



ISSN: 2231-3354  
 Received: 12-07-2011  
 Revised on: 16-07-2011  
 Accepted: 19-07-2011

## Polymeric Matrix Membrane Sensors for Stability-Indicating Potentiometric Determination of Bambuterol Hydrochloride and Its Metabolite Terbutaline

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### ABSTRACT

The construction and electrochemical response characteristics of polyvinyl chloride (PVC) membrane sensors for determination of bambuterol hydrochloride (BH) in presence of its degradation products are described. The sensors are based on the ion association complexes of BH cation with sodium tetraphenyl borate (BH-TPB) [sensor 1] or ammonium reineckate (BH-RNC) [sensor 2] counter anions as ion exchange sites in PVC matrix. Fast and stable Nernstian responses in the range  $10^{-5}$ - $10^{-2}$  M for BH over the pH range 5–8 revealed the performance characteristics of these electrodes, which were evaluated according to International Union of Pure and Applied Chemistry recommendations. The two proposed sensors are used for determination of BH, in pure form, in presence of its degradation product and in pharmaceutical formulations. Validation of the method according to the quality assurance standards showed suitability of the proposed electrodes for use in the quality control assessment of BH. The recoveries for determination of BH by the two proposed selective electrodes were  $100.07 \pm 1.008$ ,  $99.93 \pm 0.920$ , for sensor 1 and sensor 2, respectively. Statistical comparison between the results obtained by this method and the official non-a method of BH was done, and no significant difference was found.

**Key words:** Bambuterol hydrochloride, terbutaline, ion selective electrodes, potentiometry, PVC membranes electrodes, sodium tetraphenyl borate, ammonium reineckate.

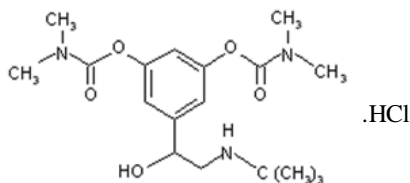
### INTRODUCTION

Bambuterol hydrochloride (BH; Figure 1), (RS)-5-(2-tert-butylamino-1-hydroxyethyl)-m-phenylene bis(dimethylcarbamate) hydrochloride is a direct acting sympathomimetic with predominantly  $\beta_2$ -adrenergic activity ( $\beta_2$ -agonist) (Sweetman et al., 2002). It is an ester prodrug of  $\beta_2$  adrenergic agonist terbutaline (O'Neil et al., 2001). It is used for the prophylaxis and treatment of chronic asthma and chronic bronchitis in pediatrics. Bambuterol hydrochloride is official in BP Pharmacopoeia and determined by non aqueous titration method (B.P., 2001). Different HPLC methods have been reported for the estimation of BH in pharmaceutical dosage form (Zhang., 2001; Bartolincic et al., 2005; Wannerberg and Persson., 1988). The drug has been also estimated by solid-state NMR spectroscopy (Harris et al., 2005). The cationic properties of BH suggested the use of anionic exchangers, such as tetraphenyl borate, and ammonium reineckate as counter ion association complexes. These complexes are embedded in polyvinyl chloride (PVC) matrix membranes plasticized with suitable solvent mediators. The high selectivity of these electrodes imparts a great advantage over other techniques (Conway, 1995). Analytes in colored, turbid, and viscous samples can be determined accurately. They show rapid response to changes in the

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concentration. Furthermore, they may be used for measurement over a wide concentration range. Ion selective electrodes (ISEs) are generally tolerant of small changes in pH. A further advantage is that they are relatively simple and cheap to develop, set up, and run. Moreover, the chemical design of the electrodes has been developed to give superior selectivity and response (Conway, 1995).



**Fig 1.** Structure of bambuterol hydrochloride; molecular formula =  $C_{18}H_{29}N_3O_5 \cdot HCl$ , molecular weight = 403.91

Consequently, ISEs have been widely used in recent years in the analysis of drugs in pure powder form and in their pharmaceutical formulations (El-Saharty et al., 2007; Ibrahim et al., 2007; Sayed et al., 2005; Arvand, et al., 2003; Susan et al., 2007; Vissers et al., 2006). Performance characteristics of these electrodes reveal low detection limit, high sensitivity, good selectivity, fast response, long life span, and applicability for accurate determination of BH in dosage forms, and in the presence of its degradation product.

