Novel Ion Selective Electrodes for Determination of Lisinopril: A Study of Plasma and Plasma Proteins Effect.

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Abstract: Three lisinopril-selective electrodes were developed with different techniques and in different polymeric matrices. Precipitation based technique with bathophenanthroline-ferrous as cationic exchanger in polyvinyl chloride (PVC) was used for the fabrication of sensor I (classical electrode) and sensor II (coated wire electrode). Hydroxypropyl ß cyclodextrin-based techniques were used for the fabrication of sensor III using tecoflex (graphite electrode).Linear responses were obtained for the three sensors in the concentration ranges $10^{-7} – 10^{-4}$ M, $10^{-6} – 10^{-3}$ M and $10^{-6} – 10^{-4}$ M with slopes of 36.6 2, 32.66 and - 50.37 mv/decade for sensors I , II and III; respectively. The average recoveries are of 99.75 ± 1.141 %, 99.51± 1.198% and 99.79 ± 1.261% for sensors I , II and III respectively The effect of pH and temperature were studied for the three sensors . The sensors show good selectivity to the drug in presence of a variety of inorganic and organic interferents including drugs of related substances. The proposed procedures were compared to the British pharmacopoeial method and showed no significant difference. The effect of serum levels of electrolytes (145 mmol/L Na^+, 4.3 mmol/L K^+ and 1.26 mmol/L Ca^{2+}) was also studied and was found to be negligible. The behavior of all three sensors in presence of bovine serum albumin (BSA), globulins and human plasma was studied. The three sensors were then used to determine lisinopril in plasma with average recoveries of 88.45 ±1.284 %, 83.42 ± 1.6% and 99.64 ± 0.972 % for sensors I , II and III; respectively.
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1. Introduction:

Lisinipril, a lysine analogue of the nonsulfhydryl angiotensin converting enzyme (ACE) inhibitor enalapril, is used for the treatment of hypertension and congestive heart failure [(1)]. Chemically, lisinopril is (2S)-1-[(2S)-6-amino-2-[[(2S)-1-hydroxy-1-oxo-4-phenylbutan-2-yl]amino] hexanoyl] pyrrolidine-2-carboxylic acid (figure 1). The measurement of this drug in biological fluids is challenging since it has poor electromagnetic absorbance due to weak benzene chromophore. Reversed phase high performance liquid chromatography (RP-HPLC) of drugs containing proline or proline related residue may show peak splitting owing to slow *cis-trans* isomerization, caused by hindered rotation around the N-substituted peptide bond [(2-4)]. Lisinopril, being an amphoteric peptide-like molecule, cannot be efficiently extracted from biological fluids with organic solvents [(5)].

The official methods for the determination of lisinopril are potentiometric acid-base titration [(6)] and HPLC [(7)]. Various methods have been developed for the determination of lisinopril in pharmaceutical preparations including spectrophotometric [(8–10)] spectrofluorimetric [(8,9)], HPLC [(9)], micellar electrokinetic chromatography [(4)] and gas liquid chromatography [(11)]. Capillary electrophoresis was also applied to the determination of lisinopril in pharmaceutical tablets [(12,13)]. Methodsfor determination of lisinopril in biological fluids include HPLC [(5,14,15)], fluoroimmunoassay [(16)], radioimmunoassay [(17)] and fluoroenzymatic assay [(18)].

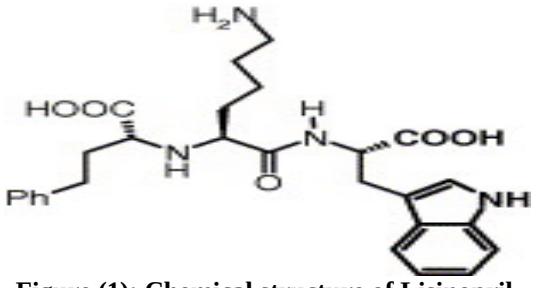

Figure (1): Chemical structure of Lisinopril.

Modern ion selective electrodes (ISEs) based on material transport across a specific membrane are now widely used in the determination of trace amounts of analytes as well as drugs in pure form and pharmaceutical dosage forms [(19)]. The material transport includes both neutral and charged

complex species, or simple ions [20,21]. The high selectivity of these electrodes imparts a great advantage over other techniques [22]. Analytes in colored, turbid or viscous samples can be determined accurately. They show rapid responses to changes in the concentration. Furthermore, they may be used for measurement over a wide concentration range. ISEs are generally tolerant of small pH changes. A further advantage is that they are relatively cheap and simple to develop, set up and run. Moreover, the chemical design of the electrodes has been developed to give superior selectivity and response [23].

