—Regular Articles—

Membrane Sensors for the Selective Determination of Tiapride in Presence of its Degradation Products

Fadia Hussein METWALLY

Analytical Chemistry Department, Faculty of Pharmacy, Cairo University, El-Kasr El-Aini St., ET–11562 Cairo, Egypt

(Received February 25, 2007, Accepted April 28, 2007)

The construction and electrochemical response characteristics of polyvinyl chloride (PVC) membrane sensors for determination of tiapride in presence of its degradation products are described. The sensors are based on the ion association complexes of tiapride cation with sodium tetraphenyl borate (Tia-TPB) [sensor 1]) or ammonium reineckate (Tia-R) [sensor 2] counter anions as ion exchange sites in PVC matrix. The performance characteristics, sensitivity and selectivity of these electrodes in presence of tiapride degradation products were evaluated according to IUPAC recommendations. It reveals a fast, stable and linear response for tiapride over the concentration range 10^{-5}–10^{-2} M with cationic slopes of 28.997 and 30.580 mV per concentration decade with sensors 1 and 2, respectively. These sensors exhibit fast response time (20–30 s), low quantitation limit (4.5×10^{-6} and 3.6×10^{-6}, respectively), and good stability (6–8 weeks). The direct potentiometric determination of tiapride hydrochloride using the proposed sensors gave average recoveries of 99.95 ± 0.678 and 99.92 ± 1.157 for sensors 1 and 2, respectively. The sensors are used for determination of tiapride hydrochloride, in pure form, in presence of its degradation products in tablets, and in plasma. Validation of the method shows suitability of the proposed sensors for use in the quality control assessment of tiapride hydrochloride and for routine analysis as stability indicating method. The developed method was found to be simple, accurate and precise when compared with a reference company spectrophotometric method.

Key words——tiapride; ion selective electrodes; potentiometry; pharmaceutical analysis stability indicating methods

INTRODUCTION

Tiapride (Fig. 1) is N-[(2-diethylamino)ethyl]-2-methoxy-5-(methyl sulphonyl) benzamide hydrochloride.[1] It is a substituted benzamide with general properties similar to those of sulpiride. It is mainly used in management of behavioral disorders and in treatment of dyskinesias. It is claimed to exert its antipsychotic action via a selective blockage of central dopamine D_2 receptors.[2]

A variety of methods have been reported for the determination of tiapride hydrochloride including non-aqueous titration,[1,3] spectrophotometric,[4] HPLC methods in tablets[5–7] or in plasma,[8] gas liquid chromatography in serum,[9] or in whole blood[10] spectrofluorimetric[11] electrochemiluminescence by capillary electrophoresis[12] and flow injection chemiluminometric analysis[13] and dispersive solid phase extraction with gas chromatography/ion trap mass spectrometry.[14] From the literature review, it was found that none of these methods analyzed tiapride HCl in presence of its degradation products (stability indicating assay). Additionally, most of these methods as HPLC and Gas Chromatography involve time-consuming procedures and use sophisticated instruments.

Tetraphenyl borate and ammonium reinickate were reported as ion exchanges[15,16] for basic drugs. They

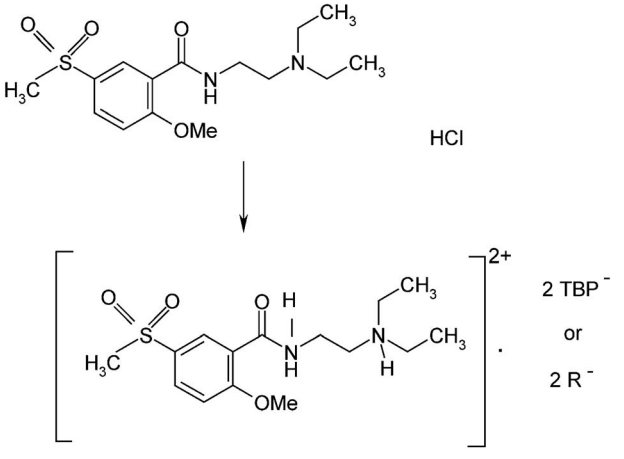


Fig. 1. Chemical Structure of Tiapride Hydrochloride and its Complexes

Molecular formula $C_{15}H_{25}ClN_2O_4S$, and molecular weight=364.9 g/mol.