## EXPERIMENTAL

### Apparatus

(a) Digital ion analyzer.—Model 3330 with Ag/AgCl double junction reference electrode No. 924017-LO3-Q11C (Jenway, Essex, UK).

(b) pH glass electrode.—No. 924005-BO3-Q11C (Jenway).

(c) Magnetic stirrer.—Rx510S (Bandelin Sonorox, Budapest, Hungary).

(d) Infrared (IR) spectrometer.—Vector 22 (Bruker Optics, Ettlingen, Germany).

(e) Mass spectrometer.—Hewlett Packard Model 5988 GC/mass spectrometry instrument (Agilent Technologies, Wilmington, DE).

### Reference Samples

Pure sample was kindly supplied by Alborg Pharmaceutical industry, Alexandria, Egypt.; it was assayed for its purity according to a pharmacopoeial method (B.P., 2001) and found to contain  $100.15 \pm 1.258\%$ .

### Pharmaceutical Formulations

(a) Probric syrup.—Manufactured by Borg Pharmaceutical industry, Batch No. 026028. labelled to contain 10 mg BH/10 mL syrup.

(b) Bamedil 10 tablets.—Manufactured by Western Pharmaceutical industry, Batch No. 09018, labelled to contain 10 mg BH/tablet.

(c) Lela Free 20 tablets.—Manufactured by Multiapex Pharma, (Badr city, Egypt), Batch No. MT1070409, labelled to contain 20 mg BH/tablet.

### Degraded Samples

500 mg of BH was refluxed with 50 mL of 1 M HCl solution for 3 hours. The solution was concentrated to a small volume and extracted with methanol. The methanolic extract was evaporated under vacuum. The structure of the isolated degradation product was elucidated using IR, and MS.

### Reagents

All chemicals and solvents used were of analytical grade (water was doubly distilled). All chemicals and solvents were handled in a fume hood wearing gloves and masks, and measurement of the solvents was done using pipettes with the aid of pipet filler.

(a) Tetrahydrofuran (THF).—BDH Ltd (Poole, UK).

(b) Ammonium Reineckate (Sigma- Aldrich) freshly prepared, aqueous saturated solution.

(c) Sodium tetraphenyl borate (Sigma- Aldrich) freshly prepared, aqueous saturated solution.

(d) PVC.—BDH Ltd.

(e) Phosphate buffer (pH 7); was prepared according to BP (B.P., 2001).

(f) Dibutylsebacate (DBS).—Sigma-Aldrich.

(g) Sodium hydroxide.—Prolabo (VWR International).

(h) Potassium chloride.—Prolabo (VWR International, West Chester, PA).

### Standard Solutions

(a) BH stock solution ( $1 \times 10^{-1}$  M)—Prepared by dissolving 1.01 g in 25 mL of double distilled water.

(b) BH working solutions ( $10^{-6}$ - $10^{-2}$  M) —Prepared by proper dilution from its stock solution using distilled water.

(c) Degradation product solution ( $1 \times 10^{-3}$  M) — Prepared by dissolving 56.25 mg in 25 mL of double distilled water.

### Precipitation-Based Technique for the Preparation of BH-TPB and BH-RNC Ion Exchangers (Electrodes 1 and 2, respectively)

BH-TPB and BH-RNC ion pair complexes were prepared by mixing 10 mL  $10^{-2}$  M aqueous solution of BH with 10 mL saturated aqueous solution of TPB for preparation of electrode 1, or with 10 mL saturated aqueous solution of RNC solution for preparation of electrode 2.

The resulting precipitates were filtered using Whatman (Florham Park, NJ) No. 42 paper, washed with cold water, dried at room temperature (about  $20^\circ\text{C}$ ), and ground to a fine powder. Elemental analysis of the formed complexes confirmed a drug: ion exchanger ratio of 1:1 in the cases of electrodes 1 and 2.

A portion (10 mg) of BH ion exchanger was thoroughly mixed with 0.19 g PVC and 0.35 g DBS in a glass petri dish (5 cm diameter), then dissolved in 5 mL THF. The petri dish was covered with filter paper and left to stand overnight to allow solvent

evaporation at room temperature. Master membranes with a thickness of 0.1 mm were obtained and used for the construction of the sensors as previously described.

Equal volumes of  $1 \times 10^{-2}$  M BH and  $1 \times 10^{-2}$  M KCl were mixed, and these solutions used as internal reference solutions.

Ag/AgCl wires (1 mm diameter) were immersed in the internal reference solutions as internal reference electrodes.

