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Novel PVC-membrane electrode for flow injection potentiometric determination of Biperiden in pharmaceutical preparations

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ABSTRACT

The construction and performance characteristics of Biperiden (BP) polyvinyl chloride (PVC) electrodes are described. Different methods for electrode fabrication are tested including; incorporation of BP-ion pairs (BP-IPs), incorporation of ion pairing agents, or soaking the plain electrode in BP-ion pairs suspension solution. Electrode matrices were optimized referring to the effect of modifier content and nature, plasticizer and the method of modification. The proposed electrodes work satisfactorily in the BP concentration range from 10^{-5} to 10^{-2} mol L^{-1}, with fast response time (7 s) and adequate operational lifetime (28 days). The electrode potential is pH independent within the range 2.0–7.0, with good selectivity towards BP in presence of various interfering species. The developed electrodes have been applied for potentiometric determination of BP in pharmaceutical formulation under batch and flow injection analysis (FIA) conditions. FIA offers the advantages of accuracy and automation feasibility with high sampling frequency. The dissolution profile for Akineton tablets (2 mg BP/tablet) was studied using the proposed electrode in comparison with the official methods.

1. Introduction

Biperiden hydrochloride (1-(5-bicyclo[2.2.1]hept-2-enyl)-1-phenyl-3-(1-piperidinyl)propan-1-ol hydrochloride) is anti-Parkinson that is used in treatment of Parkinsonism [1]. 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 [2].

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 mL^{-1} [3]. A stability-indicating HPLC procedure for BP had also been developed and validated [4]; 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 [5]. Good linearity was achieved in the concentration range from 1 to 50 μg mL^{-1}, with the limit of detection 0.4 μg mL^{-1} BP. An extractive colorimetric method for determination of BP in dosage forms have been proposed using bromophenol blue [6]. Calibration graphs were rectilinear for less than 15 μg mL^{-1} BP with coefficient of variation 3.7%. Official method was performed via direct titration of BP with 0.1 N perchloric acid using crystal violet as indicator [7].

The widespread dosefication and/or adulteration of commercially available pharmaceutical preparations demand reliable method for quality control that are preferably selective, rapid and can be undertaken with simple equipment. Nevertheless, most of the aforementioned methods [3–7], involve several manipulation steps before the final result of the analysis, have poor selectivity or require expensive equipments. This is in contrast to electrometric methods using ion selective electrodes, which is now a well established method, with advantage of simplicity, short measurement time, adequate precision and accuracy, and the ability to measure the activity of the target species in colored or cloudy samples. Although ion-selective electrodes (ISEs) had found wide applications for drug quality control [8–13], to the best of our knowledge, no ISE was reported in literature for potentiometric determination of BP.

The present study is concerned with preparation, characterization and application of simple BP potentiometric sensors. PVC

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electrodes fabricated in plain and modified forms were subjected to a series of tests to select sensor possessing the most favorable performances for BP determination.

2. Experimental

2.1. Reagents

All reagents were of the analytical grade and bidistilled water was used throughout the experiments. *o*-Nitrophenyloctylether (*o*-NPOE, Sigma 73732), dioctylphthalate (DOP, Sigma 6699), dibutylphthalate (DBP, Aldrich 84-74-2), dioctylsebacate (DOS, Avocado 122-62-3) and tricresylphosphate (TCP, Fluka 1330-78-5) were used as electrode plasticizer. PVC powder (relative high molecular weight, Aldrich 389293) was used for membrane fabrication.

Ion pairing agents, including sodium tetraphenylborate (NaTPB, Fluka 143-66-8), potassium tetrakis (4-chlorophenyl) borate (KTCPB, Fluka 14680-77-4), phosphotungstic acid (PTA, Fluka 12501-23-4), phosphomolybdic acid (PMA, Fluka 51429-74-4), were used for precipitation of different BP-IPs.