e-mail: fadiahm@yahoo.com

have been used in the formation of many sensors.[16–19] In this work, it has been found that tiapride react with tetraphenyl borate or ammonium reinickate to form water insoluble ion association complex. The high lipophilicity and remarkable stability of these complexes suggested their selective use as electroactive materials in PVC matrix membrane sensors for the determination of the studied drug in the presence of its degradates and related substances. The advantages of these electrodes are the ease of construction, rapid manipulation, low cost, fast response, wide concentration range and applicability to turbid and colored solutions. Moreover, they offer highly sensitive, selective and convenient technique for the determination of tiapride in pure form, pharmaceutical preparation and spiked human plasma.

EXPERIMENTS

Apparatus Potentiometric measurements were made at 25±1°C with a Hanna (Model 211) pH/mV meter. A single junction calomel reference electrode (Model HI 5412) was used in conjugation with the drug sensor. A WPA pH combined glass electrode Model CD-740 was used for pH measurements.

Reagents and Solvents All chemicals were of analytical grade and bidistilled water was used. Tetrahydrofuran (THF) 99% (Lab scan), high molecular weight (10000) polyvinylchloride (PVC) powder (Aldrich), sodium tetraphenyl borate (Na TPB) (Aldrich), ammonium reineckate (R) (Sigma) and phosphate buffer pH 4.9 were prepared.[20]

Materials

Pure Samples

(1) Tiapride HCl (Batch No. 20367) was kindly supplied by Memphis Co. for Pharm. and Chemical Ind. Cairo-Egypt. Its purity was reported to be 99.2% according to the company analysis certificate.

(2) 2-Diethylamino-ethylamine was supplied by Sigma-Aldrich Chemie GmbH, Germany. Its purity was reported to be 99% according to the company certificate.

Market Samples Tiapridal® tablets (Batch No. 306182), labeled to contain 100 mg tiapride per tablet) was supplied from Memphis Co. for Pharm and Chemical Ind. Cairo-Egypt.

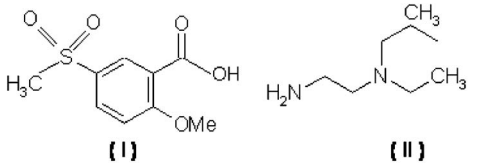
Stock Standard Solutions

Tiapride HCl Stock Solution (10^{-2} M) in water or phosphate buffer pH 4.9 was prepared by transforming 0.3649 g of tiapride powder into two separate 100 ml measuring flasks, 50 ml of either water in case of studying optimum parameters or phosphate buffer for calibration and determination with optimum pH were added, shaken and completed to volume with the same solvent.

Working Standard Solutions Tiapride working solution (10^{-7}–10^{-3} M) were prepared by suitable dilution from its stock solution using either water or phosphate buffer pH 4.9.

Preparation of Pure Degraded Samples Tiapride (0.3 g) was refluxed with 30 ml of 3 N HCl for eight hours for complete degradation. The solution was cooled and the precipitate (I) was filtered and washed with ether (3×15 ml). It was allowed to dry at room temperature until constant weight. The dried powder was identified by IR where the peak of carbonyl group present in the parent compound was shifted from 1646 cm^{-1} to 1704 cm^{-1}. A band of N-H group (of the amide group) which appeared in the parent compound at about 3323 cm^{-1} disappeared. A new band at about 3652 cm^{-1} appeared in the IR spectra of (I) indicating the presence of hydroxyl group.

