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Electrochemical Sensor for the Selective Determination of Prindopril Based on Phosphotungestic Acid Plastic Membrane

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A novel PVC membrane sensor for perindopril based on perindopril-phosphotungstate ion pair complex was prepared. The influence of membrane composition (*i.e.* percent of PVC, plasticizer, ion-pair complex, and kind of plasticizer), inner solution, pH of test solution and foreign cations on the electrode performance was investigated. The optimized membrane demonstrates Nernstian response (30.9 ± 1.0 mV per decade) for perindopril cations over a wide linear range from 9.0×10^{-7} to 1×10^{-2} M at 25 ºC. The potentiometric response is independent of the pH in the range of 4.0-9.5. The proposed sensor has the advantages of easy preparation, fast response time. The selectivity coefficients indicate excellent selectivity for perindopril over many common cations (*e.g.*, Na^+, K^+, Mg^{2+}, Cu^{2+}, Ni^{2+}, rhamnose, maltose, glycine and benzamide. The practical applications of this electrode was demonstrated by measuring the concentrations of perindopril in pure solutions and pharmaceutical preparations with satisfactory results.

Key Words : Perindopril, Phosphotungstate, Ion selective electrode, Pharmaceutical analysis, PVC-membranes

Introduction

Perindopril $C_{19}H_{32}N_2O_5$ (mol.wt. 368.468) (Figure 1) is agoitensin converting enzyme (ACE) inhibitor and used in the treatment of hypertension and heart failure.[1] Inhibition of ACE results in decreased plasma angiotensin II, leading to decreased vasoconstriction, increased plasma rennin activity and decreased aldosterone secretion. The overall effect of this is a drop in blood pressure and a decrease in the workload of the heart. Perindopril (PDL)[2-4] is chemically (2*S*, 3a*S*, 7a*S*)-1-[(2*S*)-2-{[(2*S*)-1-ethoxy-1-oxapentan-2-l] amino} propanoyl]-octahydro-1*H*-indole-2-carboxylicacid, with selective clinical activity against hypertension.

A literature of survey revealed that there are a few analytical methods have been reported, which include immunoassay,[5] spectrophotometric,[6,7] HPLC,[8,9] biosensor method,[10-12] LC3MS/MS[13,14] and capillary gas chromatographic methods[15] for the estimation of the drug in biological fluids and pharmaceutical formulations.

In the present work, PVC membrane and conventional sensors based on Perindopril–phosphotungestate ion pair complex was introduced for the first time. This facilitate the monitoring of prindopril down to a small concentrations (9×10^{-7} M) either in pure solutions or into pharmaceutical preparations. The sensors exhibited Nernstian slope with fast response time and excellent selectivity towards many organic and inorganic ions.

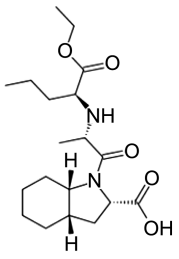

Figure 1. Structure of Perindopril.

The proposed electrode method is advantageous. No need for organic solvent like spectrophotometric methods. By comparing the propose method with a spectrophotometric method,[7] it was found that better sensitivity was recorded ($2.6 \times 10^{-6} - 2.7 \times 10^{-2}$ μg/mL) relative to the spectrophotometric method (20-40 μg/mL). For selectivity, interferences were recorded for the spectrophotometric method from (2*S*,3a*S*,7a*S*)-1-[(2*S*)-2-[[(1*S*)-1-[(1-carboxybutyl]-amino]-propanoyl]octahydro-1*H*-indol-2-carboxylic acid, (2*S*,3a*S*, 7a*S*)-1-[(2*S*)-2-[[(1*S*)-1-[(1-methylethoxy)carbonyl]-butyl]-amino]propanoyl]octahydro-1*H*-indol-2-carboxylic acid, and (2*S*,3a*S*,7a*S*)-1-[(2*S*)-2-[[(1*R*)-1-[(1-ethoxycarbonyl) butyl]-amino] propanoyl] octahydro-1*H*-indol-2-carboxylic acid. These compounds were not interfere with the proposed methods since they are anionic.

