—Regular Articles—

# Stability Indicating Electrochemical Methods for the Determination of Meclophenoxate Hydrochloride and Pyritinol Dihydrochloride Using Ion-Selective Membrane Electrodes

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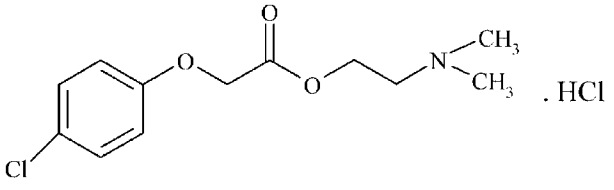
The construction and electrochemical response characteristics of polyvinyl chloride (PVC) membrane sensors for the determination of meclophenoxate hydrochloride (I) and pyritinol dihydrochloride (II) in presence of their degradation products are described. The sensors are based on the use of the ion-association complexes of (I) and (II) cation with sodium tetraphenyl borate and ammonium reineckate counteranions as ion-exchange sites in the PVC matrix. In addition $\beta$-cyclodextrin ($\beta$-CD) membranes were used in the determination of I and II. These ion pairs and $\beta$-CD were then incorporated as electroactive species with ortho nitrophenyl octyl ether (oNPOE) as a plasticizer. Three PVC sensors were fabricated for each drug, *i.e.* meclophenoxate tetraphenyl borate (meclo-TPB), meclophenoxate reineckate (meclo-RNC) and meclophenoxate $\beta$-cyclodextrin (meclo-$\beta$-CD), and the same was done for pyritinol (pyrit-TPB), (pyrit-RNC) and (pyrit-$\beta$-CD). They showed near Nernestian responses for meclophenoxate over the concentration range $10^{-5}$—$10^{-2}$ with slopes of 52.73, 51.64 and 54.05 per concentration decade with average recoveries of 99.92$\pm$1.077, 99.96$\pm$0.502 and 100.03$\pm$0.763 for meclo-TPB, meclo-RNC and meclo-$\beta$-CD respectively. Pyritinol also showed near Nernestian responses over the concentration range of $3.162\times10^{-6}$—$3.162\times10^{-4}$ for pyrit-TPB and pyrit-RNC, and $10^{-6}$—$3.162\times10^{-4}$ for pyrit-$\beta$-CD with slopes of 30.60, 31.10 and 32.89 per concentration decade and average recoveries of 99.99$\pm$0.827, 100.00$\pm$0.775 and 99.99$\pm$0.680 for pyrit-TPB, pyrit-RNC and pyrit-$\beta$-CD respectively. The sensors were used successfully for the determination of I and II in laboratory prepared mixtures with their degradation products, in pharmaceutical dosage forms and in plasma.

**Key words**——meclophenoxate hydrochloride; pyritinol dihydrochloride; ion-selective membrane electrodes PVC membranes; ammonium reineckate; $\beta$-cyclodextrin

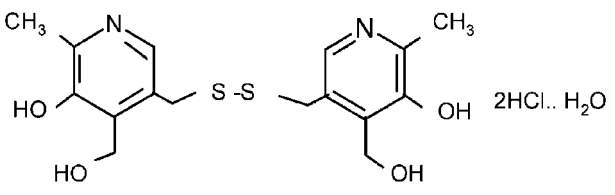
## INTRODUCTION

Meclophenoxate hydrochloride (I) [CAS number 51-68-3] [(4-chloro phenoxy) acetic acid-2-(dimethyl amino) ethyl ester] is a white powder, soluble in cold water and methanol, sparingly soluble in cold isopropanol and acetone and practically insoluble in benzene, ether, and chloroform.[1)]




It acts as cerebral stimulant. It has been claimed to aid cellular metabolism in the presence of diminished oxygen concentrations. It has been administered mainly for mental changes in the elderly or following strokes and head injury.[2)] Various chromatographic,[3—6)] colorimetric,[7)] radiochemical[8)] and proton magnetic resonance methods[9)] were used for determination of drug concentration.

