ISSN : 0974-7419 Volume 16 Issue 2

Analytical CHEMISTRY

An Indian Journal

Full Paper

ACAIJ, 16(2) 2016 [080-089]

Application of membrane selective electrodes for stability indicating determination of bambuterol HCL in presence of its metabolite terbutaline in its pharmaceutical dosage forms and in plasma

Khadiga M.Kelani[1], Wafaa E.Hassan[2], Sherief M.Eid[3]*, Abdalla A.Shalaby[4]

[1]Professor of Analytical Chemistry Department, Faculty of Pharmacy, Cairo University, Kasr El-Aini, Cairo, Postal code 11562, (EGYPT)

[2]Assistant Professor of Analytical Chemistry Department, Faculty of Pharmacy, Zagazig University, Zagazig City, Postal code 44519, (EGYPTP)

[3]Assistant lecturer of Analytical Chemistry Department, Faculty of Pharmacy, October 6 University, 6th October City, Postal code 11787, (EGYPT)

[4]Professor of Analytical Chemistry Department, Faculty of Pharmacy, Zagazig University, Zagazig City, Postal code 44519, (EGYPT)

E-mail: sherief055@yahoo.com; sherief055@gmail.com

ABSTRACT

Two polyvinyl chloride (PVC) membrane sensors for the determination and quantification of Bambuterol HCL (BH) in presence of its acid degradation product (Terbutaline) were described and characterized. The sensors are based on the use of ion association complexes of BH cation with Phosphotungestic acid (PTA) counter anions as ion exchange sites in the PVC matrix(BH-PTA sensor 1) or β- Cyclodextrin (β-CD) to form inclusion complex (BH-β-CD sensor 2). The performance characteristics of the sensors were evaluated according to IUPAC recommendations, reveal a fast, stable and linear response over the concentration range 10^{-5}- 10^{-2} M for BH.The recoveries for determination of BH by the two proposed selective electrodes were 99.96 ± 0.694, 99.98 ± 0.387, for sensor 1 and sensor 2, respectively. Statistical comparison between the results obtained by this method and the official Pharmacopoeial method of BH was done, and no significant difference was found.

INTRODUCTION

Bambuterol hydrochloride [BH] (RS)-5-(2-tert-butylamino-1 hydroxyethyl)-m-phenylene bis (dimethyl carbamate) hydrochloride[1], is an orally effective long acting sympathomimetic drug with predominantly adrenergic activity (B2-agonist)[2]. It is an ester prodrug of B2 adrenergic agonist terbutaline[3]. It is widely used for prophylaxis and treatment of asthma and chronic obstructive pulmonary disease in clinic[2, 4, 5]. BH is ofûcial in British Pharmacopoeia and determined ofûcially by potentiometric titration[6]. Different HPLC methods have been reported for the estimation of BH in different pharmaceutical dosage forms such as GC-MS[7-9], solid-state NMR spectroscopy[10] and spectrophotometric charge transfer complexometry[11].

The development and application of ionselective electrodes continue to be of interest for pharmaceutical analysis because these sensors offer the advantages of simple design and operation, reasonable selectivity, fast response, low cost, wide pH working range, broad concentration range, and applicability to turbid and colored solutions[12]. Conse-

quently, ISEs have been widely used in recent years in the analysis of drugs in pure powder form and in their pharmaceutical formulations[13, 16].

In the present work, the cationic properties of BH suggests its use for formation of two ion-selective membrane sensors based on the use of the ion association complexes of this drugs with phosphotungestic acid (PTA) as a good anionic exchanger (sensor 1) and β- Cyclodextrin (β-CD) to form inclusion complex (sensor 2). The high lipophilicity and remarkable stability of these complexes suggested their selective use as electro-active materials in PVC matrix membrane sensors for the determination of BH in the presence of its acid degradation product 'Terbutaline', excipients, and plasma without the need of preliminary extraction and separation steps. Moreover, they offer a highly sensitive, selective, and convenient technique for the determination of BH in either pure forms or in pharmaceutical preparations.

EXPERIMENTAL

Instruments

(a) Hanna (Model 211) pH /mV meterwith Ag/AgCl double junction reference electrode.
(b) Single junction calomel reference electrode (Model HI 5412).
(c) WPA pH combined glass electrode Model CD 740.
(d) Bandelin sonorex, RK 510 S, magnetic stirrer.
(e) Silver wire (3 mm diameter) immersed in the internal solutions.
(f) Shimadzu FT-IR spectrophotometer (IRAffinity-1) (Japan), connected to IBM-PC computer loaded with IRsolution software version 1.60 with laser jet printer.
(g) Hewlett Packard Mass spectrometer model 5988 GC/MS instrument (Agilent Technologies, Wilmington, DE)

Reagents

All chemicals were of analytical grades, handled in a fume hood wearing gloves and masks, and measurement of the solvents was done using pipettes with the aid of pipette filler and bidistilled water was used. Tetrahydrofuran (THF) 99% (Lab Scan), High molecular weight (10000) polyvinyl chloride (PVC) powder (BDH Ltd), dioctylphthalate (DOP) plasticizer were obtained from (Sigma-Aldrich), Phosphotungestic acid (PTA), β-Cyclodextrin 95% and Di-n-butyl sebacate 94% were obtained from (Sigma). Phosphate buffer pH 4.7 was prepared according to BP.

