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Ionophore-Based Potentiometric Sensors for Drug Analysis

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Abstract: The construction, evaluation and analytical application of ionophore-based sensors for potentiometric determination of hexoprenaline sulphate (Hx) or biperiden hydrochloride (BP) are reported. Electrode matrices compositions are optimized on the basis of the nature and content of sensing ionophore, ionic sites and plasticizers. Sensors incroporated with β-cyclodextrins (β-CDs), sodium tetrakis (4-fluorophenyl) borate (NaTFPB) and 2-fluorophenyl 2-nitrophenyl ether (*f*-NPE), showed fast and stable potentiometric responses with mean Nernstian compliance of 59.0 ± 1.0 and 56.8 ± 1.4 mV·decade^{-1} for Hx and BP, respectively in the concentration ranges 1×10^{-5}–1×10^{-2} mol·L^{-1} for Hx and 1×10^{-5}–1×10^{-2} mol·L^{-1} for BP. Incorporation of β-CD as molecular recognition element improved the electrode sensitivity and selectivity due to encapsulation of the drug molecule into β-CD cavity (host-guest interaction). The electrodes were fully characterized in terms of composition, usable pH range, life span and response time. The developed electrodes have been successfully applied for the potentiometric determination of the cited drugs in pharmaceutical formulations. Comparison of the obtained results with those provided by reference methods revealed adequate accuracy for control assay.

Keywords: Cyclodextrins; Potentiometric sensors; Hexoprenaline sulphate (Hx); Biperiden hydrochloride (BP); Pharmaceutical analysis.

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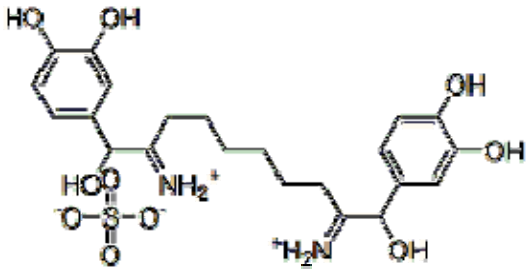
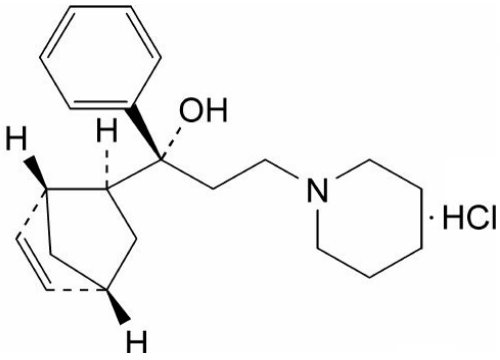
Introduction

The widespread dosification and/or adulteration of commercially available pharmaceutical preparations demand reliable methods for drug quality control that are preferably selective, rapid and can be undertaken with simple equipment. Nevertheless, most of these methods involve several manipulation steps before the final result of the analysis, have poor selectivity or require expensive apparatus. This is in contrast to potentiometric methods using ion selective electrodes, which is now a well-established method, when applied to the analysis of pharmaceutical products, can be considered to be advantageous due to their simplicity, short measurement time, low cost, adequate precision and accuracy, wide analytical range (usually more 5 decades), the ability to measure the activity of various drugs from the formulation matrix in colored or cloudy samples as well as non-destructive measurement of the analyt sample. This makes ISE potentiometry very attractive tools for pharmaceutical analysis [1–6].

Hexoprenaline sulphate (Hx), N,N-Hexamethylene bis [2-amino-1-(3,4-dihydroxy-henyl)ethanol] sulphate, is a selective *β*-sympathomimetic agent which has a double action [7]. It can be used as a bronchospasmatic agent that can reduce bronchial secretion and promotes the efficiency of the bronchial epithelium as well as being used as a sympathomimetic agent that relaxes the uterus through decreasing or arresting both the frequency and intensity of the uterine contraction, thus inhibiting both the spontaneous and the oxytocin-induced labour [8]. A limited number of methods are available in literature for the determination and assay of Hx in its pure state or pharmaceutical preparations including colorimetric determination using either $NaNO_2$ or 4-aminoantipyrine and potassium hexacyanoferrate [9,10], and HPLC methods [11].