The course of the reaction was followed by TLC on plates of silica gel 60 F_{254} using methanol: ethyl acetate (6.5:3.5 v/v) as a mobile phase. The mass spectra confirm these claims where the base peak for each compound corresponds to its molecular weight. The filtrate contains (II) which is liquid and is difficult to be separated so it was supplied by Sigma-Aldrich.[21]



(I) (II)

Stability Study The pH of the degraded samples prepared (10^{-2} M) was adjusted to 4.9 with phosphate buffer. The emf of the samples were measured and plotted as a function of time.

Laboratory-prepared Mixtures Aliquot portions 2.5, 5, 10, 25 ml of degradate I (10^{-2} M) was transferred accurately to a series of 50 ml measuring flasks. Add to each flask 5 ml portions from tiapride (10^{-2} M) solution to prepare mixtures containing 1 : 0.5, 1 : 1, 1 : 2 and 1 : 5 tiapride and degradate, respectively.

Procedures

Precipitation-based Technique for the Preparation of PVC-membrane Sensors Two membranes namely tiapride-tetraphenyl borate and tiapride-reineckate were prepared using a reported method.[19)]

Preparation of Tiapride-tetraphenyl Borate Membrane Ten milliliter of 10^{-2} M tiapride hydrochloride aqueous solution was mixed with 10 ml of a saturated aqueous solution of sodium tetraphenyl borate. The resulting precipitate was filtered, washed with cold water, allowed to dry at room temperature then grounded to fine powder. Elemental analysis for carbon, hydrogen and nitrogen was carried to study the formation of the complex.

In a glass Petri dish (5 cm diameter), 10 mg of the previously prepared ion association complex was mixed thoroughly with 0.35 ml of dibutylsebacate then 0.19 g of polyvinyl chloride was added (PVC). This mixture was dissolved in 5 ml tetrahydrofuran (THF), covered with filter paper and left to stand overnight to allow slow evaporation of the solvent at room temperature, thus a master membrane with 0.1 mm thickness was formed.[22,23)]

Preparation of Tiapride-reineckate Membrane The same procedure described in previous section was followed using saturated aqueous solution of ammonium reineckate instead of tetraphenyl borate.

Electrodes Assembly 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 THF as adhesive. A mixed solution consists of equal volumes of 10^{-2} M tiapride HCl and 10^{-2} M sodium chloride was used as internal reference solution (equimolar ratio of the highest concentration in linearity range of the drug added to NaCl solution). Ag/AgCl coated wire (3 mm diameter) was employed as an internal reference electrode. The electrochemical cell arrangement was Ag, AgCl/internal solution 10^{-2} M/membrane/sample solution//10 mM KCl/Hg/Hg_2Cl_2. The prepared sensors were conditioned by soaking for 24 hours into 10^{-2} M aqueous drug solution and stored in the same solution when not in use.

Sensors Calibration The prepared electrodes were immersed in conjugation with the single junction calomel reference electrode in phosphate buffer pH 4.9 solution of tiapride hydrochloride in the range of 10^{-6} to 10^{-2} M.

They were allowed to equilibrate whilst stirring and recording the emf readings within ± 1 mv. The membrane sensors were washed between measurements with water. The mV-concentration profiles were plotted. The regression equations for the linear part of the curves were computed and used for subsequent determination of unknown tiapride concentrations.

Selectivity Measurements Potentiometry selectivity coefficient (K_{Tia}^{Pot}) were evaluated according to IUPAC guidelines using the separate solutions method[22,23)] in which the potential of cell compromising the membrane electrode and a reference electrode in measured with two separate solutions, A and B where A (Tia ions) and B (interfering ion) at the same activity aA=aB.