The electrodes were conditioned by soaking in  $1 \times 10^{-2}$  M BH aqueous solution for 1 day and stored in the same solution when not in use. The conditioned sensors were calibrated by separately transferring 20 mL aliquots of solutions covering the concentration range of  $1 \times 10^{-6}$  to  $1 \times 10^{-2}$  M BH into a series of 100 mL beakers followed by insertion of the corresponding BH-PVC membrane sensor in conjunction with a double junction Ag/AgCl reference electrode.

The electrodes were stored in distilled water between measurements. The electrode potential was plotted vs each negative logarithmic concentration of BH. The calibration plots obtained were used for subsequent measurements of unknown samples.

#### Direct Potentiometric Determination of BH in Pure Sample

The electrodes were conditioned and calibrated as mentioned in the previous subsection starting from "The electrodes were conditioned with a double junction Ag/AgCl reference electrode." The electrodes were stored in distilled water between measurements. The electrode potential was plotted vs each negative logarithmic concentration of drug. The calibration plots obtained were used for subsequent measurements of unknown samples.

#### Analysis of Laboratory Prepared Mixtures

In a series of 25 mL volumetric flasks, 10 mL BH solution ( $10^{-3}$  M) was quantitatively transferred. Aliquots from the corresponding degradation product solution ( $10^{-3}$  M) were added, then the volume was completed with water to prepare mixtures containing 0.5:1, 1:0.5, 1:1, 1:2, and 4:1BH:degradation product, respectively.

#### Direct Potentiometric Determination of BH in Probric Syrup, Bamedil and Lela Free tablets

The content of the Probric syrup was shaken well, Twenty Bamedil tablets and 10 Lela Free tablets were accurately weighed and powdered, separately. Then different amounts equivalent to 20.2 mg BH from Probric syrup, 10.1 mg BH from Bamedil tablets and Lela Free tablets were accurately transferred to three separate 25 mL volumetric flasks and diluted to the mark to prepare  $1 \times 10^{-3}$  M aqueous solutions of BH. The potential readings produced by immersing the prepared electrodes in conjunction with the double junction Ag/AgCl reference electrode in the prepared solutions were recorded and compared with the calibration plots.

## RESULTS AND DISCUSSION

Complete degradation of BH using 1 M HCl for 3 hours, where hydrolysis of the two ester linkages to give its active

degradation product (terbutaline), (Figure 2). Its structure was elucidated by IR, MS, (Figures 3-5). The IR spectrum of intact bambuterol hydrochloride revealed carbonyl stretching band at  $1689\text{cm}^{-1}$ , Figure (3) which disappeared in the IR spectrum of terbutaline. Also a broad band of alcoholic OH stretching vibration at  $3394\text{cm}^{-1}$  confirmed the acidic hydrolysis at the two ester linkages, Figure (4). These results were confirmed using MS of degradation product which revealed molecular ion peak is at 225 which is equivalent to its molecular weight (Figure 5).

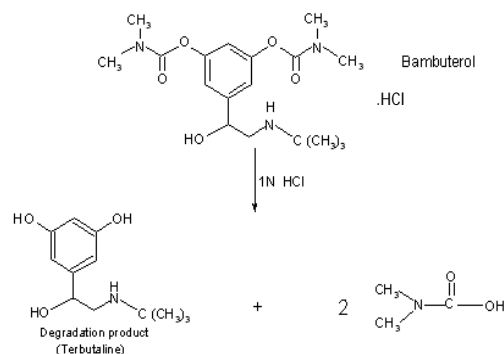


Fig 2. Suggested scheme for the degradation of bambuterol hydrochloride.

ISEs contain membranes having a selective response for a particular ion (Ma. and Hassan., 1982). Selective membranes in ISEs have shown both ion exchange and perm-selectivity properties for the sensor ions. The present work originates from the fact that BH can behave as cation; this fact suggests the use of ion exchangers of anionic types. It has been found that TPB, and RNC were optimum anionic exchangers for the studied drugs because of their low solubility product and suitable grain size (Hassan et al., 2003; El-Saharty et al., 2006). BH react with TPB, and RNC to form water-insoluble 1:1 ion association complexes as confirmed by elemental analysis. The complexes were prepared, characterized, and incorporated with a suitable solvent mediator in PVC matrix membranes. Plastic membranes prepared by using a casting solution of composition 0.1:0.19:0.35 % (w/w) ion pair complex, PVC, and DBS, respectively, were used for constructing the sensors, and this composition was an optimum membrane condition (Hassan et al., 2003).