Hexoprenaline Sulfate



Biperiden Hydrochloride

Biperiden Hydrochloride (BP) is (1*RS*)-1-[(1*RS*, 2*SR*, 4*RS*)-bicyclo[2,2,1]-hept-5-en-2-yl]-1-phenyl-3-(piperidin-1-yl) propan-1-ol hydrochloride is anti-parkinsonic that is used in treatment of Parkinsonism [12]. Parkinsonism is thought to result from an imbalance between the excitatory (cholinergic) and inhibitory (dopaminergic) systems in the corpus striatum. The mechanism of action of centrally active anticholinergic drugs such as Akineton, may be relate to competitive antagonism of acetylcholine at cholinergic receptors, which restores the balance [13]. Different official and non-official methods for BP assay were found in literature, where the chromatographic is the most common ones. Capka and Xu developed a liquid chromatographic method for simultaneous determination of BP enantiomers in human serum with limits of detection reaching 1 $ng \cdot mL^{-1}$ [14]. A stability-indicating HPLC procedure for BP had also been developed and validated [15]; the method has the requisite accuracy, selectivity, sensitivity and precision for BP assaying in bulk and pharmaceutical dosage forms. Capillary electrophoretic method has been developed and applied for the enantioselective analysis of the anti-Parkinson drug, biperiden, in pharmaceutical formulations using a modified cyclodextrin as chiral selector [16]. An extractive colorimetric method for determination of BP in dosage forms have been proposed using bromophenol blue [17]. Official method was performed via direct titration of BP with 0.1 N perchloric acid using crystal violet as indicator [18].

Although ion-selective electrodes (ISEs) had found wide applications for drug quality control, to the best of our knowledge only an ion pair based Hx and BP sensors were reported in literature [19,20]. Potentiometric sensors incorporated with ion-pair associates are generally plagued by limited selectivity and their applications are restricted to more challenging matrices; therefore more selective molecular recognition component is clearly required.

Efforts to improve ISEs characteristics have been proposed through the use of species capable of molecular recognition [21,22]. Different types of ionophores such as crown ethers, calixarenes, cyclodextrins (CDs) or porphyrins have been proposed; however, CDs were by far the most commonly used. CDs are naturally occurring macrocyclic oligosaccharides formed of 1,4-glucosidic bond linked D-(+)-glucopyranose oligomers of 6, 7, and 8 glucose units yielding α-, β-, and γ-CD, respectively, with toroidal three-dimensional cage configuration [23,24]. Due to the presence of primary and secondary hydroxyl group pointing outside the cavity, the exterior surface is hydrophilic whereas the interior surface, lined with C-H groups and ether-linked oxygen atoms, is hydrophobic. CDs can form inclusion complexes with different types of guests without the formation of chemical bonds or changing

their structure where the binding forces associated with the inclusion formation are attributed to number of factors, such as hydrophobic forces, hydrogen bonding, size of the cavity, shape of the guest molecule and electrostatic interaction [25,26]. Such unique properties introduced CDs for chiral separation of drugs based on chromatographic capillary zone electrophoretic, mass spectroscopic methods [27] and as a sensing material in potentiometric sensors for many pharmaceutically important drugs [28–31].

In this study, plastic membrane electrodes (conventional) for Hx and BP have been constructed based on the incorporation of β-CDs ionophore in polyvinyl chloride (PVC) membranes plasticized with 2-fluorophenyl 2-nitrophenyl ether (*f*-NPE). The fabricated sensors were subjected to a series of tests to select sensor possessing the most favorable analytical characteristics for potentiometric determination of BP and Hx in their pharmaceutical preparations.

Experimental

Chemicals, Reagents, Stock and Standard Solutions

All reagents were of the analytical grade, purchased form *Sigma-Aldrich* or *Fluka* (if not stated otherwise), and double distilled water was used throughout the experiments. Different cyclodextrin derivatives were used, including; heptakis (2,6-di-O-methyl)-β-CD **(I)**, heptakis (2,3,6-tri-O-methyl)-β-CD **(II)**, 2-hydroxypropyl-β-CD **(III)**, native β-CD **(IV)**, α-CD **(V)** and γ-CD **(VI)**. Different ionic sites were incorporated in the electrode matrices namely; sodium tetraphenylborate (NaTPB), sodium tetrakis (4-fluorophenyl) borate (NaTFPB), potassium tetrakis (4-chlorophenyl) borate (KTCPB), silicotungstic acid (STA), phosphotungstic acid (PTA) or phosphomolybdic acid (PMA). 2-nitrophenyl octyl ether (NPOE), 2-fluorophenyl 2-nitrophenyl ether (*f*-NPE), dioctylphthalate (DOP, *BDH*), dioctylsebacate (DOS, *Avocado*), and tricresylphosphate (TCP) were used as membrane plasticizers.

