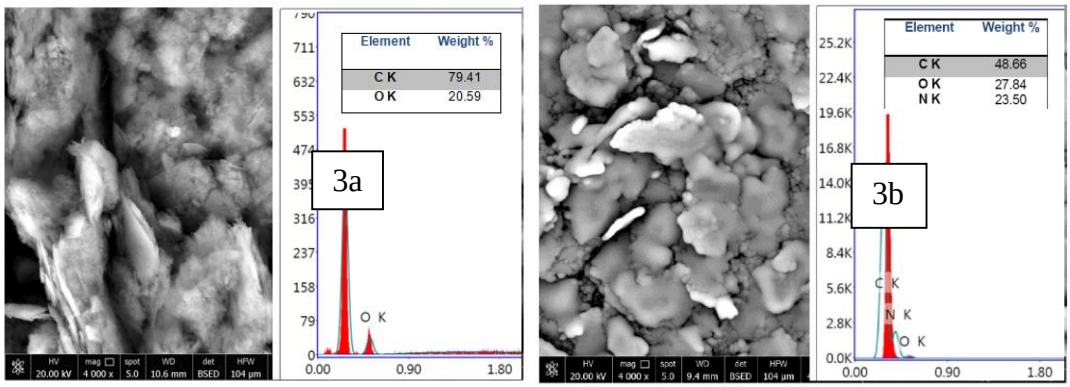


Figure 3. SEM image for sensor II surface (a) before and (b) after soaking in 1.0×10^{-3}mol L^{-1} BPF with EDX analysis showing weight % of different elements present in the paste of sensors.

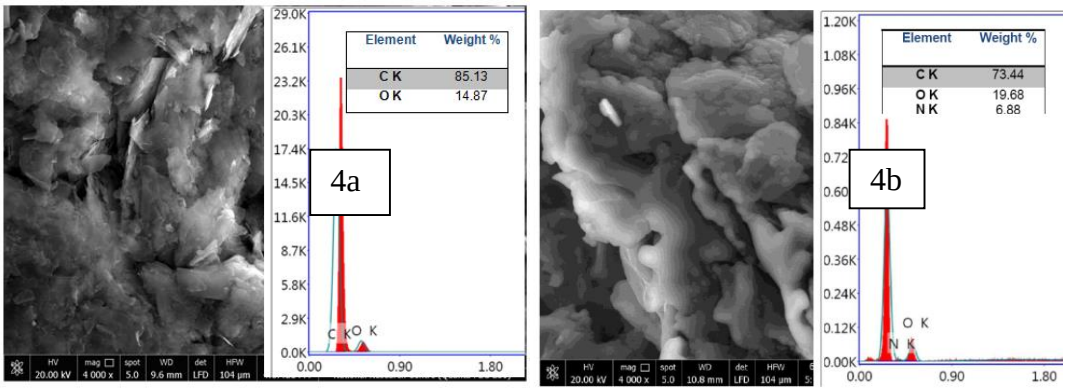


Figure 4. SEM image for III surfaces (a) before and (b) after soaking in 1.0×10^{-3}mol L^{-1} BPF with EDX analysis showing weight % of different elements present in the paste of sensors.

3.3. Effect of pH

At fixed temperature and concentration values, the pH effect of the test solution on the electrode response was examined. Over the pH range of 2.0-12.0, the variation of the potential with the pH of the