Pyritinol dihydrochloride (II) [CAS number 1098-07-1] [5,5-dihydroxy-6,6-dimethyl-3,3-dithio dimethylene bis (4-pyridyl methanol) dihydrochloride monohydrate] is a white powder soluble in water, hydrochloric acid, sodium hydroxide and methanol.[1)]




It has been described as a nootropic drug, which has no vitamin B6 activity.[2)] The determination of pyritinol dihydrochloride in tablets was studied using

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several colorimetric,[10—12] spectrophotometric,[13,14] electrochemical[15] and HPLC[16] methods.

None of the above methods indicate stability, which may not be suitable for the determination of (I) and (II) in presence of their degradates. The present study aimed to develop feasible, sensitive, and specific analytical procedures for the analysis of (I) and (II) in presence of their degradation products. Adaptation of the proposed procedure for the analysis of the available dosage form including expired ones is also an important task to solve problems encountered in quality control. The fabricated sensors also can determine I and II either in plasma or in the presence of other excepients without the need for preliminary extraction and separation steps.

## EXPERIMENTAL

**Samples** Meclophenoxate hydrochloride powder was kindly supplied by Minapharm. Its purity was checked in our laboratory according to the reported method[17] and it was found to be 100.23±0.662. Lucidril tablets batch nos. 5GE0941 and 010156 (expired March 2004) were purchased on the Egyptian market. Each tablet is claimed to contain 250 mg (I). Lucidril tablets are manufactured by Minapharm Pharmaceutical Company under license from Lipha-France.

Pyritinol dihydrochloride monohydrate powder was kindly supplied by E. Merck, Darmstadt, Germany. Its purity was checked in our laboratory according to the reported method[18] and was found to be 99.06±1.053. Encephabol tablets batch no. 13476 were purchased on the Egyptian market. Each tablet is claimed to contain 200 mg of (II). Encephabol tablets are manufactured by El Nile Pharmaceutical Company under licence from E. Merck.

**Reagents** All materials were of analytical grade and double-distelled deionized water was used. o-Nitrophenyloctyl ether (oNPOE), polyvinyl chloride (PVC; high molecular weight), ammonium reineckate (RNC), sodium tetraphenylborate (TPB), and $\beta$-cyclodextrin ($\beta$-CD) were purchased from Sigma (St. Louis, MO, USA), Tetrahydrofuran, 99% was from Lab scan. Phosphate buffer solution, pH 6, was prepared by adding 74.2 ml of 0.5 M $KH_2PO_4$ and 8.6 ml of 0.5 M $Na_2HPO_4$ to a 1-L volumetric flask and diluted to 1 L with water. Phosphate buffer solution, pH 3, was prepared by dissolving 34 g of potassium dihydrogen phosphate in sufficient water to produce 250 ml of buffer and pH was adjusted with phosphoric acid.[19]

**Apparatus** All potentiometric measurements were carried out at 25±1℃ with a Hanna (Model 211) pH/mV meter with a single-junction calomel reference electrode (Model HI5412) used in conjunction with the drug sensor. A WPA-pH combined electrode model CD 740 was used for pH measurements.

**Procedures**

Preparation of the Degradation Product of Meclophenoxate Hydrochloride: Five hundred milligrams was dissolved in 50 ml of 2 N sodium hydroxide and then refluxed at 100℃ for 25 min.

One ml was cooled to room temperature and then diluted with methanol. The degraded solution and standard solution were spotted on HPTLC plates. The plates were placed in chromatographic tanks previously saturated for 1 h with the mobile phase of chloroform : methanol : acetic acid (1 : 1 : 0.1 v/v/v) and then air-dried. The spots were visualized under UV. light at 254 nm. The medium was rendered acidic using concentrated hydrochloric acid (Prolabo) to precipitate the degradation product. The degradation product was filtered and then recrystallized from isopropyl alcohol.

