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Plastic Sensor for Losartan Potassium Determination based on Ferroin and Ionic Liquid

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In this study, a potentiometric sensor based on a plastic-membrane was introduced for the determination of losartan potassium in pharmaceutical formulations. The sensing element contained an ion-pair, which was synthesized by the interaction of losartan potassium and 1,10 phenanthroline monohydrate. The best membrane sensor response was obtained by a membrane composed of 30.6% PVC, 61.4% *o*-NPOE, 7.5% ion-pair and 0.5% ionic liquid. The proposed method was successfully applied for the determination of losartan potassium in some formulations. The proposed sensor showed a linear dynamic range between 5.0×10^{-5} and 1.0×10^{-2} M of losartan potassium with a Nernstian slope of 62.0 ±1.0 mV per decade and a lower detection limit of 3.5×10^{-5} M. It displayed a fast response time of about 10 s, and a lifetime of about three weeks without any significant loss in its performance.

Keywords: Losartan potassium, potentiometric sensor, PVC membrane electrode, ion-pair.

1. INTRODUCTION

Losartan potassium (LsK) is chemically known as 2-n-butyl-4-chloro-5-hydroxymethyl-1-((2´-(1H-tetrazol-5-yl)(biphenyl-4-yl) methyl) imidazole potassium salt (Figure1a). It is a strong antihypertensive agent, non-peptide, and exerts its action by specific blockade of angiotensin-II receptors [1-3]. LsK develops a gradual and long-lasting effect as antihypertensive, so it has become a new alternative to treat this frequent chronic disease. LsK is a light-yellow solid with molecular weight and a melting point of 461 and 183.5–184.5 °C, respectively. It is also soluble in water (3.3 mg L^{-1} at pH 7.8) with pK_a value of 4.9. The determination of losartan is carried out in tablets using HPLC, capillary electrophoresis, and super-critical fluid chromatography [4–6]; in bulk and solid dosage forms using colorimetric method [7] and spectrophotometric [8]; in drug formulations by HPLC [9]

and simultaneously, with its degradants in stressed tablets by LC-MS/MS [10] and HPTLC [11]. It could also be determined by its active metabolite in biological fluids by HPLC [12–14] and in urine by gas chromatography-mass spectrometry [15].

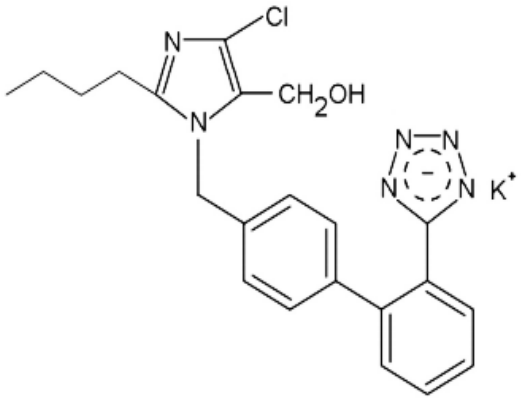

Figure 1.a. Chemical formula of losartan potassium.

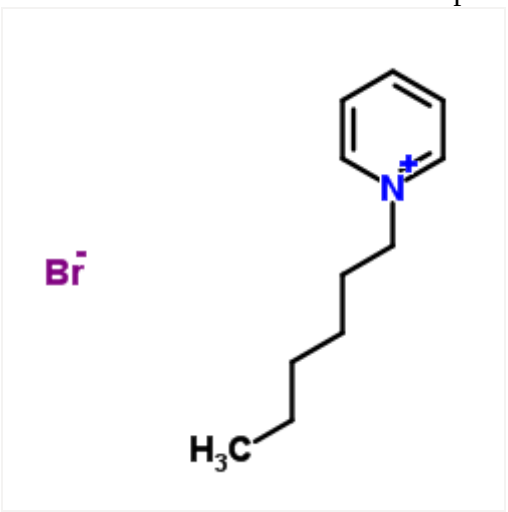

Figure 1.b. Structural formula of the used ionic liquid 1-hexylpyridinium bromide.

Different electrochemical measurement techniques have been implemented for the drug analysis in recent years. The potentiometric sensor has the advantages of rapidity and ease of preparation, fast response time, reasonable selectivity, wide linear dynamic range, and low cost, and hence, these characteristics lead to the preparation of numerous sensors for several ionic species. Owing to the importance of drug-monitoring system [16–19], polyvinyl chloride (PVC) membrane electrodes, one of the subdivisions of potentiometric sensors, have found a wide range of applications in the analysis of ionic species [20].

In the present work, a conventional PVC membrane sensor based on losartan-1, 10-phenanthroline ion-pair complex was applied for the quantification of losartan potassium in its

solutions. In addition, the membrane response was studied with the application of 1-hexylpyridinium bromide (Figure 1b) as an ionic liquid (IL).

2. EXPERIMENTAL

2.1. Equipment

All potentiometric measurements were done at 25 ±1 °C with a Wheeler (Model WD–5010EC) pH/mV meter and losartan-membrane sensor in conjunction with a Wheeler double junction Ag/AgCl reference electrode containing 10% (w/w) potassium nitrate solution in the outer compartment. A combination pH electrode (Ross-model) was also used for pH adjustment.

