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Sensitive Determination of Enalapril in its Pure Forms and in its Pharmaceutical FormulationsUsing Prepared Ion Selective Electrode

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Abstract:*A new PVC membrane sensor for enalpril based on enalpril-phosphotungstate ion pair. The influence of membrane composition (i.e. percent of PVC, plasticizer, ion-pair complex, and nature of plasticizer), inner filling solution, pH of test solution, and the presence of foreign cations on the electrode performance were be studied. The optimized membrane demonstrates Nernstian response (57.8 ± 1.0 mV per decade) forenalprilcations over a wide linear range from $1\times10^{-6}$to 1×10^{-2} M at 25 ^{o}C. The potentiometric responseis independent of the pH in the range of 1.5-4.0. The proposed sensor has the advantages of easy preparation,fast response time. The selectivity coefficients indicate excellent selectivity for enalprilover many commoncations (e.g., Na^{+}, K^{+}, Mg^{2+}, Ca^{2+}, Ni^{2+},and severalorganic compounds(rhamnose, maltose, glycine and benzamide). The practical applicationsof this electrode wasdemonstrated by measuring the concentrations of enalprilin pure solutions andpharmaceutical preparations with excellent results.*

Keywords*:Enalpril, Phosphotungstate, Ion Selective Electrode, Pharmaceutical Analysis, PVC-Membranes*

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I. Introduction

Over the last four decades, there has been growing interested in sensors area, ion selective electrode [1-6]. This is due to the fact that "ion selective electrodes (ISEs)" meet the need for rapid, simple, low cost, and accurate measurements of ionic species. In addition, ISEs measure activity rather than concentration, which is advantageous in biological and bio-chemistry studies. This is because ionic activities rather than concentration affect biological processes.

Enalapril maleate (ENP) is chemically described as (S)-1-N-[1- (ethoxycarbonyl)-3 phenylpropyl]-L-alanyl -L-proline, (Z)-2-butenedioate salt (Figure 1). It is an ester pro-drug which is hydrolyzed to pharmacologically active enalaprilate, a specific competitive inhibitor of angiotensin converting enzyme (ACE) [7].It inhibits the active sites of a zinc glycoprotein. The angiotensin converting enzyme blocking the conversion of angiotensin I to angiotensin II, whose levels are elevated in patients with hypertension.

Several analytical methods were reported for ENP include Spectrophotometric Methods [8, 9],Chromatographic Methods [10-12], and with electrochemical method [13]. This research will be presented , a PVC membrane sensor based on enalpril-phosphotungstate ion pair and o-nitrophenyloctyl ether (*o*-NPOE)as electrode plasticizer was applied for the quantification of enalapril in its pure forms and in its pharmaceutical preparations.

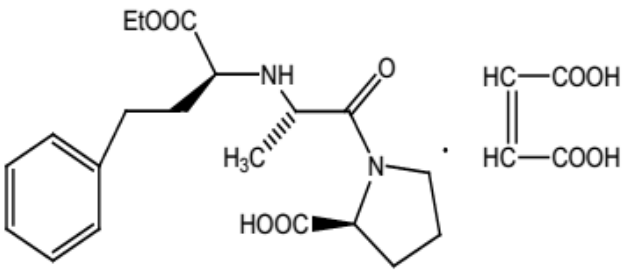

Figure (1) Structure formula of Enalapril Maleate (ENP).

II. Expermintal

2.1. Equipments:

All potentiometric measurements were made at room temperature with a Wheeler (Model WD-5010EC) pH/mV meter using membrane sensor in conjunction with a Wheeler (Model WD-5010EC) double junction Ag/AgCl reference electrode (Model Cole Parmer Vernon Hills Illinois 60061) containing 10% (w/w) potassium nitrate solution in the outer compartment. A Ross combination pH electrode was used for pH adjustment. IR spectrometer (Model FT/ IR 4100 Jasco- Japan) was used for recording IR Spectra of material under study.

2.2. Chemicals and reagents:

All chemicals were of analytical grade. Deionized water was used for all aqueous solutions. Enalapril was obtained from National Organization for Drug Control and Research, High molecular weight poly (vinyl chloride) powder (PVC), phosphotungstic acid (PTA) were purchased from Aldrich. Tetrahydrofuran (THF) was obtained from fluka. o-nitrophenyloctyl ether (*o*-NPOE), dioctylphethalate (DOP) and didecylphetalate (DDP)were purchased from Aldrich. Several salts of the highest purity (magnesium sulfate heptahydrate, nickel sulfate hyptahydrate, calcium chloride, potassium chloride, and sodium sulfate) were purchased from (El-Naser Company, Egypt). Several organic compound of the highest purity (maltose, glycose, rhamanose, ammonium citrate ammonium oxalate, benzamide, and glycine) were purchased from (Chemical Drug House (CDH), India). Standard solutions (10^{-1} M) from the mentioned salts and the previous organic compound were prepared with deionized water and subsequently dilute solutions (10^{-2}-10^{-7}M) were freshly prepared. (10^{-2} M) from enalapril maleate (ENP) solution was prepared by dissolving 0.2462 g of the solid salt in 50 ml deionized water. The obtained solution was standardized according to European Pharmacopoeia method (European Pharmacopoeia, 2016). Then, several dilutions were applied to cover lower concentration range.

2.3. Preparation of Electroactive (ENP-PTA) Ion-Pair:

The electroactive material (ENP-PTA) was prepared by mixing 20 ml of $1x10^{-2}$ M of both enalapril (ENP) and phosphotungstic acid (PTA) solutions. The resulting precipitate was filtered off through a Whatman filter paper No.42, washed with cold water several times, dried at room temperature and ground to fine powder [1,4]. The confirmation of ion-pair formation was applied by IR Spectra of (ENP), (PTA) and (ENP-PTA).

