ISSN : 0974-7419 Volume 15 Issue 8
Analytical CHEMISTRY
An Indian Journal
Full Paper
ACAIJ, 15(8) 2015 [311-318]

Development of a new potentiometric modified carbon paste electrode for losartan potassium determination in pharmaceutical formulations

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ABSTRACT

In this paper, the development of an extremely inexpensive potentiometric modified carbon paste electrode for losartan potassium is described. Commercially available graphite pencil was ground to fine powder and used to prepare the carbon paste electrode. The electrode is based on the ion-pair complex of losartan potassium with 1,10-phenanthroline-iron (II) as modifier and dissolved in 2-nitrophenylpentyl ether (2–NPPE) as pasting liquid. The proposed electrode showed a near-Nernstian slope of –58.3 ± 0.7 mV/decade over the concentration range of 1.0×10^{-4} to 1.0×10^{-2} M with the limit of detection 5.0×10^{-5} M over the pH range 6.5 – 9.0. The electrode exhibits good selectivity for losartan anions over many inorganic anions, sugars and amino acids. The electrode was applied for the determination of losartan potassium in its different pharmaceutical dosage forms. The results obtained were satisfactory with excellent percentage recovery comparable with HPLC method. © 2015 Trade Science Inc. - INDIA

KEYWORDS

Losartan potassium;
Potentiometric MCPE;
Commercially available graphite pencil;
Pharmaceutical formulation.

INTRODUCTION

In modern world, hypertension is one of the most significant causes of death. Its treatment with losartan potassium (LOS) [2-butyl-4-chloro-1-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl) benzyl] imidazole-5-methanol monopotassium salt] (Figure 1) presents advantageous effects[1,2]. LOS is the first drug in the new class of non-peptide angiotensin II antagonist (type AT_1) which acts by suppressing the effects of angiotensin II at its receptors[3].

Since LOS is being more and more used, its determination is very important. Numerous methods have been published for its analytical determination as well as high performance liquid chromatography (HPLC)[4-13], high performance thin layer chromatography (HPTLC)[14-15], capillary electrophoresis (CE)[13,16], spectrophotometry[17-20], conductimetry[21] and voltammetry[22-24]. However, most of these methods present many drawbacks, such as high cost, long analysis time and require special reagents and sophisticated instruments which limited their use in routine quality control analysis. Therefore, there is an increasing need for development of sensitive, selective and low-cost analytical method for losartan determination.

Although ion-selective electrodes (ISEs) have been used extensively for drug analysis over the last decades[25-27], there is no potentiometric reported methods for the determination of losartan in the litera-

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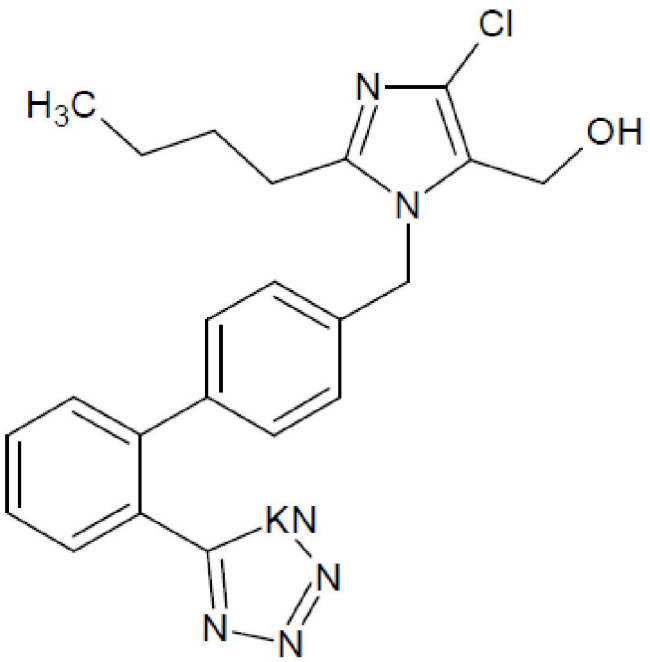