In the present work, three sensors were studied, two of which depend on the anionic properties of lisinopril which allow the use of precipitation-based technique with bathophenanthroline-ferrous both in classical and coated wire electrodes. The third sensor is hydroxypropyl ß-cyclodextrin -based using tecoflex (graphite microelectrode). This study also includes the behavior of all three electrodes in presence of plasma, bovine serum albumin (BSA) and globulins.

2. Materials and methods

2.1- Instruments

Jenco digital ion analyser Model 6209 pH/ mV/ °C meter, Orion, Ag /AgCl Double junction reference electrode, model 90-02 containing 10% w/v KNO_3 in the outer compartment and Bandolin Sonorex, Rx 510 S, Magnetic stirrer.

2.2- Materials

Lisinopril dihydrate pure sample was kindly supplied by Glopbal Napi pharmaceuticals, 6th October city, Egypt. Purity was reported to be 100 ± 0.3 %. All reagents and solvents used were of analytical reagent grade. Water used was double distilled. Bathophenanthroline (4,7-diphenyl-1,10-phenanthroline); Sigma,GmbH, Germany, (2-hydroxy propyl) ß-cyclodextrin ;Fluka Chemie Gmbh, Germany, Polyurethane (Tecoflex); Fluka Chemie Gmbh, Germany, Bovine serum albumin (BSA) ; Sigma, USA, Gamma Globulins ; Fluka , Germany , Frozen human plasma was obtained from VACCERA, Batch no 07/G.

2.3- Procedures

Precipitation- based technique for preparation of PVC sensor (sensor I)

A 5 ml aliquot of 10^{-1} M aqueous lisinopril solution was treated with two drops of 10 % ammonia solution, mixed with 5 ml bathophenanthroline – ferrous solution and shaken for 5 minutes. The resultant precipitate formed was filtered using Whatmann no. 42 filter paper, washed with cold water, dried at room temperature (≈ 25°C) and ground to fine powder. In a glass petri dish (5 cm diameter) , 10 mg of lisinopril - ion exchanger was thoroughly mixed with 0.35 ml of DOP and 0.19 g of PVC. The mixture was dissolved in 6 ml of THF. The petri dish was covered by a filter paper and left to stand for 24 hrs to allow solvent evaporation at room temperature. A master membrane of 0.1 mm thickness was obtained. From the master membrane, a disk (≈ 8 mm diameter) was cut using a cork borer and pasted using THF to an interchangeable PVC tip that was clipped into the end of the electrode glass body. Equal volumes of 10^{-2} M lisinopril and 10^{-2} M KCl were mixed and this solution was used as an internal reference solution. Ag/AgCl wire (1mm diameter) was immersed in the internal reference solution as an internal reference electrode. The electrode was preconditioned by immersing in 10^{-2} M lisinopril solution for 24 hours. Prior to use, the electrode was washed with distilled water.

Fabrication of PVC based coated wire electrode (sensor II)

The lisinopril – ion exchanger complex was prepared as mentioned previously. Then 10 mg of lisinopril - ion exchanger was thoroughly mixed with 0.35 ml of DOP and 0.19 g of PVC. The mixture was mixed with 3 ml of THF to obtain a colloidal solution. The electrode was prepared by applying 3 layers of the membrane mixture onto a platinum wire tip (15 cm length, 1 mm diameter) at 20 minutes interval using a Pasteur pipette. The electrode was left standing at room temperature for 24 hours to dry. The platinum wire was covered by insulating polymer such that only the coated tip was exposed to the solution. Preconditioning was done by immersing the sensor in 10^{-2} M lisinopril solution for 2 hours. Prior to use, the electrode was washed with distilled water.

Hydroxypropyl ß-cyclodextrin -based technique for the preparation of tecoflex-graphite sensors (sensor III)

A graphite rod is inserted in a PTFE tube such that its tip is exposed (0.5 mm diameter & 0.2 mm length). Electroactive membrane was prepared by thorough mixing of 0.04 g (2-hydroxypropyl) β-cyclodextrin and 0.4 g 2-nitrophenyl octyl ether (NPOE) and 32.8% tecoflex till homogeneity. Mixture was then dissolved in 3 ml (THF). Solvent was slowly evaporated until an oily concentrated mixture was obtained. One drop of the mixture was applied to the surface of the graphite rod. It was then left standing at room temperature for 24 hours to dry.