Authentic hexoprenaline sulphate ($C_{22}H_{32}N_2O_6.H_2SO_4$, molar weight 518.58 $g{\cdot}mol^{-1}$) and biperiden hydrochloride ($C_{21}H_{29}NO.HCl$, molar weight 346.46 $g{\cdot}mol^{-1}$) samples were supplied by the *Arab Drug Company*, *ADCo*, Egypt. Stock drug solutions (10^{-2} $mol{\cdot}L^{-1}$) were freshly prepared by dissolving the appropriate amounts of each drug in bidistilled water and kept at 4 ^{o}C.

Pharmaceutical Preparations

For sampling of tablets, (Asmadol, tablets 0.5 mg Hx per tablet, and Gynipral, 0.5 mg Hx per tablet, *Arab Drug Company*, Cairo, Egypt,), 20 tablets were ground together and appropriate weights of each were taken as samples. The required amount was dissolved in 0.1 M HCl, (about 0.1 cm^3 for one mg of tablets) and completed to 50 mL with distilled water. The exact Hx concentration was estimated according to the official method by measuring the absorbance in 0.1 M HCl at 250 nm [7].

Akineton and Achtenon tablets (2 mg BP per tablet) were purchased from local drug stores. Ten tablets were ground and dissolved in 50 mL of bidistilled water. BP content was assayed according to the proposed potentiometric method and colorimetric method using phosphate buffer–bromocresol purple solution and measuring the absorbance of the produced color at 408 nm [18].

Electrochemical Apparatus and Other Instrumentation

Potentiometric measurements were carried out using a 692-pH meter (*Metrohm*, Herisau, Switzerland, Art. no. 1.691.00100) with Ag/AgCl double-junction reference electrode (*Metrohm*, Art. no. 6.0726.100) and a combined pH glass electrode (*Metrohm*, Art. no. 6.0202.100).

Procedures

Sensor Construction. Electrode matrix cocktail composed of 2.5 mg of the native β-CD **(IV)**, 2.7 mg NaTFPB, 240 mg *f*-NPE, 240 mg PVC and 6 mL THF was poured in a Petri dish (5 cm diameter). After evaporation of THF, circular pieces (2 cm diameter) of the PVC membranes were mounted on the end of the PVC tubing, and the electrodes were filled with 10^{-2} mol·L^{-1} KCl and 10^{-2} mol·L^{-1} of drug solution using Ag /AgCl as internal reference electrode. The fabricated electrodes were soaked in 10^{-3} mol·L^{-1} of the corresponding drug for 2 h before using.

Sensor Calibration. Sensors were calibrated by immersing the sensor in conjugation with reference electrode in 25 mL aliquots of 10^{-6}–10^{-2} mol·L^{-1} HX or BP solutions [32]. The potential readings were recorded and plotted against drug concentration in logarithmic scale (log [Drug]).

Potentiometric Determination of Hx and Bp in Pharmaceutical Preparations. Hx and BP were potentiometrically determined in their pharmaceutical preparations using the developed sensors under batch conditions potentiometric titration. Aliquots of the sample solutions containing 5.0–25.0 mg Hx or 3.0–15.0 mg BP were potentiometrically titrated against standardized NaTPB solution [21]; the titration process was monitored using the corresponding drug sensor in conjugation with Ag/AgCl reference electrode. The potential readings were plotted against volume added, and the equivalence points were estimated from the first derivative of the sigmoid-shape titration curves.

Results and Discussion

The customary type of ion selective electrode is one in which the membrane is composed of a water-immiscible organic solvent containing the ion in question, usually in the form of an ion-pair [2,4,33,34]. Hx and BP present in the cationic form and can form ion pair complexes with different ion pairing agents [19,20]. In some cases, these ion pairs are in the form tinny suspended particles which cannot be separated either by filtration or precipitation in addition due to the limited stability of Hx solution and Hx-TPB ion pairs. In such a case, alternative sensing material is needed for Hx determination.

Chemically modified electrodes (CMEs) were suggested for improving the electroanalytical performance through application of molecular recognition species selective to the target analyte. In a reported work [16,35], a capillary electrophoretic method has been developed and applied for the enantioselective analysis BP and Hx using a modified cyclodextrin as the chiral selector. Based on this work, the research team tested application of cyclodextrin as a sensing ionophore for potentiometric determination of both drugs. Extensive investigation will take place for optimization of the electrode matrix composition to achieve the highest electrode sensitivity.