2.2. Chemicals and reagents

All applied chemicals were of analytical grade. Deionized water was used for all aqueous solutions. A pure losartan potassium sample was supplied by Sigma Pharmaceuticals, Quesna city, Egypt. High molecular weight PVC powder, 1-hexyl pyridinium bromide, *o*-nitrophenyloctyl ether, and potassium *tetra-kis* (4-chloro-phenyl) borate (KTClPB) were purchased from Aldrich Tetrahydrofuran (THF) and 1,10-phenanthroline monohydrate (Phen) were obtained from Fluka and Euromedex, respectively. Solid salts of maltose, ammonium citrate, ammonium oxalate, benzamide, glycine, Na_2SO_4, KCl, ammonium renieckate, $CuSO_4.5H_2O$, KCl, KNO_3, KCN of the highest purity were used during the experiment. A standard solution of 10^{-2} M losartan potassium was freshly prepared. Dilute solutions (10^{-2}–10^{-6} M) were also prepared by subsequent dilutions from the stock solution (10^{-2} M).

2.3. Electroactive materials

(Phen-iron II) or Ferroin complex was obtained by weighing 180 mg of 1,10 phenanthroline monohydrate and dissolving in 10 mL 10% v/v ethanol-water, and subsequently, mixing with 0.5 mL of 10^{-1} M iron (II) sulfate heptahydrate. The obtained mixture was added drop by drop to 40 mL of 10^{-2} M losartan potassium and then stirred for 10 min. After the formation of a red precipitate of Ls-Ferroin, it was filtered, washed with water and then dried and powdered. The IR-spectra of the prepared compounds (Figures 2 (a-c)) confirmed the formation of Ls-Ferroin ion-pair complex.

2.4. Construction of the sensors

The different amounts of Ls-Ferroin ion-pair complex (5.5–11%) along with appropriate amounts of PVC (29.5–31.5%), plasticizer (59.5–63%), and additive (2% KTpClPB 2% or 2–0.5% IL) were first dissolved in tetrahydrofuran (THF). The obtained solution was then mixed well and poured into a Petri dish of 2 cm diameter.

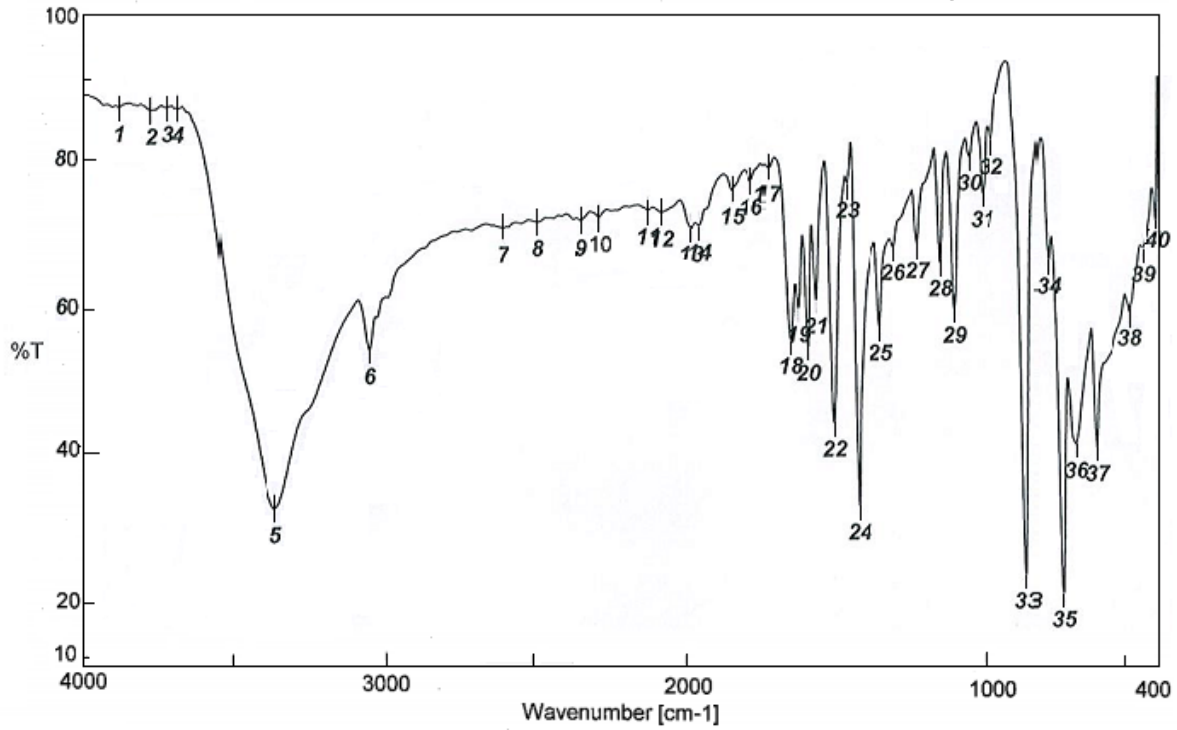

Figure 2.a. Infra-red spectra of 1,10-phenanthroline monohydrate.