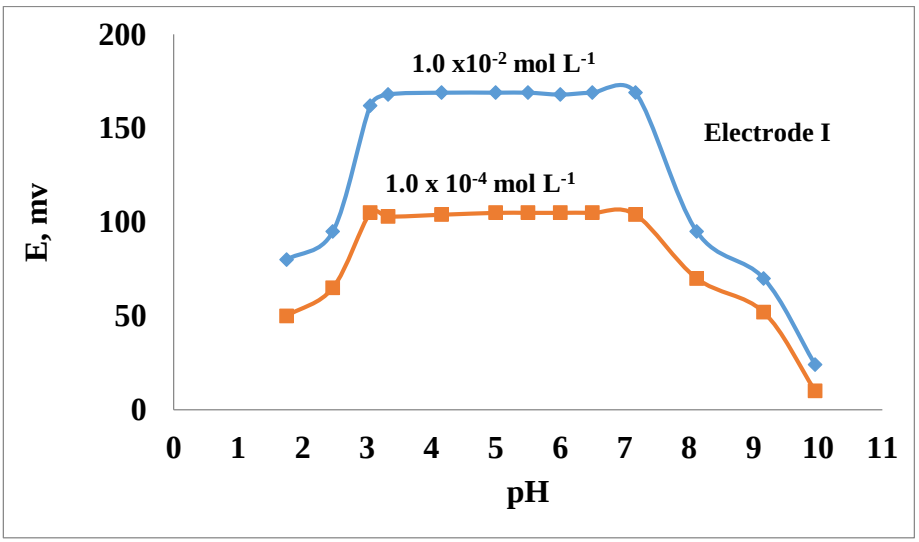
test solution ($1.0x10^{-2}$ and $1.0x10^{-4}$mol L^{-1}) was investigated. As shown in Figure (5), the potential-readings were plotted against the pH values. The results indicate that the electrode was independent on pH changes in the range 3.05-7.17 for electrodes and 3.50-7.15 for electrodes II and III. At pH< 3, the electrodes become H^+ -sensitive and the potential reading increased gradually. This can be attributed to interference of H_3O^+, while the diminution that occurs at pH higher than 7.0 is most probably attributed to the formation of the free drug base which appeared as white precipitate leading to a diminution in the concentration of protonated drug in the test solution.

3.4. Response time

Response time is that the average time needed for the electrode to achieve a gradual potential response at intervals ±1 mV by immersion of the projected electrodes during a series of BPF solutions, every having a 10-fold difference in concentration [39]. The dynamic response time of the sensors below study was investigated for the concentration vary from 1.0 $x10^{-5}$ to 1.0 x 10^{-2} mol $L^{-1}$for electrodes I and III and from 1.0 $x10^{-6}$ to 1.0 x 10^{-2} mol L^{-1} for electrode II. The proposed sensor has a very short response time of 9, 5 and4 s for electrodes I, II and III, respectively as shown in Figure (6), which reflect that the calibration time does not exceed few minutes and also confirm that the paste composition and plasticizer that were chosen show the best performance.

3.5. Effect of temperature

Calibration graphs were created at different solution temperatures (10, 25, 40, 50 and 60 ºC), to study the thermal stability of the modified BCD sensors. At different temperatures, the standard cell potentials (Eº cell) were determined from the various calibration plots as the intercepts of those plots at [BPF] = zero and were plotted versus (t−25).