Preparation of the Degradation Product of Pyritinol Dihydrochloride: The preparation of the degradation product depends on the oxidation of the disulphide linkage of (II) to sulphonate using hydrogen peroxide 30% (v/v).[20] First 200 mg of the drug was added to 10 ml of hydrogen peroxide 30% (v/v) in a stoppered test tube and left for 1 h at room temperature. The solution was heated to evaporate excess oxygen until the final volume was about 1 ml. The degraded solution was applied as a band versus spots of the standard solution on HPTLC plates using n-butanol (Prolabo) : acetic acid (Prolabo) : water (4 : 1 : 1 v/v/v) as a developing system. The separated band was scraped off and extracted in the least amount of methanol. The filtrate was dried at atmospheric temperature to obtain the degradation product.

Preparation of Membranes: The method of Hassan et al.[21] was used for the preparation of the membranes.

Preparation of Meclo-TPB and Pyrit-TPB Membranes: Ten milliliters of $10^{-2}$ M (I) or (II) aqueous solution was mixed with 10.00 ml of a saturated aqueous solution of (TPB). The resulting precipitate was

filtered, washed with cold water, allowed to dry at room temperature and ground to fine powder. The resultant ion-association complex was confirmed using elemental analysis.

In a Petri dish (5-cm diameter), 0.01 g of the previously prepared ion-association complex was mixed with 0.35 g of oNPOE then 0.19 g of PVC was added and repeated mixing. This mixture was dissolved in 5 ml tetrahydrofuran, and the dish was covered with a filter paper and left to stand overnight to allow slow evaporation of the solvent forming the master membrane with 0.1-mm thickness.[21)]

Preparation of Meclo-RNC and Pyrit-RNC Membranes: The same procedure as above was followed using saturated aqueous solution of ammonium reineckate instead of TPB.

Preparation of Meclo-$\beta$-CD and Pyrit-$\beta$-CD Membranes: In a Petri dish (5-cm diameter), 0.04 g of $\beta$-CD was mixed with 0.4 g oNPOE and 0.01 g of ammonium reineckate, then dissolved in 5 ml tetrahydrofuran. The dish was covered with a filter paper and left to stand overnight to allow slow evaporation of the solvent forming the master membrane with 0.1-mm thickness.[21,22)]

Electrode Assemble: A disk of an appropriate diameter (about 8 mm) was cut from the previously prepared master membranes and cemented to the flat end of PVC tubing with an adhesive of PVC dissolved in tetrahydrofuran. The other end of the PVC tubing was then connected to an appropriate glass outer casing.

A mixture of equal volumes of $10^{-2}$ M (I) or $10^{-2}$ M (II) and $10^{-2}$ M sodium chloride was used as an internal reference solution. The membranes were conditioned by soaking in $10^{-2}$ M aqueous drug solution overnight and stored in the same solution when not in use.

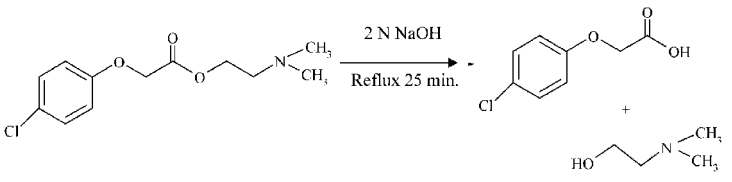
Sensor Calibration: The prepared electrodes in conjunction with the single-junction calomel reference electrode were immersed in aqueous solutions of (I) and (II) in the range of $10^{-6}$—$10^{-1}$ M and $10^{-6}$—$10^{-3}$ M respectively. They were allowed to equilibrate while stirring and recording the e.m.f readings within $\pm 1$ mV. The membrane sensors were washed between measurements with water. The e.m.f values were recorded as a function of drug concentration and then calibration graphs of the recorded potentials versus log drug concentration were plotted. These calibration graphs or the computed regression equations for the linear part of the curves were used for subsequent determination of unknown concentrations of (I) and (II).