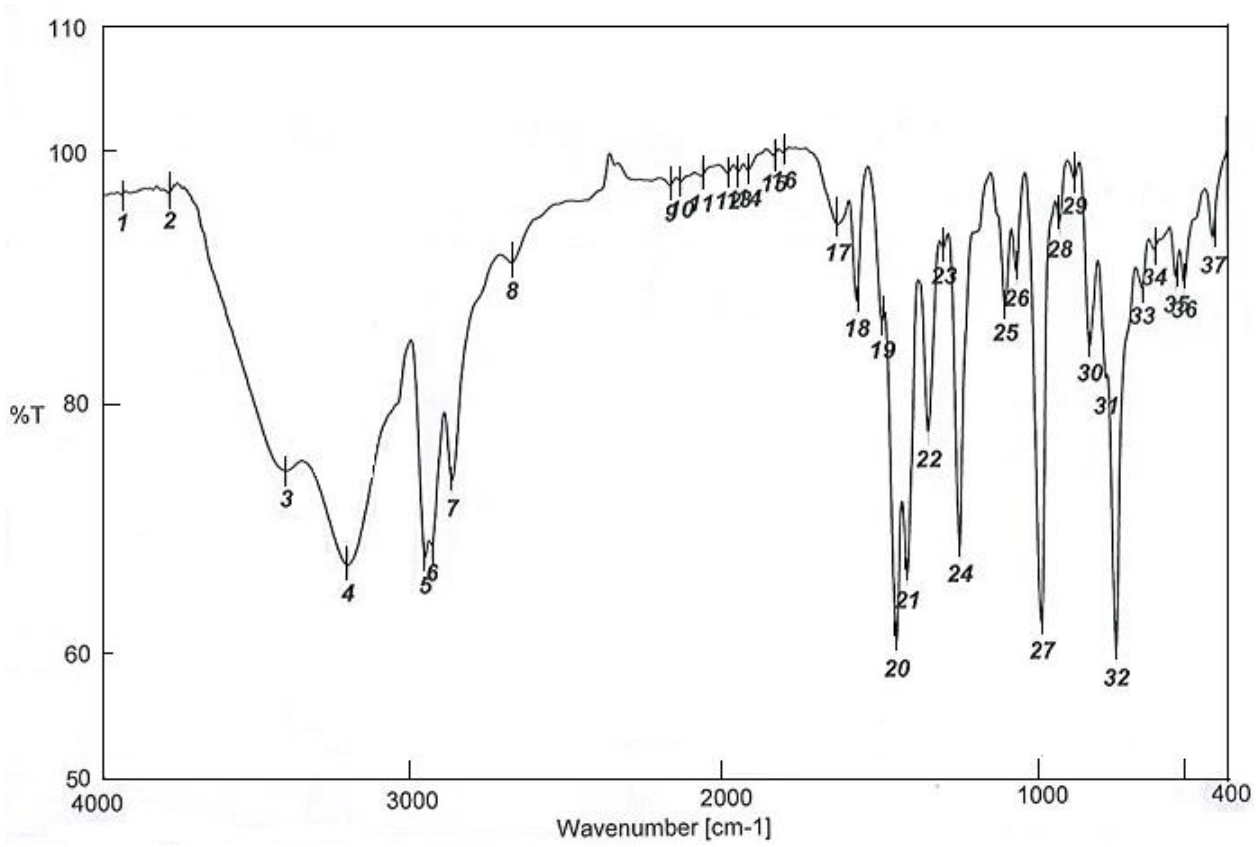

Figure 2.b. Infra-red spectra if losartan potassium (LsK).

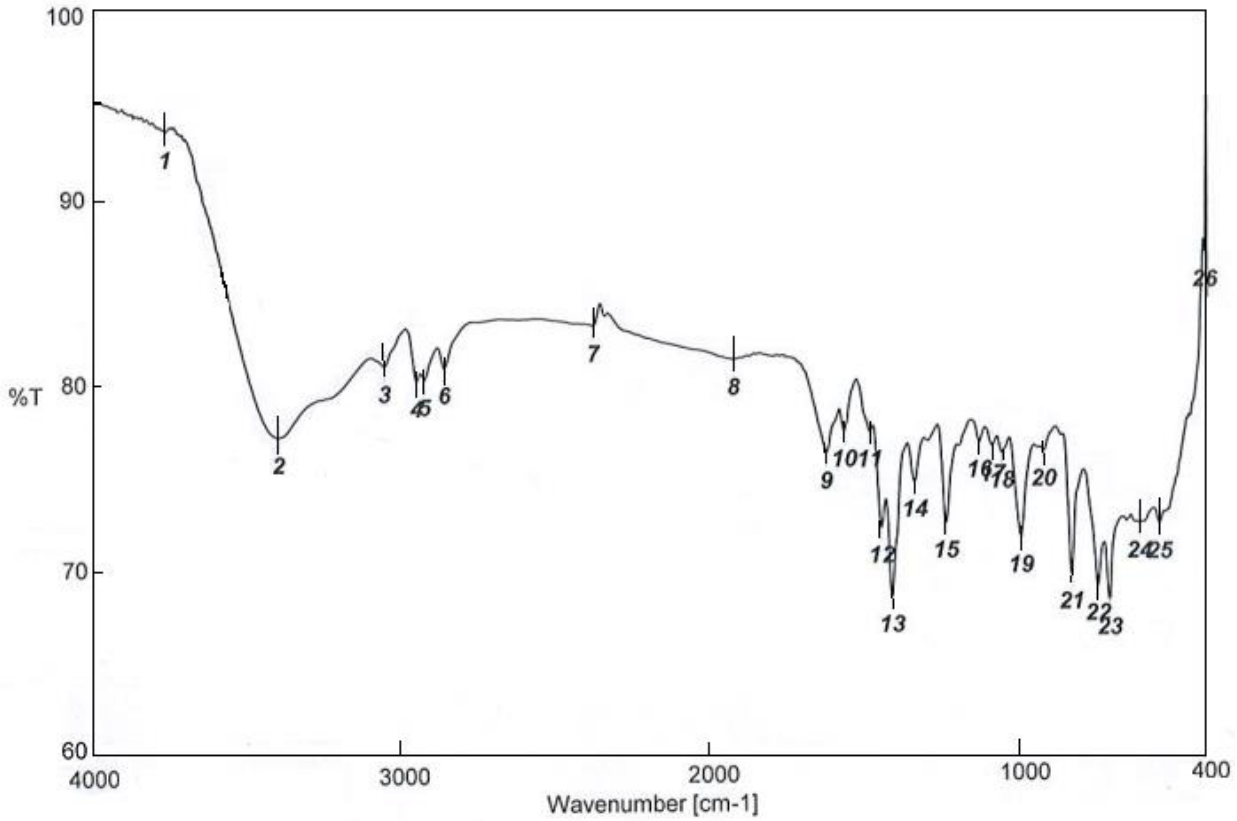

Figure 2.c Infra-red spectra for (Ls-Ferroin) ion-pair association.