#### Sensor Fabrication

The electrochemical performance characteristics of the sensors were systematically evaluated according to International Union of Pure and Applied Chemistry (IUPAC) recommendations (Pure Appl. Chem., 2000). The results are given in Table 1.

In the present study, DBS was found to be the most suitable plasticizers for sensors 1 and 2.

It plasticized the membranes, dissolved the ion association complexes, and adjusted the selectivity of the membranes; therefore, it gave the optimal results. The membrane constituents were dissolved in THF, which was slowly evaporated at room temperature leading to membrane formation.

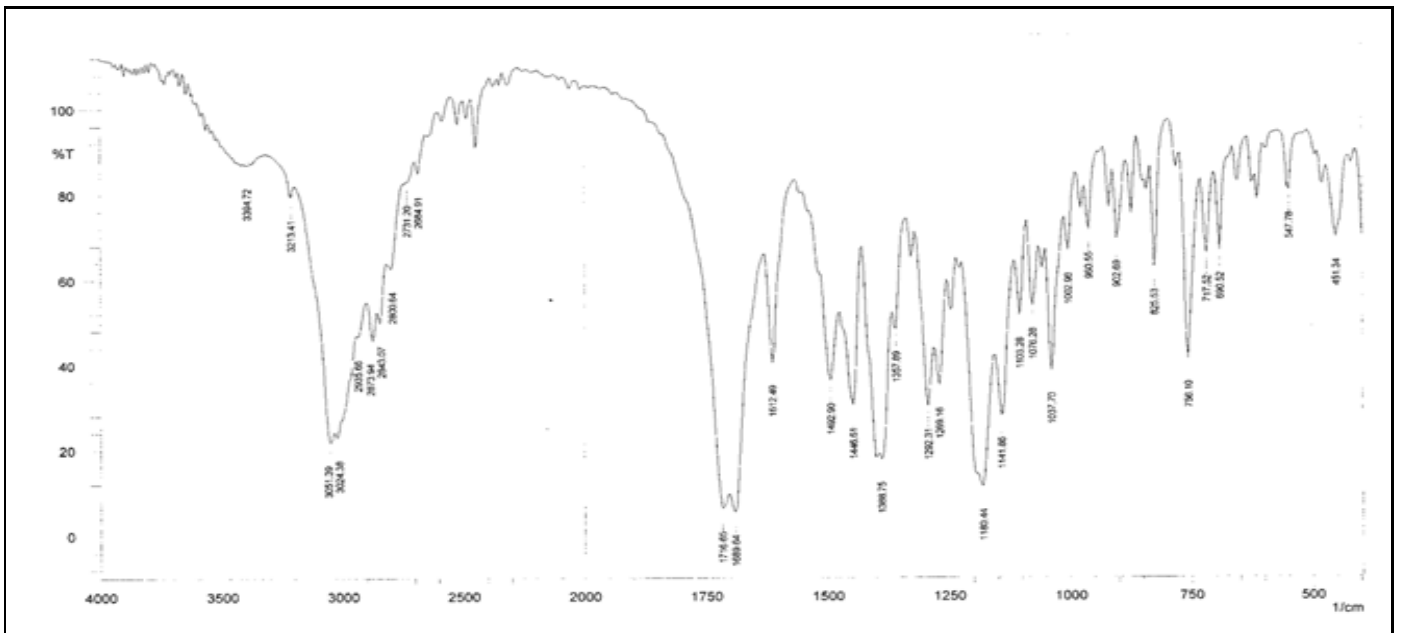


Fig 3. IR spectrum of intact bambuterol hydrochloride.