Figure 1 : The chemical structure of losartan potassium

ture. Ion-selective electrodes are potentiometric sensors that respond selectively to the activity of the target ion. They are characterized by low-cost, easy to fabricate, accuracy, and can be used without pretreatment steps[28]. It needs only a pre-dilution or dissolution of tablets in the measuring solvent. Recently, many efforts have been focused on the development of new potentiometric electrodes more and more simple and low-cost. Chemically modified carbon paste electrodes (CMCPEs) are the subject of many researches. Generally, carbon paste electrodes consist of Teflon well into which is inserted a platinum, copper, steel, or graphite contact. The well is filled with a paste made by mixing powdered graphite with a suitable mulling liquid[29]. Due to their ease of preparation, simple operation, renewability, fast and stable response, reasonable selectivity and low ohmic resistance, the carbon paste electrodes were used as attractive methods for the potentiometric determination of many organic and inorganic species[30-32].

In the recent year, graphite obtained from pencil writing device has emerged as a low-cost material for the construction of various electrodes, sensors and biosensors. It have been used as substrate electrodes in either rod or paste form due to their low background current, good electrical conductivity, chemical inertness, low-cost and commercial viability[33-36]. Therefore, in this paper, we have used powdered graphite obtained from pencil writing device in the preparation of a new potentiometric MCPE for losartan potassium. The influence of the paste composition on the response of the losartan sensor was investigated. The electrode with optimum performances was successfully applied with minimal sample pre-treatment to the determination of losartan in pharmaceutical tablets.

EXPERIMENTAL

Reagents and materials

All used reagents were of analytical grade purity. Dipentyl phthalate (DPP), dibutyl phthalate (DBP), dioctyl phthalate (DOP), 2–nitrophenyl pentyl ether (2–NPPE) were all obtained from Fluka (Switzerland). Losartan potassium (LOS) pure powder was kindly supplied by The National Laboratory of Drug Control (Tunis, Tunisia). The pharmaceutical preparations containing LOS (Losar®50 mg/tablet and Zartan®50 mg/tablet) were purchased from local drug stores.

For the preparation of the ion-pair complexes, the 1,10-phenanthroline-metal (II) (Figure 2) aqueous solutions were obtained by dissolving 100 mg of 1,10-phenanthroline in 20 mL of 2×10^{-2} M iron (II) ammonium sulphate, nickel (II) sulphate, cobalt (II) chloride or copper (II) sulphate solutions.

For all potentiometric measurements, LOS stan-

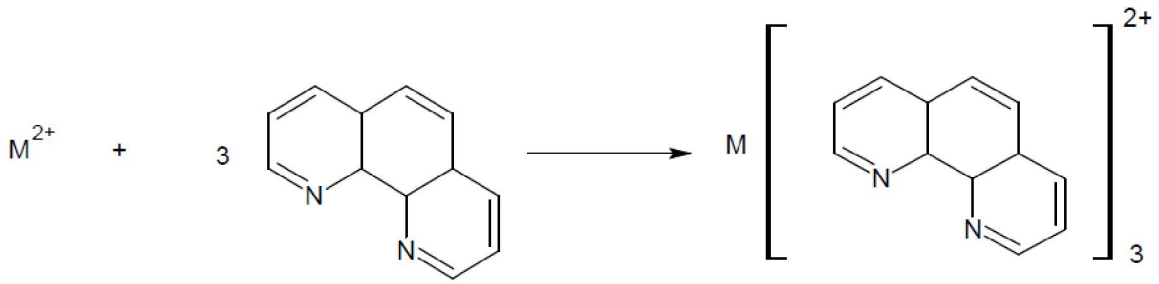

Figure 2 : Reaction of metal (II) with 1,10-phenathroline

dard solutions (1.0×10^{-5} to 1.0×10^{-2} M) were freshly prepared in 40 mM phosphate buffer (NaH_2PO_4/Na_2HPO_4) solution of pH = 8.0.

Apparatus

An EL 20 model pH–mV meter, a reference electrode (Ag-AgCl) and a pH double junction glass electrode (Mettler Toledo, Switzerland) were used for the potentiometric and pH measurements at room temperature (25 ± 1° C).