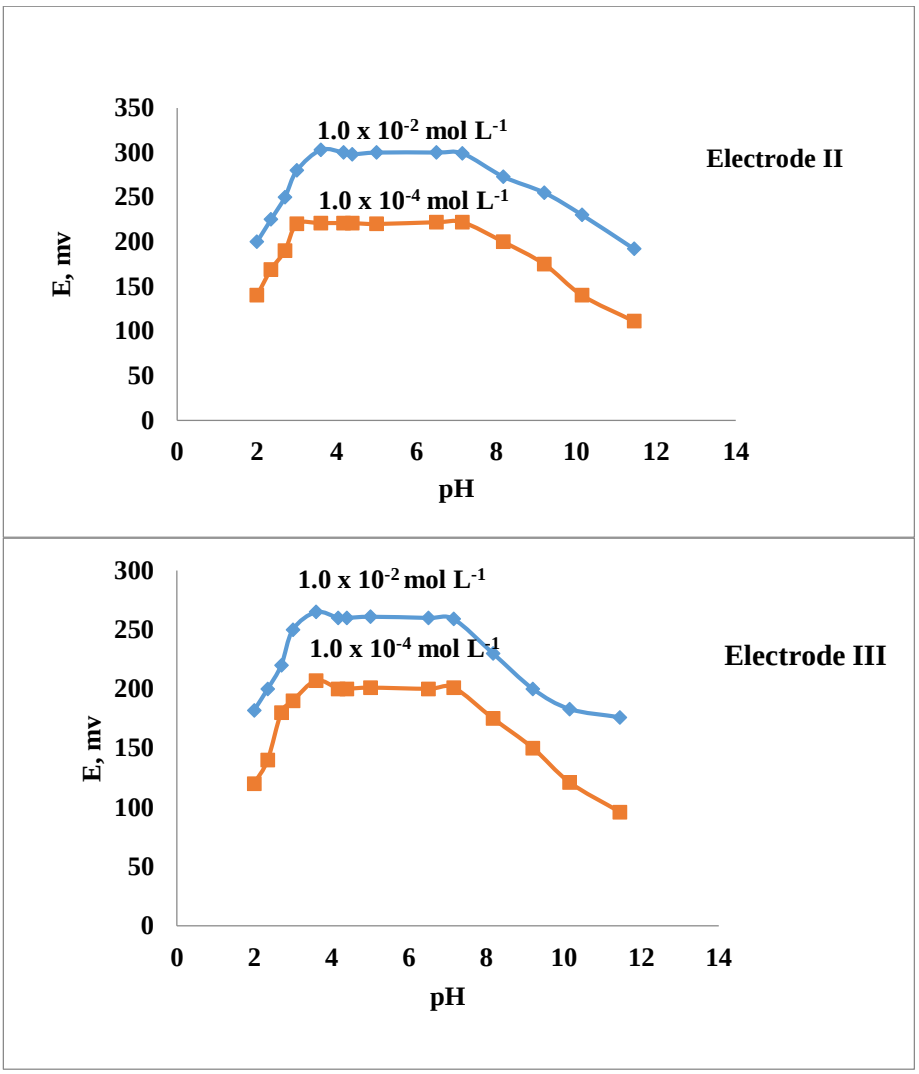
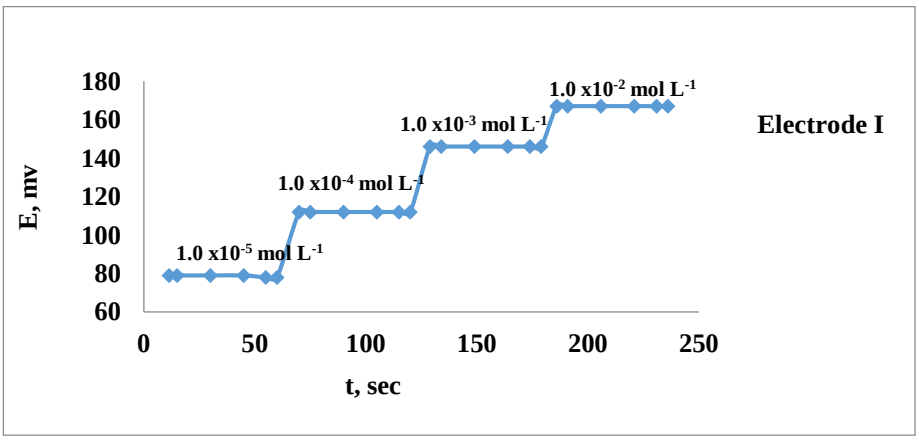


Figure 5. The pH effect on the performance of the proposed electrodes I, II and III.