2.4. Construction of the ENP-PTA sensors:

Different amounts of ion-pair (3-9 %) along with the appropriate amounts of PVC(30-32%) with a several types (62-65%) of plasticizers (DOP, o-NPOE or DDP) were dissolved in tetrahydrofuran (THF). The solution was mixed well and poured into a glass dish of 2 cm diameter. Then, THF was evaporated slowly at room temperature until the membrane was obtained. Sections of the resulting membrane were cut out with a cork borer (10 mm diameter) and glued to polyethylene tubing. The tube was then filled with inner filling solution containing different concentrationsfrom both enalapril and potassium chloride to study the infulance of inner filling solution on membrane behavior.

2.5. Response time:

It is well known that the response time of the electrode is one of the most important factors in its evaluation. Response time was determined by recording the time after which the sensor potential reached its steady value (±1 mV) [14].Different ENP solutions aliquots (1×10^{-6}, 5×10^{-6}, 1×10^{-5}, 5×10^{-5}, 1×10^{-4}, 5×10^{-4}, 1×10^{-3}, 5×10^{-3} and 1×10^{-2} M) were prepared. 25 ml aliquots of the prepared solutions were transferred to 50 ml beakers. The proposed electrode in conjunction with the reference electrode were immersed into the measured solution with simultaneous recording of potential -time values. The potential (mV-values) were recorded for each case to reach the steady potential (±1mV). For each case, the response time values were estimated according to IUPAC definition. The potential reading was recorded after stabilization and the emf was plotted as a function of time for enalapril concentration.

2.6. Lifetime:

The life time of the electrode was determined by preparing calibration graphs at soaking time intervals, at room temperature. 25 ml aliquots of ENP solutions (1×10^{-6}, 5×10^{-6}, 1×10^{-5}, 5×10^{-5} 1×10^{-4}, 5×10^{-4}, 1×10^{-3}, 5×10^{-3} and 1×10^{-2} M) were prepared. The proposed sensor in conjunction with the reference electrode were immersed in each drug solution. The calibration graphs for the drug were constructed after soaking periods 1, 4, 7, 10, 13, 17, 21, 24, 28, 32, 35 days. The slope, LOD and linear range were calculated in each case and correlated to the electrode performance.

2.7. Effect of pH on the sensor response:

In an approach to understanding the impact of pH on the drug-electrode response, the potential was measured at two concentrations (1×10^{-3} M and 1×10^{-4} M) of ENP solutions. Aliquots of the drug solutions (20 ml) were transferred to 50 ml volumetric flask. The tested sensor in conjunction with Ag/AgCl reference electrode, and a combined glass electrode were immersed in the same solution. The testing pH-range was varied over a wide pH-range (1.5 -12.0 for ENP solutions) by addition of small volumes of (0.1M) HCl and/or NaOH solution. The mVreadings were plotted against the pH-values for the different concentrations.

2.8. Effect of the inner filling solution:

The influence of concentration of inner filling solution on the potential response of the developed drug selective membrane sensors was studied. In order to study this effect, three inner filling solution concentrations were used. Stock solutions (10ml) of $5x10^{-2}$ M of the drug solution and 10ml from ($5x10^{-2}$ M) KCl solution were prepared. Equal volume from the mentioned, drug solution and KCl solution were mixed together. Then, three inner filling solution concentrations were prepared (A) 10^{-2} M, (B) 10^{-3} M and (C) 10^{-4} M inner filling solutions concentrations. The electrode body was filled with 2 ml of each of the prepared inner filling solution to study the effect of concentration of internal filling solution on the potential response. Calibration graphs were constructed for the three sensors comprising the inner filling A, B, or C. The performance characteristics for each electrode were calculated and compared to each other.

2.9. Determination of selectivity coefficient:

The selectivity coefficient of the sensor was determined using the separate solution method (SSM) **[15]**. 25 ml aliquots of 10^{-2} M solutions of each of the drug and the interferent were transferred to 50 ml beaker. The potential values for each of the drug and the interferent solutions were measured. The $K_{D,J}^{pot}$ values were calculated by using Nicolsky equation.

$$log\boldsymbol{K}_{D,J}^{pot} = [\boldsymbol{E}_J\text{-}\boldsymbol{E}_D/S] + log\boldsymbol{a}_J^{(Z_D/Z_J)} + log\boldsymbol{a}_D$$

Where:

E_D: is the potential measured in 10^{-2} M drug solution.

E_J : is the potential measured in a 10^{-2} M solution of the interfering anions.

S: slope of the electrode calibration plot.

2.10. Determination of enalapril in its pharmaceutical preparations:

The content of 5 tablets (Acapril, 5 mg /tablet), (Ezapril, 10 mg/tablet) and (Enalap, 20 mg/tablet) were weighed separately and finely powdered in a small dish. The equivalent weight for one tablet was transferred to 25ml beaker and dissolved in a minimum volume of 10^{-2} M HCl, then diluted to the mark with deionized water. The obtained solution was shaken, adjusted at working range pH (1.5-4) and filtered off into 50 ml volumetric flask through Whatman filter paper No.42. Several dilutions were prepared from the previous solution of the pharmaceutical drugs to obtain concentrations equivalent to $1x10^{-4}$, $5x10^{-5}$ and $1x10^{-5}$ M enalapril. The sensor type no.3 in conjunction with double-junction Ag/AgCl reference electrode were immersed in the beaker and the mV of the test solutions were directly measured and compared with a previously prepared calibration graph. The accuracy of the results was compared with those indicated by the manufacturing company according to recommended method by the European Pharmacopoeia **[16]**.