Samples

Reference sample

BH was kindly supplied from Astra Zeneca, Egypt. The purity of the samples were 99.00% conûrmed by HPLC method[17].

Market samples

Bambec® tablets, product of AstraZeneca Co., Egypt, Bach no. 120111, labeled to contain 10 mg BH per tablet.

Bambedil® tablets, product of western pharmaceutical industries Co., Bach no. 12337, labeled to contain 10 mg BH per tablet.

Lelafree® tablets, product of Multiapex Pharma, Co., Egypt), Bach no. MT0280113, labeled to contain 10 mg BH per tablet.

Degrade sample

Dissolve accurately weighed 500 mg of BH in 20 ml water and reflux with 50 ml 1 M HCL for about 4 hours at 100 °C. The solution was concentrated to a small volume and extracted with methanol. The methanolic extract was evaporated under vacuum. Complete degradation was confirmed by spotting on TLC plates usingethyl acetate: methanol: ammonium hydroxide (7: 3: 0.01 by volume) as a developing system. The spots were dried and visualized under UV light. The structure of the isolated degradation product was elucidated using IR, and MS.

Prepared solutions

Stock solution of BH (10^{-2} M)

BH stock solution (10^{-2} M) in either water or phosphate buffer pH 4.7 were prepared by transferring 0.4039 gm of BH into two separate 100-ml measuring flasks. To each flask 50 ml of either water or

phosphate buffer pH 4.7 were added, shacked for few minutes and completed to volume with the same solvent.

Working solution of BH(10^{-6} - 10^{-3} M)

Prepared by proper dilution from its stock solution using distilled water or phosphate buffer.

Working solution of the degrade (10^{-3} M)

Prepared by dissolving 56.25 mg in 25 mL of double distilled water or phosphate buffer.

Laboratory prepared mixtures

Aliquot 1, 2, 3, 5, 6, 7 and 9 ml of BH from its stock solution 10^{-2} M were transferred accurately into a series of 10 ml measuring flasks. Aliquot portions from its acid degradation 10^{-2} M solution were added to prepare mixtures containing 10%, 30%, 40%, 50%, 70%, 80% and 90% degradation, respectively.

Procedure

Precipitation-based technique for the preparation of PVC-membrane sensor (sensor 1 and 2)

10 ml of 10^{-2} M BH aqueous solution was mixed with 10 ml of a saturated aqueous solution of phosphotungestic acid (PTA). The resulting precipitate was filtered, washed with cold water, allowed to dry at room temperature and grounded to fine powder

In a glass petri dish (5 cm diameter), 10 mg of the previously prepared ion association complex was mixed thoroughly with 0.35 ml of dioctylphthalate (plasticizer) then add 0.19 gm of poly vinyl chloride (PVC). This mixture was dissolved in 5 ml tetrahydrofuran (THF), cover the dish with a filter paper and leave to stand overnight to allow slow evaporation of the solvent at room temperature forming master membrane with 0.1 mm thickness.

The first sensor was assembled using a disk of an appropriate diameter (about 8 mm) was cut from the previously prepared master membrane and cemented to the flat end of PVC tubing with THF. A mixed solution consisting of equal volumes of 10^{-2} M BH and 10^{-2} M potassium chloride was used as an internal reference solution. Ag/AgCl coated wire (3 mm diameter) was employed as an internal reference electrode. The sensors were conditioned by soaking for 24 hours in a solution of 10^{-2} M of the drug and stored in the same solution when not in use.

β-CD sensor 2 was prepared by weighing 0.04 gm of β-CD,mixed with 0.35 ml of di-n-butyl sebacate and 0.01 gm of ammonium reineckate. About 0.19 gm of PVC, previously dissolved in 6 ml THF was added and procedure was completed as above.

Effect of pH on the electrode response

The effect of pH on the potential values of the two electrode systems was studied over pH range 1 - 13 by immersing electrodes in 1 x 10^{-3} and 1 x 10^{-4} M BH solutions. The pH was gradually increased or decreased by adding aliquots of diluted sodium hydroxide or hydrochloric acid solutions, respectively. The potential obtained at each pH was recorded.