Application to Plasma Samples: 4.5 ml of plasma was placed in 6 stoppered shaking tubes, then spiked with 0.5 ml of $10^{-2}$ and $10^{-3}$ M (I) and 0.5 ml of $3.162\times10^{-3}$ and $10^{-4}$ M (II) separately and shaken. The e.m.fs produced by immersing the prepared electrodes in conjunction with the single-junction calomel reference electrode in the spiked plasma were recorded and then was determined the concentration of (I) and (II) from their calibration curves from the corresponding electrode.

Application to Pharmaceutical Formulations: Ten tablets of both drugs were weighed and powdered. An amount of the powdered tablets equivalent to 0.01468 g of (I) and 0.0023 g of (II) was transferred to two 50-ml volumetric flasks and phosphate buffer, pH 6, was added to prepare a $10^{-3}$ M aqueous solution of (I) and phosphate buffer, pH 3, to prepare a $10^{-4}$ M aqueous solution of (II). The e.m.f values produced were recorded by immersing the prepared electrodes in conjunction with the single-junction calomel reference electrode in the prepared solutions and then the concentration of (I) and (II) was determined from their calibration curves from the corresponding electrode.

## RESULTS AND DISCUSSION

**Degradation of Meclophenoxate Hydrochloride** The proposed scheme for preparing the degradation product is shown below.

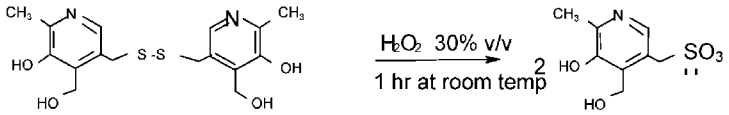



Mass spectroscopy was performed for the degradation product (p-chloro phenoxy acetic acid) and the parent peak was identified at m/z = 187 which is the molecular weight of the product. N,N-dimethyl ethanolamine is a volatile compound characterized by a fishy odor and it cannot be detected on TLC plates.

(I) can be hydrolyzed in aqueous solution[23)] but it was stable in water for 6 h. This was confirmed in TLC.

**Degradation of Pyritinol Dihydrochloride** The proposed scheme for preparing the degradation

product is shown below.




In the GC-MS chart, the parent peak was identified at m/z=233, which is the molecular weight of the degradation product.

Using the NMR spectra to identify the structure of the precursor and the degradation product was useless as no change in the type of hydrogen occurs. In the IR spectra, no change in the functional groups occurs, except for the SH group in the precursor and the S=O group in the degradation product. The SH group appears at the same wave number as the OH group, and thus will be masked. S=O appears in the region of the double bond (1600—1800 $cm^{-1}$) and thus will be masked by the C=C of the aromatic pyridine ring, *i.e.*, the IR spectra also will not change.[24]

The drug contains no ester or amide group that can be hydrolyzed by acids, bases, moisture or heat and thus the only pathway for degradation is through oxidation.

Applying the ICH guidelines for the degradation of the tablets showed no degradation, and we decided to force degradation under stressed conditions. Alkyl hydroperoxides, hydrogen peroxide and peroxy acid oxidize the drug through a free radical mechanism resembling that of photodegradation which oxidizes the disulphide linkage to sulphoxide and then sulphonate, which is why the ICH considers it to be a method of degradation.

Following the rapid developments at the end of the 1960s and the beginning of the 1970s, the field of potentiometry with ion-selective electrodes (ISEs) has stabilized.[25] The 1980s and 1990s were characterized by enormous exploratory efforts in the theory and methodology of ISEs and their possible application to chemical problems.[26] In the present study, the membranes used were supported ion-exchange sensors fabricated with PVC as a polymer matrix.

In the proposed PVC sensors, (I) and (II) act as a cation, which suggests the use of ion exchangers of the anionic type. TPB and reineckate were found to be the optimum anion exchangers for the studied drug. The resulting precipitates have low solubility products and suitable grain size. (I) and (II) reacted with TPB and reineckate to form a stable 1 : 1 and 1 : 2, water-insoluble ion-association complex respesctively. This ratio was confirmed by the elemental analysis data and by the Nernest response of the suggested sensors, which was about 60 mV and 30 mV, the typical value for monovalent and divalent drugs, respectively.