III. Results and Discussion

3.1. Optimization of Membrane Composition of Enalapril- Electrodes:

The optimization of PVC membrane composition is very important because the sensitivity and selectivity of the PVC membrane sensor are highly influenced by the amount of the ion-pair, nature of the plasticizer and the plasticizer/PVC ratio. In order to study the effect of varying the membrane composition on the response of the developed sensors, eight different compositions for the PVC membrane were prepared. All the active ingredients of the membrane matrix were changed so as to obtain an optimum composition for the membrane. Three types of plasticizers were used, o-NPOE (ε = 24), DOP (ε = 7), and DDP (ε = 4) corresponding to electrode types no. 3, 7 and 8. They showed calibration graph slopes of 57.8, 39.2 and 22.08 mV decade-1 with linear ranges of 1×10^{-2} - 1×10^{-6}, 1×10^{-2} - 5×10^{-5} and 1×10^{-2} - 5×10^{-4} with limits of detection of 1×10^{-6}, 4×10^{-5} and 1.0×10^{-4}M, respectively (Figure 2). It can be seen from table (1) that the proposed sensor based on the ENP-PTA ion-pair with o-NPOE plasticized membrane showed the highest slope and the best detection limit among other tested sensors with membranes plasticized with DDP and DOP. This was due to the highest dielectric constant (ε) of o-NPOE than DDP and DOP, which is an important factor to be considered in liquid membranes [17]. It is expected that the values of the dielectric constants of the liquid membranes are similar to that of the pure liquid plasticizer. This is due to the fact that most liquid membranes

used as sensors contain between 60 to 70% by weight of a plasticizer. The latter can be explained by considering that the pKa of the plasticized PVC is above its glass transition temperature (Tg) at room temperature. The variation observed in sensor response using different plasticizers may be attributed to different carrier mechanisms [18].

The content of the ion-pair was found to influence the sensitivity of the sensors. The amount of ion-pair in the fabricated electrode matrices was varied from 3% to 9%. It was found that incorporation of 7%(w/w) of the ENP-PTA ion-pair was sufficient to the proper performance of the sensor (slope values were 57.8±0.2 mV decade^{-1}). Figure (2) shows the calibration graphs for selected examples of each composition.Table (1) clearly shows how the slopes of the sensors vary with changing the composition of the membrane. The best membrane composition (ENP- electrode type no.3) was containing the ratios (7.0:31.0:62.0) % (w/w) (ion association: PVC: plasticizer). This sensor exhibited a linear response over the range 1x10^{-6}-1x10^{-2} M of ENP with a lower detection limit of 1x10^{-6} M. According to these results the ENP-electrode type no.3 was applied for performing the following studies.

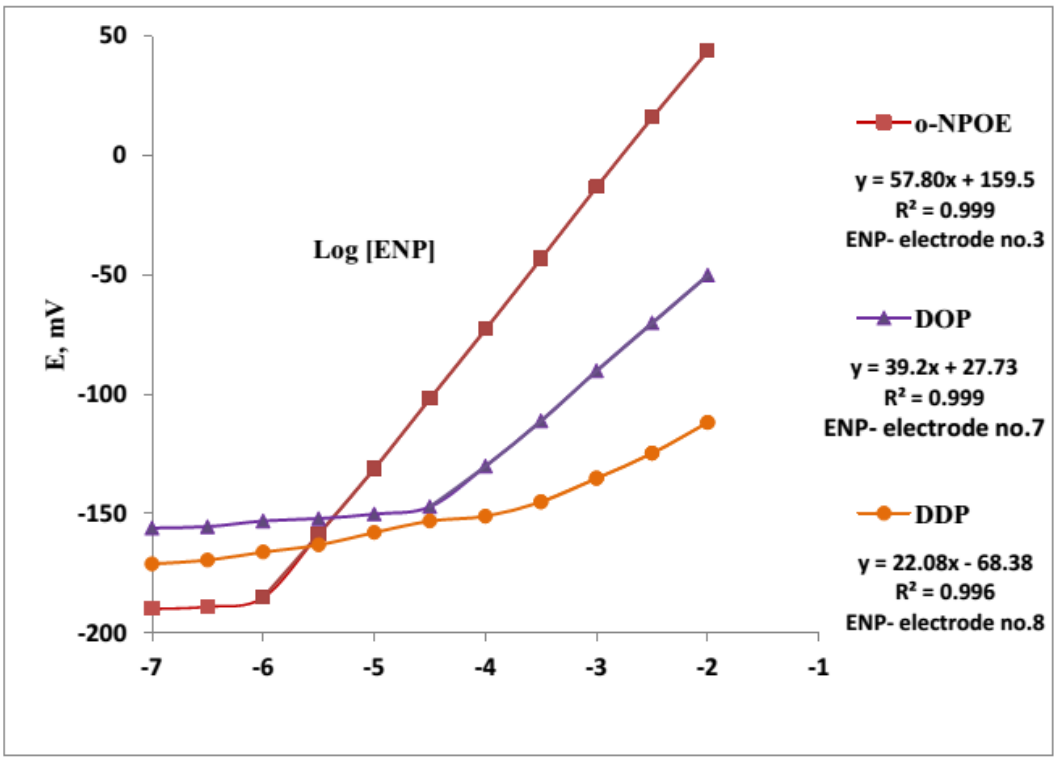

Figure (2) Calibration graph of ENP- electrode (type no. 3, 7 and 8) when using *o*-NPOE, DOP and DDP as a plasticizer.