Chromatographic measurements were carried out using a Thermo Separation Products HPLC model spectra system P 1000 equipped with an isocratic pump and an Eclipse plus C_{18} separator column (Agilent®, 5 µm, 250 × 4.6 mm) coupled with an UV detector model Spectra series UV 100. The eluent used was acetonitrile:buffer (40:60) mixture at a flow rate of 1.0 mL.min^{-1}. The detection was performed at 230 nm.

Preparations of the ion-pair complexes

The ion-pair complexes used in this work were prepared according to the previously reported methods[37,38]. A 5 mL aliquot of 1.0 M aqueous LOS solution was mixed with 5 mL of one of the following solutions: 1,10-phenathroline-iron (II), 1,10-phenanthroline-nickel (II), 1,10-phenanthroline-cobalt (II) or 1,10-phenanthroline-copper (II) and shaking for 5 min. The precipitates formed were filtered off on Whatman No. 42 paper, washed with cold water, dried at room temperature for at least 24 h, grounded and kept.

Electrode preparation and potentiometric measurements

The graphite powder obtained from the commercially pencil writing device was prepared as well: The pencil graphite rod was obtained by completely removing the plastic sleeve of the 3B pencil, PITT® Graphite Pure 2900, Faber-Castell, Germany, using a cutter. The pencil rod was grounded manually into powder using a mortar and pestle. The powder was then kept until used.

The MCPE was constructed as indicated by[30] by mixing the pencil graphite powder with the ion-pair complex by means of a mortar and pestle for at least 10 min. Then, a desired weight of plasticizer was added and the mixture was merged until a uniform paste was obtained. Sensor body was prepared from 1 mL polypropylene syringe (3 mm i.d.) which the needle tip had been cut off with a cutter. The paste was packed powerfully into the end of the syringe and a copper wire was inserted to establish electrical contact. To obtain a polished surface, the small amount of paste was pushed and the excess was removed against a paper. The sensor was used directly without pre-conditioning.

Performances of the electrodes were investigated at room temperature (25 ± 1 °C) by measuring the potential of LOS standard solutions (1.0×10^{-5} to 1.0×10^{-2} M). All potentiometric measurements were carried out with the following cell assemblies:

Modified carbon paste electrode | test solution || Ag-AgCl, KCl (sat.)

Analytical determination of losartan potassium in pharmaceutical preparations

For the losartan determination in tablet dosage forms (Losar®50 mg/tablet and Zartan®50 mg/tablet), ten tablets were weighed and using a mortar, a finely powder was obtained. An accurately weighed p,ortion of the tablet powder equivalent to 50 mg of the LOS was weighed and dissolved in about 30 mL, filtered in a 100 mL measuring flask and with the phosphate buffer solution (40 mM, pH = 8.0) the volume was completed. The sample solutions were subjected to potentiometric determination of LOS by the calibration curve method. In this method, the calibration plot was made by measuring the potential of LOS standards solutions ranging from 1.0×10^{-5} to 1.0×10^{-2} M. The displayed potentials were plotted versus the negative logarithm of the LOS concentration then; the obtained graph was used to determine directly unknown drug concentration.

For the LOS determination in pharmaceutical dosage forms using the reference HPLC method[13], the mobile phase was a mixture of acetonitrile/ phosphate buffer (pH = 2.0, 10 mM of H_3PO_4/NaH_2PO_4) solution of in a proportion of 40/60 (v/v).

RESULTS AND DISCUSSION

Optimization of the paste composition

The influence of the past ingredients (the modifier and the plasticizer) on the response of the LOS sensor

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TABLE 1 : Analytical performances of various losartan potassium carbon paste electrodes