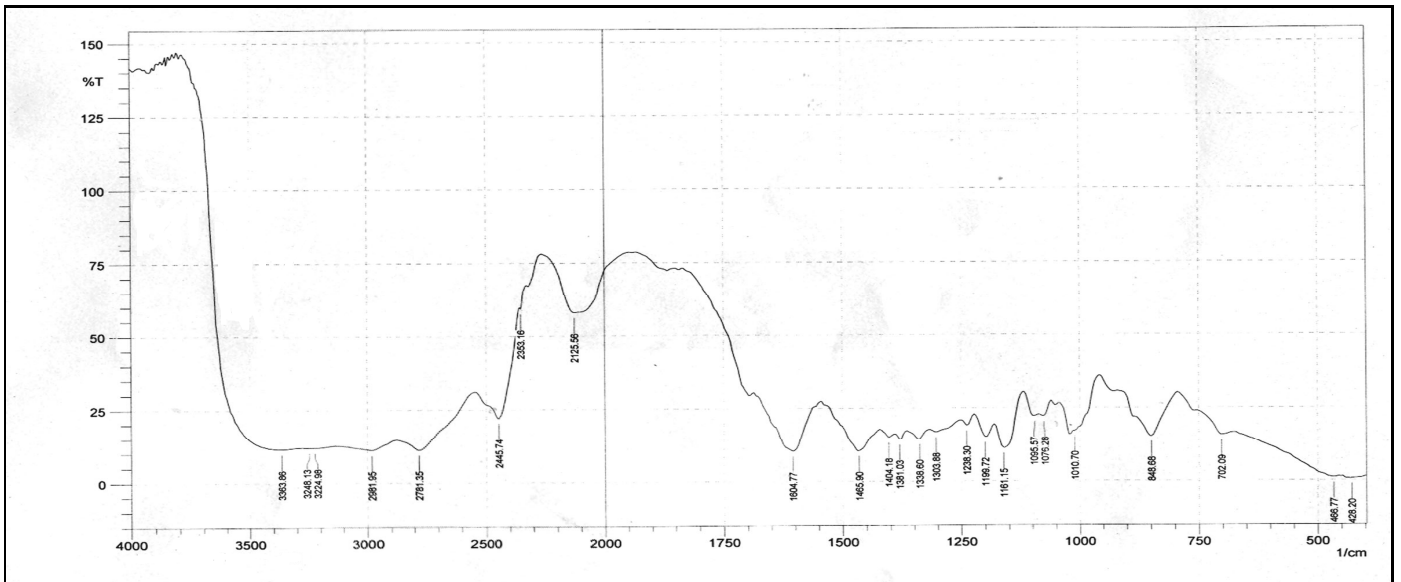


Fig 4. IR spectrum of bambuterol hydrochloride degradation product.

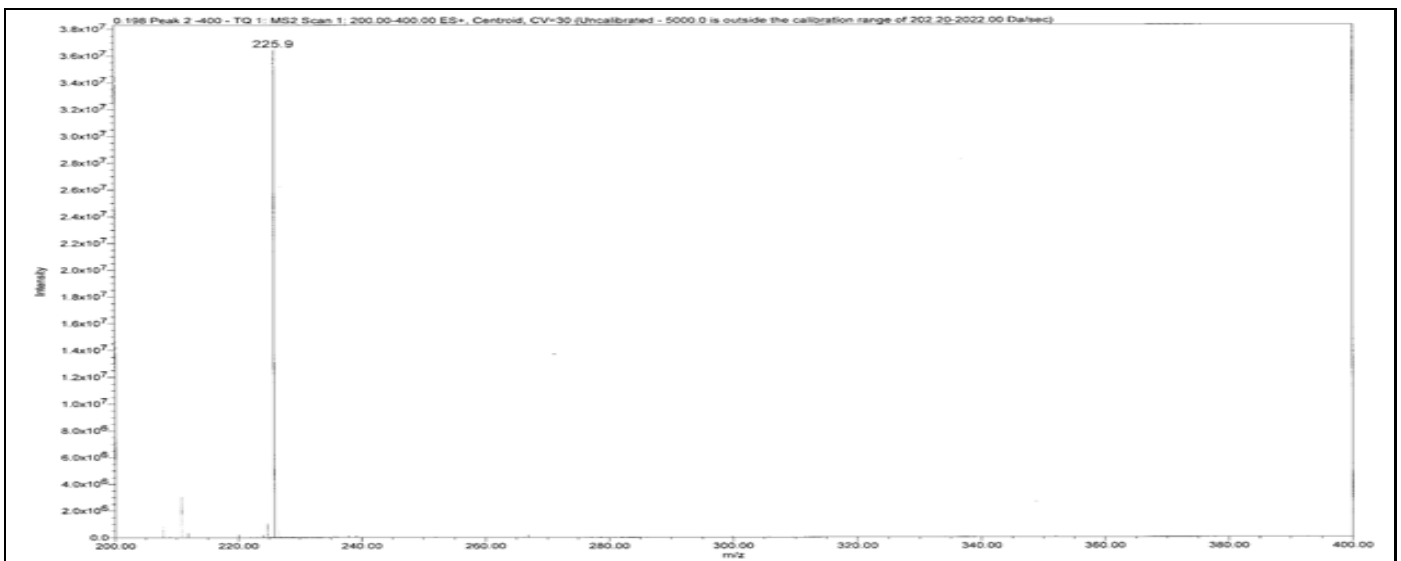


Fig 5. Mass spectrum of bambuterol hydrochloride degradation product.