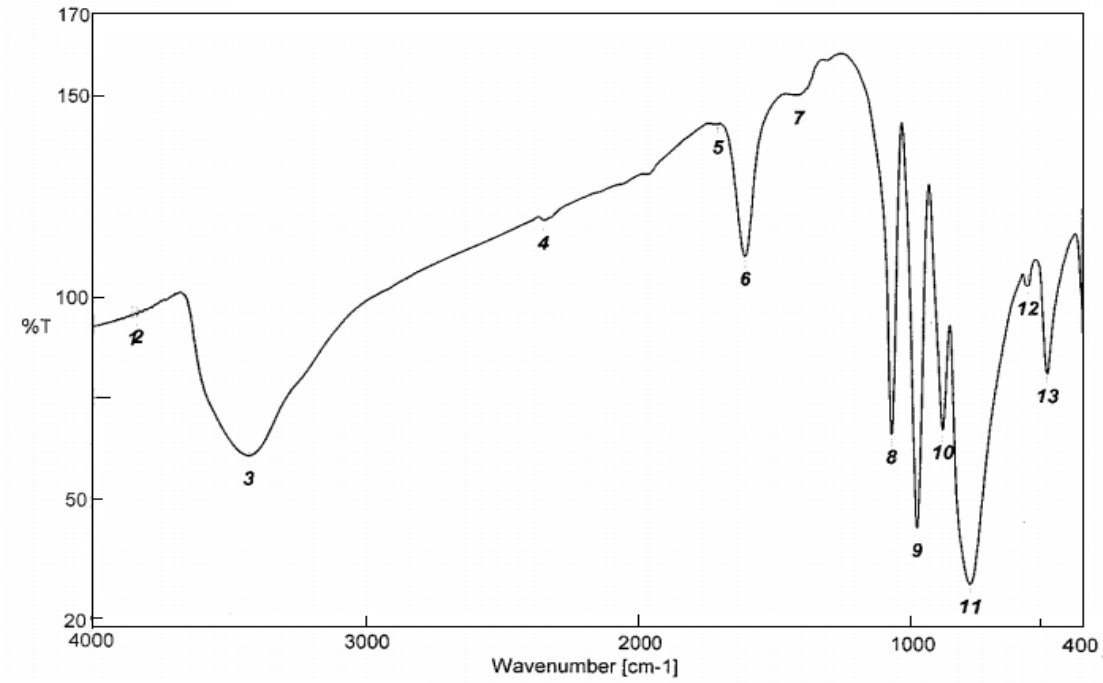

Figure (3) Infra-Red spectrum of (PTA)

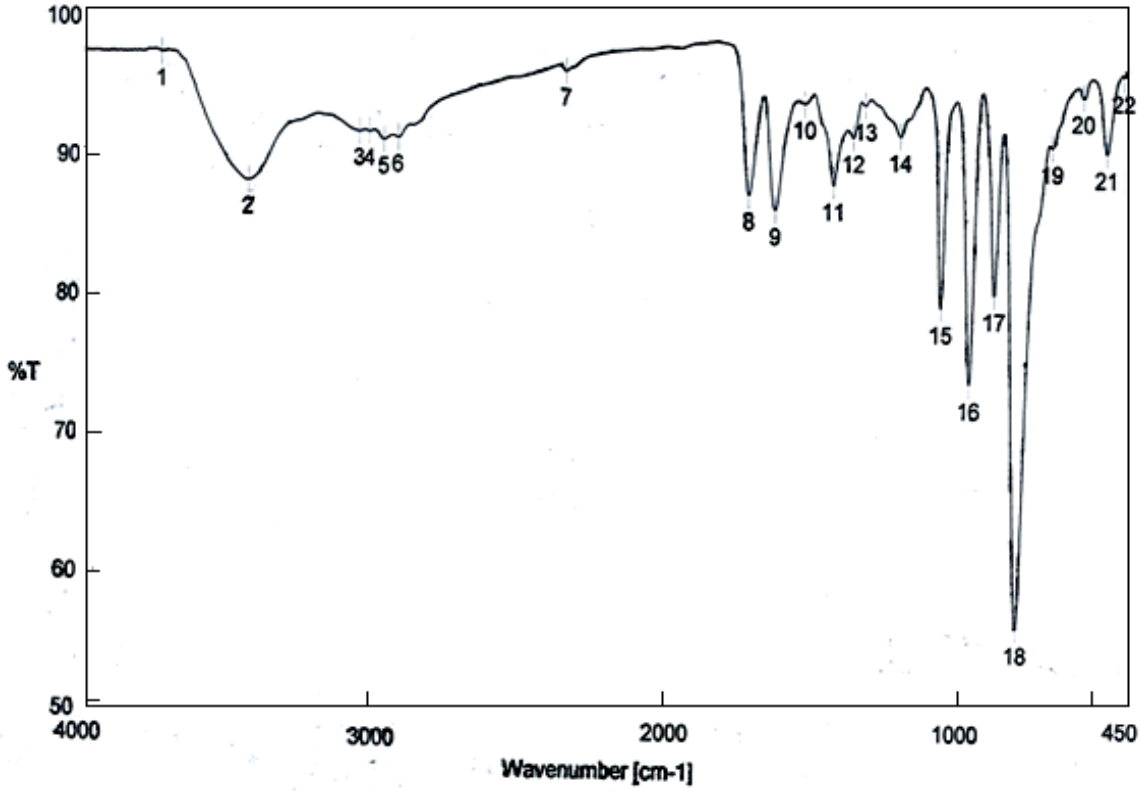

Figure (4) Infra-Red spectrum of (ENP) drug.

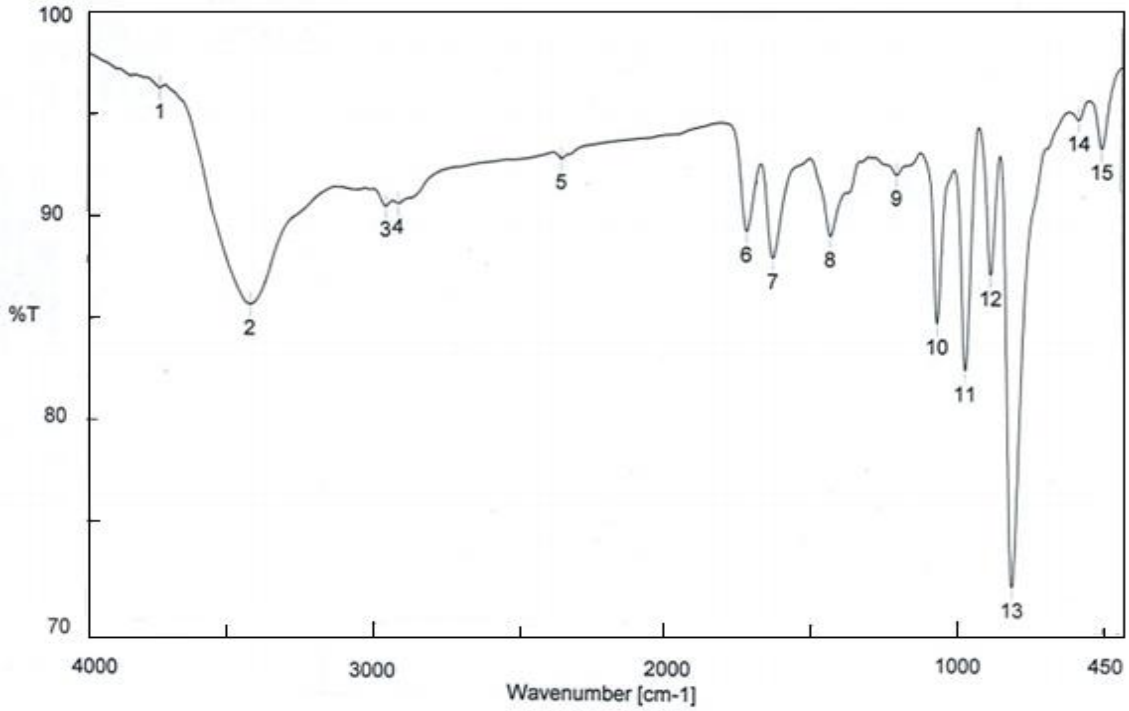

Figure (5) Infra-Red spectrum of (ENP-PTA).

