Full Paper

Ion Selective Electrode Approach for In-line Determination of Benzydamine Hydrochloride in Different Matrices of Pharmaceutical Industry

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Abstract- This work demonstrates a comparative study between six fabricated ion selective electrode sensors to determine Benzydamine HCL (BZ) by direct potentiometry in pure form and in its different pharmaceutical formulations. Precipitation based technique was only used for fabrication of BZ/phosphotungestate (BZ/PT) sensor, where BZ was incorporated in the membrane composition. For other sensors, the BZ association complexes with different cationic exchangers were obtained in situ by soaking the sensors membranes in 1×10^{-2} M BZ solution. Sensors 1-5 were named BZ/Na-tetraphenylborate, BZ/phosphomolybdate, BZ/Na-phosphotungestate, BZ/K-tetrakis and BZ/ammonium-reineckate, respectively. Dioctylphthalate (DOP) and Nitrophenyloctyl ether (NOPE) were used as plasticizers. The proposed sensors showed fast, stable Nernstian responses across a relatively wide BZ concentration range (5×10^{-5} to 1×10^{-2} M) in pH range of 4-7. The suggested sensors could be used for several weeks without any measurable change in sensitivity. Validation of the method according to IUPAC recommendations showed the suitability and selectivity of these electrodes in the quality control assessment of BZ in presence of different interferents. Sensor 4 showed the best results regarding sensitivity and accuracy. The proposed sensors were

successfully applied for the determination of BZ in pure powder form and in its different pharmaceutical formulations where good recoveries were obtained.

Keywords- BenzydamineHCL, Ion selective electrode, Na-phosphotungestate, K-tetrakis, Cationic exchangers and pharmaceutical dosage form

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1. INTRODUCTION

BenzydamineHCl (BZ) is an official tertiary amine compound; it is chemically designated as 3-(1- benzylindazol-3- yloxy) propyldimethylamine hydrochloride (Figure 1) [1]. It acts as a non-steroidal anti-inflammatory drug (NSAIDs), which is used topically in order to reduce the unwanted systemic side effects of the ordinary systemic NSAIDs in addition to reducing the synthesis of prostaglandins at the pain site [2,3]. It is a white crystalline powder, very soluble in water, freely soluble in ethanol (95%) and in chloroform, practically insoluble in ether.

Several methods have been reported for quantitative determination of BZ, including non-aqueous titration method [1], different high-performance liquid chromatography methods [4-6],several spectroscopic methods [7-9], electrochemical determination [10-12] and a stability indicating method has been reported for determination of BZ in presence of its toxic photodegrdation products [13].

Remote sensing and direct measurements of untreated samples are of global interest to reach greenest analytical methodologies as no hazardous reagents or organic solvents will be needed. Modern techniques based on material transport across a selective membrane as ion selective electrodes (ISEs) are now widely used in the determination of trace amounts of analytes as well as drugs in pure form and pharmaceutical dosage form [14]. The material transport includes both neutral and charged complex species and simple ions [15,16]. The high selectivity of these electrodes imparts a great advantage over other techniques [17]. From the great advantages of ISE is the no need for sample preparation and analytes in colored, turbid or viscous samples can be determined accurately. Besides, they have the advantage of a limited reagent consumption, easy automation and good impact on the environment. Furthermore, ISEs show rapid response to changes in concentration and are tolerant to small changes in pH. A further advantage is that they are relatively cheap and simple to develop, set up and run with no need for sophisticated apparatus.

Recently, four publications described the use of electrochemical sensors as bench-top real-time analyzer for in-line tracking of the concentration of active principle ingredients [18-21].

In-line determination of drug concentrations is recently applied in the pharmaceutical field in order to provide rapid and time saving method of analysis during manufacture. It also avoids sample withdrawal and extra sample preparation steps. Several traditional analytical techniques were used for in-line analysis as spectroscopic and HPLC techniques, but they

require high cost setup and additional time for analysis [21]. According to the previously mentioned advantages of potentiometric electrodes, they can be successfully applied for in-line determination of pharmaceutical drugs. The required concentrations are determined by just dipping the sensor in the solution to be measured.