The emf for A and B are measured values, respectively. Different interfering anions at a concentration of 1×10^{-3} M at a suitable pH (phosphate buffer) were utilized and the results were obtained using the equation:

$$\text{Log}\quad K_{A.B}^{pot}=\frac{EB-EA}{S}+\frac{1-ZA}{ZB}\log aA$$

Where $K_{A,B}^{pot}$ is the potentiometric selectivity coefficient, S the slope of the calibration plot, aA the activity of tiapride, ZA and ZB are charges on degradation product (I) and interfering anion, respectively.

Application to Laboratory Prepared Mixtures The membrane sensor was immersed in conjunction with the single junction calomel reference electrode in different laboratory mixtures containing 1×10^{-2} M tiapride solution was mixed separately with proportions from the degradate (I) solution in different ratios. The membrane sensor was washed with water between measurements. The emf produced for each mixture was measured by the 2 proposed electrodes then the concentration of tiapride in presence of it's degradate was determined from the corresponding regression equation.

Application to Pharmaceutical Preparation Ten tablets of tiapridal tablets (B.N. 306182) was weighed and powdered. An amount of the powdered tablets equivalent to 18.245 mg tiapride was accurately transferred into a 50 ml volumetric flask and the volume was completed to the mark with phosphate buffer (pH 4.9) to prepare a 10^{-3} M solution of tiapride hydrochloride. The emf produced by immersing the prepared electrodes in conjunction with single junction calomel reference electrode in the prepared solution was determined then the concentration of tiapride hydrochloride was calculated from the

regression equation of the corresponding electrode.

Application to Plasma Sample 4.5 ml of spiked human plasma were placed into two stoppered shaking tubes, and then 0.5 ml of 10^{-2} and 10^{-3} M tiapride hydrochloride were added separately and shaked. The membrane sensor was immersed in conjunction with the single junction calomel reference electrode in this solution and complete as previous section.

RESULTS AND DISCUSSION

Sensors for cationic and basic drugs are based on the use of the ion association complexes of these species with one of anionic compounds forming ion-association complexes embedded in PVC matrix membrane with suitable solvent and mediators.[24]

In the present work tiapride[1] hydrochloride behave as a cation in acidic medium, due to presence of the amino groups. This fact suggests the use of anionic type of ion exchangers, sodium tetraphenyl borate and ammonium reineckate with their low solubility. The PVC was used as a polymer matrix in fabrication of membrane sensors. The drug was found to form 1 : 2 ion association complexes with each Na TPB and amm R as proved by elemental analysis. Calculated results were agreed with the found ones, also the Nernstian response of the suggested sensors was about 30 mV; which is the typical value for divalent drugs.[22] The suggested structural formulae are shown in Fig. 1.

The PVC acts as a regular support matrix for the membrane but its use creates a need for a plasticizer.[25] In the present investigation, dibutylsebacate was found to be the optimum available plasticizer for the PVC membrane sensors. It plasticizes the membrane, dissolves the ion-association complexes and adjust both of the membrane permittivity and ion-exchanger sites mobility to give highest possible selectivity and sensitivity.[16,26] Other plasticizers such as nitrophenyl phenyl ether, tricresyl phosphate and castor oil failed in dissolving the ion association complexes and thus gave noisy response.

Electrochemical performance characteristics of the proposed sensors were systematically evaluated according to IUPAC standards.[22]

Table 1 shows the slopes of lines, response times, detection limits and intervals of linearity over a period of 2 months for 5 different assemblies of each sensor at optimal pH and temperature at 25°C±1°C using the recommendations of IUPAC.[22] The sensors displayed constant potential readings within 1 mV from day to day and the calibration slopes did not change by more than 2 mV per decade over a period of 1 month for PVC sensors.