Construction of calibration graphs for direct potentiometric determination of BH using the proposed sensors

The sensors were conditioned by soaking in 10^{-2} M BH solution for 24 h. Storage was in the same solution when not in use. The conditioned electrodes were immersed in conjunction with the single junction calomel reference electrode in solutions of BH in the range of 1 x 10^{-5} - 1 x 10^{-2} M. They were allowed to equilibrate whilst stirring and recording the e.m.f readings within ± 2 mV. The membrane sensors were washed between measurements with water. The potential concentration profiles were plotted. The regression equations for the linear part of the curves were computed and used for subsequent determination of unknown concentrations of BH.

Effect of foreign compounds on the electrode selectivity

The response of the two studied electrodes was also examined in the presence of a number of other related substances. The potentiometric selectivity coefficients ($K_{BH,I}^{pot}$) were evaluated according to IUPAC guidelines using the separate solutions method in which the potential of cell consisting of the membrane electrode and a reference electrode

were measured for 1 x 10^{-3} M BH solution and then for 1 x 10^{-3} M interfering solutions, separately, then potentiometric selectivity coefficients were calculated using the following equation:

$$Log\ K_{A,B}^{pot} = \frac{(EB - EA)}{S} + \left(1 - \frac{BA}{BB}\right) Log\ aA$$

Where $K_{A,B}^{pot}$is the potentiometric selectivity coefficient,S is the slope of the calibration plot, *aA* is the activity of BH, while BA and BB are the charges of BH and the interfering ion, respectively, the EB and EA are the potential of interfering ions and BH ions at 1 x 10^{-3} M, respectively.

Application to laboratory prepared mixtures

The membrane sensors were immersed in conjunction with the single junction calomel reference electrode in the different laboratory prepared mixtures of BH and its acid degradation product. The membrane sensors were washed with water between measurements. The e.m.f. produced for each mixture was measured by the three proposed electrodes then the concentration of BH was determined from the corresponding regression equations.

Application to pharmaceutical dosage forms

Bambec, Lela free and Bambedil tablets: Ten tablets of each were weighed and powdered separately. An amount of the powdered tablets equivalent to 20.18 mg BH was accurately transferred separately to a 50 ml volumetric flask and the volume was completed to the mark with phosphate buffer pH 4.7 and sonication for 15 minutes was made to prepare 1 x 10^{-3} M solution of BH. The e.m.f. produced by immersing the prepared electrodes in conjunction with single junction calomel reference electrode in the prepared solutions were determined then the concentration of BH was calculated from the regression equation of the corresponding electrode.

Application to plasma samples

4.5 ml of plasma were placed into Stoppard tube, and then 0.5 ml of 1 x 10^{-2} M BH was added and the tube was shaken. The membrane sensor was immersed in conjunction with the single junction calomel reference electrode in the solution. The membrane sensor was washed with water between measurements. The e.m.f produced was measured by the three proposed electrodes then the concentration of BH was determined from the corresponding regression equation

RESULT AND DISCUSSION

BH is liable to acid hydrolysis where complete degradation was obtained after reflux with 1 M HCL at 100 °Cfor about 4 hours.

The obtained degradation product was separated by TLC on silica gel G F_{254} plates, usingethyl acetate: methanol: ammonium hydroxide (7: 3: 0.01 by volume) as a developing system.

The acid hydrolysis of BH cause cleavage of the two-ester linkages to give its active metabolite (Terbutaline) as degradation product (Figure 1).The degrade structure was elucidated by IR, MS spectroscopy(Figure 2-4).

The IR spectrum of intact BH(Figure 2) revealed carbonyl-stretching band at 1710 cm-1, which disappeared in the IR spectrum of Terbutaline (Figure 3), also a broad band of alcoholic OH stretching vibrating at 3334 cm-1 confirmed the acidic hydrolysis at the two ester linkages.