The aim of this work was to develop new, eco-friendly, economic and portable ion selective electrodes which can be used for routine quality control analysis and in-line determination of BZ in its drug substance and available pharmaceutical formulations without the need of preliminary derivatization, extraction or separation steps.
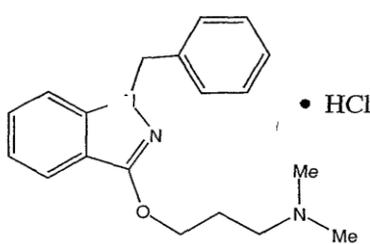

Fig. 1. Chemical structure of Benzydamine HCl

2. EXPERIMENTAL

2.1. Instrument

A Jenway digital ion analyzer model 3330 (UK) with Ag/AgCl double junction reference electrode No. Z113107-1EAPW (Aldrich Chemical Co.) was used. The influence of pH on the response of the electrodes was studied using pH glass electrode Jenway (Jenway, UK) No. 924005-BO3-Q11C. The determination of the samples was occurred using Magnetic stirrer, BandelinSonorox, R×510S (Budapest, Hungaria).

2.2. Materials and reagents

2.2.1. Pure standard

BZ working standard was obtained as kind gift sample from EIPICO Company (10th of Ramadan city, Cairo, Egypt). Its purity was found to be 99.90% according to its official BP method [1].

2.2.2. Market samples

- Tantum verde[®] mouthwash and gargle manufactured by EIPICO, Cairo, Egypt (Batch No. 1306203) each 100 mL gargle was labeled to contain 0.15 g BZ.
- Tantum[®] gel manufactured by EIPICO, Cairo, Egypt (Batch No. 1300465) each 100 g gel was labeled to contain 5.00 g BZ.

- Tantum verde® lozenges manufactured by EIPICO, Cairo, Egypt (Batch No. 1301813) each lozenge was labeled to contain 3.00 mg BZ.

2.2.3. Chemicals and reagents

All chemicals and solvents used throughout this work,were of pure analytical grade and water used was bi-distilled.

- Dioctyl phthalate (DOP), Nitrophenyloctyl ether (NPOE), sodium phosphotungestate tribasic hydrate (Na-PT) and potassium Tetrakis (4-chlorophenyl) borate (TpClPB) (Sigma-Aldrich, Germany).
- Ammonium reineckate (ARN), sodium tetraphenylborate (Na-TPB), phosphomolybdate (PM), tetrahydrofuran (THF) and polyvinyl chloride (PVC) of high molecular weight (BDH, England).
- Sodium hydroxide (NaOH), hydrochloric acid (HCl) (37.00% w/v) and potassium chloride (KCl) (Prolabo, USA).

2.3. BenzydamineHClstandard stock solution(1×10^{-2} M)

It was prepared by transferring 0.35 g of BZ, accurately into100-mL volumetric flask then dissolving in 90-mL bi-distilled water and completing to volume with the same solvent. The stability of the prepared solution was studied and it was found to be stable with no apparent degradation throughout the experimental time at 25 °C.

2.4. Procedures

2.4.1. Preparation of the membrane sensors

(a) For BZ/PT loaded complex membrane

An accurate volume of 10 mL of 1×10^{-2} M aqueous solution of BZ was mixed with 10 mL of a saturated aqueous solution of 1×10^{-2} PT solution. The resulting precipitate was filtered, washed with cold water, allowed to dry at room temperature and ground to fine powder. In a glass petri dish (5 cm diameter), 10.00 mg of the previously prepared association complex was mixed with 0.4 mL of DOP, then 0.19 g of PVC was added. The mixture was dissolved in 5 mL THF, and then the petri dish was covered with a filter paper and left to stand for one hour to allow slow evaporation of the solvent, producing a thick homogeneous master coating PVC solution

(b) For Plain membranes

In separate petri dishes, 10.00 mg of Na-TPB, PM, Na-PT, K-TpClPB and ARN for sensors 1, 2, 3, 4 and 5, respectively was thoroughly mixed with 0.19 g PVC and 0.4 mL NOPE for sensors (1,4&5) and DOP for sensors (2 and 3) in a 5 cm glass petri dish then all membrane components were dissolved in 5 mL THF. The petri dishes were covered with

filter paper and left to stand overnight to allow solvent evaporation at room temperature. Master membranes with thickness of 0.10 mm were obtained and used for the construction of the electrodes.