The response of ionophore-based potentiometric sensors is usually governed by the molecular recognition ability between the analyte (guest) and the host molecule. The most important property of CDs is their ability to form supramolecular (inclusion) complexes with many appropriately sized organic ions and molecules, where the driving forces for the complexation are non-covalent, including van der Waals forces and directed hydrogen bonding. Preliminary experiment declared that sensor fabricated without incorporation of CD showed non-significant response towards both drugs (slope 22 $mV \cdot decade^{-1}$), while those modified with different CDs derivatives gave Nernstian responses with different slope values, demonstrating the crucial rule of the ionophore on the electrode response. Sensors modified with both α- and γ-CDs showed low Nernstian response (30–45 $mV \cdot decade^{-1}$), which may be attributed to the incompatible cavity size for inclusion complex formation. Contrary, electrodes incorporated with different β-CDs ionophores **(I–IV)** showed reasonable responses and β-CD **(IV)** was the best among other tested ionophores (Nernstain slope values were 59.1 ± 1.5 and 55.4 ± 0.6 mV $decade^{-1}$ for Hx and BP, respectively). Such variation in electrode performances can be explained on the basis of the stability constants of the formed inclusion complexes and fitting of the drug molecule within the CD cavity.

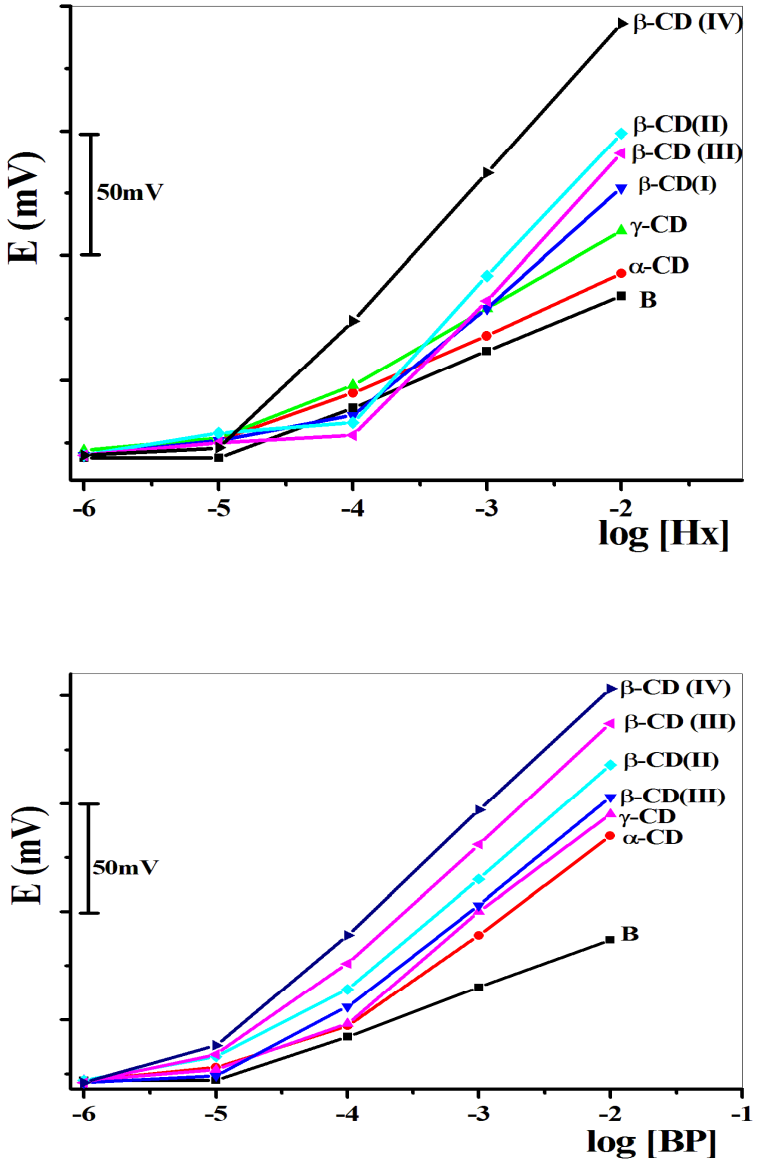


Fig. 1: *Effect of the sensing ionophore on the sensor performances*.

On constructing an ISE, the amount of the sensing material in the electrode matrix should be sufficient to obtain reasonable complexation at the electrode surface that is responsible for the electrode potential. β-CD **(IV)** content in the fabricated electrode matrices was varied from 1 to 10 mg, incorporation of 2.5 mg of β-CD was sufficient to get the proper performance (slope values were 55.6 ± 0.9 and 60.3 ± 0.6 mV·decade^{-1} for Hx and BP respectively).