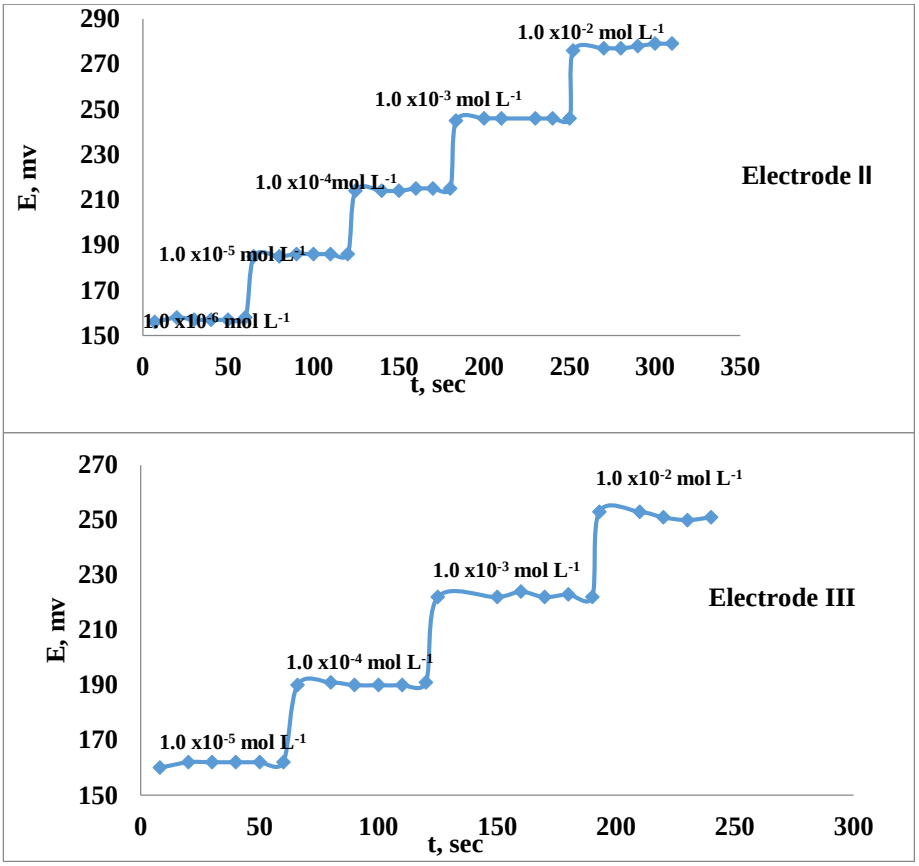


Figure 6. The response time of modified BCD potentiometric electrodes I, II and III.

A straight line plot is obtained according to Antropov's equation [40-41] and therefore the slope of this line refers to the isothermal coefficient of the electrodes of the value of 0.45 x 10^{-3}, 2.70 x 10^{-3} and 1.19 x10^{-3} V/°C for electrodes I, II and III, respectively. The obtained values of the isothermal coefficient confirmed that the proposed electrodes have high thermal stability at the used range of temperature. It's noticed that the electrodes display good Nernstian behavior within the tested temperature range.

3.6. Selectivity

The response of the proposed electrodes was also studied in the presence of a variety of foreign substances. By using the separate solutions (SSM) and matched potential (MPM) methods, the potentiometric selectivity coefficients ($K_{A,B}$) were evaluated in keeping with IUPAC guidelines [42-44].

The results presented in Table (4) show no significant interference from inorganic cations nor carbohydrates which reflect a high selectivity of the electrodes toward the drug under investigation.

3.7. Method validation

Method validation is that the method is vital so as to substantiate that the analytical procedure used for a particular test is suitable for its intended use [45]. From method validation results the

reliability, quality ,and consistency of analytical results can be judged. By using the proposed electrodes validation parameters like accuracy, linearity, precision, specificity, and limit of quantification (LOQ) and detection (LOD) were achieved.

From linear regression analysis, as shown in the table (5) the linearity was evaluated, that was calculated by the least squares regression method.

The LOD is the lowest amount of analyte in a sample which can be detected but not needed to be quantitated as an exact value. LOQ is considered to be the lowest amount of the investigated compound that may be detected within the sample at a suitable level of accuracy and precision known [46]. The values listed in Table (5), indicate that the proposed sensors are sensitive to detect the low concentrations of BPF.

Three solutions with different concentrations of pure BPF or concor tablets were prepared and analyzed in five replicates over five days to evaluate intermediate precision (inter-day precision) and within the same day to evaluate repeatability (intra-day precision), to determine the precision of the proposed methods. From the data listed in Tables (6, 7), we conclude that the low values of the relative standard deviation (% RSD) indicate the precision and repeatability of the proposed sensors.

3.8. Determination of BPF in concor tablets and spiked human plasma and urine

Table 4. Calculation of selectivity coefficients for the electrodes I, II and III using matched potential and separate solution methods.