2.4.2. Preparation of the electrodes assemblies

From the prepared master membranes, a disk (≈5 mm diameter) was cut using a cork borer and pasted using THF to an interchangeable PVC tip that was clipped into the end of the glassy electrode body. Equal volumes of 1×10^{-4} M BZ and 1×10^{-4} M KCl was mixed and this equimolar mixture was used as internal solution for electrodes. Ag/AgCl wire (1 mm diameter) was immersed in the internal reference solution as an internal reference electrode. The electrodes were conditioned by soaking in 1×10^{-4} M BZ solution for one day and were stored dry when not in use.

2.4.3. Sensors calibration

The conditioned sensors were calibrated by transferring 25 mL of 1×10^{-2} M BZ solution into 50 mL beakers, separately. Different concentrations of BZ were determined by a stepwise dilution of 1×10^{-2} M solution with deionized water and continuous electromotive force (EMF) measurements. The electrode system was immersed in BZ standard solution in conjunction with an Ag/AgCl reference electrode. The emf readings of equilibrium state was recorded within ±1 mV. Linear correlation was obtained in the range of 6.05×10^{-5} M to 1×10^{-2} M (for sensors BZ/PT, 4&5), 1.01×10^{-4} M to 1×10^{-2} M (for sensors 1&2) and 7.84×10^{-6} M to 1×10^{-2} M (for sensor 3). The membrane sensors were stored in deionized bi-distilled water. The electrode potential was plotted versus logarithmic concentration of each sensor. The obtained calibration plots were used for subsequent measurements of unknown concentration of BZ samples using the corresponding electrode.

2.4.4. Effect of pH

The effect of pH on the response of the investigated electrodes was studied using 1×10^{-2} M solutions of BZ with pH ranging from 1 to 11. The pH was adjusted with 2 M hydrochloric acid and 2 M sodium hydroxide solutions.

2.4.5. Sensors selectivity

The potentiometric selectivity coefficients (K^{Pot}_{AB}) of the proposed sensors towards different substances were evaluated according to IUPAC guidelines using separate solution method [22].

2.4.6. Determination of BZ in different pharmaceutical matrices

Accurate portions equivalent to 8.65 mg BZ of Tantum® different pharmaceutical formulations were accurately transferred to 25 mL volumetric flasks to prepare 1×10^{-3} M BZ. The volume was completed to the mark with distilled water

A volume of 5.77 mL of Tantum verde® mouthwash was accurately transferred to 25 mL volumetric flask.

Accurate weight of 0.17 g of Tantum® gel was first dissolved in 5 mL distilled water, then magnetically stirred for 10 minutes and accurately transferred to 25 mL volumetric flask. Five tablets of Tantum verde® lozenges were weighed and finely powdered in a small dish, then an accurately weighed portion of the powder (3.93 g) was transferred to 25 mL volumetric flask.

The potentiometric measurements were performed using the proposed sensors in conjunction with the Ag/AgCl reference electrode, and the recovery % was obtained either by comparing the potential readings with those of the same concentrations of standard BZ or from the corresponding regression equation. Standard addition technique has been carried out to assess the validity of the developed method.

3. RESULTS AND DISCUSSION

Selective membranes in ISE have shown both ion exchange and perm-selectivity for the sensor ion [23]. The suggested ion selective electrodes for determination of BZ offer many advantages over other reported electrochemical methods [11,12]. The developed electrodes were established using several numbers of cationic exchangers and different strategies were used for membrane preparation.In this study, six ion selective membrane sensors were proposed for determination of BZ either in its pure powder form or in its different pharmaceutical matrices.

3.1. Membrane compositions and response characteristics of sensors

Sensors for basic drugs are based on the use of the ion association complexes of these species with one of cationic exchanger compounds forming ion-association complexes embedded in PVC matrix membrane with suitable solvent and mediators [17]. In the present work BZ behaves as a cation, due to the presence of tertiary amine functional group (Figure 1). The type of the ion exchanger affects the response of the sensor [23], therefore, different cationic exchangers were used in order to study there effect on the drug sensors. Cationic exchangers as Na-PT, PM, Na-TPB, K-TpClPB and ARN were used for the preparation of the membrane sensors as they form insoluble ion association complexes with suitable grain size with BZ. The ratio of BZ to the ion exchangers in the formed complexes was found to be 1:1 (about60 mV/decade) so BZ acts as a monoionic species. The cationic exchangers were

incorporated with a suitable solvent mediator in PVC matrix to produce plasticized membranes which were used for the construction of the electrodes.