Effect of Anionic Sites

Addition of lipophilic ionic sites promotes the interfacial ion-exchange kinetics and decrease the bulk resistance by providing mobile ionic sites in the electrode matrix [36,37]. β-CDs behave as neutral carrier ionophores and their ISEs are functional only when anionic sites are incorporated. Addition of NaTFPB to the electrode matrix afforded the highest slope value (59.2 ± 0.6 and 57.2 ± 1.0 mV·decade^{-1} for Hx and BP, respectively) compared with NaTPB, KTClPB, PTA or PMA. Furthermore, the content of NaTFPB was changed from 0 to 7.0 mg and addition of 2.70 mg was selected.

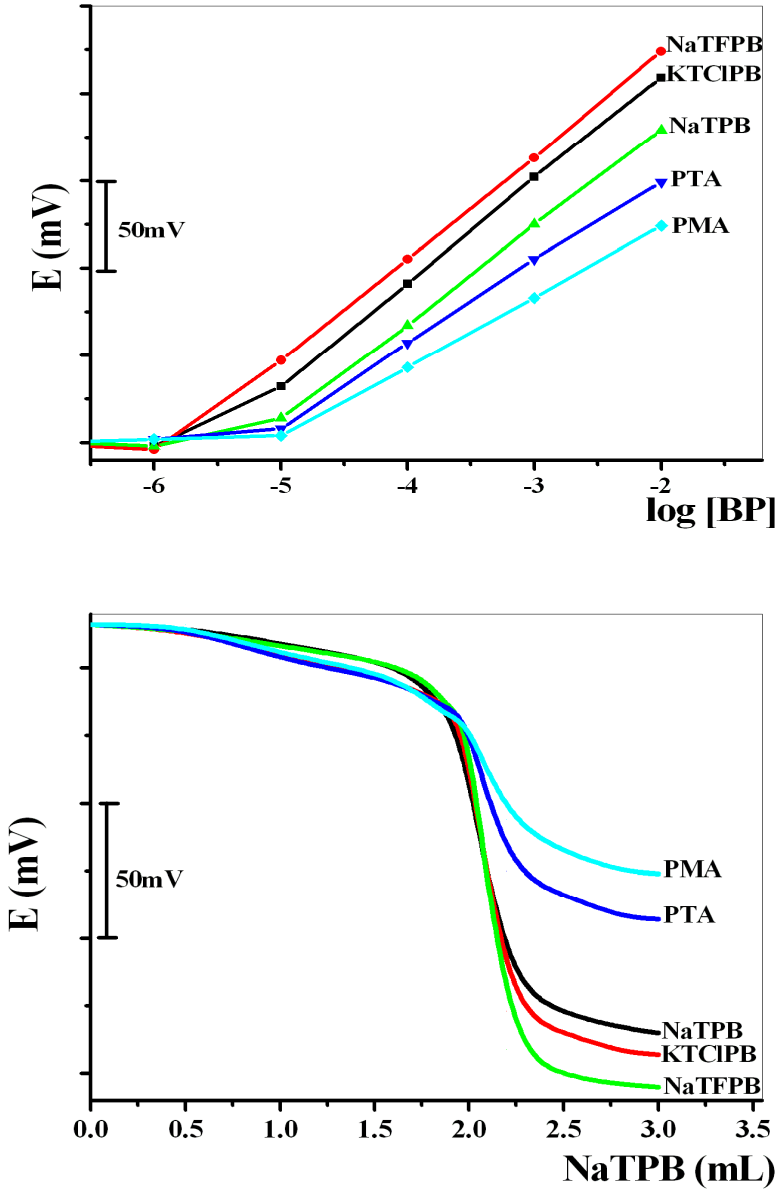


Fig. 2: *Effect of ionic sites type on BP sensor performance.*

Effect of Membrane Plasticizer

Sensitivity and selectivity obtained for a given ionophore based ion-selective electrode is greatly influenced by the polarity of the electrode matrix, which is defined by the dielectrical constant of the electrode plasticizer [38,39]. It should be noted that the nature of the plasticizer affects not only the polarity of the electrode phase but also the mobility of ionophore molecules and the state of the formed complexes.