CDs are optically active oligosaccharides that form inclusion complexes in the aqueous and in solid state with organic molecules. They were previously applied as sensor ionophores to potentiometric ISEs for the determination of protonated amines[27] and chiral molecules incorporating aryl rings.[28] $\beta$-CD based sensors showed accurate results in both response and selectivity.

It has been reported that the PVC matrix is a regular support and reproducible trap for ion-association complexes in ISEs. Nevertheless, its use creates a need for plasticization and places a constraint on the choice of mediator.[29] In the present study, oNPOE plasticizer was used in the fabrication of the proposed sensors. It plasticized the membrane and adjusted both permittivity of the final organic membranes and mobility of the ion-exchanger sites. Such adjustments influence the partition coefficient of the studied drug with subsequent effects on electrode selectivity.

Electrochemical performance characteristics of the proposed sensors were evaluated according to the IUPAC recommendation data.[30]

For Meclophenoxate Hydrochloride: The electrodes displayed constant and stable potential readings within $\pm$2.0 mV, 2.4 mV, and 1.0 mV from day to day using the sensors meclo-TPB (1), meclo-RNC (2), and meclo-$\beta$-CD (3), respectively. Calibration slopes did not change by more than 2 mV/decade over a period of 3 weeks for the three sensors.

The response times of the electrodes were tested for drug concentrations of $10^{-4}$ and $10^{-3}$ M. The measurements were characterized by a fast, stable response within 40, 40 and 30 seconds for sensors 1, 2, and 3, respectively. The slopes of the calibration curves were typically $-52.73$, $-51.64$ and $-54.05$ mV/concentration decade for electrodes 1, 2, and 3, respectively (Table 1). Deviation from the ideal Nernestian slope (60 mV) stems from the fact that the electrode responds to the activities of drug cation rather than its concentration.

The effect of pH on the electrode potential was investigated and it was found that the investigated elec-

Table 1. Electrochemical Response Characteristics of Meclophenoxate Electrodes

| Parameter | Meclo-TPB | Meclo-RNC | Meclo-$\beta$-CD |
|---|---|---|---|
| Slope (mV/decade)* | −52.73 | −51.64 | −54.05 |
| Slope relative error (mV) | ±2.0 | ±2.4 | ±1.0 |
| Intercept (mV) | 222.03 | 227.84 | 268.6 |
| Response time (seconds) | 40 | 40 | 30 |
| Working pH range | 4—7.5 | 5.5—7 | 4—7.5 |
| Concentration range (M) | $1\times10^{-5}$—$1\times10^{-2}$ | $1\times10^{-5}$—$1\times10^{-2}$ | $1\times10^{-5}$—$1\times10^{-2}$ |
| Stability (weeks) | 3 | 3 | 3 |
| Average recovery (%) | 99.92 | 99.96 | 100.03 |
| Standard deviation | 1.077 | 0.502 | 0.763 |
| Correlation coefficient | 0.9995 | 0.9998 | 0.9996 |

* Calculated using 4 points.