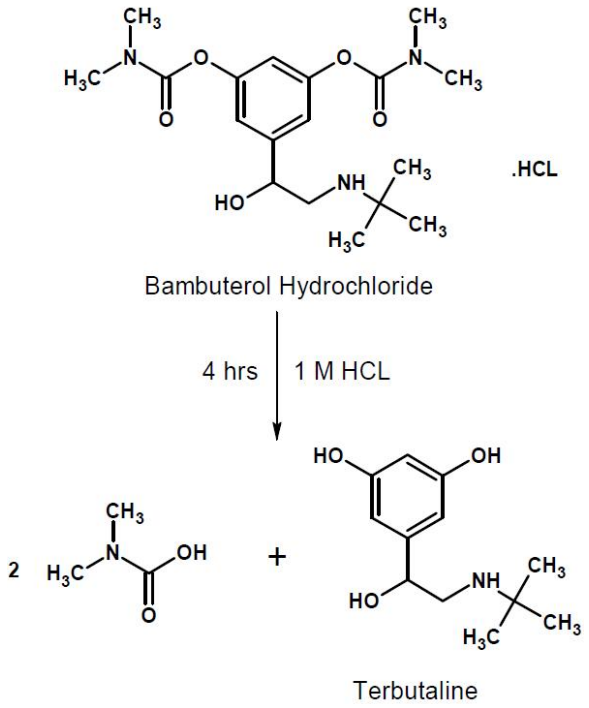

Figure 1 : The suggested scheme for the acid degradation of Bambuterol Hcl

Full Paper

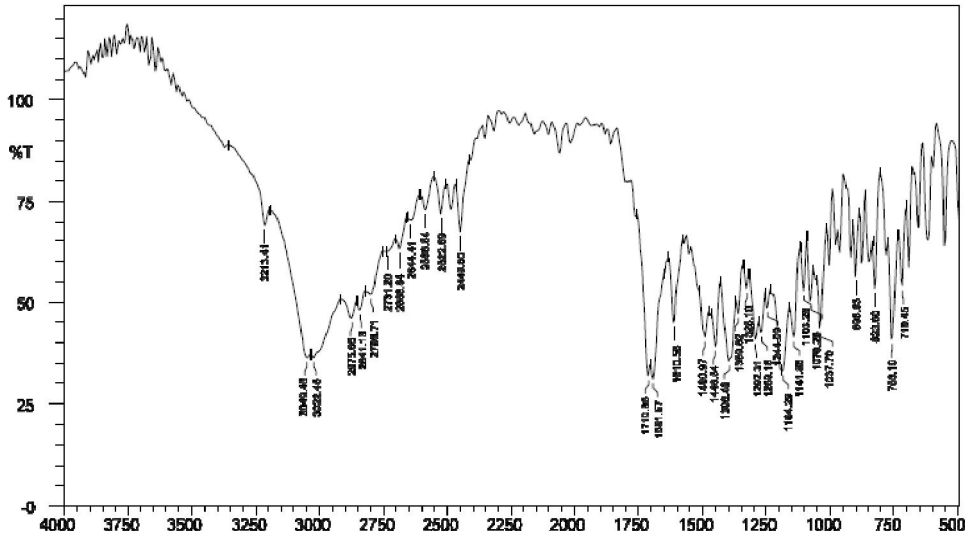

Figure 2 : IR spectrum of bambuterol Hcl

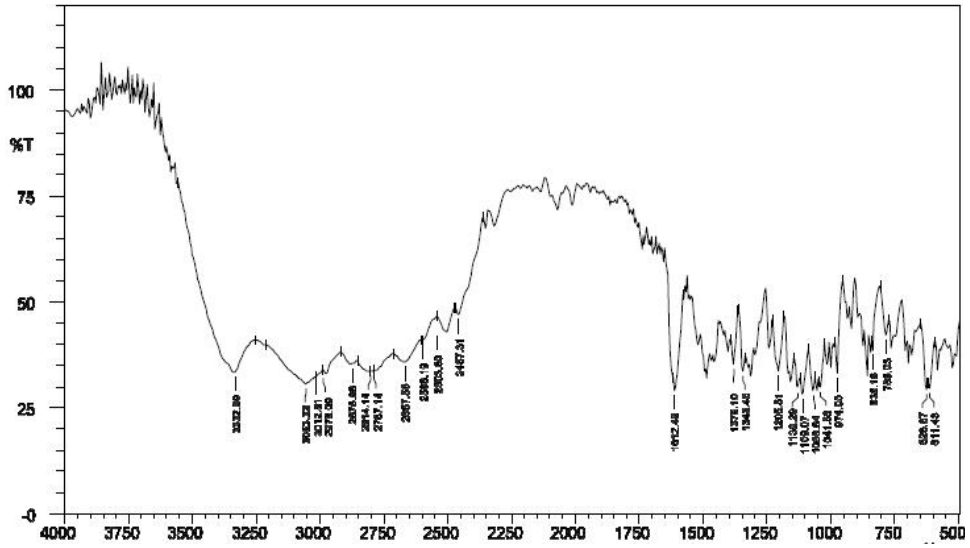

Figure 3 : IR spectrum of bambuterol Hcl degradation product

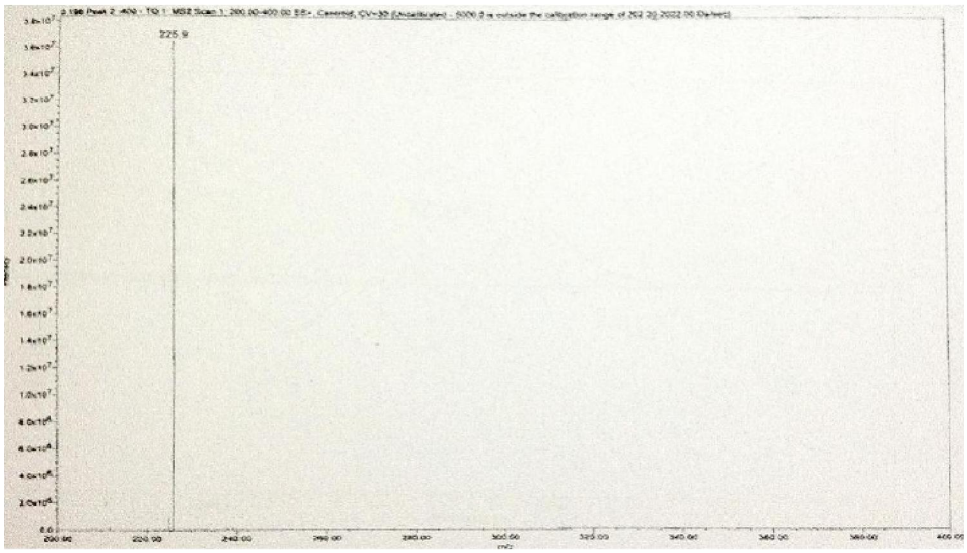

Figure 4 : Mass spectrum of bambuterol Hcl degradation product

These results confirmed using MS of the degradation product, which revealed molecular ion peak at 225, which is equivalent to its molecular weight (Figure 4).

The aim of this work was to develop and validate stability indicating methods for the determination of BH in pure form, pharmaceutical dosage forms and in plasma. ISEs contain membranes having a selective response for a particular ion. Selective membranes in ISEs have shown both ion exchange and selectivity properties for the sensor ions.

The present study originates from the fact that BHcan act as a cation, which suggests the use of ion exchangers of the anionic type like Phosphotungestic acid and ammonium reineckate with low solubility product and suitable grain size of the resulting precipitate.

BH reacted with Phosphotungestic acid to form stable 1:1 water insoluble ion association complex having the following suggested composition (Figure 5). This ratio confirmed by the Nernstian response

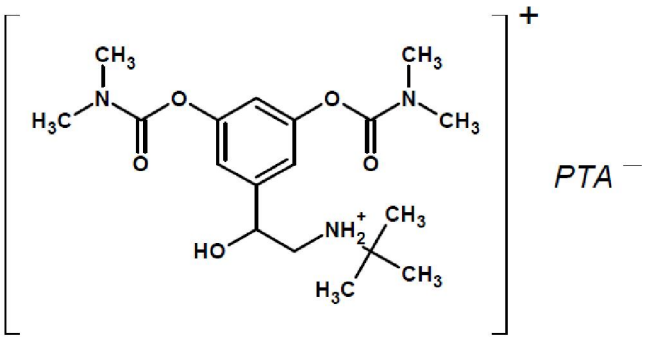

Figure 5 : Suggested composition for product of the reaction of bambuterol with phosphotungestic acid (PTA)