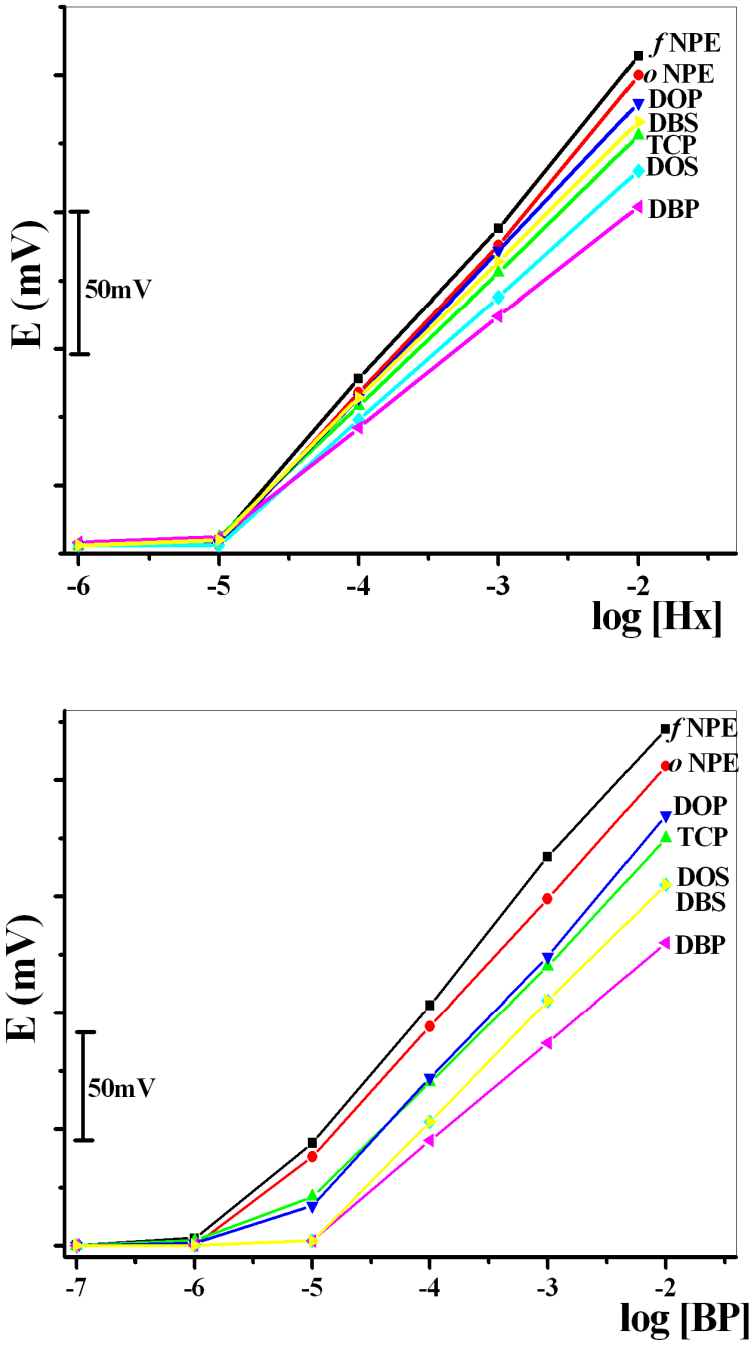


Fig. 3: *Effect of the plasticizer on the performance of Hx and BP sensors*.

The influence of the plasticizer on the performance of both Hx and BP sensors modified with β-CD **(IV)** and NaTFPB as ionic sites was studied using six plasticizers having different dielectric constant, namely *f*-NPE, *o*-NPOE, TCP, DOS, DBS, DBP and DOP (ε = 50, 24, 17.6, 5.2, 4.8, 4.7 and 3.8, respectively). Plasticizer selection was crucial for appropriate sensor performance, as application of the less polar plasticizers decreased the sensitivity while the proper sensitivity was observed for electrodes containing high polar plasticizer, *f*-NPOE (Nernstain slope was 57.1 ± 1.2 and 56.1 ± 2.2 mV·decade^{-1} for Hx and Bp, respectively) (Fig. 3).

Sensor Performances

The potentiometric response characteristics of the developed sensors, at the optimal matrices compositions, were evaluated according to the IUPAC recommendation [32]. The fabricated sensor displayed Nernstian cationic responses towards Hx and BP (Table 1). Data obtained indicated that the developed sensors can be successfully applied for the potentiometric determination of cited drugs with LOD was 10^{-6} mol·L^{-1}. It is noteworthy to mention that the sensors based on β-CD as sensing material showed higher sensitivity with fast response time than those based on ion pairs as sensing materials [19,20], which may be attributed to the encapsulation of drug molecule into the CDs toroidal cavity (host-guest interaction) rather than equilibrium at the membrane surface.

Table 1: *Analytical performances of Hexoprenaline sulphate and Biperiden hydrochloride sensors*.

Sensors	**Hx**	**BP**
Concentration range (mol·L^{-1})	10^{-5}–10^{-2}	10^{-6}–10^{-2}
Slope (mV·decade^{-1})	59.0 ± 1.0	56.8 ± 1.4
R	0.99982	0.99761
LOD (mol·L^{-1})	8.0×10^{-6}	10^{-6}
Response time (s)	8	6
Lifetime (Day)	30	30
Working pH range	3–7	2–7

* Results are average of five different calibrations.