Table (1) Performance Characteristics of ENP Sensors with Different Membrane Compositions.

Membrane No.	**Composition, (%) (**w/w**)**			**Slope, (mV decade^{-1})**	**Linear range, M**	**(LOD), (M)**	**Lifetime, (Week)**	**Response time, (Sec.)**
	Ion pair	*PVC*	*Plasticizer*					
1	3.0	32.0	65 (***o***-NPOE)	51.8	$1x10^{-2}$- $1x10^{-5}$	$9x10^{-6}$	2	10-15
2	5	32.0	64 (***o***-NPOE)	55.3	$1x10^{-2}$- $1x10^{-5}$	$8x10^{-6}$	3	10-15
3	7	31.0	62 (*o*-NPOE)	57.8	$1x10^{-2}$- $1x10^{-6}$	$1x10^{-6}$	5	10-15
4	9	30.0	61 (***o***-NPOE)	54.7	$1x10^{-2}$- $1x10^{-5}$	$9x10^{-6}$	5	15
5	3	32.0	65 (*DOP*)	10	$1x10^{-2}$- $1x10^{-3}$	$5x10^{-4}$	2	40
6	5	31.0	63 (*DOP*)	15.2	$1x10^{-2}$- $5x10^{-4}$	$5x10^{-4}$	2	30
7	7	31.0	62 (*DOP*)	39.2	$1x10^{-2}$- $5x10^{-5}$	$4x10^{-5}$	2	30
8	7	31.0	63 (*DDP*)	22.08	$1x10^{-2}$- $5x10^{-4}$	$1x10^{-4}$	1	30

3.2. Effect of pH:

In order to study the effect of pH on the performance of the sensor, the potentials were determined at two concentrations (1.0×10^{-3} and 1.0×10^{-4} M) of (ENP) ions as a function of pH. As can be seen from the results shown in Figure (6), the potential was independent on the pH changes in the range of 1.5–4.0. Thus, this range was chosen as the working pH for the electrode assembly. Below pH4, the potential value was almost steady due to protonation of ENP-molecule. Above pH 4 till 5.5, sudden change of potential occur due to the added OH^- was working to neutralize the diprotonated ENP. After pH 5.5, slight decrease in potential values due to interference from OH^- ion was observed.

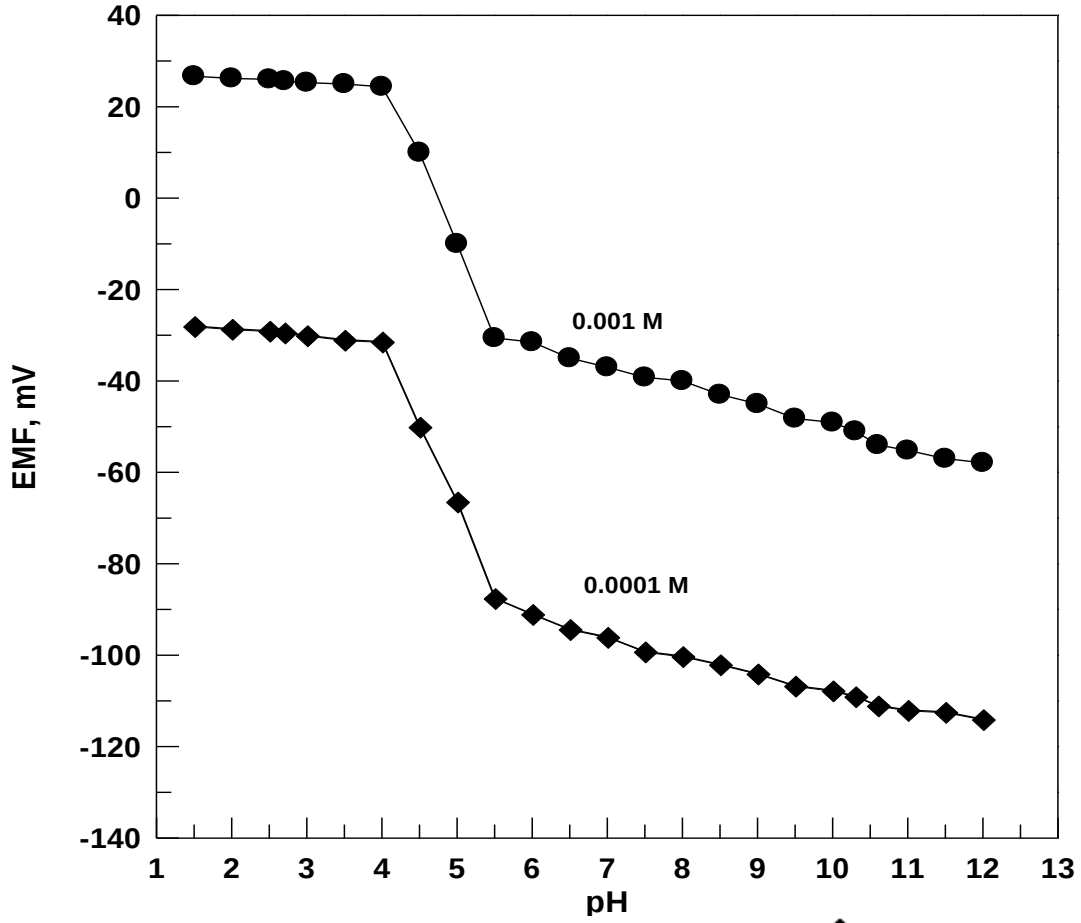

Figure (6) Potential pH curves for ENP- electrode type no.3 for (●) 0.001and (◆) 0.0001M ENP solution.