Two different strategies were applied for the membrane preparations using PT ion exchanger. The drug association complex was prepared by precipitation as in BZ/PT sensor or by soaking the prepared sensor in 1×10^{-4} M BZ solution as in sensor 3. According to the obtained results regarding performance characteristics, no significant differences were found (Table1). This provides an evidence of the ability of the applied method for the preparation of BZ selective membrane without the incorporation of drug-ion exchanger association complex in membrane composition. Preparation of the plain membrane is more simple, economic and less time consuming. That is why BZ-complexes in sensors 1, 2, 3, 4 and 5 were prepared in situ by soaking the PVC membranes of different cationic exchangers in 1×10^{-4} M BZ solution after construction of the electrodes. Also, method validation was applied using sensors 1-5 only.

The results of using different ion exchangers where represented by the slopes obtained for all studied sensors, as shown in Table 1. The PVC acts as a regular support matrix for the membrane but its use creates a need for a plasticizer [24]. The plasticizer is the second factor that allows BZ ions to be extracted from an aqueous solution in to the membrane, as an organic phase. After the evaluation of different plasticizers, namely DOP and NOPE, better results were obtained using NOPE represented in significant change in the slopes (Table 1). It plasticizes the membrane, dissolves the ion-association complexes and adjusts both the membrane permittivity and ion-exchanger sites mobility to give highest possible selectivity and sensitivity[25]. Based on the IUPAC recommendations [22], the response characteristics of the designed electrodes were assessed.

Table1. Effect of different cationic exchangers and plasticizers on the slope and concentration range of Benzydamine HCl

Sensor	Cationic exchanger	Plasticizer	Slope (mV/ concentration decade)	Concentration range (M)
BZ/PT	Na-PT	DOP	46.40 ± 0.89	6.05×10^{-5}-1×10^{-2} M
1	Na-TPB	NOPE	50.09 ± 1.56	1.01×10^{-4} -1×10^{-2} M
2	PM	DOP	49.85 ± 0.82	1.01×10^{-4}-1×10^{-2} M
3	Na-PT	DOP	46.22 ± 1.78	7.84×10^{-6}-1×10^{-2} M
4	K-TpClPB	NOPE	56.00 ± 1.77	6.05×10^{-5}-1×10^{-2} M
5	ARN	NOPE	43.67 ± 1.53	6.05×10^{-5}-1×10^{-2} M

Table 2 displays the slopes, linear ranges and validation parameters for the BZ ion-selective electrodes. Also it shows the response times and intervals of linearity over a period of two months for 3 different assemblies of each sensor at optimal pH and temperature at 25±1 °C. The suggested electrodes displayed constant potential readings for day to day measurements, and the calibration slopes did not change by more than ±2 mV/decade over a period of 6 weeks. The calibration plots were presented in Figure 2. The deviation of the slopes of the suggested sensors from the ideal Nernestian slope (60 mV/decade), is due to the fact that the electrodes respond to activities of the drug rather than the concentration. The detection limits of the sensors were estimated according to the IUPACdefinition [22].

Table 2. Validation of the response characteristics of the investigated sensors

Parameters	Sensor 1 BZ-TPB-NOPE	Sensor 2 BZ-PM-DOP	Sensor 3 BZ-PT-NOPE	Sensor 4 BZ- TpCIPB-NOPE	Sensor 5 BZ-RN-NOPE
Linearity **Slope (mV/decade)[a]**	50.09±1.56	49.85±0.82	46.22±1.78	56.00±1.77	43.67±1.53
Intercept (mV)[a]	156.47±15.07	166.35±9.28	202.56±8.19	199.12±8.62	231.04 ± 4.19
Correlation coefficient (r)	0.9965	0.9960	0.9904	0.9943	0.9915
Concentration Range (M)	1.01×10^{-4}-1×10^{-2}	1.01×10^{-4}-1×10^{-2}	7.84×10^{-6}-1×10^{-2}	6.05×10^{-5}-1×10^{-2}	6.05×10^{-5}-1×10^{-2}
Response time (s)	25	25	45	15	25
Working pH range	4-7	3-7	4-7	3-7	3-7
Stability (weeks)	6-8	6-8	6-8	6-8	6-8
Accuracy [b] (% ± SD)	98.67±1.48	98.73±1.88	98.99 ± 1.06	99.29±1.54	97.89±1.64
Precision [c] (%RSD) **Repeatability**	1.50	1.80	0.88	1.55	1.68
Reproducibility	0.73	0.56	2.41	1.78	1.95
Ruggedness [d]	0.08	1.04	1.36	0.60	0.98