Experimental

Equipment. All potentiometric measurements were made at 25 ± 1 ºC with a Wheeler (Model WD-5010EC) pH/mV meter using Perindopril membrane sensor in conjunction with an Wheeler double junction Ag/AgCl reference electrode containing 10% (w/w) potassium nitrate solution in the

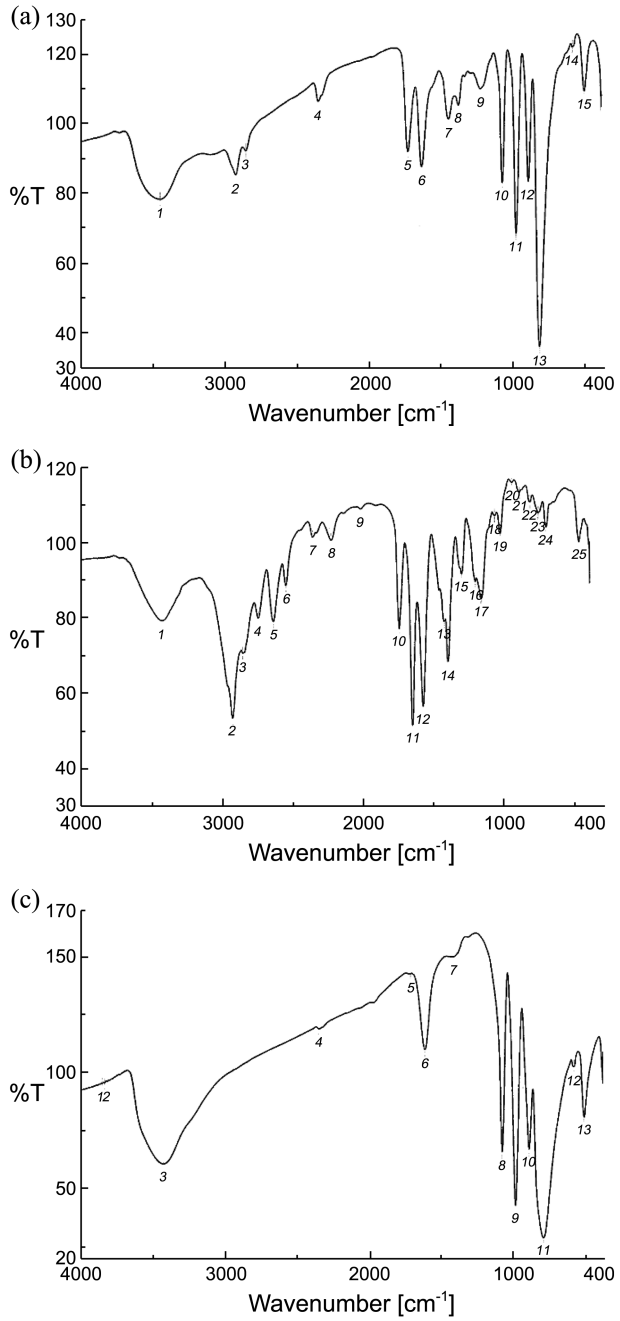

Figure 2. (a) Infra-red spectra for (PDL-PTA) ion-pair association. (b) Infra-red spectra for (PDL). (c) Infra-red spectra for (PTA).

outer compartment. A Ross combination pH electrode was used for pH adjustment.

Chemicals and Reagents. All chemicals were of analytical grade. Deionized water was used for all aqueous solutions. Perindopril was obtained from "National Organization for Drug Control and Research", Cairo, Egypt. 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) and dioctylphethalate (DOP), didecylphetalate (DDP) were purchased from Aldrich. Cation salts of the highest purity were used. Standard (10^{-2} M) solution was prepared using deionized water, then dilutions were applied to cover lower concentration range (10^{-3}-10^{-7} M). For selectivity measurements the standard solutions were adjusted to pH 6.