3.3. Effect of the inner filling solution on performance of ENP-electrode

The influence of the concentration of inner solution on the response of ion-selective electrodes were studied and the results showed that variation in the concentration (1×10^{-2} to 1×10^{-4} M) of the inner filling solution did not significantly change the electrode response of slope, while parameters like linear range and detection limit changed to a considerable extent. From the obtained results which were observed in figure (7), it was found that 1×10^{-3} M inner filling solution showed the best electrode response. This was recognized from the performance of the electrode characteristics (slope 57.8 mV decade^{-1}, linear range 1.0×10^{-6} to $1x10^{-2}$ M, and LOD 1×10^{-6} M).

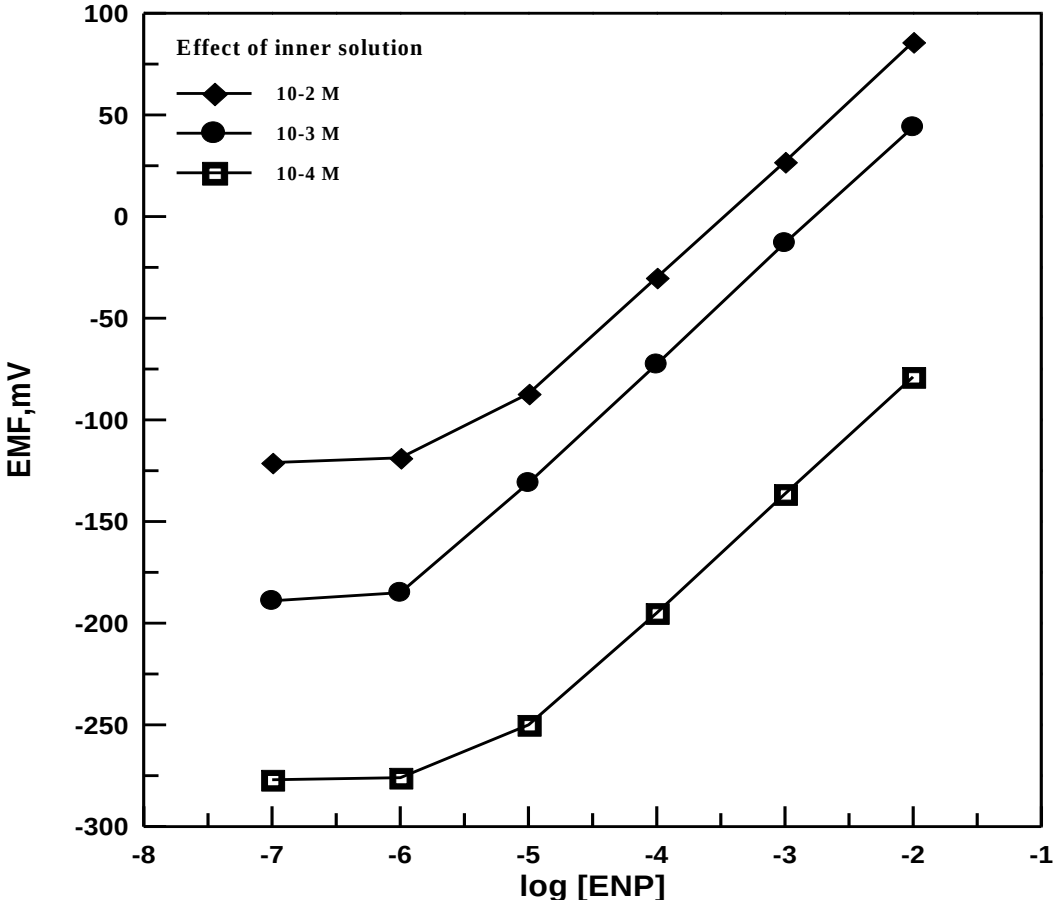

Figure (7) Calibration graph of ENP- electrode (type no. 3) when using different concentrations (◆) 10^{-2} M, (●) 10^{-3}Mand (■) 10^{-4} M of the inner filling solutions.

3.4. Response Time

Response time was defined as the time after which the sensor potential reached its steady value (±1 mV) [14]. In this study, the practical response time was recorded for different ENP concentration from 1.0×10^{-6} to 1.0×10^{-2} M. The actual potential vs. time traces showed that the proposed electrode reached the equilibrium response in a short time (10s) for concentrations from 1.0×10^{-6} to 1.0×10^{-4} M and 15 s for concentration from 1.0×10^{-3} to 1.0×10^{-2} M. Figure (8) shows the dynamic response time of the ENP membrane sensor (no. 3).