[a] Results of three determinations.
[b] Average recovery % of three concentration levels, each repeated three times.
[c] Three concentration levels each repeated three times.
[d] Relative standard deviation % of the potential produced by 10^{-4} M solution using Jenway 3505 digital ion analyzer instead of 3510 in another laboratory

The response time of the electrodes was tested for concentrations of the drug from 6.05×10^{-5} M to 1×10^{-2} M (for sensors BZ/PT, 4&5), 1.01×10^{-4} M to 1×10^{-2} M (for sensors

1&2) and 7.84×10^{-6} M to 1×10^{-2} M (for sensor 3). The measurements were characterized by a fast stable response within 15-45 seconds.

The optimum equilibration time for the electrodes after soaking in 1×10^{-4} M BZ was 12 h. After this time period, the electrodes generated stable potentials in contact with the BZ solution. On soaking for a longer time the slopes decreased gradually and this may be attributed to the gradual leaching of the electroactive species into the bathing solution [26]. Therefore, when not in use for a longtime, the electrodes should be kept dry.

To evaluate the accuracy and precision of the electrodes measurements, three concentrations within the linear concentration range of BZ were chosen. Three solutions of each concentration were prepared and analyzed in triplicate (repeatability assay). This assay was repeated on three different days (reproducibility assay), as shown in Table 2.
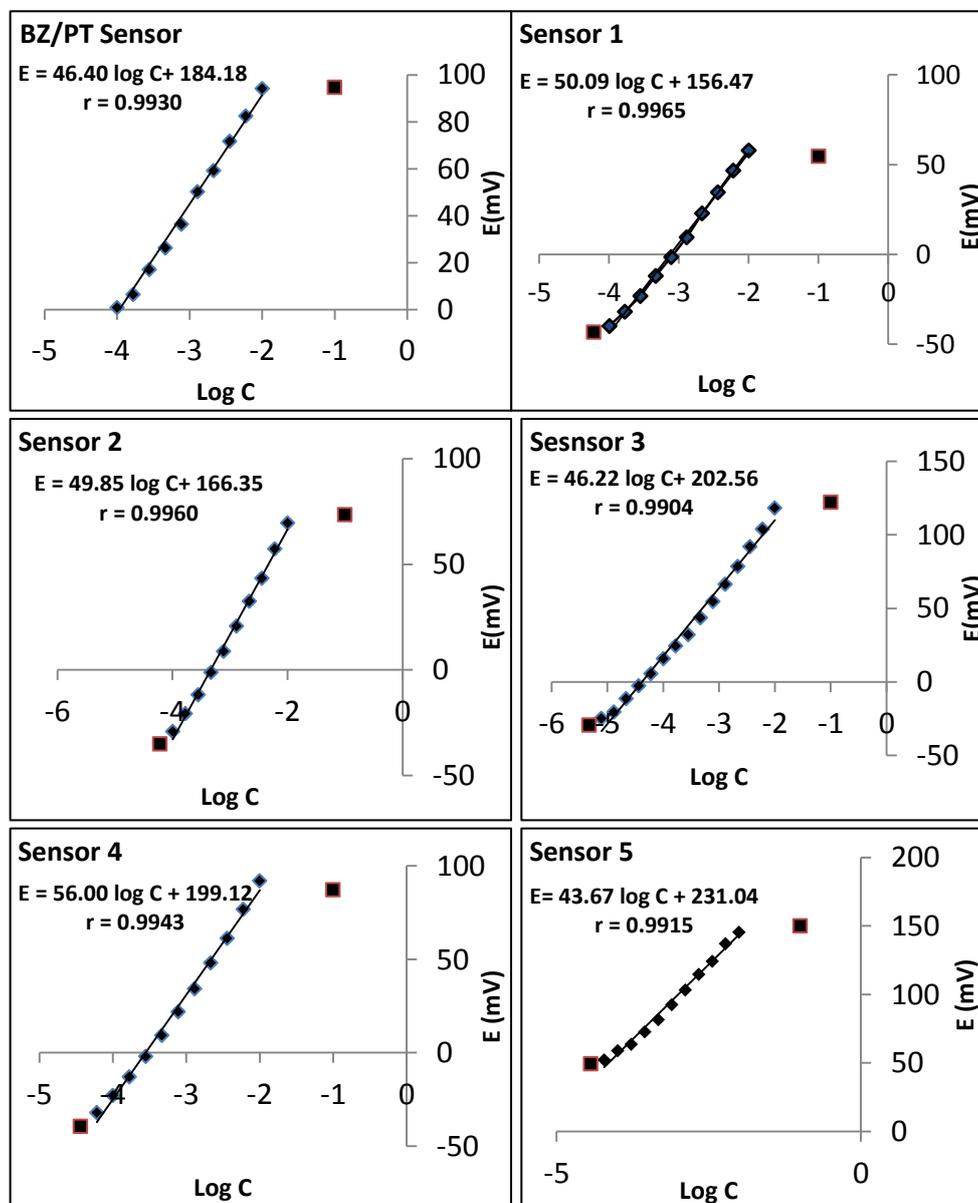
Fig. 2. Potentiometric profiles of the suggested sensors