Interfering compound	$K_{A,B}$ (SSM)			$K_{A,B}$ (MPM)		
	I	II	III	I	II	III
Pb^{2+}	1.85×10^{-5}	9.86×10^{-9}	2.08×10^{-8}	---	---	---
Ca^{2+}	2.06×10^{-2}	1.07×10^{-9}	3.05×10^{-8}	---	---	---
Na^{+}	1.53×10^{-6}	1.90×10^{-6}	6.90×10^{-8}	---	---	---
Zn^{2+}	2.95×10^{-4}	1.51×10^{-8}	1.12×10^{-7}	---	---	---
K^{+}	6.45×10^{-7}	2.75×10^{-7}	8.12×10^{-8}	---	---	---
Cd^{2+}	3.70×10^{-4}	5.67×10^{-8}	3.44×10^{-8}	---	---	---
Co^{2+}	4.76×10^{-5}	6.60×10^{-8}	1.70×10^{-8}	---	---	---
Mn^{2+}	4.36×10^{-4}	1.99×10^{-9}	1.77×10^{-7}	---	---	---
Ni^{2+}	5.50×10^{-4}	2.82×10^{-9}	8.12×10^{-8}	---	---	---
Starch	---	---	---	3.45×10^{-3}	2.55×10^{-8}	1.55×10^{-6}
Lactose	---	---	---	4.55×10^{-4}	8.93×10^{-8}	1.09×10^{-6}
Sucrose	---	---	---	9.02×10^{-6}	3.43×10^{-9}	1.87×10^{-8}
Fructose	---	---	---	6.40×10^{-2}	7.39×10^{-6}	1.85×10^{-5}
Maltose	---	---	---	5.56×10^{-3}	8.48×10^{-9}	7.18×10^{-4}
Glucose	---	---	---	7.88×10^{-5}	1.88×10^{-9}	2.99×10^{-6}

The modified sensors were found to be important in the potentiometric determination of BPF not only in pure solution and in concor tablets but also in spiked biological fluids with high precision and accuracy as shown in Tables (6 and 7). HPLC is the reported method for determination of BPF [18], it is a sophisticated tool but suffers from using an expensive solvent well as time-consuming, but the

proposed method (potentiometric sensors) is easy, inexpensive and fast. In electroanalytical methods, accuracy is considered as one of important requirement. The closeness between the obtained value and the true or accepted reference value expressed about accuracy [47]. The proposed method accuracy using CPEs was investigated for the determination of BPF in pure solutions and in concor tablets. The results obtained by the proposed sensors listed in Tables (6, 7) indicated the effective use of the sensors for determination of BPF with a good agreement with those obtained by the reported HPLC method regarding on the percentage recovery, student's t-test and F-test.

Table 5. Response characteristics of sensors I, II and III.

Parameters	**Electrode I**	**Electrode II**	**Electrode III**
Slope, mV decade $^{-1}$	28.2 ±0.85	29.3±0.34	29.40±0.33
Correlation coefficient (r^2)	0.999	0.999	0.999
Concentration rang, mol L^{-1}	1.0 $x10^{-5}$- 1.0 $x10^{-2}$	1.0 $x10^{-6}$- 1.0 $x10^{-2}$	1.0 $x10^{-5}$- 1.0 $x10^{-2}$
Working pH range	3.05-7.17	3.50-7.15	3.50-7.15
Response time, s	9	4	5
Isothermal coefficient, V/°C	0.454$x10^{-3}$	2.702 $x10^{-3}$	1.195$x10^{-3}$
LOD, mol L^{-1}	1 $x10^{-5}$	1$x10^{-6}$	1$x10^{-5}$
LOQ, mol L^{-1}	3.33$x10^{-5}$	3.33$x10^{-6}$	3.33 $x10^{-5}$
SD	0.01-0.08	0.02-0.09	0.01-0.09
RSD%	0.30-1.11	0.29-1.08	0.29-1.08
Recovery %	98.50-101.3	98.4-101.30	97.80-101.30

Table 6. Evaluation of intra- and inter-day precision and accuracy of the modified electrodes in pure form and Concor tablets.