of the suggested sensors, which was about 60 mV; the typical value for monovalent drugs.

PVC acts as standard support matrix and as traps for the sensed ions, but its use creates a need for a plasticizer[18]. In the present investigation, dibutylsebathete was chosen as plasticizers from di-esters of carboxylic acids. With PVC, the di-esters of carboxylic acids were found to be the optimum plasticizers; they dissolve the ion association complex, and adjust of both the membrane permittivity and ion exchange sites mobility to give highest possible selectivity and sensitivity. Other plasticizers such as tricresyl phosphate and castor oil failed in dissolving the ion association complexes and thus gave noisy responses.

Cyclodextrins are optically active oligosaccharides that form inclusion complex compounds in the aqueous and in solid state with organic molecules. They were previously applied as sensor ionophores to potentiometric ISEs for the determination of protonated amines[19] and chiral molecules incorporating aryl rings[20]. β-CD-based sensors showed accurate results in both response and selectivity. Ammonium reineckate previously used as anionic exchanger[21] with bambuterol hydrochloride in concentration range of $1 \times 10^{-5} - 1 \times 10^{-2}$ M although on application of β-Cyclodextrin it forms an inclusion complex that increase the sensitivity range to reach $1 \times 10^{-6} - 1 \times 10^{-2}$ M.