2.2. Authentic sample

Biperiden hydrochloride ($C_{21}H_{29}NO{\cdot}HCl$, assigned to be 99%) authentic sample, was kindly provided from Arab Drug Company, Cairo, Egypt. Stock drug solution (10^{-2} mol L^{-1}) was prepared by dissolving the appropriate amount of BP in bidistilled water and kept at 4 °C.

2.3. Pharmaceutical preparations

Akineton and Achtenon tablets (2 mg BP/tablet; Knoll Pharmaceutical Company and Arab Drug Company, Cairo, Egypt, respectively) were purchased from local drug stores. Ten tablets were grinded and dissolved in 50 mL 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 [14].

2.4. Apparatus

Potential measurements were carried out using 692-pH meter (Metrohm, Herisau, Switzerland, art. no. 1.691.00100) accompanied with Ag/AgCl double-junction reference electrode (Metrohm, art. no. 6.0726.100) and pH glass electrode (Metrohm, art. no. 6.0202.100). Single line flow injection system composed of four channel peristaltic pump (MCP Ismatec, Zurich, Switzerland), sample injection valve with exchangeable sample loops 5.0–500 μL (ECOM, Ventil C, Czech Republic), and contentious flow cell [15] was illustrated. The continuous flow cell was simply manufactured from Perspex cube with two cylindrical holes for fixation of electrodes, and internal tube within for connecting the two electrodes and carrier stream. The change of electrode potential was monitored using 46-Range Digital Multimeter (Radioshack, China) with PC interface.

2.5. Procedures

2.5.1. Preparation of the sensing material

BP ion-pairs synthesis protocol included dropwise addition of 10^{-2} mol L^{-1} of different ion pairing agent solutions, namely, NaTPB, PTA or PMA, to BP solution with continuous stirring. The resulting precipitates were then filtered off and left to dry at 60 °C. Chemical compositions of BP-IPs were confirmed by elemental analysis.

2.5.2. Sensor construction

Modified electrodes were fabricated using membrane matrix composed of 7.5 mg BP-TPB or 20 mg NaTPB, 240 mg *o*-NPOE, 6 mL THF and 240 mg PVC powder. Matrices cocktails were poured into "5 cm" diameter Petri dish, after 24 h of slow solvent evaporation, a master PVC membrane with 0.11 mm thickness was obtained. Circular pieces 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} BP solution. The fabricated electrodes were soaked in 10^{-3} mol L^{-1} BP for 24 h before using. Soaked electrodes were prepared in the same manner using the dummy PVC membrane (prepared without addition of modifier) and soaked in the BP-TPB suspension for 24 h before using.

2.5.3. Sensor calibration

For batch measurements, BP-sensors were calibrated by immersing the sensor in conjugation with reference electrode in 25 mL aliquots of 10^{-6}–10^{-2} mol L^{-1} BP solutions. The potential readings were recorded and plotted against drug concentration in logarithmic scale (log [BP]).

Under FIA conditions, 500 μL of freshly prepared BP solutions covering the concentration range from 10^{-5} to 10^{-2} mol L^{-1}, were injected in the flowing stream (10^{-6} mol L^{-1} BP) at a flow rate 45 mL min^{-1}. The corresponding peak heights were recorded and used to draw the calibration graphs.

2.5.4. Potentiometric determination of BP in pharmaceutical preparations

BP was potentiometrically determined in pure solution and pharmaceutical preparations using the developed sensors under batch (by standard addition and potentiometric titration) and FIA conditions. In standard addition method, known increments of 10^{-2} mol L^{-1} BP solution were added to 25 mL aliquot of the sample solutions. The change in the potential readings was recorded for each increment and used to calculate the concentration of BP in sample solution.

Aliquots of the sample solutions containing 3.1–15.5 mg BP were potentiometrically titrated against standardized NaTPB solution [16]; the titration process was monitored using BP sensor in conjugation with the conventional 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.

FIA analysis included injection of 500 μL sample solutions in the carrier stream under the optimum conditions, where the peak heights were compared to those obtained from injecting standard solutions of known concentrations.