Drug type	Electrode type	BPF taken mg mL^{-1}	Inter-day			Intra-day		
			Found mg mL^{-1}	Recovery %	RSD %	Found mg mL^{-1}	Recovery (%)	RSD %
Pure form	I	0.7669	0.7739	100.9	1.11	0.7738	100.9	0.54
		0.0766	0.0773	100.90	1.07	0.0776	101.3	0.39
		0.0076	0.0074	98.50	0.30	0.0075	98.9	0.73
	II	0.7669	0.7765	101.2	0.42	0.7621	99.4	0.31
		0.0766	0.7566	98.6	1.21	0.0754	98.4	0.86
		0.0076	0.0077	101.3	0.43	0.0078	101.3	1.05
	III	0.7669	0.7545	98.4	1.01	0.7769	101.3	1.08
		0.0766	0.0759	99.1	0.45	0.0773	100.9	0.32
		0.0076	0.0075	98.7	0.89	0.0076	100.0	0.61
	I	0.7669	0.7611	99.2	0.72	0.7539	98.3	0.92
		0.0766	0.0779	101.6	0.69	0.0767	100.2	0.55
		0.0076	0.0075	98.6	1.04	0.0076	100	1.06

Concor	II	0.7669	0.7597	99.1	0.63	0.7611	99.3	0.51
		0.0766	0.0761	99.3	0.29	0.0768	100.3	0.86
		0.0076	0.0077	101.3	1.03	0.0076	100	1.13
	III	0.7669	0.7589	98.9	1.01	0.7590	98.9	0.48
		0.0766	0.0772	100.7	0.39	0.0761	99.3	1.02
		0.0076	0.0076	100.0	0.33	0.0075	98.6	0.68
Reported method [18]		0.76697	0.7779	101.4	1.08			
		0.0766	0.0772	100.7	1.02			
F-test: 0.04 – 0.8 t-test: 0.095 -4.46								

At (n = 5) and 95% confidence limit: tabulated t value = 2.571 and tabulated F value = 5.05.

Table 7. Evaluation of inter- and intra-day precision and accuracy of the modified electrodes in biological fluids.

Biological fluids type	Electrode type	BPF	Inter-day			Intra-day		
		taken mg mL^{-1}	Found mg mL^{-1}	Recovery (%)	RSD %	Found mg mL^{-1}	Recovery (%)	RSD %
Urine	I	0.7669	0.7620	99.5	1.03	0.0759	99.1	0.90
		0.0766	0.0765	99.87	0.95	0.0761	99.35	1.01
		0.0076	0.0075	98.7	0.43	0.0076	100.0	0.66
	II	0.7669	0.0769	100.4	0.67	0.7638	99.6	0.77
		0.0766	0.0766	100.0	0.56	0.0768	100.3	1.03
		0.0076	0.0076	100.0	0.56	0.0075	98.68	1.03
	III	0.7669	0.7776	101.4	0.95	0.7768	101.3	0.92
		0.0766	0.0776	101.3	0.55	0.0768	100.3	0.43
		0.0076	0.0075	98.7	1.03	0.0076	100.0	0.65
Blood serum	I	0.7669	0.7669	100.0	1.01	0.7638	99.6	0.75
		0.0766	0.0766	100.0	1.09	0.0763	99.6	0.47
		0.0076	0.0076	100. 0	0.91	0.0076	100.0	0.89
	II	0.7669	0.7566	98.65	0.95	0.7631	99.5	0.88
		0.7669	0.0756	98.7	1.01	0.0762	99.5	0.43
		0.0076	0.0076	100.0	0.38	0.0074	97.4	0.33
	III	0.7669	0.7718	100.6	0.33	0.7659	99.9	0.98
		0.0766	0.0771	100.6	0.29	0.0765	99.9	0.88
		0.0076	0.0074	97.4	0.73	0.0075	98.7	1.06

4. CONCLUSION

Potentiometric sensors have several advantages over HPLC such as very simple, cheap, short response time and quick preparation process. The proposed sensors modified with BCD were good detectors for determination of BPF in different forms like pure, pharmaceutical preparation and spiked biological fluid form. Different parameters were studied and the results obtained show high selectivity, good response time, high sensitivity, high thermal stability over reasonable temperature and high stability over reasonable pH. Different method validation parameters were studied and they were in good agreement with results obtained by the HPLC method.

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