### Sensor Calibration and Response Time

The potential displayed by the two proposed electrodes for measurements of the standard solutions of BH in the same day and from day-to-day did not vary by more than  $\pm 1$  mV. Calibration slopes did not change by more than  $\pm 1$  mV/decade concentration over a period of 4 weeks for two electrodes (Table 1).

**Table 1.** Electrochemical response characteristics of the two investigated bambuterol hydrochloride electrodes.

Parameter	BH-TPB	BH-RNC
Slope (mV / decade)	-54.1	-51.7
Intercept (mV)	185.60	172.20
LOD ( M )*	$6.2 \times 10^{-6}$	$6.1 \times 10^{-6}$
Response Time (Sec.)	15	15
Working pH Range	5-8	5-8
Concentration Range (M)	$10^{-5}$ - $10^{-2}$	$10^{-5}$ - $10^{-2}$
Stability (days )	30	30
Accuracy (mean $\pm$ S.D.)	$100.07 \pm 1.008$	$99.93 \pm 0.920$
Correlation coefficient	0.9997	0.9997

M: Molar solution

The dynamic response times for the electrodes to reach values within  $\pm 1$  mV of the final equilibrium potential after increasing the drug concentration 10-fold were found to be 15 s for the two electrodes (Table 1). The slopes of the calibration plots were -54.1, and -51.7 mV/concentration decade for BH-TPB (electrode 1), BH-RNC (electrode 2), respectively (Table 1; Figures 6 and 7). Slope values of two sensors were about 60, which is a typical value for monovalent substances; BH behaved as monovalent cation. Figures 6 and 7 show a decrease in negative potential as the concentration increases, due to the decrease in negative charge on the membrane. The response characteristics of the two electrodes are summarized in Table 1.

Deviation from the ideal Nernstian slope (60 mV/decade) for two sensors arise from the fact that the electrodes respond to the activities of the drugs, rather than their concentrations. The investigated electrodes exhibit fast response time (15 s) and fair stability (4 weeks). The fabricated ISEs gave a Nernstian response within the  $1 \times 10^{-5}$ – $1 \times 10^{-2}$  M concentration range (Table 1).

The official method of BH (B.P., 2001) was non aqueous titration in which the drug was dissolved in alcohol and titrated with 0.1 M sodium hydroxide; the end point was determined potentiometrically. Results obtained by the proposed methods for the determination of pure samples of the drugs were statistically compared to those obtained by the official method (B.P., 2001), and no significant differences were observed (Table 2).

**Table 2.** Statistical comparison for the results obtained by the proposed electrodes and the official method for the analysis of BH in pure powder form.

Item	BH-TPB	BH-RNC	Official method*
Mean	100.07	99.93	100.15
S.D.	1.008	0.920	1.258
Variance	1.016	0.846	1.583
n	4	4	5
Student's t-test	0.111 (2.365)**	0.311 (2.365)**	
F value	1.558 (9.120)**	1.871 (9.120)**	

\*\* The values in parenthesis are the corresponding tabulated t and F values at P=0.05.

### Sensor pH

Studies were carried out to determine the optimum pH range. The effect of pH on the response of the two investigated electrodes was evaluated using phosphate buffers over the pH range from 2–11 by immersing the two electrodes in  $1 \times 10^{-3}$ , and  $1 \times 10^{-4}$  solutions of BH. pH was gradually increased or decreased by adding drops of 1 M NaOH or 1 M HCl solutions, respectively. It is apparent from Figures 8–9 that the responses were fairly constant over pH range 5–8 for the two electrodes

Above and below these ranges, the potentials displayed by the electrodes were noisy. Based on the above considerations, BH was dissolved in phosphate buffer (pH 7).