THF was then kept at room temperature till the plastic membrane was obtained. The sections of the obtained membrane were cut with a cork borer (10 mm diameter) and glued to the bottom of polyethylene tubing. The tube was then filled with an internal filling solution that was prepared by mixing an equal volume of losartan potassium and potassium chloride. Several compositions were tried to reach the optimum membrane composition.

2.5. Sensor calibration

Aliquots (25 mL) of standard losartan potassium solution (10^{-6}–10^{-2} M) were transferred into a 50 mL beaker. The proposed LS-sensor with the reference Ag/AgCl electrode was then immersed in the solution. The solutions were stirred and the potentials were recorded and plotted as a function of losartan potassium concentration. The obtained graphs were used for the subsequent determination of unknown concentrations of losartan potassium. The lower detection limit of the sensor was taken at the point of intersection of the extrapolated linear segments of the LsK calibration curve.

To study the effect of pH on the electrode response, the EMFs of different LsK concentrations (10^{-2}–10^{-4} M) were recorded at various pH values. The solutions of 0.1M NaOH and 0.1M HCl were used for the pH adjustments.

2.6. Lifespan and response time

Sensor lifespan was examined by monitoring the slope of losartan potassium calibration curve. The potential reading was recorded after stabilization (±1mV), and the emf was plotted as a function of logarithm losartan potassium concentration. The dynamic response of the sensors was studied by measuring the time required to reach a steady potential within ±1 mV after the successive immersion of the sensor in different drug concentrations (10^{-5}–10^{-2} M).

2.7. Determination of selectivity coefficient

The selectivity coefficient of the sensor was determined by the separate solution method (SSM) [21] for 10^{-2} M solution of (LsK) and interferents at solution pH. The coefficient was calculated by rearranging the Nikolsky equation:

$$\log K^{pot}_{Ls^-,J^{z-}} = [(E_J - E_{Ls})/S] + \log [Ls^-] - \log[J^{Z-}]^{1/Z}$$

where

E_{Ls}: The measured potential in 10^{-2} M losartan potassium solution

E_J: The measured potential in 10^{-2} M solution of the interfering cations

S: Slope of the electrode calibration plot

2.8. Determination of losartan in pharmaceutical preparation

Lozapress (25 mg/tablet), Lozapress (50 mg/tablet), Amosar (25 mg/tablet), Amosar (50 mg/tablet), and Aratins 50 mg/tablet were weighed and finely powdered in a small dish. The powder was then dissolved in a minimum volume of 10^{-2} M HCl solution and filtered in a 50 mL volumetric flask using a Whatman filter paper until the pH value reached 7. Both the Ls-sensor and the reference electrodes were immersed in 10 mL of tablet solution. The potential of the solution was directly measured and compared with the calibration graph. The results of losartan amount in some pharmaceutical samples are shown in Table 3. Our results were in satisfactory agreement with the stated content.

3. RESULTS AND DISCUSSION

3.1. Optimization of the Membrane Composition

The performance of an electrode mainly depends on its components [22–24]. The main components of a membrane are PVC matrix, plasticizer, and the ion-pair as a sensing material. Each membrane component plays a specific role in the membrane function and electrode response.

The prepared ion-pair complexes were used as an electroactive material in the construction of the new LsK sensors. Ls-Ferroin was applied as an electroactive ion-pair for the Ls-sensor. The

formation of Ls-ferroin was proved by comparing the IR-spectra of LsK, ferroin, and Ls-ferroin (Figures 4–6). The ion-pairs were incorporated in a membrane containing *o*-NPOE (ε=24) as a plasticizer in PVC matrix, and the performance characteristics of the proposed sensor were evaluated according to the IUPAC recommendations [25].

Table 1. Optimization of membrane components

Membrane No.	**Composition (%)**					**Slope (mV decade^{-1})**	**Linear range (LR), M**	**LD, (M)**	**Life time (Week)**
	ion pair	*PVC*	*plasticizer*	*Add. (KTClPB)*	*ILs*				
1	5.5	31.5	63	_	_	–49.4	1×10^{-2} – 5×10^{-5}	5×10^{-5}	1
2	7.7	30.7	61.6	_	_	–52.6	1×10^{-2} - 5×10^{-5}	4×10^{-5}	2
3	11	29.5	59.5	_	_	–30.5	1×10^{-2} - 1×10^{-4}	9×10^{-5}	2
4	7.5	30	60.5	2	_	–46.3	1×10^{-2} - 1×10^{-4}	6×10^{-5}	3
5	7.5	30	60.5	_	2	–62.2	1×10^{-2} - 1×10^{-4}	9.5×10^{-5}	3
6	7.5	30.2	61	_	1.3	–67.5	1×10^{-2} - 5×10^{-5}	5×10^{-5}	3
7	7.5	30.5	61.2	_	0.8	–62	1×10^{-2} - 1×10^{-4}	1×10^{-4}	3
8	7.5	30.6	61.4	_	0.5	–62	1×10^{-2} - 5×10^{-5}	3.5×10^{-5}	3