Table 1. Response Characteristics for Tiapride HCl, PVC Membranes Using the Proposed Sensors

Parameter	Sensors	
	Sensor I	Sensor II
Slope (mV/decade)	28.997	30.58
Intercept (mV)	73.00	68.80
Correlation coefficient (r)	0.9998	0.9994
Response time (s)	20—30	20—30
Working pH range	3—7	4—7
Concentration range (M)	10^{-5}—10^{-2}	10^{-5}—10^{-2}
Life time (weeks)	6—8	6—8
Average recovery (%)	99.95	99.92
R.S.D.[a]	0.678	1.157
Lower limit of linear range (mol/l)	6×10^{-6}	8.8×10^{-6}
Detection limit LOD (M)	4.5×10^{-6}	3.6×10^{-6}
Between day-variability	0.983	1.213

a) Results of 6 determinations.

In measurements with the investigated sensors the experimental conditions were studied to reach the optimum. The potential response displayed by each investigated electrode was monitored as a function of the temperature and the drug concentration in the range of 20–40°C. Both electrodes exhibited constant slope value and gradual increase in their potentials as the temperature increased. A pH value within the range of 3–7 for Tia-TPB and 4–7 for tia-R sensors respectively was found optimum. Figure 2 shows the potential-pH profiles for 10^{-3} and 10^{-4} M drug solutions using sensors I and II, respectively. It is apparent that the sensor responses are fairly constant in phosphate buffer solution of pH 4.9.

Above pH 8, drug precipitation occurs while in highly acidic solution less than pH 3 unstable nernestian responses were displayed by the sensors. At pH range of 4–7, drug cations are dissociated and therefore they become sensible.

The response time of the electrodes was tested for concentrations of the drug from 10^{-6} to 10^{-2} M. The measurements was characterized by a fast stable response within 20–30 s for concentrations less than 10^{-4} M and less than 20 s for concentrations more than 10^{-4} M.

Long term potential stability of the proposed sensors was fairly good as it practically unchanged over a

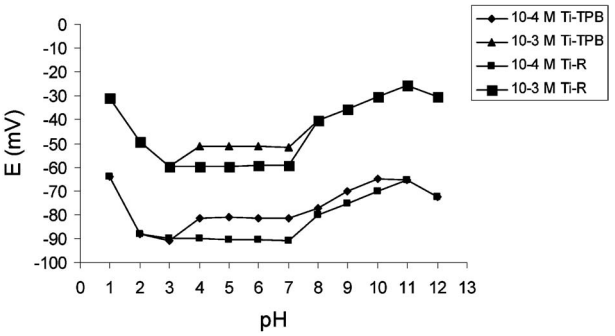


Fig. 2. Effect of pH on the Response of Tiapride-tetraphenyl Borate Electrode (Ti-TPB) and Tiapride-reineckate Electrode (Ti-R)

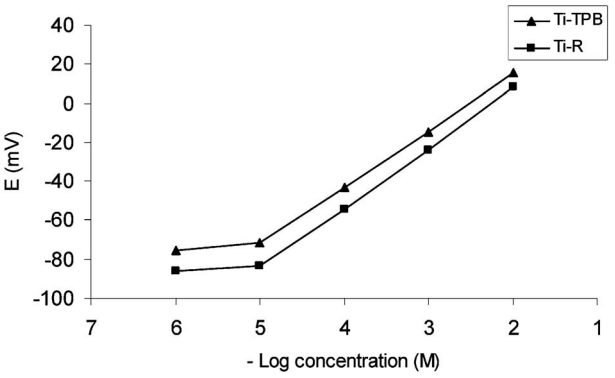


Fig. 3. Profile of the Potential in mV to the -Log Concentration of Tiapride Hydrochloride with TPB and R

period of 6–8 weeks.

The potentiometric response of the two studied electrodes at the optimum pH was linear with constant slopes over a drug concentration range 10^{-5}–10^{-2} M of tiapride hydrochloride (Fig. 3). The accuracy and precision of the proposed membrane sensors for the quantitation of blind samples of tiapride hydrochloride was assessed by using Tia-TPB and Tia-R sensors, respectively. The results showed average recoveries of 99.95 ± 0.678 and 99.92 ± 1.157 for Tia-TPB and Tia-R, respectively. Low detection limits are one of the advantages of the investigated sensors as declared in Table 1.