### Sensor Selectivity

The influence of various basic substances (i.e., amino compounds of biological interest, such as urea, hydroxylamine, and degradation product) and a number of pharmaceutical additives commonly used in drug formulations (e.g., starch, magnesium chloride, methylcellulose, and lactose) on the response of sensors was investigated by measuring the potentiometric influence of some potentially interfering species. The selectivity coefficients were calculated by the separate solution method (Pure Appl. Chem., 2000), where potentials were measured for  $1 \times 10^{-3}$  M aqueous drug solution, then for  $1 \times 10^{-3}$  M aqueous interferent solution separately. The selectivity coefficients were calculated from the following equation (Ma. and Hassan., 1982).

$$-\log(K^{\text{pot}}_{\text{interferent}}) = E_1 - E_2/S$$

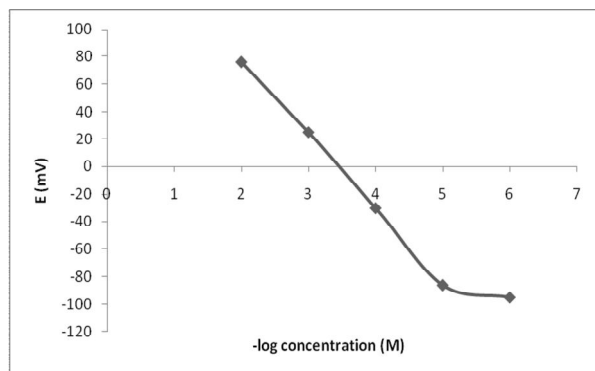
where  $E_1$  and  $E_2$  are the potential readings recorded after exposing the electrode to the same concentration of the studied drug and the interferent, respectively, and S is the slope of the calibration curve. The results in Table 3 reveal that the investigated sensors have reasonable selectivity.

**Table 3.** Potentiometric selectivity coefficients( $K^{\text{pot}}_{\text{BH},1}$ ) of the two proposed electrodes.

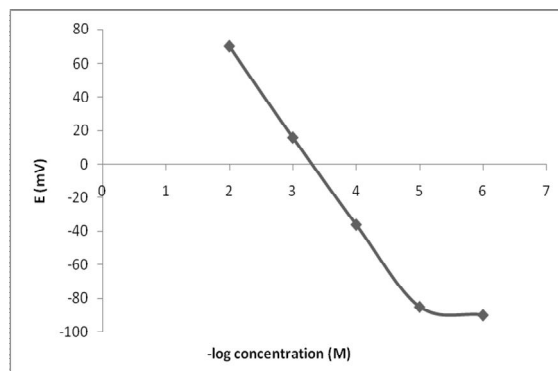
Interferent**	Selectivity coefficient*	
	BH-TPB	BH-RNC
Degradate	$2.1 \times 10^{-3}$	$2.2 \times 10^{-3}$
NaCl	$9.1 \times 10^{-3}$	$3.9 \times 10^{-3}$
KCl	$6.5 \times 10^{-3}$	$3.5 \times 10^{-3}$
NH <sub>4</sub> Cl	$5.3 \times 10^{-3}$	$2.2 \times 10^{-3}$
CaCl <sub>2</sub>	$3.2 \times 10^{-3}$	$3.2 \times 10^{-4}$
MgCl <sub>2</sub>	$1.2 \times 10^{-3}$	$2.2 \times 10^{-4}$
Glucose	$1.6 \times 10^{-3}$	$1.9 \times 10^{-3}$
Lactose	$1.5 \times 10^{-3}$	$2.1 \times 10^{-3}$
Starch	$8.1 \times 10^{-4}$	$6.3 \times 10^{-4}$
Urea	$6.2 \times 10^{-4}$	$4.8 \times 10^{-4}$

\*Average of 3 different determinations. \*\*All interferents are in the form of  $1 \times 10^{-3}$  M solution.

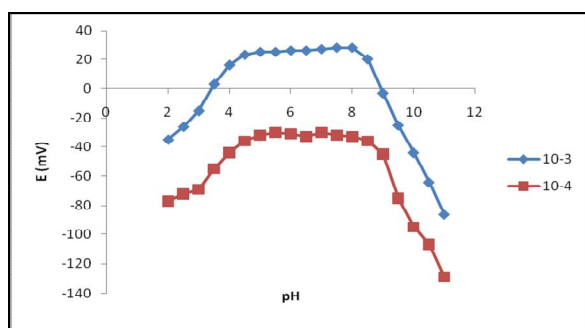
The specificity of the method was proved by the analysis of laboratory mixtures containing different percentages of the degradation product and satisfactory results were obtained, (Table 4).