Table 1 shows the different parameters of the membrane compositions. Membranes 5, 7, and 8 comply with the Nernstian slope (62.0–62.2 mV/decade) and other membranes (1–4 and 6) show deviations from Nernstian slope (30.5–52.6 and 67.5 mV-decade). Among all tested membranes, it was found that the electrode with membrane 8 showed the best performance (62 mV/decade) because of its best LOD (3.5×10^{-5} M) and wide linear range (5×10^{-5}- 10^{-2} M). This composition contributed to the smallest percentage of IL (0.5%) with IP of 7.5%. Table 2 shows a comparison of the obtained results to that of a carbon paste electrode based sensor [26]. It was noticed that the present electrode with membrane type 8 exhibited a better sensitivity (LR 1×10^{-2} –3.5×10^{-5} M and DL 5×10^{-5} M) (Table 2). Bagheri et al. [27] introduced the carbon paste electrode based on a molecularly imprinted polymer for losartan determination. In their work, the electrode manifested a positive Nernstain response, however, the authors did not give any explanation about their results; this disagrees with both studies [26] and our present work. Nano-based sensor [27] showed the best sensitivity (1.82×10^{-9} M) for losartan.

Table 2. Comparison between performance characteristics of different losartan electrodes with the proposed losartan electrode

No.	Ion pair	Slope (mV decade^{-1})	ILs	Linear range (LR), M	pH	LD, (M)	Life time,	Response time, s	Ref.
1	$(Phen_3\text{-}Fe)^{2+}$ Ls_2)/NPOE	–62	0.5	1×10^{-2} - 5×10^{-5}	6.5–8.5	3.5×10^{-5}	3 weeks	10	Present sensor
2	$(Phen_3\text{-}Fe)^{2+}$ Ls_2)/NPPE	–58.3	-	1×10^{-2} - 1×10^{-4}	6.5–9	5×10^{-5}	2 months, regenerate surface after each 5 times calibration	5–10	26*
3	Nanographene carbon paste/mol. imprint polymer	+59.64	-	1×10^{-2} - 3×10^{-9}	6.0–8.5	1.82×10^{-9}	3 months	6	27**

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Several methods based on 1, 10-phenanthroline-Fe ($Phen_3$-Fe) were applied for the determination of different compounds (either cationic or anionic species). Koch employed 1, 10-phenanthroline-Fe^{3+} as a spectrophotometric reagent for the determination of phenolic compounds [28]. Gayathri and Kumar [29] studied the electrochemical behavior of multi-walled carbon nanotube surface to recognize Cu^{2+} and H_2O_2. Hassan and Marzouk [30] described the use of ferroin-TPB for fabricating the plastic sensor for Fe^{2+} and Fe^{3+}. Marzouk et al. [31] prepared a Ls-sensor based on 1, 10-$Phen_3$-cation TPB for the determination of Hg^{2+} and Cu^{2+}. Hassan et al. [32] utilized [Phen-Fe^{2+}]-ethamsylate ion-pair to prepare a sensor for ethamsylate. Sugihara et al. [33] prepared ISE based on 1, 10-phenanthroline for the determination of Li^+. Abdel-Fattah et al. [34] devised an ion-selective electrode based on diphenyl-1, 10-phenanthroline-Fe^{2+}-lisinopril ion-pair for lisinopril sensing. It can be noticed that most of the previous works did not introduce a new sensor for losartan, so it is important to report more sensitive losartan sensors.

3.2. Effect of Ionic Liquids

Ionic liquids (ILs) are a new class of ionic salt-like materials that are liquid at unusually low temperatures. The official definition of ILs uses the boiling point of water as a reference point: “Ionic Liquids are ionic compounds which are liquid below 100 °C” [35]. ILs have some unique properties, such as low vapor pressure, good thermal stability, high polarity, and tunable viscosity. According to these advantages, the incorporation of lipophilic ILs in the ion-selective membrane electrode as an ion-exchanger diminishes the Ohmic resistance and enhances the response behavior and selectivity, and at the same time, in case of poor extraction capability, increases the sensitivity of the membrane electrodes. Thus the use of ionic liquids (ILs) increases the extraction of Ls^- ions and improves the

response of the sensor (Table 1). The exchange of ions at the membrane-solution interface for type-I (with only ion-pair) can be shown as:

$$2(Ls)^{-}K^{+} + Ph_3\text{-}Fe^{2+}SO_4^{--} \rightleftharpoons [(Ls^{-})_2\ Ph_3\text{-}Fe^{+2}] + 2\ K^{+} + SO_4^{2-}$$

$$K_{eq} = [(Ls^{-})_2\ Ph_3\text{-}Fe^{+2}]/[(Ls)^{-}K^{+}]\ [Ph_3\text{-}Fe^{2+}SO_4^{2-}]$$

$$(Ls^{-})_2\ Ph_3\text{-}Fe^{++} \rightleftharpoons 2Ls^{-} + Ph_3\text{-}Fe^{2+}$$

$$K_{eq} = [(Ls^{-})]^2\ [Ph_3\text{-}Fe^{2+}]/[(Ls^{-})_2\ Ph_3\text{-}Fe^{2+}]$$

In case of type-II (contains IP, HP^{+}, Br^{-} as IL), the following equilibrium can be achieved:

$$(Ls^{-})_2\ Ph_3\text{-}Fe^{2+} \rightleftharpoons 2Ls^{-} + Ph_3\text{-}Fe^{2+}$$

$$HP^{+}\ Br^{-} + Ls^{-} \rightleftharpoons (\ HP^{+}\ )\ Ls^{-} + Br^{-}$$

$$K_{eq} = [(\ HP^{+}\ )\ Ls^{-}]\ [Br^{-}]/[HP^{+}\ Br^{-}]\ [\ Ls^{-}]$$

From the above equilibrium equations, it can be observed that in case of Type-I, there was an equilibrium between Ls^{-}, $[Ph_3\text{-}Fe^{2+}Ls_2]^{-}$, and Ph^{2+}. But in Type-II, different types of ions (Ls^{-}, $[Ph_3\text{-}Fe^{2+}Ls_2]^{-}$, and $Ph_3\text{-}Fe^{2+}$, $HP^{+}\ Br^{-}$, Ls^{-}, $(HP^{+})\ Ls^{-}$, Br^{-}) were present due to the presence of an ionic liquid.