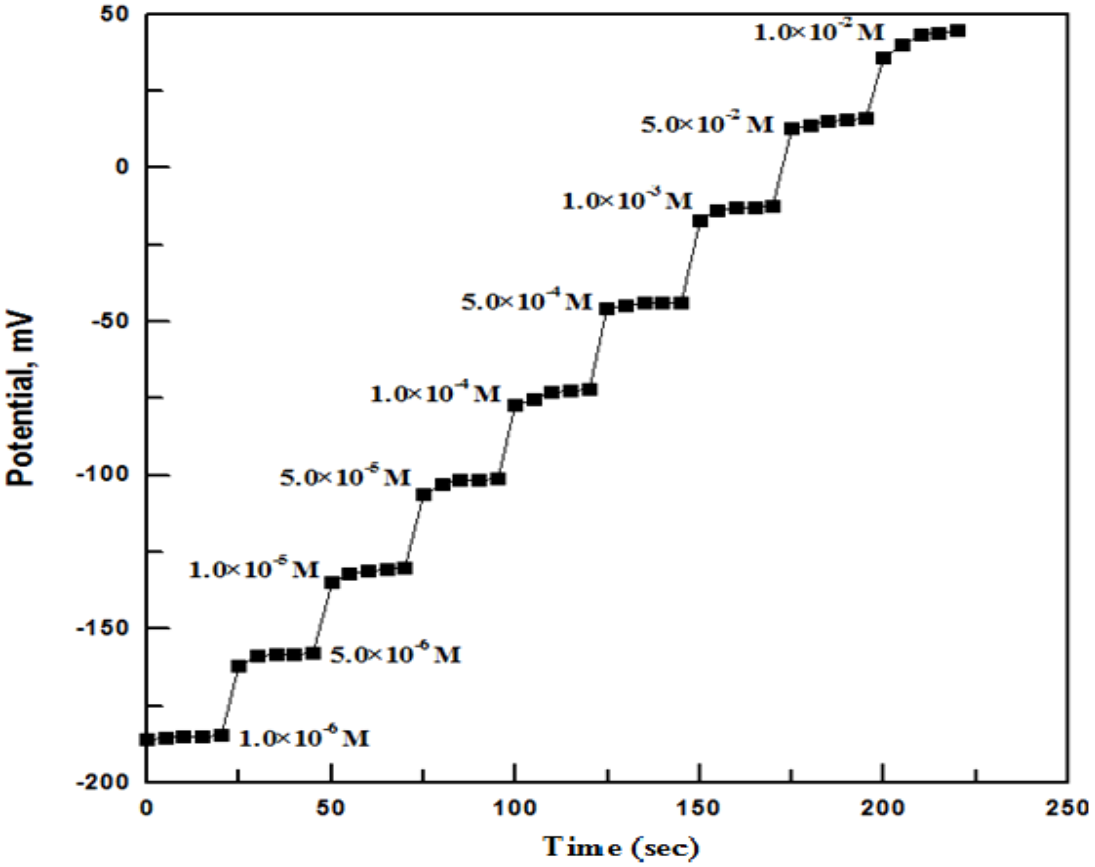

Figure (8) Dynamic response time of the ENP membrane sensor (no.3).

3.5. Lifetime of ENP-electrode

Lifetime may be defined as the storage or operational time for the sensitivity of the sensor to decrease by a factor of 10% to 50%, within the concentration range [19]. The stability and lifetime of the developed sensors were monitored. All sensors were tested for a period extended up to 7 weeks. The lifetime for these sensors was in the range of 1-5 weeks, according to the differences in chemical composition. For the main membrane (ENP-electrode type no.3), detectable loss of performance characteristics has not been found upto 5 weeks. After this time the slope of the sensor decreased, and the detection limit increased. So, the main sensor had been used for 5 weeks. After six weeks, there was a decrease in the slope (-5.8mV decade^{-1}) and an increase in the LOD compared to the first week. These changes in the electrode performance were attributed to the loss of the plasticizer and the ion-pair (ENP-PTA) due to the leaching into the measured solution (Table 2).

Table (2) Lifetime of PVC membrane ENP-electrode type no.3

Soaking time, (Week)	Slope, (mV decade^{-1})	LOD, (M)
First	57.8	1x10^{-6}
Second	57.5	1.2x10^{-6}
Third	57.3	1.5x10^{-6}
Fourth	57.0	1.9x10^{-6}
Fifth	56.8	2.1x10^{-6}
sixth	52.0	5.5x10^{-6}
seventh	50.4	9.1x10^{-6}

*The results based on five measurements.

3.6. Selectivity of ENP-sensor

The most important characteristic of any ion selective sensor is its response to the primary ion in the presence of other ions in the solution, which is expressed in terms of the potentiometric selectivity coefficient$K_{A,B}^{pot}$. The potentiometric selectivity coefficient $K_{ENP,J}^{pot}$ of Enalapril sensor was evaluated for Enalapril towards differentinterferents by using the separate solution method (SSM) [15]. The results shown in figures (9) and (10) revealed that the sensor showed a reasonable good selectivity for ENP as compared to many basic and acidic compounds. No interference was caused by the selected organic and inorganic cationic diluents commonly used in drug formulations (e.g. maltose, rhamnose and glycine). The non-charged property of some interferent molecules such as maltose, rhamnose, glucose and amines was the reason of small selectivity coefficient values. Sodium cations showed the highest selectivity coefficient values ($2.5x10^{-3}$), which still suitable for measurements. This was expected due to the similar mono cationic charge. Divalent molecules such as Ni^{++}, Ca^{++} and Mg^{++} exhibited the smallest selectivity coefficient values (order of 10^{-6}), because of the difference in the number of positive charge and ionic size.