2.5.5. BP tablet dissolution profile

Two Akineton tablets were placed in the dissolution vessel containing 50 mL hydrochloric acid (10^{-2} mol L^{-1}) at 37 ± 0.5 °C and rotation speed 50 rpm [7]. At appropriate time intervals (5 min), the amounts of BP released in the dissolution medium were evaluated using the proposed BP-potentiometric sensor and the official method using bromocresol purple solution [14].

3. Results and discussion

Biperiden is a tertiary amine cation which forms water insoluble ion pair complexes with different anions such as NaTPB, PTA or PMA. The resultant Bp-IPs can be used as ion exchangers for construction of BP potentiometric sensors. From this point of view,

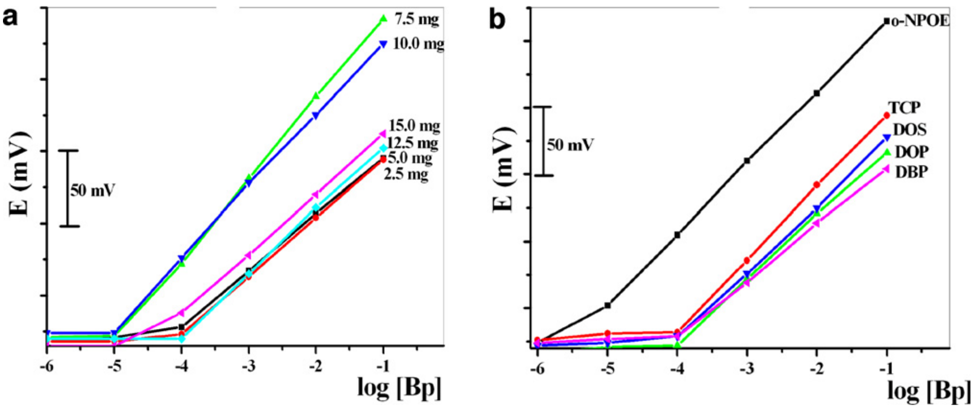

Fig. 1. Performance characteristics of BP-TPB modified sensor: (a) containing different amounts of BP-TPB ion pair, and (b) different plasticizers.

different types of BP-IPs were prepared and their stoichiometric ratios were estimated from elemental analysis. BP forms 1:1 (reagent:drug) IPs with TPB, while PTA and PMA showed ratio 1:3, respectively.

3.1. Optimization of the electrode matrices compositions

For quantitative and qualitative composition optimization of the developed PVC sensors, selection scheme was followed. Both modified (with either BP-IPs or ion pairing agents) and unmodified (soaked) electrodes were prepared and optimized referring to the effect of nature and content of modifier, plasticizer, pH, response time, sensitivity and applications.

3.1.1. Electrodes modified with BP ion pairs

BP sensors modified in bulk with different BP-IPs as electroactive components were fabricated and conditioned in 10^{-3} mol L^{-1} BP solution for 24 h. Preliminary experiments declared that electrodes contain no electroactive material and plasticized with *o*-NPOE showed non-Nernstian response (about 15–18 mV $decade^{-1}$) towards BP; while those modified with different BP-IPs gave Nernstian responses depending on the nature of IP used. Incorporation of BP-TPB showed the best performance (slope 54.0 ± 1.0 mV $decade^{-1}$) compared with other BP-IPs. Moreover, the obtained results were sustained by performing the potentiometric titration of BP with NaTPB using BP sensors modified with different BP-IPs. Electrode incorporated with BP-TPB gave the best titration curve indicated by the highest total potential change and the potential break at the inflexion point.

Constructing ion selective electrode, the amount of sensing material in electrode matrix should be sufficient to obtain reasonable ionic exchange and equilibrium at the membrane gel layer–test solution interface that is responsible for the membrane potential. Thus, the BP-TPB content in the electrode matrix was varied from 2.5 to 15.0 mg; addition of 7.5 mg gave the best performance (slope 55.6 ± 0.8 mV $decade^{-1}$). Higher BP-TPB concentrations lowered the slope value and the measuring concentration range (Fig. 1a).