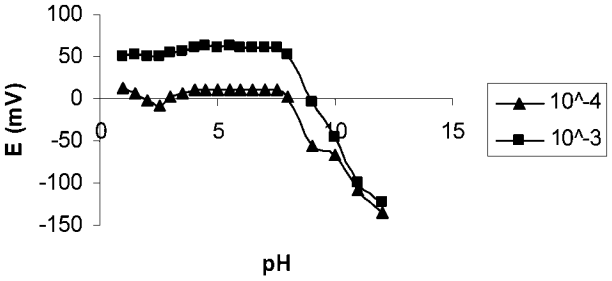



Fig. 1. Effects of pH on the Response of the Meclo-TPB Electrode

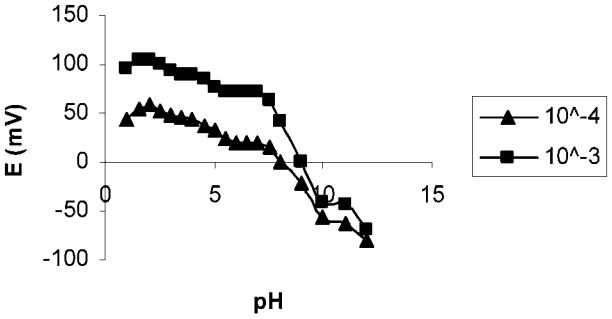



Fig. 2. Effects of pH on the Response of the Meclo-RNC Electrode

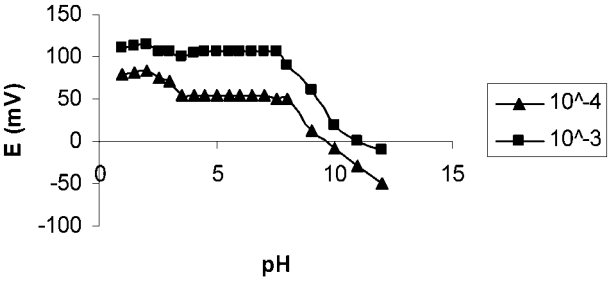



Fig. 3. Effects of pH on the Response of the Meclo-$\beta$-CD Electrode

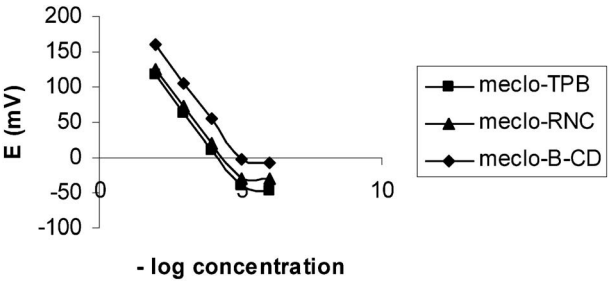



Fig. 4. Profile of the Potential (in mV) to the −Log Concentration of Meclophenoxate Hydrochloride with Meclo-TPB, Meclo-RNC, and Meclo-$\beta$-CD

trodes gave a useful pH range from 5—7. Above this pH range, the potential showed a sharp decrease due to the formation of the nonprotonated tertiary amino group of meclophenoxate. Below pH 4, the potentials displayed by the electrodes were noisy as the membrane may extract $H^+$ from the medium at such high acidity (Figs. 1—3).[31] The potentiometric responses of the three studied electrodes at the optimum pH and at 20—25℃ were linear with constant slopes over the drug concentration range $10^{-5}$—$10^{-2}$ M (0.00293—2.937 mg/ml) for sensors 1, 2, and 3 (Fig. 4).

For Pyritinol Dihydrochloride: The electrodes displayed constant and stable potential readings within ±2.2 mV, 2.0 mV, and 1.6 mV from day to day using sensors pyrit-TPB (4), pyrit-R (5), and pyrit-$\beta$-CD (6), respectively. Calibration slopes did not change by more than 2.8 mV/decade over a period of 4 weeks for the three sensors.

Table 2. Electrochemical Response Characteristics of Pyritinol Electrodes

| Parameter | Pyrit-TPB | Pyrit-RNC | Pyrit-$\beta$-CD |
|---|---|---|---|
| Slope (mV/decade) * | −30.600 | −31.100 | −32.891 |
| Slope relative error (mV) | ±2.2 | ±2.0 | ±1.6 |
| Intercept (mV) | 266.84 | 286.89 | 317.07 |
| Response time (seconds) | 40 | 40 | 40 |
| Working pH range | 2.5—4 | 2.5—4 | 2.5—4 |
| Concentration range (M) | $3.162\times10^{-6}$—$3.162\times10^{-4}$ | $3.162\times10^{-6}$—$3.162\times10^{-4}$ | $1\times10^{-6}$—$3.162\times10^{-4}$ |
| Stability (weeks) | 4 | 4 | 4 |
| Average recovery (%) | 99.99 | 100.00 | 99.99 |
| Standard deviation | 0.827 | 0.775 | 0.680 |
| Correlation coefficient | 0.9994 | 0.9996 | 0.9990 |

* Calculated using 4 points.