The influence of pH on the response of the fabricated electrodes was studied by recording the electrode potential readings at different pH values (pH 2–10). The electrode responses were found to be pH independent in the range 3–7 and 2–7 for Hx and BP electrodes, respectively. The lifetimes of the fabricated electrodes were tested by performing day-to-day calibration. Both electrodes showed useful lifetime of 30 days during which the Nernstian slopes did not change significantly (±2 mV·decade^{-1}), while the detection limit was shifted by one order of magnitude at the end of this period.

In pharmaceutical analysis, it is important to test the selectivity of the method towards the excipients added to the pharmaceutical preparations, such as glucose, starch, talc, lactose, sucrose. Potentiometric selectivity coefficient defines the ability of the ISE to differentiate a particular (primary) ion from others (interfering ions) [40]. The matched potential method (MPM) was used to determine selectivity coefficients; in this method the selectivity coefficient is defined as the activity (concentration) ratio of the primary ion and the interfering ion which gives the same potential change in a reference solution [41]. This method can be used in the case of differences in the charge number between primary and interfering ions and does not require Nernstian responses to the activity (concentration) of primary or interfering ions. This is only one method suitable for determination of selectivity coefficients concerning the neutral compounds. Results (Table 2) revealed a high selectivity toward Hx and BP in the presence of other interferents, additives and fillers commonly introduced in pharmaceutical formulations and inorganic cations, indicating the high selectivity of the proposed methods and applicability to use for routine determination of Hx and BP in pure and in dosage forms.

Table 2: *Potentiometric selectivity coefficient for Hx and BP sensors*.

Interferent	**–log $K_{A,B}$**		**Interferent**	**–log $K_{A,B}$**	
	Hx	BP		Hx	BP
Li^+	3.16	3.30	Maltose	3.40	3.30
NH_4^+	3.00	3.25	Starch	3.60	3.60
Ca^{2+}	3.50	3.20	Sucrose	3.10	3.00
Mg^{2+}	3.03	3.10	Glucose	2.03	2.59
Ni^{2+}	2.95	2.62	Fructose	2.40	2.84
Fe^{2+}	2.45	2.80	Glycine	2.95	3.20
Co^{2+}	3.10	3.30	Caffeine	2.80	2.65
Phosphate	2.65	3.05	Glycine	2.45	3.05
Citrate	2.25	2.29	Cysteine	2.60	2.90

Average of five measurements.

Potentiometric Titration

In contrast to direct potentiometric measurements requiring careful calibrations of measuring cells, the potentiometric titration techniques offers the advantage of high accuracy and precision; although the cost of increased time and increased consumption of reagents used as titrants. In the potentiometric titration of Hx and BP with NaTPB, membrane sensors plasticized with *f*-NPE gave the highest magnitude of both the potential break and sharpness at the inflexion point of the titration curve compared with the other plasticizers (Fig. 4).