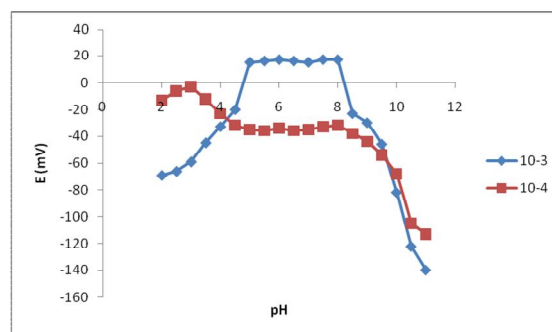
**Fig 6.** Profile of the potential in mV versus  $-\log$  concentration (M) of BH-TPB = bambuterol hydrochloride – sodium tetraphenyl borate (electrode 1).



**Fig 7.** Profile of the potential in mV versus  $-\log$  concentration (M) of BH-RNC = bambuterol hydrochloride – ammonium reineckate (electrode 2).



**Fig 8.** Effect of pH on the response of bambuterol hydrochloride–sodium tetraphenyl borate (electrode 1).



**Fig 9.** Effect of pH on the response of bambuterol hydrochloride–ammonium reineckate (electrode 2).

**Table 4.** Determination of bambuterol hydrochloride in laboratory prepared mixtures containing different ratios of bambuterol hydrochloride and its degradation product by the proposed electrodes.

** Ratio drug : degradate	Drug recovery* %	
	BH-TPB	BH-RNC
0.5:1	100.75	100.89
1:0.5	101.51	101.61
1:1	101.01	101.05
1:2	98.92	100.17
4:1	100.71	100.91
Mean	100.58	100.93
S.D.	0.981	0.514
R.S.D.%	0.975	0.509

\*Average of 3 different determinations.

\*\*  $1 \times 10^{-3}$  M phosphate buffer of pH 7 (BH-TPB, BH-RNC)

Table 5 shows that the proposed sensors were successfully used for the determination of BH in Probric Syrup, Bamedil and Lela Free Tablets without the need of prior separation of the drugs from excipients and additives.

Linearity was assessed by the determination of the same concentration range as the calibration plot. The mean accuracies are given in Table 1.

Validation of the proposed potentiometric method for determining BH was made by measuring range, LOD, accuracy, precision, linearity, selectivity, and sensitivity (slope). Results obtained are depicted in Table 1. These data render the proposed method applicable for the quality control of the drug formulations.

**Table 5.** Determination of bambuterol hydrochloride in certain pharmaceutical formulations by the proposed electrodes.

Pharmaceutical Formulations	Recovery % $\pm$ S.D.*	
	BH-TPB	BH-RNC
Probric syrup Batch No. 026028	99.32 $\pm$ 0.596	99.58 $\pm$ 0.719
Bamedil 10 tablets Batch No. 09018	100.27 $\pm$ 0.328	99.87 $\pm$ 0.370
Lela Free 20 tablets Batch No.MT1070409	99.97 $\pm$ 0.420	99.79 $\pm$ 0.980

\*Average of three different determinations.

## CONCLUSIONS

The use of ISEs in analytical chemistry has several advantages over other techniques. These advantages include the ease of construction, rapid manipulation, low cost, fast response, wide concentration range, and applicability to turbid and colored solutions (Conway, 1995). Consequently, ISEs are currently widely used to solve some analytical problems, such as determination of drugs in the presence of their degradation products (Hassan et al., 1998; Hassan et al., 1996).

The electrodes are simple and sufficiently specific for quantitative determination of the studied drug. BH is determined in pure powder and in dosage forms. The sensors offer the advantages of fast response, reasonable selectivity, elimination of drug pretreatment or separation steps, and low cost. Further advantages offered by using the TPB-, and RNC- based membrane sensors are

a low detection limit extended working concentration range, wide pH range, stability, and specificity. These are probably due to the extremely poor solubility and low leachability of TPB, and RNC drug exchangers from the membrane of the sensors.

The proposed method is precise, accurate, and simple. It is more rapid and does not require expensive and sophisticated apparatus or expensive and special grade solvents. Also, it is more sensitive and selective if compared with the official titrimetric methods of the drug. So, the proposed method can be used for the routine analysis of BH, either in pure form, in pharmaceutical formulations, or in the presence of its degradation product.

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