From the above observation, it can be concluded that the total number of ions in the second case was more than that in the first case, so the conductivity of Type-II membrane was more than that of Type-I. Figure 3 shows the equilibrium of the membrane components for Ls-sensor in the presence of IL. The slope of the calibration graph and the better LDL and linear range confirm an improvement in the sensor response.

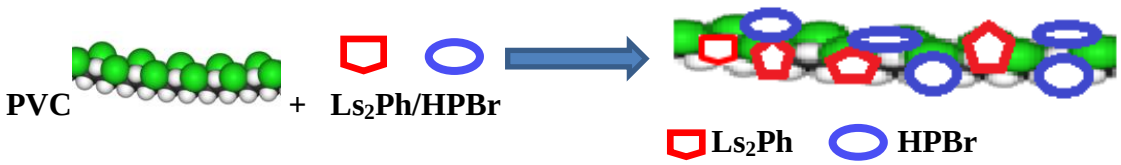

Figure 3. Graphical representation of the equilibrium between the membrane components

3.3. Calibration graph

The slope of the calibration curve for PVC membrane electrode no.8 was 62.0 mV per decade, and a standard deviation of ±1.0 mV was obtained after five measurements. The linear response of the losartan potassium concentration was in the range of 5.0×10^{-5}–1.0×10^{-2} mol. L^{-1}. In this work, the detection limit of the sensor was 3.5×10^{-5} mol L^{-1}, which was calculated by extrapolating the two segments of the calibration curves. As a conclusion, membrane 8 with the composition of 30.6% PVC, 7.5% ion-pair, 0.5% IL, and 61.4% *o*-NPOE was the optimal choice for sensor design.

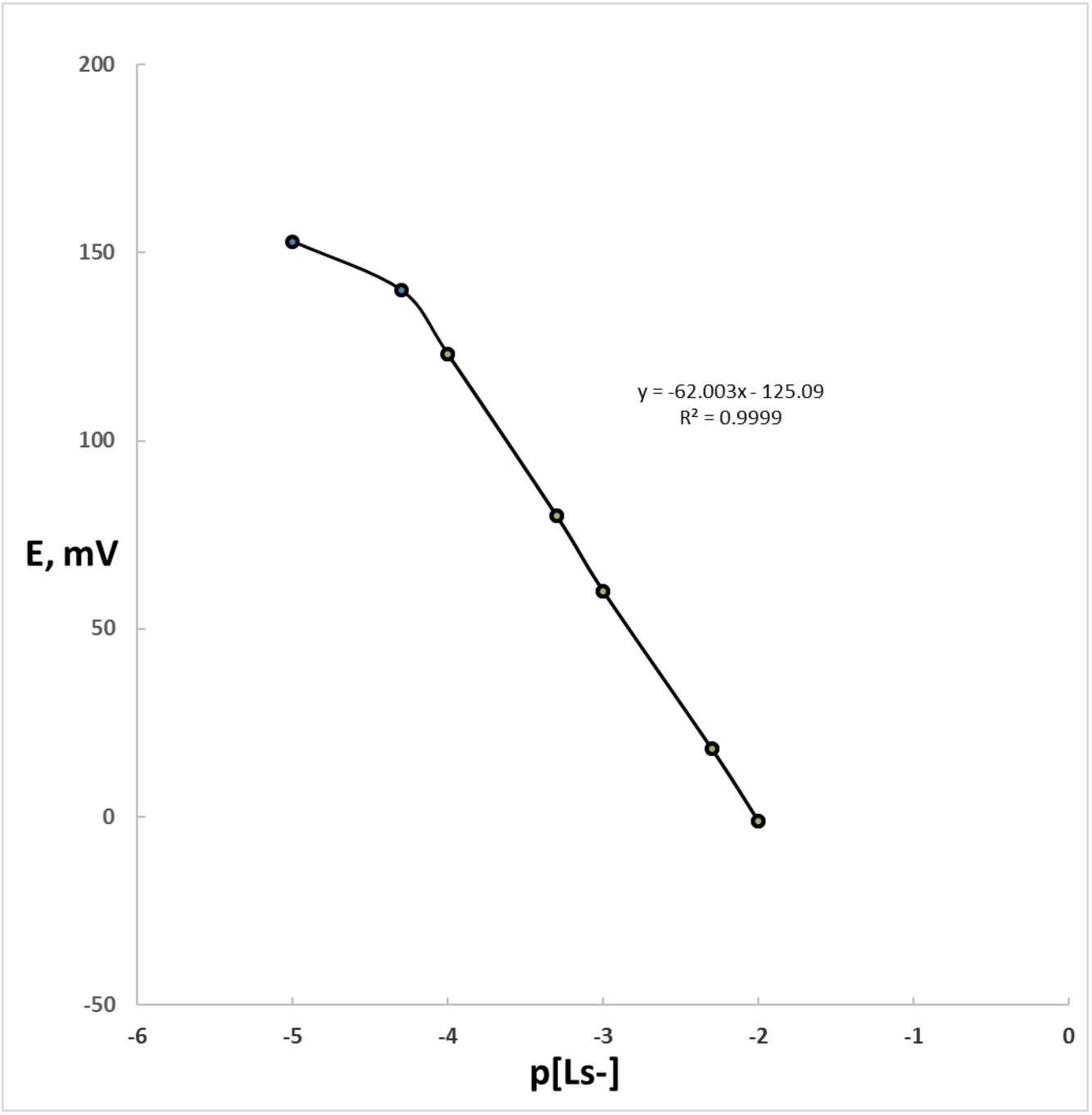

Figure 4. The calibration curve of the Losartan potassium membrane sensor type no. 8.