3.1.2. Electrode modified with the ion pairing agents (in situ mode)

Incorporation of a suitable ion pairing agent in the membrane matrix followed by soaking the electrode in the drug solution, led to formation of drug–ion pair complexes at the electrode surface, which subsequently extracted by the plasticizer into the electrode bulk [17–19]. The effect of the ion pairing agent on the electrode performance was tested by incorporation of different ion pairing agents; namely, NaTPB, KTCPB, PTA or PMA. Incorporation of NaTPB in the electrode matrix was selected with the highest slope value (53.1 ± 1.8 mV $decade^{-1}$). The content of NaTPB was varied from 5.0 to 40.0 mg, and addition of 20.0 mg NaTPB in the electrode matrix showed the highest Nernstian slope value in the working concentration range from 10^{-5} to 10^{-2} mol L^{-1}.

3.1.3. Soaked electrodes

In addition to the aforementioned methods for electrode fabrication, a simple and reliable suggested procedure could be applied by soaking the plain electrodes in the aqueous suspension of the lipophilic IP, where the electrode mediator (plasticizer) extracts IP and becomes gradually saturated with this IP. In such case, there is no need to incorporate either IP or the ion pairing agent into the electrode matrix during its fabrication [20–22]. Herein, the constructed electrodes were soaked in different BP-IPs aqueous suspensions for 24 h before using. Results obtained showed that, electrodes soaked in BP-TPB possessed the best sensitivity compared with other tested ion pairs (57.8 ± 0.4, 50.3 ± 0.5 and 53.3 ± 0.5 mV $decade^{-1}$, for BP-TPB, BP-PMA and BP-PTA, respectively), which may be directly related to the solubility products of these IPs and their extractability in the membrane matrix [20–22].

3.1.4. Effect of the membrane plasticizer

Plasticizers play important roles in the behavior of the ISEs, since they improve the solubility of the sensing materials and lower the overall electrode bulk resistance [23,24]. The performance of electrode plasticized with *o*-NPOE was compared with other tested plasticizers; namely, TCP, DOS, DOP or DBP (Fig. 1b). The best performance was achieved using *o*-NPOE as membrane plasticizer (Nernstain slope values were 63.2 ± 0.8, 50.9 ± 4.6, 50.5 ± 2.0, 49.7 ± 6.2 and 47.5 ± 2.2 mV $decade^{-1}$ for *o*-NPOE, TCP, DOS, DBP, and DOP, respectively).

3.2. Sensors performance

The potentiometric response characteristics of different BP sensors were evaluated according to IUPAC recommendations [25]. Data obtained (Table 1) indicated that, the developed sensors can be successfully applied for potentiometric determination of BP in the concentration range from 10^{-5} to 10^{-2} mol L^{-1}, with Nernstian cationic slopes depending on the method of electrode fabrication. Soaked electrodes showed limit of detection (4.7×10^{-6} mol L^{-1}) compared with other tested electrodes.

For analytical applications, the response time of a new fabricated sensor is of critical importance, especially when the sensor is incorporated in FIA system. According to the IUPAC recommendation, the electrode dynamic response time was tested by measuring the time required to achieve a steady state potential (within ±1.0 mV)

Table 1
Performance characteristics[a] of BP sensors fabricated with different techniques.

Sensor	Modified	In situ	Soaked
Concentration range (mol L^{-1})	10^{-5}–10^{-2}	10^{-5}–10^{-2}	10^{-5}–10^{-2}
Slope (mV decade^{-1})	55.7 ± 1.4	58.8 ± 0.4	57.0 ± 0.9
r	0.9999	0.9997	0.9998
Limit of detection (mol L^{-1})	1.0×10^{-5}	1.0×10^{-5}	4.7×10^{-6}
Response time (s)	7	10	10
Lifetime (Day)	28	21	28
Working pH range	2–7	2–7	2–7

[a] Results are average of five different calibrations.