Electrochemical performance characteristics of the proposed sensors were evaluated according to the IUPAC recommendation data[22] (TABLE 1). It

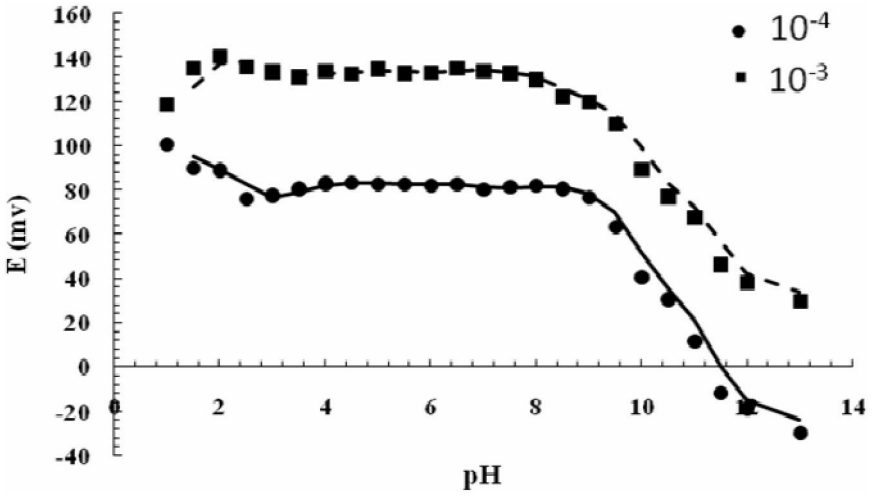

Figure 6 : Effect of pH on the response of sensor 1 (BH-PTA)

Full Paper

TABLE 1 : Response characteristics of the two investigated electrodes

Parameter	Sensor 1 (BH-PTA)	Sensor 2 (BH-β-CD)
Slope (mv/decal)	-50.2	-50.08
Intercept (mv)	208.8	201.73
Correlation coefficient	0.9995	0.9999
Response time	20 - 30	20 - 30
Working PH range	2 - 8	2 - 8
Concentration range (M)	10^{-5} - 10^{-2}	10^{-6} - 10^{-2}
Life span (weeks)	6 - 8	5 - 6
Average recovery (%)	99.96	99.98
R.S.D (%)	0.694	0.387

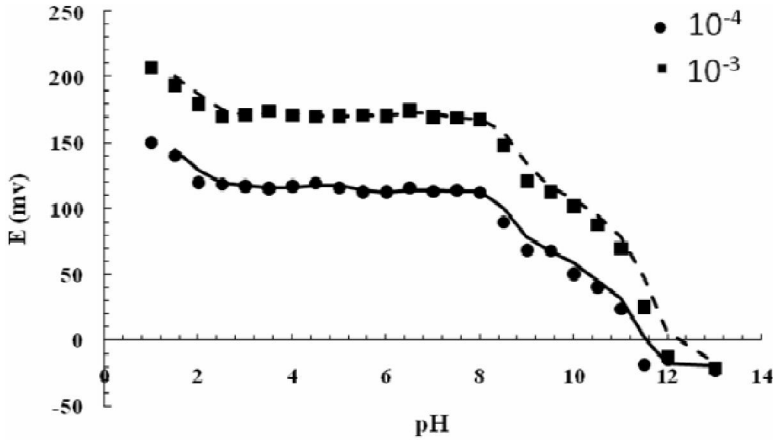

Figure 7 : Effect of pH on the response of sensor 2 (BH-β-CD)

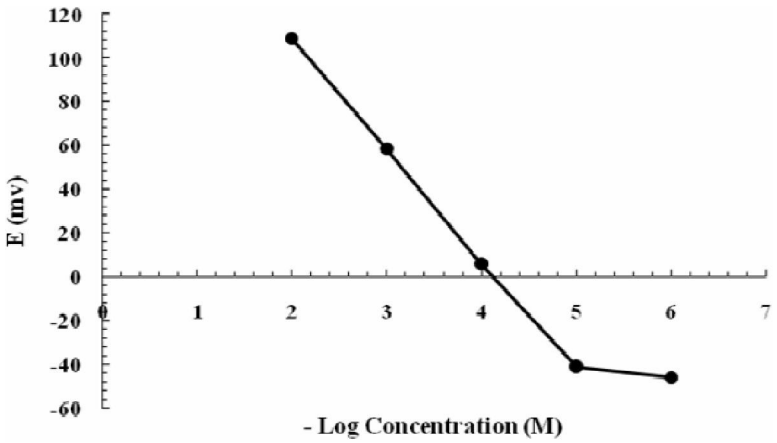

Figure 8 : Profile of the potential in mv versus –log concentration for sensor 1 (BH-PTA)

was found that the electrodes displayed constant and stable potential readings within 2 mV from day-to-day and the calibration slopes did not change by more than 2 mV per decade over a period of 1 month for the two sensors.

The response time of the electrodes were tested for concentrations of the drug from 10^{-5}- 10^{-2} M. The measurements were characterized by a fast stable response within 20-30 seconds for concentrations less than 10^{-4} M and 10-20 seconds for concentrations more than 10^{-4} M.

The effect of pH on the electrodes potential was investigated and it was found that the electrodes gave a useful pH range from 2 - 8 for sensors 1 and 2 (Figure 6-7). Above and below this pH range, the potentials displayed by the electrodes were noisy.