3.2. PH effect on the electrodes responses

The potentiometric response of the suggested electrodes was found sensitive to pH changes. Figure 3 shows a typical pH response curve for the prepared electrodes, over a pH range of 1–11, where the pH was adjusted with hydrochloric acid and sodium hydroxide solutions. The electrode response was barely affected by the pH change from 3 up to 7. In this pH range BZ is completely ionized, dissociated and sensed and this allowed working in water without using a buffer solution. Below pH 3, the electrodes response increased with the increase in solution acidity as the membrane may extract H^+ leading to a noisy response [27]. The decrease in potential at pH>7.5 was due to the gradual decrease in the concentration of the BZ mono cation due to the formation of the non-protonated amino group.
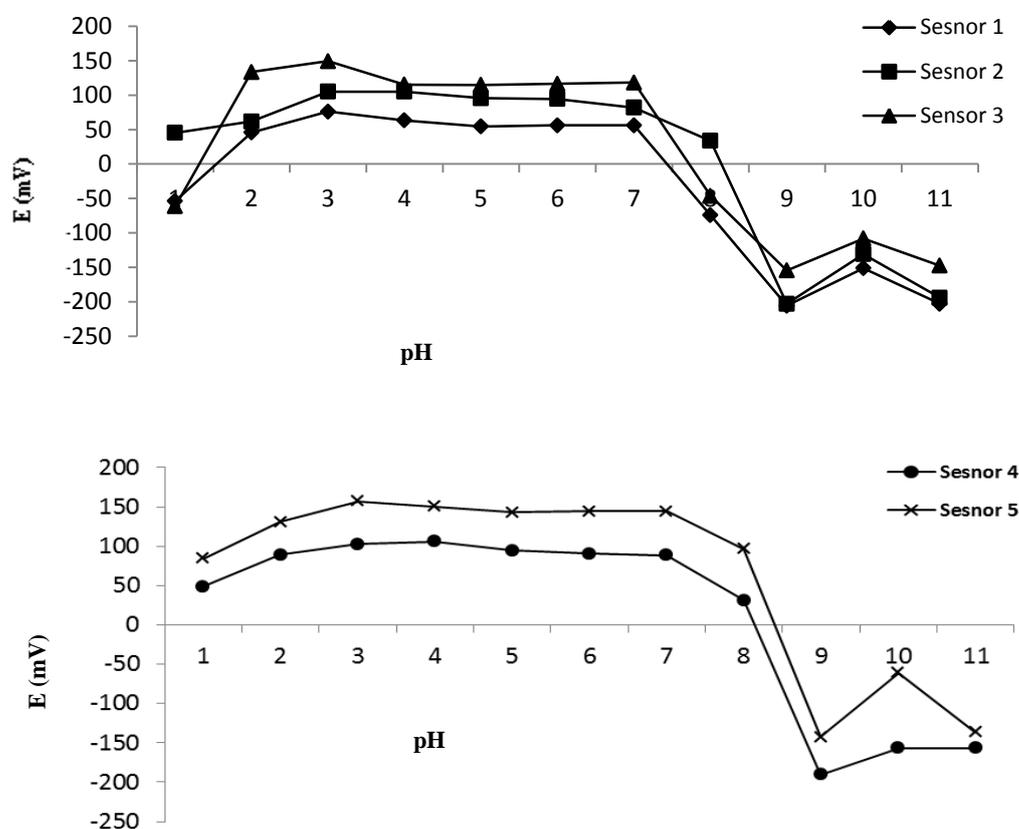