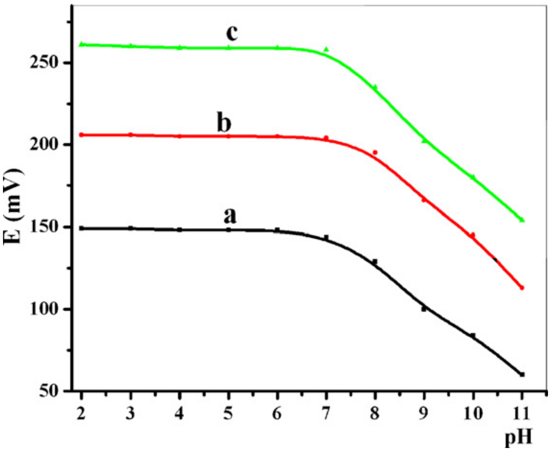

Fig. 2. Effect of pH on the potential readings of BP-PVC electrode, (a) 1×10^{-4}, (b) 1×10^{-3}, and (c) 1×10^{-2} mol L^{-1}.

Table 2
Selectivity coefficients for Bp sensors under batch and FIA conditions.

Interferent	$-\log K_{A,B}$	
	Batch[a]	FIA[b]
Na^+	3.30	3.45
K^+	2.75	2.95
Li^+	3.10	3.51
$NH_4{}^+$	2.90	3.06
Ca^{2+}	2.61	2.93
Mg^{2+}	3.16	3.31
Starch	3.57	
Maltose	3.00	
Sucrose	2.80	
Citrate	2.49	
Caffeine	3.38	
Glycine	2.46	

[a] Performed with MPM.
[b] Performed with SSM.

after sudden 10-fold increase in the BP concentration. Sensors modified with BP-TPB ion pair showed more stable potential readings and faster response time (7 s). Lifetimes of the fabricated electrodes were tested by performing day-to-day calibration. Sensors showed useful lifetime of about 21–28 days, during which the Nernstian slopes did not change significantly, while the detection limits were shifted from 10^{-5} to 10^{-4} mol L^{-1} at the end of the period.

The influence of pH on the electrode response was studied by recording the potential readings at different pH values (2–11). Change in pH has a negligible affect (±2.0 mV) within the range of 2–7; at higher pH values the electrode potential decreased due to precipitation of BP (Fig. 2). In addition, the effect of the temperature was tested by performing sensor calibrations at different temperatures ranging between 25 and 70 °C. Results (not shown) declared that, calibration graphs had stable Nernstian slopes in the temperature range 25–60 °C. Isothermal coefficient, estimated by plotting the standard cell potentials versus (T-25), was found to be 0.4 mV °C^{-1} [26].

The selectivity of the prepared BP sensor was tested towards different interfering species using matched potential method (MPM) [27]. The determined selectivity coefficients (Table 2), reflects the high selectivity of the investigated electrode; additives and fillers commonly introduced in pharmaceutical formulations (such as glycine, caffeine, citrate, maltose, sucrose, and starch) as well as inorganic cations, have no effect on the electrode potential.

3.3. Potentiometric titration

In addition to the direct potentiometric determination of BP, the fabricated PVC electrodes were applied as indicator electrodes in potentiometric titration of BP with NaTPB. The effect of electrode plasticizer on the titration performance was investigated using BP sensors containing different membrane plasticizer (Fig. 3a). *o*-NPOE gave the highest total potential change compared with other tested plasticizers (ΔE were 231, 150, 115, 192 and 96 mV, for *o*-NPOE, TCP, DOP, DOS and DBP, respectively), which may be attributed to the difference in dielectric constants of the tested plasticizers (ε = 24, 17.6, 4.5, 5.2 and 4.7 in the same order) [28].

Under the optimum conditions, titration curves were symmetrical with well-defined potential jumps allowing the determination of 3.1 mg BP (Fig. 3b). Between day assays was tested by performing three different titration runs on three different days. The values for the end-point volumes were highly reproducible within the each series compared with official method.