The response times of the electrodes were tested for drug concentrations of $10^{-5}$ and $10^{-4}$ M. The measurements were characterized by a fast, stable response within 40 seconds for sensors 4, 5, and 6.

The slopes of the calibration curves were typically −30.60, −31.10 and −32.89 mV/concentration decade for electrodes 4, 5, and 6, respectively (Table 2). Deviation from the ideal Nernestian slope (30 mV) stems from the fact that the electrode responds to the activities of drug cation rather than its concentration.

The effect of pH on the electrode potential was investigated and it was found that the investigated electrodes gave a useful pH range from 2.5—4. Above this pH range, the potential showed a sharp decrease. Below pH 2.5, the potentials displayed by the electrodes were noisy as the membrane may extract $H^+$ from the medium at such high acidity.[31] The pH range from 8.5—10 was also suitable but the disadvantage was that concentrations of $10^{-3}$ and greater were insoluble at pH from 5.5—10.5 (Figs. 5—7). The potentiometric responses of the three studied electrodes at the optimum pH and at 20—25℃ were linear with constant slopes over the drug concentration range of $3.162\times10^{-6}$—$3.162\times10^{-4}$ M (0.0014—0.1452 mg/ml) for sensors 4 and 5 and a concentration range of $10^{-6}$—$3.162\times10^{-4}$ M (0.000459—0.1452 mg/ml) for sensor 6 (Fig. 8).

The performance of the six electrodes in the presence of the degradation products or any interferent, which may be pharmaceutical additives and diluents commonly used in drug formulation such as NaCl, KCl, $NH_4Cl$, $CaCl_2$, $MgSO_4$, lactose, glucose, sucrose, and L-phenyl alanine was assessed. Selectivi-

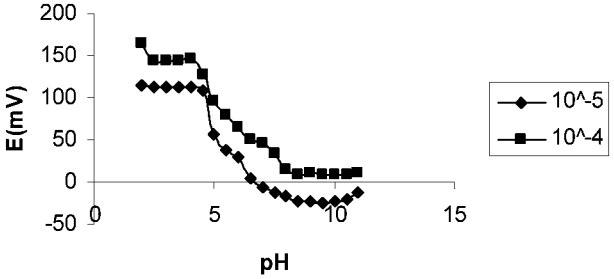



Fig. 5. Effects of pH on the Response of the Pyrit-TPB Electrode

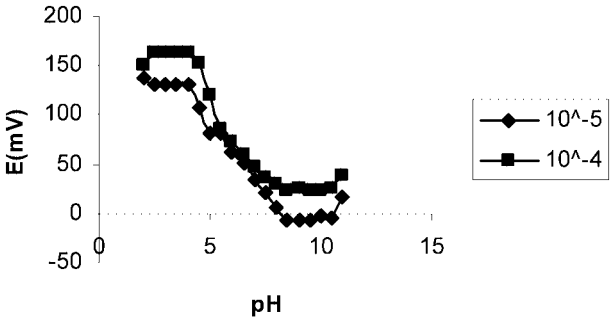



Fig. 6. Effects of pH on the Response of the Pyrit-RNC Electrode

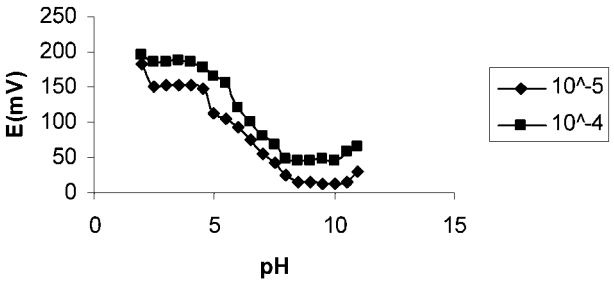



Fig. 7. Effects of pH on the Response of the Pyrit-$\beta$-CD Electrode

ty coefficient values ($K^{Plot}_{primary\ ion,\ interferent}$) were measured with the separate solution method[32] using a fixed concentration of the interferent and the degradation product [$10^{-3}$ M for (I) and $10^{-4}$ M for (II)]. The small values of K obtained show reasonable selectivity for (I) and (II).