Calibration of the sensors.

The sensors were conditioned by soaking in 10^{-2} M aqueous lisinopril solution for 24 , 2 and 2 hours for sensors I, II and III; respectively. Storage was in the same solution when not in use. The conditioned sensors were calibrated by separately transferring 50 ml aliquots of solutions covering the concentration range of (1×10^{-8} to 1×10^{-3} M) lisinopril into a series of 100 ml beakers. The sensor and the reference electrode were immersed in each solution with constant stirring using a magnetic stirrer and recording the potential readings within ± 1 mv. The sensor was washed in distilled water between measurements. The electrode potential was plotted versus negative logarithmic concentration of lisinopril.

Study of the effect of plasma proteins.

PVC and Tecoflex lisinopril selective electrodes were transferred back and forth between aqueous solutions containing a simulated clinical electrolyte background (145 mmol/L Na^+ , 4.3 mmol/L K^+ and 1.26 mmol/L Ca^{2+}) , electrolytes solutions that contained BSA (10 g/L) and electrolytes solutions that contained gamma globulins (5 g/L). The ISE and the reference electrode were placed first in the aqueous analyte solution and the potential difference recorded after 20 min. The electrodes were then transferred to the protein containing solution and the potentials recorded after 20 min. This is a standard method for measuring protein induced asymmetry potentials in calcium ISEs [24,25]. All calibration measurements were made at 25 ± 1ºC using a continuous dilution method described previously [26,27].

Potentiometric determination of lisinopril in plasma.

Lisinopril solutions were prepared by mixing 5 ml plasma with aliquots of stock solution and the volume was completed to 25 ml using phosphate buffer pH 8 to obtain concentrations (1×10^{-6}, 1×10^{-5} M and 1×10^{-4}). The measurements were made using the procedure mentioned above.

3. Results and Discussion:

Lisinopril behaves both as anion in basic medium and cation in acidic medium as it has four dissociation constants (pK_a) of 2.5, 4, 6.7 and 10.1[28]. The present study is based on the anionic properties of the drug in sensors I and II, where bathophenanthroline-ferrous was found to be optimum anionic exchanger due to its low solubility product and suitable grain size. Lisinopril was found to form 1:1 ion association complex with bathophenanthroline-ferrous as proven by elemental analysis and the obtained Nernstian slopes.

The third sensor is hydroxypropyl β-cyclodextrin-based coated on graphite matrix. Cyclodextrins are optically active oligosaccharides that form inclusion compounds in the aqueous and in solid state with organic molecules because their chemical structure provides well-defined inclusion cavities with a specific receptor function [29]. Hydroxypropyl β- cyclodextrin shows better interaction with guest molecules than β- cyclodextrin owing to its greater hydrophobicity and its larger diameter relative to β- cyclodextrin [30]. They can be applied as sensor ionophores to potentiometric ISEs [29,31].

The electrochemical cell of the suggested electrodes for the determination of lisinopril can be illustrated diagrammatically as follows:

Sensor I

Double junction Ag/AgCl reference electrode	Test solution (Lisinopril)	Membrane (lisinopril-association complex in PVC/DOP)	Internal reference solution : 10^{-2} M KCl + 10^{-2} M lisinopril in 1:1 ratio	Ag/AgCl internal reference wire

Sensor II

Double junction Ag/AgCl reference electrode	Test solution (Lisinopril)	Membrane (lisinopril-association complex in PVC/DOP	Platinum wire

Sensor III

Double junction Ag/AgCl reference electrode	Test solution (Lisinopril)	Membrane (Tecoflex/NPOE/ HP-β-CD)	Graphite rod	Metallic Mercury

The electrochemical performance characteristics of the three investigated lisinopril-selective electrode were evaluated according to the IUPAC recommendation data [32,33] and summarized in table (2). The electrodes displayed constant potential readings which did not vary by more than ± 2 mV on the same day. Linearity range from day-to-day and calibration slope did not change by more than ± 2.5 mV/decade concentration over a period of 8, 6 and 12 weeks for sensors I, II and III; respectively (figure 2).