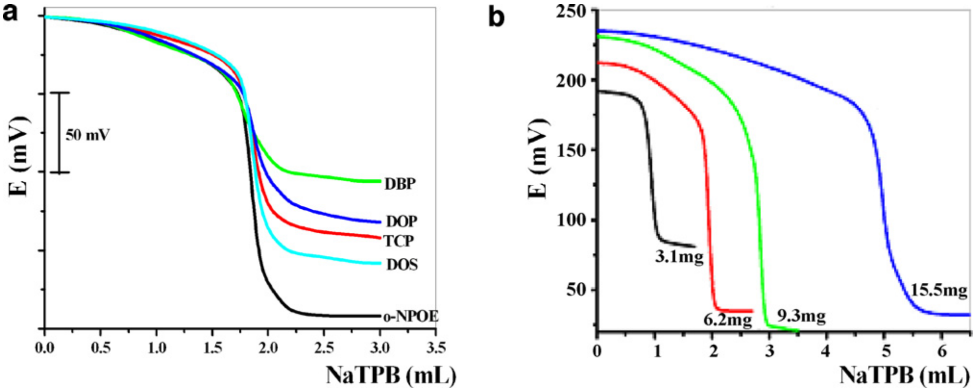

Fig. 3. Potentiometric titration of BP with NaTPB: (a) using PVC membranes fabricated using different plasticizers, and (b) at different BP concentrations.

Table 3
Potentiometric determination of BP in pharmaceutical preparations.

Sample	Taken (mg)	Found							
		Official method		Proposed potentiometric method					
				Standard addition		Titration		FIA	
		Recovery %	R.S.D[a]	Recovery %	R.S.D	Recovery %	R.S.D	Recovery %	R.S.D
Pure BP	3.1	101.45	1.90	99.70	2.00	98.95	1.90	99.52	1.10
	6.2	99.52	1.70	99.00	1.80	98.59	1.46	98.52	1.20
	9.3	100.10	1.85	100.95	2.10	100.22	0.95	99.70	1.70
	15.3	100.20	1.50	99.81	1.85	99.10	1.35	101.25	1.40
Akineton tablets	3.1	101.90	1.30	100.75	1.50	102.26	1.31	100.25	0.95
Achtenon tablets	3.1	98.56	1.65	101.60	1.30	104.66	1.78	101.35	1.10

[a] Mean recovery and relative standard deviations of five determinations.

3.4. Electrode response under FIA conditions

Flow injection analysis (FIA) becomes a wide spread methodology characterized by versatility, ease of automation and high sampling frequency [29–31]. In the present work, a home-made Perspex flow through cell was used, providing low dead volume, fast response, good washing characteristics, ease of construction and compatibility with electrodes of various shapes and sizes. FIA parameters such as flow rate and injected sample volume were optimized as previously described in details [15].

Fig. 4 showed peaks from the BP sensor when 500 μL of BP solutions at various concentrations were injected in the flowing stream (45 mL min^{-1}). Calibration graphs were linear in the concentration range from 10^{-5} to 10^{-2} mol L^{-1} with Nernstian slopes of 55.5 ± 0.4 mV decade^{-1} and sampling output of 30 sample h^{-1}. Reproducibility was evaluated from repeated 10 injections of 500 μL of 10^{-2} mol L^{-1} BP solution, the average peak heights were found to be 64.0 ± 1.8 mV.

Fig. 4 FIA is viewed as a well efficient mean for improving the performance characteristics of ISEs as the action of the flowing stream continuously cleans the electrode surface and the transient nature of the signal may help to overcome the effect of interfering ions. Under FIA conditions, the selectivity coefficients were calculated according to the separate solution method (SSM), based on potential values corresponding to the peak heights for the same concentrations of the drug and the interferents. The fabricated electrodes were highly selective which and the selectivity coefficients were improved compared with batch measurements (Table 2).

3.5. Analytical applications

3.5.1. Potentiometric determination of BP in pharmaceutical formulations

The proposed electrodes were successfully employed for BP assaying in authentic samples and pharmaceutical formulations. Results (Table 3) clearly indicated satisfactory agreement between the BP contents in different samples determined by the developed sensor compared with official method. The time required for sample analysis was short in case of FIA (about 2 min) compared to more than 10 min for potentiometric titration method, with the advantage of accuracy and automation feasibility.