No	Composition (%)			Electrode characteristics			
	IP	PG	P	Slope ± S.D. (mV/decade)	L.R. (M)	L.L.D. (M)	R
1	2.0 (LOS-phen-Co (II))	63	35 (2–NPPE)	–42.8 ± 0.5	1.0×10^{-4} 1.0×10^{-2}	9.9×10^{-5}	0.9909
2	2.0 (LOS-phen-Ni (II))	63	35 (2–NPPE)	–50.4 ± 1.1	1.0×10^{-4} 1.0×10^{-2}	7.4×10^{-5}	0.9990
3	2.0 (LOS-phen-Cu (II))	63	35 (2–NPPE)	–52.5 ± 0.7	1.0×10^{-4} 1.0×10^{-2}	9.3×10^{-5}	0.9994
4	2.0 (LOS-phen-Fe (II))	63	35 (2–NPPE)	–58.3 ± 0.7	1.0×10^{-4} 1.0×10^{-2}	5.0×10^{-5}	0.9996
5	0.5 (LOS-phen-Fe (II))	64.5	35 (2–NPPE)	–54.2 ± 0.9	1.0×10^{-4} 1.0×10^{-2}	6.4×10^{-5}	0.9988
6	1.0 (LOS-phen-Fe (II))	64	35 (2–NPPE)	–56.9 ± 0.3	1.0×10^{-4} 1.0×10^{-2}	7.3×10^{-5}	0.9972
7	3.0 (LOS-phen-Fe (II))	62	35 (2–NPPE)	–53.1 ± 1.3	1.0×10^{-4} 1.0×10^{-2}	9.8×10^{-5}	0.9975
8	4.0 (LOS-phen-Fe (II))	61	35 (2–NPPE)	–43.1 ± 0.5	1.0×10^{-4} 1.0×10^{-2}	1.0×10^{-4}	0.9982
9	2.0 (LOS-phen-Fe (II))	63	35 (DPP)	–50.7 ± 0.7	1.0×10^{-4} 1.0×10^{-2}	6.3×10^{-5}	0.9989
10	2.0 (LOS-phen-Fe (II))	63	35 (DOP)	–56.7 ± 0.5	1.0×10^{-4} 1.0×10^{-2}	9.8×10^{-5}	0.9910
11	2.0 (LOS-phen-Fe (II))	63	35 (DBP)	–56.2 ± 1.1	1.0×10^{-4} 1.0×10^{-2}	6.2×10^{-5}	0.9995

IP: ion-pair, PG: pencil graphite powder, P: plasticizer, S.D.: standard deviation based on three replicate analyses, L.R.: linear range, L.L.D.: lower limit of detection, *R*: correlation coefficient

was considered. The potentiometric performances were evaluated according to IUPAC recommendation[39] and the results are potted in TABLE 1.

The ion-pair complex used as a modifier material plays an important role to generate the selective potentiometric response of the MCPE[31]. For this, a water insoluble ion-pair complexes of losartan potassium with 1,10-phenathroline-iron (II), 1,10-phenanthroline-nickel (II), 1,10-phenanthroline-cobalt (II) or 1,10-phenanthroline-copper (II) were prepared and tested as modifiers. Then electrodes containing one of these ion-pair complexes were made and evaluated. The results of TABLE 1 revealed that the paste contains losartan-phenanthroline-iron (II) showed the best sensitivity. For this reason ion-association complex of LOS with 1,10-phenanthroline-iron (II) was considered as the selected modifier for the following experiences. For the production of the sensor response, the amount of the modifier in the paste should be sufficient[40]. Therefore, several pastes with composition ranging from 0.5% to 4.0% (w/w) were elaborated and the results are potted in TABLE 1 and presented in Figure 3.

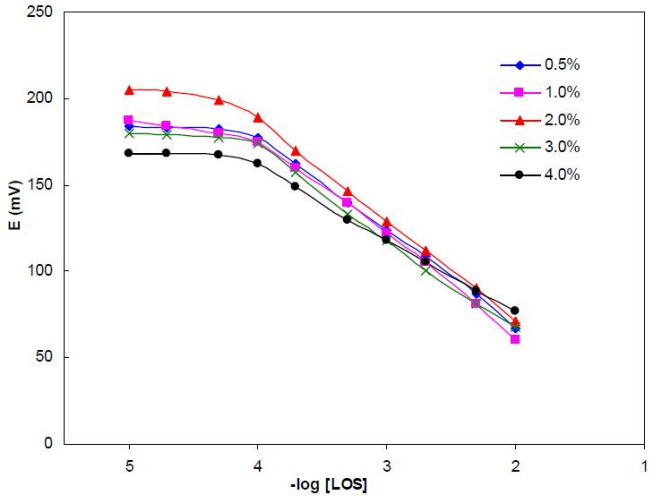

Figure 3 : Effect of different amount of losartan-phenanthroline-iron (II) on the response of the losartan potassium carbon paste electrodes (40 mM phosphate buffer, pH=8.0)