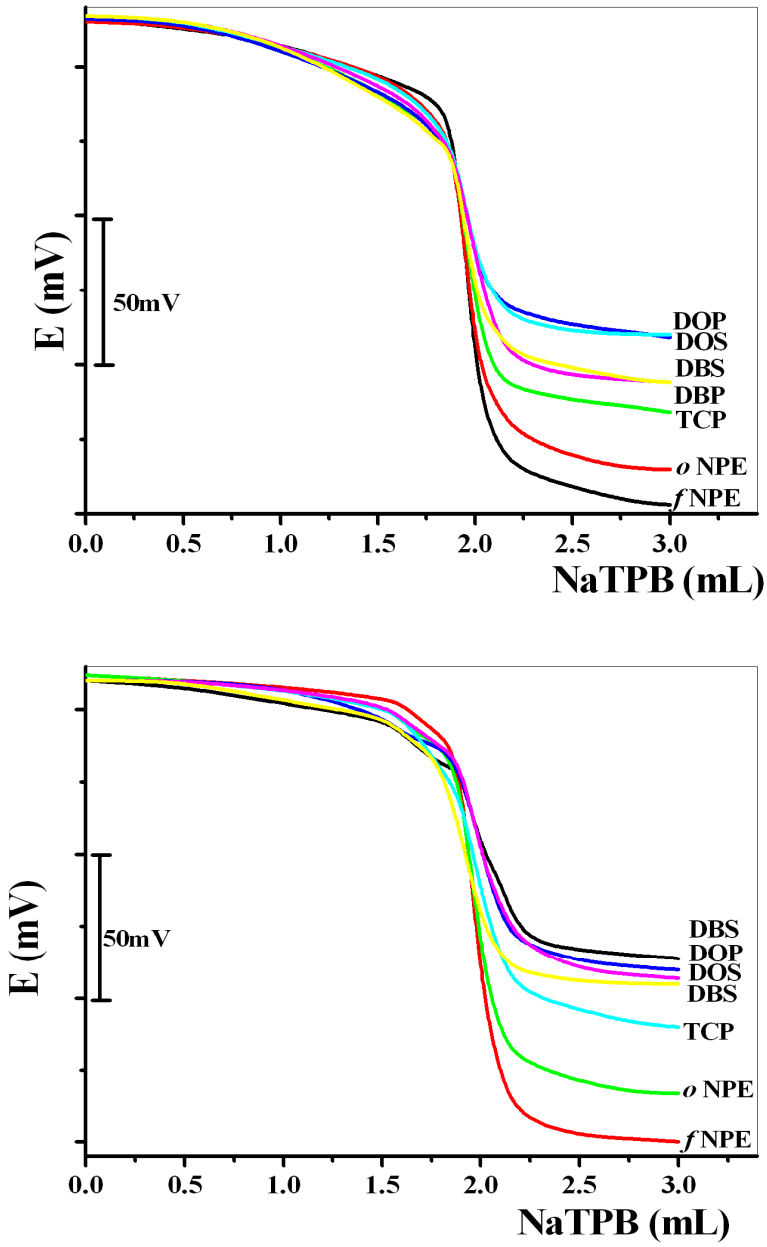


Fig. 4: *Effect of the membrane plasticizer on potentiometric titration of 2 mL 10^{-2} mol·L^{-1} Hx and Bp solutions with 10^{-2} mol·L^{-1} NaTPB.*

For Hx, the total potential change during the titration process was improved in case of DOP from 106 mV to 166 mV using *f*-NPE. Similar profile was obtained with Bp as ΔE increased from 96 mV with DBS to 162 mV with *f*-NPE. Under the optimum conditions, the fabricated sensors can be used as indicator electrode for potentiometric titration of Hx and BP in the concentration range 4.5–23 mg Hx or 3.1–15.5 mg BP, respectively.

Analytical Applications

The proposed electrodes were successfully employed for the assay of Hx and BP in their authentic samples and pharmaceutical formulations applying potentiometric titration method. The results clearly indicated satisfactory agreement between the Hx contents in different samples determined by the developed sensor and official method (Table 3, 4).

Table 3: *Potentiometric determination of Hx in pharmaceutical preparations*.

Sample	Taken (mg)	Found					
		Official method		Proposed potentiometric method			
				Standard addition		Titration	
		Recovery %	R.S.D	Recovery %	R.S.D	Recovery %	R.S.D
Pure Hx	5.0	97.50	3.00	98.2 0	2.10	97.50	1.90
	10.0	98.20	1.70	99.50	1.50	99.10	1.80
	25.0	99.10	1.80	100.00	1.75	101.00	1.20
Asmadol tablets	2.50	97.20	2.40	98.10	2.10	99.00	2.00
Gynipral tablets	2.50	98.90	2.40	98.50	2.10	99.50	1.80

a) Mean recovery and relative standard deviations of five determinations.

Table 4: *Potentiometric determination of Bp in pharmaceutical preparations*.

Sample	Taken (mg)	Found					
		Official method		Proposed potentiometric method			
				Standard addition		Titration	
		Recovery %	R.S.D	Recovery %	R.S.D	Recovery %	R.S.D
Pure BP	3.0	98.20	2.00	99.0 0	1.80	98.50	2.10
	6.0	99.80	1.70	100.50	1.60	100.00	1.70
	9.0	100.10	1.65	101.05	1.45	102.00	0.90
Akineton tablets	3.0	101.90	1.30	101.90	1.60	99.00	1.21
Achtenon tablets	3.0	98.56	1.65	99.60	1.80	98.40	1.90

a) Mean recovery and relative standard deviations of five determinations.

Conclusions

The present work demonstrates the fabrication of novel cyclodextrin-based sensors for potentiometric determination of hexoprenaline sulphate (Hx) or biperiden hydrochloride (BP). The proposed sensors showed Nernstian slopes in the concentration range from 10^{-6} to 10^{-2} mol·L^{-1} with fast response time (8 s) and long operational lifetime. The detection limit was improved compared with those based on drug-ion pairs as sensing material. The fabricated electrodes were successfully applied for the potentiometric determination of both drugs in pure and pharmaceutical forms with average recoveries comparable to the official methods. These results may be the base for further research leading to improvement of the analytical parameters for preparation of simple drug potentiometric sensors. The advantages offered by the present methods suggest their use for the routine analysis of drugs in pharmaceutical preparations.

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