3.5.2. Potentiometric monitoring of BP tablet dissolution

Biperiden is readily absorbed from the gastrointestinal tract, its bioavailability is only about 30%, suggesting that it undergoes extensive first-pass metabolism. For studying the dissolution profiles of BP tablet, the released BP in the dissolution medium was evaluated using the developed BP sensor and official spectrophotometric method. In the potentiometric method, the potential values were continuously recorded at 5 min time intervals, and the BP content was estimated from the calibration graph. Results obtained (Fig. 5) showed agreements in recoveries obtained by both methods as the differences in recoveries were about ±2.0%.

Taking into account the S-shape of the dissolution curve, it is revealed that the dissolution process involves one main step, uncoated tablet dissolute and the method proved that the release of the active principle of the tablets in simulated duodenum fluid follows the Wagner model [32].

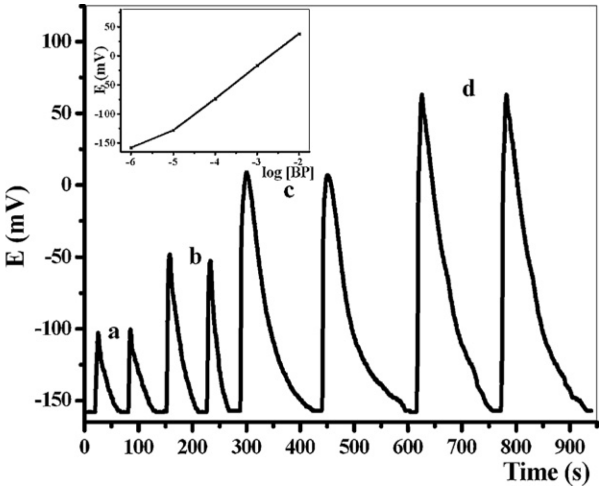

Fig. 4. FIA potentiometric determination of BP using BP sensor: (a) 1×10^{-5}, (b) 1×10^{-4}, (c) 1×10^{-3}, and (d) 1×10^{-2} mol L^{-1}.

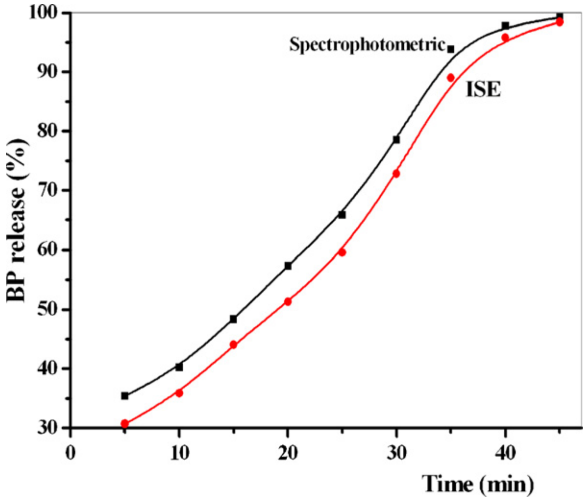

Fig. 5. Dissolution profile of Akineton tablet (2 mg BP/tablet) using proposed potentiometric and official methods.

4. Conclusion

The present work demonstrates the fabrication of novel Biperiden potentiometric sensors utilizing different fabrication methods. The proposed electrodes showed Nernstian responses in the tested BP concentration range from 10^{-5} to 10^{-2} mol L^{-1} with fast response time (7 s) and adequate operational lifetime (28 day). The method was successfully applied for monitoring of BP tablet dissolution and potentiometric determination of BP in pharmaceutical formulations. FIA allows high sampling output with the possibility for incorporation in routine analysis for drug quality control. High selectivity and rapid response make these electrodes suitable for measuring the concentration of BP in a variety of samples without the need for pretreatment or manipulation steps.

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