As can be seen, for all developed electrodes (electrodes 4–8), nearly Nernstian anionic response slopes (–43.1 to –58.3 mV/decade) are obtained over approximately 2 orders of magnitude in concentration. This result implies that the electrode response characteristics were considerably influenced by the concentration of the modifier incorporated in the paste. The amount of the modifier between 1.0% and 2.0% (w/w) was found to generate the better response. However, more increase in the modifier percentage from 2 to 4 % has led to a decrease in the electrode response (electrode 7 and 8). This may be explained by the decrease in the conductance of the electrode material with increasing the percentage of the modifier[32]. Therefore, 2 % of ion-pair complex was chosen as the optimum amount of the modifier for preparing the LOS electrode.

On the other hand, the plasticizer effect was stud-

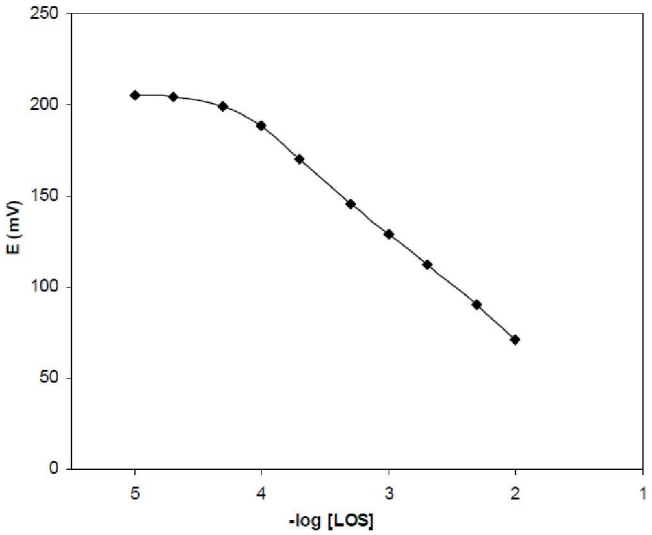

Figure 4 : Response of the proposed losartan potassium carbon paste electrode under the optimum conditions (40 mM phosphate buffer, pH=8.0)

TABLE 2 : Response characteristics* for the losartan potassium carbon paste electrode

Parameter	Value
Slope (mV/decade)	– 58.3 ± 0.7
Correlation coefficient	0.9987
Linearity range (M)	$1.0 \times 10^{-4} – 1.0 \times 10^{-2}$
Limit of detection(M)	5.0×10^{-5}
Response time (s)	5–10
Working pH range	6.5 – 9.0
Life span (weeks)	8

*** Results are average of three different calibrations**

ied. Therefore, several plasticizers with different polarities including 2–NPPE, DPP, DBP and DOP were employed and the results are potted in TABLE 1. It is clear that the paste plasticised with *2*–NPPE, with higher value of dielectric constant (ε ~ 24) produced the best response. This plasticizer may solvates and adjusts the mobility of the ion-pair complex. For that reason, 2–NPPE was chosen as the best plasticizer in the rest of experiments.

The potentiometric characteristics of sensor No. 4, witch have optimum performances, are collected in TABLE 2.

A typical calibration graph for the new LOS sensor presented in Figure 4 and showed that the slope was – 58.3 ± 0.7 mV/decade in the range of 1.0×10^{-4} to 1.0×10^{-2} M with a limit of detection equal to 5.0×10^{-5} M.