When it was applied for the determination of (I) and (II) in the presence of their degradation products in laboratory prepared mixtures, the sensors were valid until 83.33% of the degradation product for (I) as its degradation product lost its tertiary amine group and only 33.33% degradation product for (II) because its degradation product is still somewhat similar in structure to the intact molecule, and this confirms the specificity of the method. The proposed procedure was also successfully applied for the determination of (I) and (II) in lucidril and encephabol tablets, respectively, including expired lucidril tablets, with good recovery.

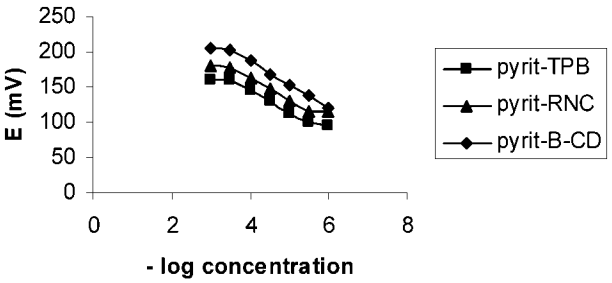



Fig. 8. Profile of the Potential in (mV) to the—Log Concentration of Pyritinol Dihydrochloride with Pyrit-TPB, Pyrite-RNC, and Pyrit-$\beta$-CD

The validity of the proposed procedure was assessed by applying the standard addition technique. On application to the spiked human plasma, the six electrodes gave stable results as revealed by the high precision and accuracy of recovery results (Tables 3,4)

Statistical analysis of the results of analysis of pure (I) and (II) by the proposed electrodes and the reference method showed that there is no significant difference between the proposed and the reference method in terms of accuracy and precision.

## CONCLUSION

The use of the proposed sensors offers the advantage of fast response, elimination of drug pretreatment or separation steps, wide pH range, low detection limit, and direct determination of drugs in turbid and colored solutions. The proposed procedure is simple, sensitive, selective, and stability indicating and can be used for the routine analysis of (I) and (II) either in the pure powdered form or their available pharmaceutical dosage forms.

## REFERENCES AND NOTES

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Table 3. Determination of Meclophenoxate Hydrochloride in Spiked Human Plasma with the Proposed Electrodes

| Concentration (M) | Meclo-TPB | Meclo-RNC | Meclo-$\beta$-CD |
|---|---|---|---|
| | Recovery % ± S.D.* | Recovery % ± S.D.* | Recovery % ± S.D.* |
| $1\times10^{-3}$ | 101.77 ± 0.612 | 101.58 ± 0.663 | 101.03 ± 0.497 |
| $1\times10^{-4}$ | 102.14 ± 0.550 | 101.97 ± 0.601 | 101.24 ± 0.404 |

* Average of three determinations.

Table 4. Determination of Pyritinol Dihydrochloride in Spiked Human Plasma with the Proposed Electrodes

| Concentration (M) | Pyrit-TPB | Pyrit-RNC | Pyrit-$\beta$-CD |
|---|---|---|---|
| | Recovery % ± S.D.* | Recovery % ± S.D.* | Recovery % ± S.D.* |
| $3.162\times10^{-4}$ | 100.92 ± 0.671 | 99.74 ± 0.601 | 100.76 ± 0.341 |
| $1\times10^{-4}$ | 101.14 ± 0.770 | 100.41 ± 0.826 | 100.11 ± 0.475 |

* Average of three determinations.

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