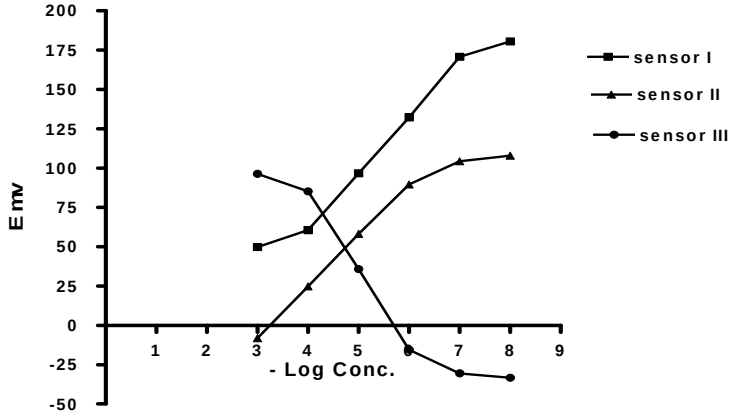

Figure (2): Profile of the potential in mV vs. –log concentration of lisinopril in M using the three studied electrodes: Lisinopril-bathophenanthroline-iron-PVC classical (sensor I), Lisinopril-bathophenanthroline-iron-PVC coated wire (sensor II) and hydroxypropyl ß-CD-Tecoflex graphite (sensor III)

The influence of pH on the potential response of the three electrodes was studied using concentrations 10^{-4} ,10^{-5} , 10^{-6} and 10^{-7} M for sensor I , concentrations 10^{-3} ,10^{-4} ,10^{-5} , and 10^{-6} M for sensor II and concentrations 10^{-4} ,10^{-5} , and 10^{-6} over the pH range 7.5 - 10. The studied pH range was selected based on the fact that lisinopril decomposes rapidly in acidic media and the decomposition is minimal at pH higher than 7[28]. Fairly constant potentials were obtained over the pH range of 8-9, 8-10 and 8-9 for sensors I , II and III; respectively .The suggested electrodes exhibit slight increase in their potentials as the temperature rises in the range of 25 ─ 45 ◦C; however, the calibration graphs obtained at different temperatures were parallel. The limit of detection, slope and response time did not significantly vary with variation of temperature, indicating reasonable thermal stability up to 35 ◦C.

Table (1): General characteristics of the three lisinopril -selective electrodes and validation parameters of assay.

Parameter	Sensor I	Sensor II	Sensor III
Slope (mV/ decade) a	36.62	32.66	-50.367
Intercept (mV)	-86.31	-105.85	287.01
LOD (M) b	7.94 *10-8	4.25 *10-7	4.98 *10-7
Response Time (Sec.)	30 for conc ≥ 10-5 to 60 for conc ≤ 10-5	40	40
Working pH Range	8 – 9	8-10	8-9
Concentration Range (M)	10-7 – 10-4 M	10-6 – 10-3 M	10-6 – 10-4 M
Stability (weeks)	8	6	10
Average Recovery (%) ± SD a	99.75 ± 1.141	99.51 ± 1.198	99.79 ± 1.261
Correlation coefficient	0.9997	0.9998	0.9999
Repeatability (SDr)	0.423	0.407	0.849
Intermediate Precision (SDint)	0.421	0.406	0.961
Ruggedness c	98.29 ±1.021	98.89 ± 1.313	99.22 ± 1.352

[a] Average of five determinations [b] Limit of Detection (measured by interception of the extrapolated arms of figure) [c] average recovery percent of determining 10^{-6}, 10^{-5} and 10^{-4} M lisinopril for the studied electrode using Jenway 3310 digital ion analyzer instead of Jenco digital ion analyser Model 6209

The effect of twelve interfering substances upon the performance of the sensor was studied by separate solution method using the rearranged Nicolsky–Eisenman equation [32]:

$$\log K^{Pot.}_{A,B} = [(E_B - E_A) / (2.303\ RT / Z_A F)] + [1 - (Z_A / Z_B)] \log [A]$$

Where E_A is the potential measured in 10^{-4} M lisinopril solution, E_B is the potential measured in 10^{-4} M interferent solution, Z_A and Z_B are the charges of drug and interferent, respectively, and 2.303 RT/Z_AF represents the slope of the calibration plot (mV / concentration decade).

As shown in table (2), the selectivity of the three studied sensors in the presence of related substances, substances which may be present with lisinopril in dosage forms, amino acid and other antihypertensives. These include sodium lauryl sulphate, EDTA disodium salt, calcium chloride, zinc sulphate, hydrochlorothiazide diuretic, cystine, glycine, perindopril erbutamine, valsartan, losartan potassium, and candesartan. The results obtained prove that the proposed sensors have excellent selectivity in the presence of excipients, amino acids and electrolytes and reasonable selectivity in the presence of other antihypertensives.