3.4. Inner Filling solution

The influence of the concentration of an internal solution on the potential response of the polymeric membrane electrode for LsK was studied. The concentration of IF solution was varied from 1.0×10^{-2} to 1.0×10^{-4} M and the potential response of the sensor was recorded. It was found that the best results in terms of slope and working concentration range were obtained when the concentration

of the IF solution was 1.0 $\times 10^{-2}$ M. So it can be recommended that the inner filling solution concentration of 1.0 $\times$ 10^{-2} M is perfect for the Ls^--sensor to work accurately.

3.5. Dynamic Response Time

The dynamic response time is defined as the required time for an electrode to achieve the potential values within ±1 mV of the final equilibrium potential [36–38]. In our experiment, the dynamic response time of the sensor was calculated by varying the LsK concentration from 1.0×10^{-5} to 1.0×10^{-2} M. It was noticed that the proposed sensor was able to quickly reach its equilibrium response in the whole concentration range. The recorded time for PVC membrane electrode type 8 was about 10 s. Figure 5 displays the obtained dynamic response results for the Ls-membrane sensor no.8.

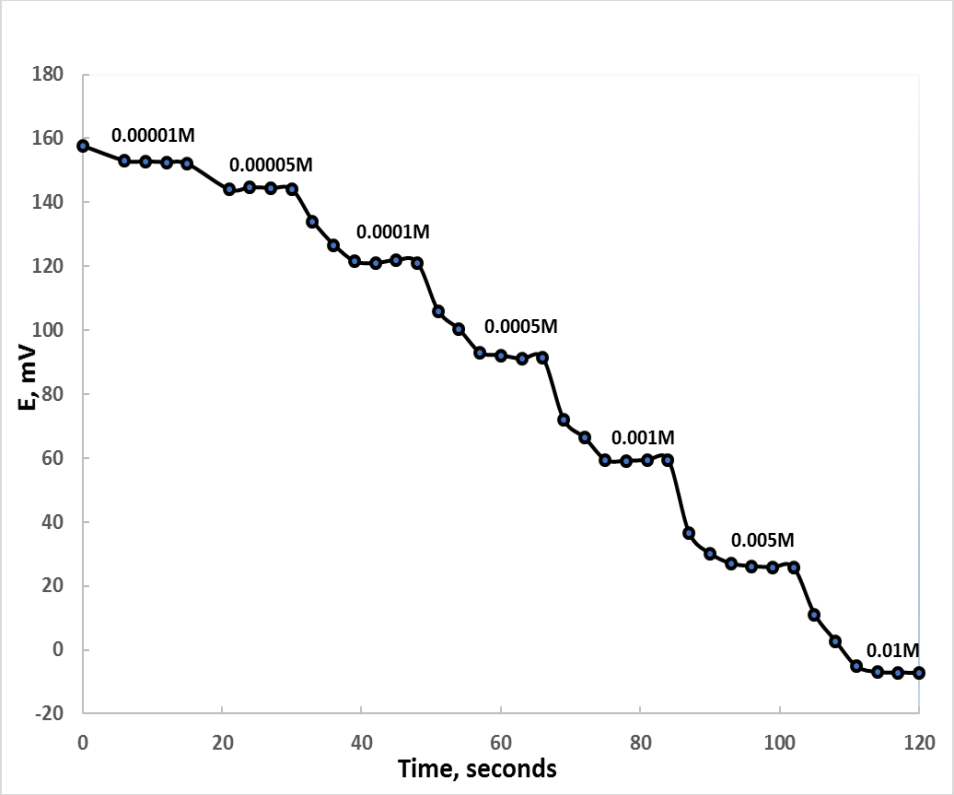

Figure 5. Potential-time curves of the proposed Ls^--sensor for different concentrations of LsK.

3.6. Lifetime

The lifetime of the sensor was detected by measuring the slope of the potential versus Ls^- ion concentration over the concentration range of 1×10^{-5}–1×10^{-2} M for a period of four weeks. The lifetime of the ion-selective sensor is in the range of 1–3 weeks according to the membrane composition. The proposed sensor was used safely for three weeks. After this period, there was a slight gradual decrease in the slopes (–2 mV per decade), hence, the detection increased. It has been well

established that the loss of plasticizer, (Ls-Ferroin) complex, and the ionic liquid from the membrane into the measured LsK-solution is the controlling factor of sensor lifetime.

3.7. Effect of pH

The wide applications of an ISE require the knowledge of the working pH range of the proposed electrode. The medium acidity may affect the state of ion-associated and other membrane components [39]. In order to study the effect of pH on the performance of the proposed sensor, the potentials were determined at two concentrations (1.0×10^{-3} M and 1.0×10^{-4} M) of LsK ions as a function of pH. The pH of the solution was varied by adding 0.1 M NaOH and 0.1 M HCl. It can be seen from Figure 6 that the potential did not change in the pH range of 6.5–8.5, therefore the mentioned range was considered as an ideal pH for the electrode. At pH < 6.5, the LsK worked like a base and accepted H^+ forming conjugate acid. At pH <5, the second protonation occurred due to the formation of quaternary amine. For pH>8.5, the potentials were decreased suddenly due to the excess concentration of $[OH^-]$.