Fig. 3. Effect of pH on the response of the suggested sensors using 1×10^{-2} M Benzydamine HCl solution with pH ranging 1-11, the pH was adjusted with 2 M HCl and NaOH solutions

3.3. Sensors selectivity

The selectivity of an ion-pair based membrane electrode depends on the physico-chemical characteristics of the ion-exchange process at the membrane. For example, sample solution interface, mobility of the respective ions in the membrane and on the hydrophobic

interactions between the primary ion and the organic membrane [28]. Table 3 shows the potentiometric selectivity coefficients of the proposed sensors in the presence of number of organic and inorganic related substances or industrial excipients, in order to study their effect on the assay method.

The selectivity coefficients were determined by the separate solution method and calculated from the rearranged Nicolsky Eisenman equation [22]:

$$-LogK_{AB}^{pot} = \frac{E_1 - E_2}{2.303RT/ZAF}K + \frac{1 - Z_A}{Z_B}Loga_A$$

Where E_1 and E_2 are the potential readings recorded after exposing the electrode to the same concentration of the studied drug and the interferent, respectively. Z_A and Z_B are the charges on BZ and the interfering ion, respectively and 2.303 RT/ZAF represents the slope of the investigated sensor (mV/decade). Results in Table 3 show obviously, that none of the tested interfering species had a significant influence on the potentiometric responses of the electrodes towards BZ.

Table 3. Potentiometric selectivity coefficients (K^{pot}_{BZ}) of Benzydamine HCl for the proposed sensors by separate solution method

Interferent 1×10^{-3} M	Selectivity coefficient*				
	Sensor 1 BZ-TPB-NOPE	**Sensor 2 BZ- PM-DOP**	**Sensor 3 BZ-PT-NOPE**	**Sensor 4 BZ-TpClPB-NOPE**	**Sensor 5 BZ -RN-NOPE**
CaCl₂	1.23×10^{-3}	4.22×10^{-3}	7.04×10^{-4}	3.68×10^{-3}	4.52×10^{-3}
Starch	1.61×10^{-3}	1.64×10^{-3}	5.46×10^{-4}	4.81×10^{-3}	5.57×10^{-3}
NaCl	1.74×10^{-3}	2.13×10^{-3}	4.92×10^{-4}	3.82×10^{-3}	3.62×10^{-3}
Glucose	2.35×10^{-4}	3.89×10^{-4}	1.04×10^{-4}	1.16×10^{-3}	2.22×10^{-3}
Lactose	9.46×10^{-4}	1.74×10^{-3}	3.10×10^{-4}	4.18×10^{-3}	7.03×10^{-3}
KCl	5.55×10^{-4}	1.93×10^{-3}	6.57×10^{-4}	3.01×10^{-3}	5.38×10^{-3}
Urea	5.18×10^{-4}	9.01×10^{-3}	1.60×10^{-4}	9.88×10^{-3}	5.40×10^{-3}

*Average of three determinations

3.4. Potentiometric determination of BZ in different pharmaceutical matrices

The new proposed sensors were successfully applied for BZ determination in its different dosage forms without prior extraction, as none of the commonly used additives show significant interference with the determination of BZ, as shown in Table 4. Results obtained

prove the applicability of the method as demonstrated by the accurate and precise recovery percentages.

The validity of the suggested methods was further verified by applying the standard addition technique on sensor 4 as a representative example. Statistical evaluation of the results of analysis of pure BZ by the proposed electrodes and the official pharmacopeial method showed no significant difference between the proposed and the official method in terms of accuracy and precision as shown in Table 5.