Table (2): Potentiometric selectivity coefficients for Lisinopril – selective electrode

Interferent*	Sensor I	Sensor II	Sensor III
$CaCl_2$	5.48×10^{-4}	2.23×10^{-4}	2.08×10^{-4}
$ZnSO_4$	6.06×10^{-4}	5.73×10^{-4}	1.2×10^{-4}
Sodium lauryl sulphate	8.19×10^{-4}	5.52×10^{-4}	2.45×10^{-4}
EDTA	2.78×10^{-4}	3.98×10^{-4}	3.89×10^{-4}
O-phenanthroline	1.45×10^{-4}	2.36×10^{-4}	1.25×10^{-4}
Glycine	5.87×10^{-4}	3.96×10^{-4}	5.48×10^{-4}
Cystine	3.7×10^{-4}	8.4×10^{-5}	4.59×10^{-4}
Perindopril	5.48×10^{-4}	4.62×10^{-4}	4.85×10^{-4}
Candesartan	7.048×10^{-4}	1.39×10^{-4}	2.56×10^{-4}
Hydrochlorothiazide	5.7×10^{-4}	9.56×10^{-5}	2.66×10^{-4}
Losartan K	6.45×10^{-4}	3.7821936	1.56×10^{-4}
Valsartan	9.53×10^{-4}	4.20×10^{-4}	2.82×10^{-4}

*Aqueous solutions of 1×10^{-4} M were used

ISEs have been widely applied in the study of binding of ionic drugs to macromolecules such as proteins by monitoring the change in physicochemical property (potential) of the protein – drug system upon binding [34]. The principle is based on the fact that in a solution containing protein molecules, free ionic ligand (drug) and protein bound ionic ligand, the ISE responds only to the free ionic ligand species. Because of their highly hydrophobic character, neither the protein molecules nor the protein - bound ions can penetrate into the organic solvent of the electrode membrane to cause a change in potential [35,36]. Basic drugs tend to bind to α_1 acid glycoprotein whereas acidic drugs mainly bind to albumin [37-39]. However, in case of lisinopril protein binding is negligible as it only binds to Angiotensin converting enzyme to produce its pharmacological action [40,41]. Thus the effect observed is attributed to the interaction of proteins with the sensors not the drug.

For each of the three sensors, 3 calibration graphs were plotted by switching the sensor between aqueous electrolytes solution (145 mmol/L Na^+, 4.3 mmol/L K^+ and 1.26 mmol/L Ca^{2+}) , electrolytes solution containing BSA (10g/L) and electrolytes solution containing gamma globulins (5g/L). In all graphs, the slope of each electrode was checked within its linearity range. Nernestian responses were maintained despite the shifts in original electromotive forces (figures 3-5). For sensor I, BSA caused a drop in potential (≈2.82 mv) in comparison to original electromotive forces. Gamma globulins caused a drop in potential (≈1.92 mv). For sensor II, BSA caused a drop in potential (≈3.7 mv) in comparison to original electromotive forces. Gamma globulins caused a drop in potential (≈2.86 mv). Sensor III was not affected by the presence of neither BSA nor gamma globulins. Table (3) summarizes the average recoveries of lisinopril in BSA, gamma globulins and plasma for the three sensors.

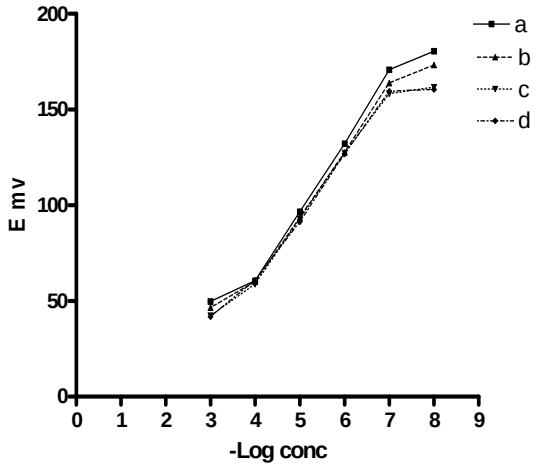

Figure (3): Response curves for calibration of lisinopril (a) aqueous solution ; in presence of (b) 145 mmol/L Na^+ , 4.3 mmol/L K^+ and 1.26 mmol/L Ca^{2+}, (c) 145 mmol/L Na^+ , 4.3 mmol/L K^+ and 1.26 mmol/L Ca^{2+}) and BSA (10 g/L) , (d) 145 mmol/L Na^+ , 4.3 mmol/L K^+ and 1.26 mmol/L Ca^{2+}) and gamma globulins (5 g/L) for sensor I