Effect of pH

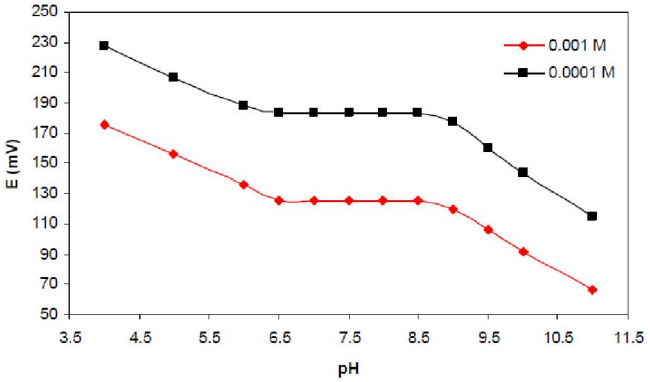

Figure 5 : Effect of pH of the test solution on the potential response of the proposed losartan potassium carbon paste electrode

The influence of pH on the LOS sensor response was examined for 1.0×10^{-3} and 1.0×10^{-4} M drug solutions at various pH values. The pH was varied by potassium hydroxide and hydrochloric acid addition. The results observed are shown in Figure 5. As can be seen, the prepared LOS sensor can be correctly used in the pH range 6.5 – 9.0. The acidic (pH > 6.5) and highly basic regions (pH > 9.0) exhibit a potential variation of the proposed electrode compared to the pH range of 6.5 – 9.0 where the potential remains stable. A possible explanation of this phenomenon is the varying ratio of the ionic forms of LOS at different pH values, or the effect of the hydroxide ions on the electrode response.

Response time, homogeneity and stability of the electrode

The response time is a crucial parameter when evaluating the performances of any ion selective electrodes[41]. It was estimated by instantaneous changing

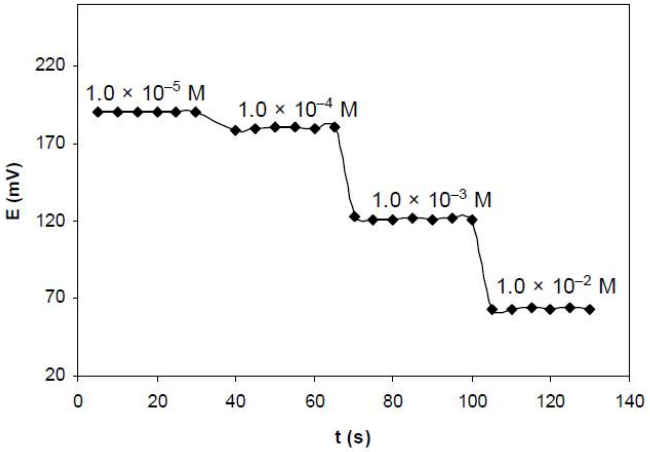

Figure 6 : Dynamic response time of the proposed losartan potassium carbon paste electrode

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TABLE 3 : Potentiometric selectivity coefficients of the proposed losartan potassium carbon paste electrode using the matched potential method (MPM)

Interferent	$\log K^{Pot}_{LOS,J}$
NO_3^-	- 1.27
Cl^-	- 2.63
CH_3COO^-	- 2.98
$H_2PO_4^-$	- 3.00
I^-	- 2.94
Glycine	- 3.13
Lactose	- 3.23
Sacarose	- 3.17
Glucose	- 3.29
Fructose	- 3.26

the LOS concentration in solution from 1.0×10^{-5} to 1.0×10^{-2} M. As seen from Figure 6, it was found that the response time for LOS sensor was to be 5 s for a high concentration level. At lower concentrations the response time was slightly longer 10s.

To test the paste homogeneity, the new LOS sensor was used to measure the potential of a 1.0×10^{-4} M standard drug solution. After each measurement, the past surface was regenerated as described in the paragraph 2.4. For ten repetitions, the results show an average of 177.0 mV for potential measurements with a relative standard deviation of 2.7, which can be an acceptable value.

Moreover, after five times of use, we observed that the slope was decreased slightly from -58.9 ± 0.9 to -56.4 ± 0.7 mV/decade. This decrease may be attributed to surface contamination and memory effect[42]. Therefore, the sensor surface should be polished to expose a new fresh layer ready for use after each calibration.