The potentiometric responses of the two studied sensors at the optimum pH were linear with constant slopes over a drug concentration ranges of 1 x 10^{-5} – 1 x 10^{-2} M and 1 x 10^{-6} – 1 x 10^{-2} M for sensor 1 and 2, respectively (Figure 8-9).

The accuracy of the proposed membrane sensors for the quantification of blind samples of BH assessed by using the two sensors. The results showed average recoveries of 99.96 ± 0.694, and 99.98 ± 0.387 for sensor 1 and 2, respectively.

The performance of the two sensors in the presence of some nitrogenous compounds such as amines, amino acids, some inorganic cation and its degradation product was assessed. Selectivity coefficient valueswere measured using a fixed concentration of the interfering substance (1 x 10^{-3} M). The results obtained by the developed sensors (TABLE 2), showed reasonable selectivity of the two sensors for BHin presence of its degradation product.

BHanalyzed in different laboratory prepared mixtures with its degradation product and good recoveries obtained,(TABLE 3).

Pharmaceutical additives did not show any interference. Thus, analysis was carried out without prior treatment or extraction. The two sensors were successfully used for the determination of BH in its different pharmaceutical dosage forms, (TABLE 4).

On application to the biological fluids, plasma electrolyte did not show any interference. It was found that the two electrodes gave stable results as revealed by high precision and accuracy of recoveries of the spiked plasma samples, (TABLE 5).

Statistical evaluation of the results of analysis of pure BH by the proposed electrodes and the Pharmacopoeial method[6] showed that there is no sig-

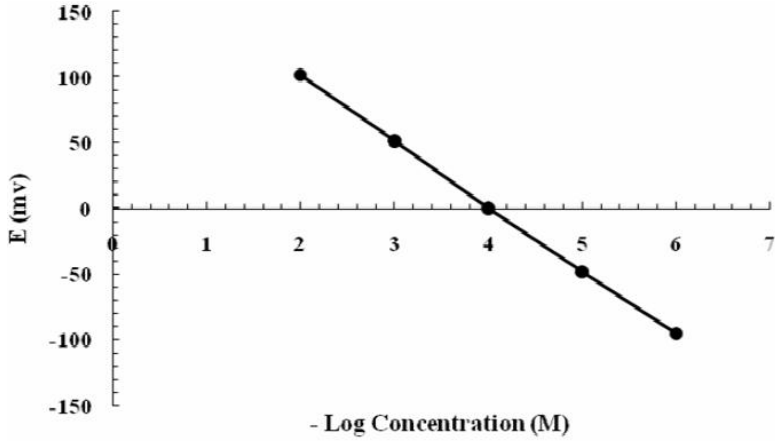

Figure 9 : Profile of the potential in mv versus –log concentration for sensor 2 (BH-β-CD)

TABLE 2 : Potentiometric selectivity coefficient $(K_{A,B}^{pot})$ for the two proposed sensors

Interfering substance	Selectivity coefficient			
	Sensor 1	(BH-PTA)	Sensor 2	(BH-β-CD)
degradation product	32.36 x 10^{-3}		58.79 x 10^{-3}	
Na+	9.97 x 10^{-3}		59.9 x 10^{-3}	
K+	8.98 x 10^{-3}		43.96 x 10^{-3}	
NH4+	9.91 x 10^{-3}		49.92 x 10^{-3}	
Mg2+	5.77 x 10^{-3}		49.95 x 10^{-3}	
Ca2+	7.96 x 10^{-3}		69.88 x 10^{-3}	
Glycine	5.17 x 10^{-3}		49.96 x 10^{-3}	
Lactose	5.57 x 10^{-3}		69.87 x 10^{-3}	
Urea	5.87 x 10^{-3}		50.16 x 10^{-3}	
Glucose	9.88 x 10^{-3}		47.79 x 10^{-3}	
Citric acid	10.97 x 10^{-3}		81.86 x 10^{-3}	

Full Paper

TABLE 3 : Results of the analysis of BAM in different laboratory prepared mixtures with its acid degradation product by the two sensors

Percentage		BAM recovery %*			
BAM	DEG	Sensor 1	(BH-PTA)	Sensor 2	(BH-β-CD)
90%	10%	100.95		100.67	
70%	30%	98.91		101.61	
60%	40%	101.15		99.04	
50%	50%	101.23		100.77	
30%	70%	100.52		101.02	
20%	80%	98.47		98.09	
10%	90%	101.37		101.68	
Mean ± S.D		100.37	± 1.186	100.41	± 1.349

*** Average of three determinations**

TABLE 4 : Quantitative determination of BAM in different pharmaceutical dosage forms by the proposed two sensors

Pharmaceutical dosage form	Mean Recovery % ± S.D*			
	Sensor 1	(BH-PTA)	Sensor 2	(BH-β-CD)
Bambec	99.76 ± 0.371		100.41 ± 0.733	
Bambedil	99.4 ± 1.588		98.66 ± 0.85	
Lelafree	99.06 ± 0.897		99.366 ± 0.833	