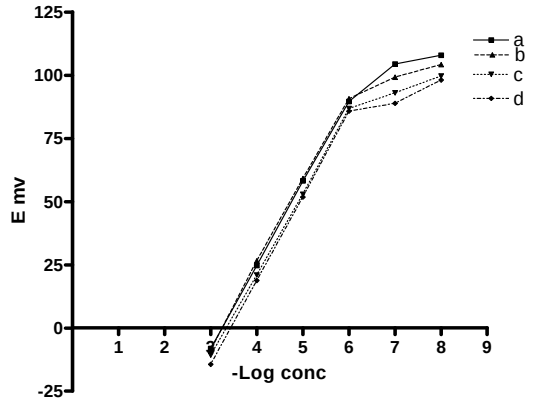

Figure (4): Response curves for calibration of lisinopril (a) aqueous solution ; in presence of (b) 145 mmol/L Na^+ , 4.3 mmol/L K^+ and 1.26 mmol/L Ca^{2+}, (c) 145 mmol/L Na^+ , 4.3 mmol/L K^+ and 1.26 mmol/L Ca^{2+}) and BSA (10 g/L) , (d) 145 mmol/L Na^+ , 4.3 mmol/L K^+ and 1.26 mmol/L Ca^{2+}) and gamma globulins (5 g/L) for sensor II

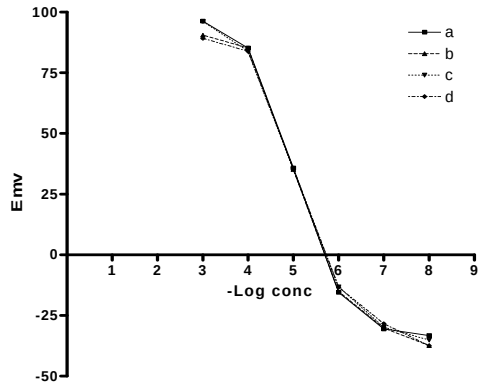

Figure (5): Response curves for calibration of lisinopril (a) aqueous solution ; in presence of (b) 145 mmol/L Na^+ , 4.3 mmol/L K^+ and 1.26 mmol/L Ca^{2+}, (c) 145 mmol/L Na^+ , 4.3 mmol/L K^+ and 1.26 mmol/L Ca^{2+}) and BSA (10 g/L) , (d) 145 mmol/L Na^+ , 4.3 mmol/L K^+ and 1.26 mmol/L Ca^{2+}) and gamma globulins (5 g/L) for sensor III

The results obtained prove that, tecoflex-based sensor gives stable results in both slopes and mv readings as revealed by the high accuracy and precision obtained in presence of proteins and plasma[42]. Whereas, sensors incorporated in PVC polymer suffered a drop in potential accompanied by noise. This may be attributed to the fact that protein adherence to PVC matrix may lead to its fouling [42,43].

Table (3): Average recoveries of lisinopril in presence of BSA (10 g/L), gamma globulins (5 g/L) and plasma

	Recovery %		
	Sensor I	Sensor II	Sensor II
BSA	91.78 ± 0.933	90.17 ± 1	99.7 ± 0.58
Globulins	95.38 ± 1.061	90.86 ± 1.129	99.86 ± 0.751
Plasma	88.45 ± 1.284	83.42 ± 1.6	99.64 ± 0.972

4-Conclusion:

Three lisinopril-selective sensors were constructed and successfully applied in the potentiometric determination of lisinopril. The advantages of the proposed sensors are the ease of construction, rapid manipulation, low cost, fast response, wide concentration range and applicability to to turbid and colored solutions. The methods offer sensitive, selective and convenient techniques for the determination of lisinopril in concentration ranges $10^{-7} - 10^{-4}$ M, $10^{-6} - 10^{-3}$ M and $10^{-6} - 10^{-4}$ M for

sensors I , II and III ; respectively. The three sensors were applied to study the effect of proteins such as BSA and gamma globulins as well as plasma. The results obtained were used to compare between the efficiency of polymers. Tecoflex proves to be more accurate and sensitive to the drug in plasma than PVC. Thus, tecoflex based sensor can be used for lisinopril determination in biological samples such as plasma without any pretreatment procedures.

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