Reproducibility of the losartan MCPE was assessed by plotting the calibration graph of five different sensors with the identical paste composition. The reproducibility for the proposed electrode is also satisfactory (for five plots, the average slope is -57.3 ± 0.8 mV/decade).

In order to evaluate the stability of the proposed electrode, calibrations were performed periodically (week to week). The obtained data confirmed that sensor exhibit a stable and an acceptable response during tow months.

Selectivity of the electrode

The selectivity behaviour of the new LOS sensor was demonstrated using the recommended matched potential method (MPM)[43]. The obtained selectivity coefficient values were compiled in TABLE 3. The value of selectivity coefficient should be found smaller than 1.0 to confirm that the developed sensor responds more to LOS ions than interfering ions.

The obtained values, presented in TABLE 3 reveal that the proposed electrode displays high selectivity for losartan and lower response for the interfering species present in solutions. No interference was observed with the inorganic anion (NO_3^-, Cl^-, CH_3COO^-, $H_2PO_4^-$ and I^-); they can thus be used as reagent to prepare the buffer solution. The effect of some pharmaceutical excipients (glycine, lactose, glucose and fructose) was also examined. No interference was noted for those com-

TABLE 4 : Determination of losartan potassium in its pharmaceutical formulations

Sample	Potentiometric method		HPLC method	
	X ± S.E.	R.S.D (%)	X ± S.E.	R.S.D (%)
Lozar® (50 g/tablet)	99.80 ± 0.40	1.07	101.03 ± 0.63	1.43
t-test	1.221 (2.306)			
F-test	1.796 (6.388)			
Zartan® (50 g/tablet)	100.43 ± 0.71	1.63	98.72 ± 0.46	1.04
t-test	1.429 (2.306)			
F-test	1.886 (6.388)			

The number of replicate measurement = 5; X ± S.E.: recovery ± standard error; R.S.D. : relative standard deviation; The values in parentheses are the corresponding theoretical values for t and F at P = 0.05

pounds used in tablet, is mainly explained by the dissimilarity in their polarity and lipophilicity relative to those of LOS ions.

Analytical determinations

The new electrode was successfully applied for determination of losartan potassium content in tablet dosage forms by using direct potentiometry method as can be seen in TABLE 4.

Using the new LOS sensor, the recoveries, from 5 replicate measurements, ranging from 99.8 % to 100.43 % were obtained and small relative standard deviations were also obtained ranging from 1.07 to 1.63. All of those results indicate a good selectivity, sensitivity and precision of the proposed method.

Also the results obtained were compared with the reported HPLC method[13]. The calculated values of F- and t-test [44], compiled in TABLE 4, were less than the critical (tabulated) ones. Thus, there is no important difference between the precision and the accuracy of the potentiometric and HPLC methods at 95% confidence levels. In summary, the obtained results showed that the new fabricated LOS sensor has good efficiency in terms of sensitivity, selectivity and accuracy. It can be considered as an interesting method for quality control analysis. Here it should be mentioned another time that there are no papers reporting on potentiometric methods for the determination of LOS in pharmaceutical formulations. Considering the advantages of the suggested ISE, such as their simplicity of fabrication and use, easy of maintenance, low-cost especially the use of the graphite from pencil, stability and lifetime, it can be considered as a competitive method in comparison with sophisticate technique as the chromatographic method.

CONCLUSION

In this paper, a novel losartan potassium ion-selective electrode is described by using a modified carbon paste electrode. The proposed electrode based on losartan- phenanthroline-iron (II) as modifier might be a useful analytical tool in the determination of losartan potassium in different pharmaceutical formulations. The electrode shows high sensitivity, high selectivity and fast response time with extremely low-cast. The present study shows that the new LOS potentiometric MCPE offers an attractive solution for investigation of losartan potassium over other costly analytical methods.

ACKNOWLEDGMENTS

This work was supported by the Tunisian Ministry of Higher Education and Scientific Research. We would like to thank "The National Laboratory of Drug Control, Tunis, Tunisia" for providing LOS pure sample.

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