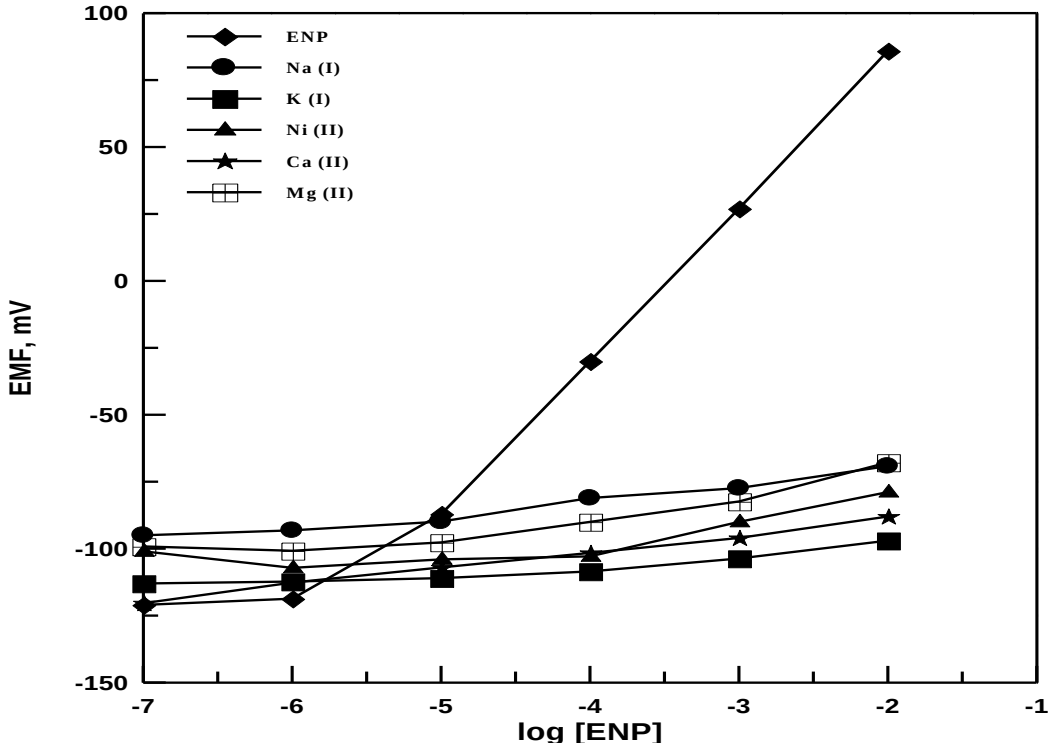

Figure (9) Calibration graph of ENP-Electrode (type no.3) for different interferent cations

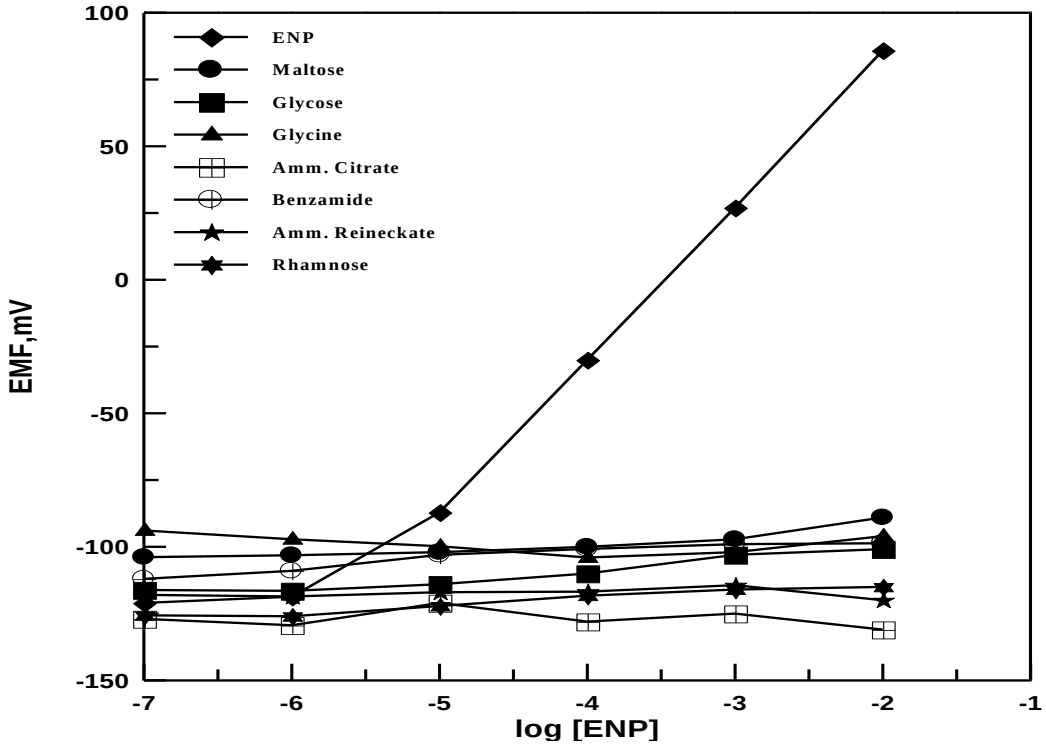

Figure (10) Calibration graph of ENP-Electrode (type no.3) for different interferent cations

3.7. Determination of Enalapril in its pharmaceutical preparations

Three selected ENP-pharmaceutical formulations were determined by the direct potentiomerty method by using the proposed ENP-electrode type no.3. The results, shown in Table (3), indicated that recovery ranges were 99.56-100.4%, 99.28-99.76%and 100.04-100.22% for the different concentrations of the selected ENP-formulations Acapril (5 mg/tablet), Ezapril (10 mg/tablet) and Enalap (20 mg/tablet) tablets, respectively. The obtained results were in satisfactory agreement with those indicated by the manufacturing company according to recommended method by the European Pharmacopoeia [16].

Table (3) Determination of Enalapril in its pharmaceutical preparations by ENP-electrode.

Sample	Company name	Stated content in drug	Taken, (M)	Recovery, (%)	RSD, (%)
ACAPRIL	Alpha Chem Advanced Pharmaceutical Co. (Acapi), Egypt	5mg/ tablet	$1x10^{-4}$	99.77-100.26	0.259
			$5x10^{-5}$	99.64-100.33	0.291
			$1x10^{-5}$	99.56-100.4	0.44
EZAPRIL	Multi-Apex, Egypt	10mg/ tablet	$1x10^{-4}$	99.32-99.74	0.2
			$5x10^{-5}$	99.30-99.76	0.2
			$1x10^{-5}$	99.28-99.65	0.211
ENALAP	Eipico, Egypt	20mg/ tablet	$1x10^{-4}$	100.05-100.17	0.114
			$5x10^{-5}$	100.04-100.22	0.128
			$1x10^{-5}$	100.055-100.21	0.13

*The results based on five measurements for each sample.

IV. Concolosion:

The described potentiometric method has simple workup procedure and requires no sophisticated instrumentation. The main membrane shows fast response time, Nernstian behavior, exellent selectivity, and chemical stablillity. The sensor was successfully applied to the direct determination of enalapril in its pure forms and in its pharmaceutical formulations.

Table (4) Potentiometric response characteristics of ENP-Electrode type no.3.

Parameter	Membrane number (3) Present work
Slope, (mV decade^{-1})	57.8
Linear range, (M)	1.0×10^{-6}-1×10^{-2}
Working pH range	1.5 - 4
Life span, (day)	35
Response time, (Sec)	10-15

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