Preparation of Electroactive Perindopril-Phosphotungstic Acid (PDL-PTA) Ion-Pair. The electroactive material (PDL-PTA) was prepared by mixing 20 mL of 1×10^{-2} M of both Perindopril and PTA solutions. The resulting precipitate was filtered off through a Whatman filterpaper No. 42, washed with cold water several times, dried at room temperature and ground to fine powder.[16,17] IR data of PDL, PTA and the PDL-PTA are shown (Figure 2(a)-(c)) to prove the formation PDL-PTA ion pair complex.

Construction of the Sensors. Different amounts of ion-pair (3.5-6.0%) along with appropriate amounts of PVC (30.5-48.3%), and plasticizer (84.2-65%) were dissolved in tetrahydrofuran (THF). The solution was mixed well into a petri-dish of 2 cm diameter. Then, THF was evaporated slowly until an oily concentrated mixture 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 internal filling solution consisted of equal volumes of 1×10^{-2} M of both Perindopril and potassium chloride. Several concentrations (10^{-2}-10^{-4} M) were made to reach to the optimum composition.

Potential Measurements. Aliquots (25 mL) of 10^{-7}-10^{-2} M standard solution of Perindopril were transferred into 50 mL beakers. Then the proposed PDL sensor in conjunction with reference electrode was immersed in the solution. The solutions were stirred, the potentials were recorded after stabilization and plotted as a function of Perindopril concentration. These graphs were used for the subsequent determination of unknown concentrations of Perindopril.

The life span of the sensor was examined by repeated monitoring of the slope of Perindopril calibration curve after soaking different periods (1 day-5 weeks) into 10^{-2} M solution, at 25 °C. The potential reading was recorded after stabilization and the emf was plotted as a function of logarithm Perindopril concentration. The detection limit was taken at the point of intersection of the extrapolated linear segments of the Perindopril calibration curve. The dynamic response of the sensors was tested by measuring the time required to reach a potential steady to within ± 1 mV after successive immersion of the sensor in different drug solutions each having a 10 fold difference in concentration.

The sensors response for different drug concentrations were also tested at various pH values. NaOH and HCl were used for pH-adjustments.

Selectivity of the Sensor. Selectivity coefficient of the sensor was calculated by using the separate solution method (SSM)[18] with 10^{-2} M solutions of Perindopril and interferent at pH 6. The selectivity coefficient values were calculated from the rearranged Nicolsky equation.

$$\log K_{PDLM}^{pot} = [E_M - E_{PDL}/S] + \log a_{PDL} - \log a_M^{(Z_{PDLM}|Z_M)}$$

Where:

E_{PDL}: is the potential measured in 10^{-2} M Perindopril solution.

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

S: slope of the electrode calibration plot.

Results and Discussion

Phosophotungestic acid (PTA) $H_3PW_{12}O_{40}$ is one of the ionic ionophores used for preparing ion-selective electrodes.[19,20] The different ionization forms of PTA, at different pH values, facilitate its interaction with many compounds.[21] At pH 1 the ionic species of PTA is $[PW_{12}O_{40}]^{3-}$, pH 2.2 they are $[PW_{12}O_{40}]^{3-}$, $[P_2W_{21}O_{71}]^{6-}$, $[PW_{11}O_{39}]^{7-}$, at pH 3.5 they are $[PW_{12}O_{40}]^{3-}$, $[P_2W_{21}O_{71}]^{6-}$, $[PW_{11}O_{39}]^{7-}$, $[P_2W_{18}O_{62}]^{6-}$, $[P_2W_{19}O_{67}]^{10-}$, at pH 5.4 they are $[P_2W_{21}O_{71}]^{6-}$, $[PW_{11}O_{39}]^{7-}$, $[P_2W_{18}O_{62}]^{6-}$, at pH 7.3 it is $[PW_9O_{34}]^{9-}$, and at pH 8.3 they are PO_4^{3-}, WO_4^{2-}.

For PDL-solution, pH 5-6, the $[P_2W_{21}O_{71}]^{6-}$, $[PW_{11}O_{39}]^{7-}$, $[P_2W_{18}O_{62}]^{6-}$ species are the most probable species which are involved into ion-pair formation.