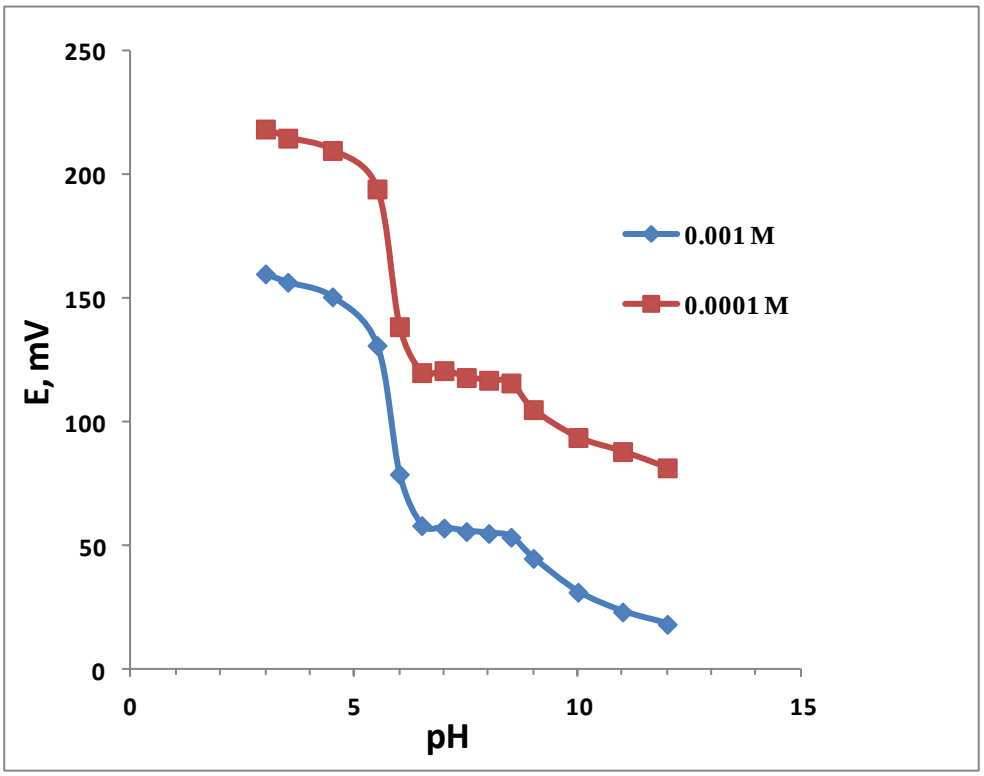

Figure 6. The relation between the solution pH and potential values of Ls^--electrode for 10^{-3} and 10^{-4} M solutions.

3.8. Selectivity of the sensor

The potentiometric selectivity coefficient ($K^{pot}_{Ls^-,J^{-z}}$) of losartan sensor was evaluated at different concentrations of both LsK and the interferents using separate solution method (SSM) [21].

The obtained data (Table 2) reveals that the sensor had a good selectivity for Ls^- ions as compared to many basic and acidic compounds. No interference was caused by the pharmaceutical ingredients and diluents.

Table 2. $\mathbf{K^{pot}_{Ls^-,J^{z-}}}$ values for the proposed Ls-sensor type 8.

Interferent	$\mathbf{K^{pot}_{Ls^-,J^{z-}}}$
Maltose	7.8×10^{-5}
Amm. Citrate	7.7×10^{-3}
Amm. oxalate	3.5×10^{-5}
Benzamide	3.1×10^{-5}
Glycine	5.6×10^{-5}
SO_4^{2-}	2.0×10^{-5}
Cl^-	3.3×10^{-4}
Amm. reineckate	2.2×10^{-3}
$CuSO_4$	1.8×10^{-4}
KCl	7.4×10^{-3}
KNO_3	3.1×10^{-3}
KCN	2.2×10^{-3}

Table 3. Determination of losartan in different pharmaceutical preparations

Sample	**Stated content in drug**	**Found ***
Lozapress	25 mg/tablet	24.9 ±0.06 mg
Lozapress	50 mg/tablet	49.85 ±0.04 mg
Amosar	25 mg/tablet	25.04 ±0.04 mg
Amosar	50 mg/tablet	50.03 ±0.05 mg
Aratins	50 mg/tablet	49.89 ±0.05 mg

*****The results are based on five measurements.

Maltose and amines showed the smallest $\mathbf{K^{pot}_{Ls^-,J^{z-}}}$ values in the order of 10^{-5}, it can be attributed to the non-charged property of the interferent molecules. In case of citrate and oxalate, the $\mathbf{K^{pot}_{Ls^-,J^{z-}}}$ value was 10^{-3} because of the similar anionic charges. For Cl^- ions, the selectivity coefficient increased to the order of 10^{-2}, while sulfate showed the smallest selectivity coefficient value (10^{-5}). Other anions, such as reineckates, also presented small value (10^{-3}).

3.9. Determination of Losartan in pharmaceutical preparation

Different losartan potassium products, such as (Lozapress 25 mg/tablet), (Lozapress 50 mg/tablet), (Amosar 25 mg/tablet), (Amosar 50 mg/tablet), and (Aratins 50 mg/tablet) were assessed by the proposed sensor. The measured values were in the range of 24.9–50.03 mg/tablet and the range of the recovery values was 99.6–100.1%.

4. CONCLUSIONS

Our described sensor has a simple working procedure and requires no sophisticated instrumentation. It determines only the therapeutically active non-degraded drug in the presence of its ingredients. The obtained results confirm that the constructed sensor is a suitable candidate for the determination of losartan in drug bulk powder. Apart from high accuracy and sensitivity, they also had high selectivity and reproducibility. From another point of view, the application of ionic liquids in PVC membrane sensors significantly improved the electrode response, this point will be elaborated in our future work.

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