*** Average of three determinations**

TABLE 5 : Determination of BAM in spiked human plasma by the proposed two sensors

Concentration (M)	Recovery % ± S.D* of BAM			
	Sensor 1	(BH-PTA)	Sensor 2	(BH-β-CD)
1×10^{-3}	101.5 ± 1.48		102.01 ± 1.98	

*** Average of three determinations**

TABLE 6 : Statistical analysis of the results obtained by the proposed methods and the manufacturer method for the analysis of Bambuterol HCL in pure powder form

Item	BH-PTA	BH- β-CD	Pharmacopoeial method**
Mean R%	99.96	99.98	100.18
S.D	0.694	0.387	1.06
R.S.D %	0.694	0.387	1.06
N	5	5	5
S.E	0.310	0.173	0.47
Variance	0.482	0.150	1.1236
Student's t-test	0.388 (2.306*)	0.396 (2.306*)	
F-value	0.429 (6.39*)	0.133 (6.39*)	

*** Average of three determinations; * The values in parentheses correspond to the theoretical values of t and F at P=0.05; ** Pharmacopoeial potentiometric titration(Ref [6]).**

nificant difference between the proposed and manufacturer method in terms of accuracy and precision, (TABLE 6).

CONCLUSION

The two fabricated electrodeswere sufficiently

simple and selective for the quantitative determination of BH at a wide concentration range in its pure form, in plasma and in pharmaceutical formulations in presence of its acid degradation product. The use of the proposed sensors offers the advantages of fast response, elimination of drug pretreatment or separation steps. They can therefore be used for routine analysis of BH in quality control laboratories.

REFERANCES

[1] S.Sweetman; London: Pharmaceutical Press, **192**, 761 **(2007)**.
[2] G.Persson, A.Baas, A.Knight et al.; European Respiratory Journal, **8**, 34 **(1995)**.
[3] D.S.Sitar, C.P.Warren, F.Y.Aoki; Clinical Pharmacology & Therapeutics, **52**, 297 **(1992)**.
[4] B.Waldeck; European journal of pharmacology, **445**, 1 **(2002)**.
[5] M.Cazzola, F.Calderaro, C.Califano et al.; European journal of clinical pharmacology, **54**, 829 **(1999)**.
[6] British Pharmacopoeia, Stationery Office, **(2001)**.
[7] A.Bartolinčić, V.Drušković, A.Šporec, V.Vinković; Journal of pharmaceutical and biomedical analysis, **36**, 1003 **(2005)**.
[8] Y.Zhang; Jiangsu Pharm Clin Res., **9**, 13 **(2001)**.
[9] O.Wannerberg, B.Persson; Journal of Chromatography A, **435**, 199 **(1988)**.
[10] R.K.Harris, P.Hodgkinson, T.Larsson, A.Muruganantham; Journal of pharmaceutical and biomedical analysis, **38**, 858 **(2005)**.
[11] W.E.Hassan, S.M.Eid, K.M.Kelani, A.A.Shalaby; Drug Invention Today, **5**, 2 **(2013)**.
[12] K.N.Mikhelson; Ion-Selective Electrodes, Springer, **(2013)**.
[13] Y.El-Saharty, F.Metwaly, M.Refaat, S.El-Khateeb; Talanta, **72**, 675 **(2007)**.
[14] Y.El-Saharty, F.Metwaly, M.Refaat, S.El-Khateeb; Journal of pharmaceutical and biomedical analysis, **41**, 720 **(2006)**.
[15] S.S.Hassan, R.M.Abdel-Aziz, A.B.Abbas; Analytica chimica.acta, **321**, 47 **(1996)**.
[16] S.S.Hassan, M.Abou-Sekkina, M.El-Ries, A.Wassel; Journal of pharmaceutical and biomedical analysis, **32**, 175 **(2003)**.
[17] A.Guptha, C.Bhargavi, Y.Runa et al.; International Journal of Research and Review in Pharmacy and Applied Sciences, **1**, 186 **(2011)**.
[18] J.Novak, J.Drozd, J.Zyka; Ellis Horwood, Chichester, **1**, **(1991)**.
[19] J.Lima, M.Montenegro; Microchimica Acta, **131**, 187 **(1999)**.
[20] A.M.Pimenta, A.N.Araújo, M.C.B.Montenegro et al.; Journal of pharmaceutical and biomedical analysis, **36**, 49 **(2004)**.
[21] N.M.Mostafa, A.M.Badawey, El-Aleem AE-ABA, Lamie NT; **1**, 191 **(2011)**.
[22] L.A.Currie; Analytica Chimica Acta, **391**, 105 **(1999)**.