The interaction between PDL and PTA is based on the interaction between the cationic part of PDL (two ammonium groups, one is quaternary and the other is a secondary amine) and anionic side of PTA^- as counter ion. The equilibrium interaction between both molecules can be expressed as:

$$[PDL\text{-}N_2H_2]^{++} + PTA^{6-} = \{[PDL\text{-}N_2H_2]^{++} - (PTA^{6-})\}^{4-}$$

It is well established that the sensitivity, linearity and selectivity of the electrode depend significantly on the membrane composition.[22] For this purpose, the effects on ISE-response according to its composition, inner solution, the presence of interfering ions, the concentration of ion pair in the membrane and polymer content (viscosity) of the membrane were studied experimentally. Six membrane compositions were prepared, Table 1.

The prepared ion-pair complex was used as an electroactive material in the construction of a new sensor selective for PDL drugs. The ion-pair incorporated in a membrane containing *o*-NPOE, DOP or DDP as plasticizers in PVC matrix and the performance characteristics of the proposed sensor was evaluated according to IUPAC recommendations.[23] Membrane sensors based on Perindopril-phosphotungstate were plasticized with DDP (ε = 4), DOP (ε = 7), and *o*-NPOE (ε = 24). They showed calibration graph slopes of 18.3, 21.3 and 28.9 mV per decade with linear ranges of 1×10^{-2} - 7×10^{-5}, 1×10^{-2} - 3×10^{-5} and 1×10^{-2} - 7×10^{-6} and lower detection limits of 5.5×10^{-5}, 1×10^{-5} and 4.5×10^{-6} M, respectively. It can be seen from Table 1 that sensor based on the Perindopril-phosphotungstate with *o*-NPOE plasticized membrane shows highest slope and detection limit than sensors with membranes plasticized with DDP and DOP. This may be due to the highest dielectric constant of *o*-NPOE than DDP and DOP. The divalent behaviour of prindopril was attributed to the presence of secondary and quaternary amine groups.

Diffusion coefficients in the membrane can be widely varied by changing the concentration ratio of polymer to plasticizer.[21] An increase of the polymer content of the membrane of ISE from the value of 31.5% to 48.3% leads to an almost ideal response and linear range Figure 3.

As it is shown from Table 1, the membrane number-6 has the optimum properties relative to others. This membrane composition was selected to perform the measurements. The high (PDL) extraction into the liquid membrane was a result of ion-pair tendency to exchange with the (PDL) cation in the aqueous solution. From Table 1, 9% ion-pair (PDL-PTA) is the optimum amount that showed the best response.

Effect of Internal Solution Concentration. The influence of the concentration of internal solution on the emf response of ion-selective electrodes were studied. The results showed that variation in the concentration (1×10^{-2} to 1×10^{-4} mol L^{-1}) of the internal solution does not significantly change the electrode response of slope while parameters like measuring range and detection limit[24] changed to considerable extent (Table 2). A 1×10^{-3} mol L^{-1} concentration of internal solution gave the best response.

Effect of pH. Wide application of an ISE requires the knowledge of the pH range of the functioning of given

Table 1. Optimization of membrane components

No.	Composition (%)			Slope (mV decade^{-1})	Linear range (mol L^{-1})	Life time (Week)	Response time, (s)
	Ion-pair	PVC	plasticizer				
1	3.5	31.5	65 (*o*-NPOE)	28.4	7×10^{-6} - 1×10^{-2}	2	10 for conc. ≥ 10^{-3} 20 for conc. ≥ 10^{-3}
2	3.5	31.5	65 (*DOP*)	21.3	1×10^{-2} - 3×10^{-5}	2	40 for conc. ≥ 10^{-4} 55 for conc. ≥ 10^{-4}
3	3.5	31.5	65 (*DDP*)	18.3	1×10^{-2} - 7×10^{-5}	2	60
4	3.5	48.3	48.2 (*o*-NPOE)	30.2	4.2×10^{-6} - 1×10^{-2}	3	10 for conc. ≥ 10^{-3} 30 for conc. ≥ 10^{-3}
5	6	31.5	62.5 (*o*-NPOE)	31.0	5.2×10^{-6} - 1×10^{-2}	3	10 for conc. ≥ 10^{-3} 20 for conc. < 10^{-3}
6	9	30.5	60.5 (*o*-NPOE)	28.9	4.0×10^{-6} - 1×10^{-2}	5	10 for conc. ≥ 10^{-3} 20 for conc. ≥ 10^{-3}