From the obtained validated results, the proposed sensors can be used for in-line determination of BZ containing pharmaceutical formulations, as they are used by just dipping the electrode in the solution to be measured without any prior sample preparation steps. Besides, they offer many advantages, including being portable, economic, highly sensitivite, fast in response and time saving. For the stated advantages, they can be applied for the routine analysis of BZ in quality control laboratories.

Table 4. Determination of Benzydamine HCl in Tantum$^{®}$ different dosage forms by the proposed sensors and application of standard addition technique

Pharmaceutical Dosage Form	Recovery% (Mean ± SD)*				
	Sensor 1 BZ-TPB-NOPE	Sensor 2 BZ-PM-DOP	Sensor 3 BZ-PT-NOPE	Sensor 4 BZ-TpClPB-NOPE	Sensor 5 BZ -RN-NOPE
Tantum$^{®}$ Mouthwash (0.15 g BZ /100 mL).Batch No. 1306203.	99.32±1.06	99.45±0.79	98.05±1.38	99.58±0.84	97.22±1.02
Tantum$^{®}$ Lozenges (3.00 mg BZ/ tablet). Batch No. 1301813	100.68±0.54	98.06±0.72	100.26±1.96	99.11±1.07	97.86±1.35
Tantum$^{®}$ Gel (5.00 g BZ/ 100 g). Batch No. 1300465.	96.38±1.02	97.93±0.52	98.05±0.36	99.11±0.07	97.98±1.85
Recovery % of standard added (Mean ± SD)*^{a}	Tantum$^{®}$ Mouthwash			99.81±1.34	
	Tantum$^{®}$ Lozenges			99.08±2.02	
	Tantum$^{®}$ Gel			100.61±0.44	

** Results of analysis $1×10^{-3}$ M 3 times.
[a]The concentrations of the added standards were $0.50×10^{-3}$, $1.00×10^{-3}$ and $1.50×10^{-3}$ M.

Table 5. Statistical comparison of the results obtained by the proposed sensors and the official BP method for the determination of Benzydamine HCl in pure powder form

	Sensor 1 BZ-TPB-NOPE	Sensor 2 BZ-PM-DOP	Sensor 3 BZ-PT-NOPE	Sensor 4 BZ-TpCIPB-NOPE	Sensor 5 BZ-RN-NOPE	Official method*
Mean	98.67	98.73	98.99	99.29	97.89	98.97
SD	1.48	1.88	1.06	1.54	1.64	1.66
RSD%	1.50	1.90	1.07	1.55	1.68	1.68
n	9.00	9.00	9.00	9.00	9.00	9.00
Variance	2.19	3.53	1.12	2.37	2.69	2.76
F-value	1.26 (3.44)	1.28 (3.44)	2.46 (3.44)	1.16 (3.44)	1.03 (3.44)	-
Student's t-test	0.41 (2.12)	0.29 (2.12)	0.03 (2.12)	0.42 (2.12)	1.39 (2.12)	-

*The official assay for determination of BZ by non-aqueous titration and determining the end point potentiometrically [1].

- The figures between parenthesis are the corresponding theoretical values of t and F at Probability=0.05.

4. CONCLUSION

The new sensors described for the determination of BZ proved to be sufficiently simple and selective for the quantitative determination of BZ in pure form and pharmaceutical formulation especially sensor 4. According to the results described before, the utility of K-TpCIPB as a cationic exchanger in the development of sensor 4 gives better results than other cationic exchangers as it increased the membrane sensitivity and selectivity. It showed the best Nernestian slope as well as the fastest response. Sensor 3 had the best sensitivity according to the obtained results. The response time was more or less instantaneous (up to 15 seconds for electrode 4), while those of 1, 2&5, were 25 seconds and it was 45 seconds for sensor 3. From applicability point of view, sensor 4 showed the most stable responses in all BZ different pharmaceutical dosage forms. Accuracy of applying the proposed method for determination of BZ in its pharmaceutical formulations was assessed by applying the standard addition technique.

The proposed sensors offer advantages of being economic, portable and the elimination of drug pre-treatment or separation steps. Therefore, they can be the mean of choice for in-line system determination of BZ and for routine analysis in quality-control laboratories.

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