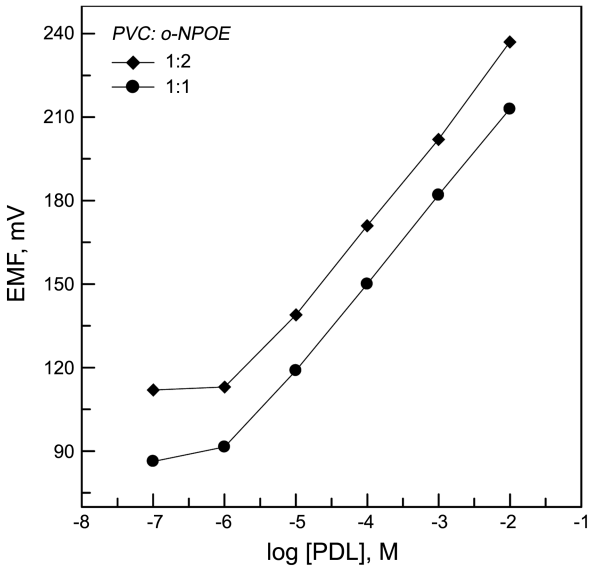

Figure 3. Influence of the viscosity of the membrane on the response of the ISE.

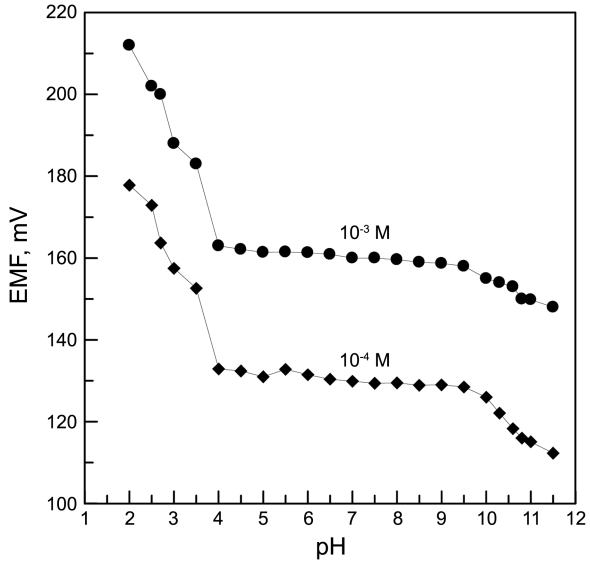

Figure 4. Effect of pH on PDL-electrode performance.

Table 2. Effect of internal solution concentration on electrode performance

Membrane no	Internal solution, conc. (M), mol L^{-1}	Slope, (mV decade^{-1})	Linear range, (mol L^{-1})
4	10^{-2}	30.2	4.2×10^{-6}-1×10^{-2}
	10^{-3}	30.4	8.3×10^{-7}-1×10^{-2}
	10^{-4}	28.8	4.6×10^{-6}-1×10^{-2}
6	10^{-2}	28.9	4.0×10^{-6}-1×10^{-2}
	10^{-3}	30.9	9.0×10^{-7}-1×10^{-2}
	10^{-4}	29.0	4.5×10^{-6}-1×10^{-2}

electrode. The acidity of the medium may affect the state of an ion associate and other membrane components.[25] 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}; 1.0×10^{-4} M) of $(PDL)^{++}$ ions as a function of pH. The pH of the solution was varied by the addition of NaOH and HCl. As it is seen from the results, Figure 4, the potential is independent on the pH changes in the range of 4-9.5. Thus, this range may be chosen as the working pH for the electrodes assembly. At pH < 4, the (PDL) cation was protonated, whereas, at relatively high pH the potential decreases more significantly probably due to membrane interference from OH . The observed potential changes at the lower and higher pH values could be caused by the ion carrier protonation as well as the formation of free base of (PDL) ion in the solution was the reason of potential changes at high pH.

Response Time. For analytical applications, the dynamic response time is an impotant parameter for any sensor.[26] In this study, the practical response time was recorded by changing solution with different concentration from 1.0×10^{-6} to 1.0×10^{-2} M. The actual potential vs. time traces shows that the electrode reaches the equilibrium response in a short time of < 12 s with concentration from 1.0×10^{-6} to 1.0×10^{-4} M and 20 s with concentration from 1.0×10^{-3} to 1.0×10^{-2} M. Table 1 shows the obtained results.

Lifetime. The lifetime of the sensors was detected by measuring the slope of the potential versus (PDL) ion concentration over the concentration range of 1×10^{-6} - 1×10^{-2} M each week over a period of five weeks while the electrodes were in continuous use. The lifetime for the ion-selective sensors is in the range of 3-5 weeks according to the membrane composition. The proposed sensor can be used for 5 weeks. After this period there is a slight gradual decrease in the slopes (−2 mV per decade) and the detection limit will increase. It is well known that the loss of plasticizer, (PDL-PTA) complex from the polymeric film due to leaching into the sample is the primary reason for the lifetimes of the sensors.

Selectivity of the Sensor. The potentiometric selectivity coefficient $K^{pot}_{PDL,M}$ of Perindopril sensor was evaluated at different concentrations of both Perindopril and the interferents using the separate solution method (SSM)[18] as it is

Table 3. Selectivity coefficient $\log K^{pot}_{PDL,M}$

Interferent	Log $K^{pot}_{PDL,M}$
Maltose	-4
Amm. Citrate	-2.23
Amm. oxalate	-3.03
Rhamnose	-4.43
Benzamide	-4.06
Glycine	-4.0
Mg^{++}	-4.06
Ni^{++}	-4.5
Amm. Renieckate	-3.26
Cu^{++}	-4.2
K^{+}	-4.24
Na^{+}	-4.56

Table 4. Determination of perindopril in its pharmaceutical preparations

Sample	Stated content in drug	Found[a]
Adwepril	4 mg/tablet	3. 9 ± 0.06 mg
Coversyl	5 mg/tablet	5.05 ± 0.04 mg
Coversyl	10 mg/tablet	10.04 ± 0.04 mg

[a]The results based on three measurements

shown in Table 3. These data reveal that the sensor gave a reasonable good selectivity for PDL as compared to many basic and acidic compounds. No interference were caused by many pharmaceutical expients and diluents commonly used in drug formulations (*e.g.* maltose, rhamnose and glycine).

Determination of Perindopril in Pharmaceutical Preparation. The content of 5 tablets (Adwepril 4 mg/tablet), (Coversyl 5 mg/tablet) and (Coversyl 10 mg/tablet) were weighed and finely powdered in a small dish, dissolved in a minimum volume of 10^{-2} M HCl solution and filtered off into 50 mL volumetric flask through Whatman filter paper No. 42, the filtrate was diluted to the mark with deionized water or a suitable buffer, shaken and adjusted at pH = 6. The sensors in conjunction with double-junction Ag/AgCl reference electrode were immersed in 25 mL beaker 2.5 mL of the prepared solution was transferred to the beaker and completed to 10 mL. The mV of the test solution was directly measured and compared with the calibration graph. The results for determination of Perindopril amount in some pharmaceutical samples from local pharmacy are shown in Table 4. The results are in satisfactory agreement with the stated content on drug.

Conclusion

The described potentiometric method has simple workup procedure and requires no sophisticated instrumentation. It determines only the therapeutically active undegraded drug in the presence of its excipients without separation. The results obtained also show that the constructed sensors provide response suitable for analytical use in the determination of Perindopril in drug bulk powder. Apart from showing linear response within wide pH and concentration ranges with high accuracy and sensitivity, they also have high selectivity, reproducibility and it offers distinct advantages in rapidity and simplicity.

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