The reliability of the proposed membrane sensors for the quantitations of tiapride was assessed by determining 1×10^{-2}–1×10^{-6} M tiapride solutions using both the calibration graph and the standard addition (spiking) methods. The results obtained showed mean accuracies of 99.63 ± 0.861, and 99.70 ± 1.31 for use of sensors I and II, respectively.

The performance of the two sensors in the presence of some nitrogenous compounds such as degradate II, amines, amino acids and some inorganic cation, were assessed by measuring and comparing the potentiometic selectivity coefficient values (K^{pott}_{Tia}). The separate solution method[18,19] with a fixed concentration of the interferent (10^{-3} M) was used for evaluation of the selectivity. The results obtained by the developed sensors, Table 2, showed reasonable selectivity for the two sensors for tiapride hydrochloride in presence of any of the mentioned interferent.

Pharmaceutical additives, diluents and ingredients commonly used in drug formulations such as lactase, sucrose, magnesium sulphate and methyl cellulose did not show any interference Table 2. Thus, analysis was carried out without prior treatment or extraction.

In the British[1] and European[27] pharmacopeias the presence of degradates I and II was mentioned to be present as impurities. Tiapride should be kept in well closed container. Improper storage conditions can cause degradation which may decrease the potency of the drug.

This fact motivated us to determine the intact drugs in the presence of their degradates. Table 3 shows the results obtained upon analysis of synthetic mixtures of intact drug and its degradates. It is obvious from the results in Table 3 that the proposed sensors (I and II) can be successfully used for selective determination of the intact tiapride in presence of its degradate.

Thus Tia-TPB and Tia-R were successfully used for the determination of tiapride in tiapridal tablets with average recoveries of 99.19 ± 0.51 and 100.19 ± 0.60 for Tia-TPB and Tia-R, respectively.

The reliability of the proposed membrane sensors for the quantitation of tiapride was assessed by determining 1×10^{-2} and 1×10^{-6} M tiapride solutions using both the calibration graph and the standard addition (spiking) methods. The results obtained showed mean accuracies of 99.63 ± 0.861, and 99.70 ± 1.31 for use of sensors I and II, respectively.

On application to the biological fluids, it has been found that the two electrodes gave stable results as revealed by high precision and accuracy of recoveries of the spiked human plasma samples without interference from any components in the plasma which represent the main advantage of ion selective electrode method (Table 4).

Statistical evaluation of the results of analysis of pure tiapride by the proposed electrodes and the manufacturer spectrophotometric method[28] showed

Table 2. Potentiometric Selectivity Coefficients (K^{pot}_{Tia}) of Tiapride PVC Membrane Based Sensors

Interferent[a]	Selectivity coefficient	
	Tia-TPB	Tia-R
Degradate II	9.64×10^{-3}	9.57×10^{-3}
Urea	13.20×10^{-3}	8.34×10^{-3}
Glycine	0.40×10^{-3}	1.01×10^{-3}
Na^+	7.80×10^{-3}	9.57×10^{-3}
K^+	7.43×10^{-3}	9.51×10^{-3}
NH_4^+	5.42×10^{-3}	9.82×10^{-3}
Ca^{++}	3.61×10^{-3}	8.18×10^{-3}
Mg^{2+}	3.60×10^{-3}	9.38×10^{-3}
Glucose	5.38×10^{-3}	9.04×10^{-3}
Lactose	5.85×10^{-3}	8.26×10^{-3}
Sucrose	4.49×10^{-3}	9.53×10^{-3}
Talc	6.28×10^{-3}	9.68×10^{-3}
Methyl-cellulose	4.27×10^{-3}	8.87×10^{-3}

a) All interferent above were in the form of 10^{-3} M, buffer phosphate pH 4.9.

Table 3. Determination of Tiapride HCl in Synthetic Mixtures with its Degraded Samples

Ratio drug : degraded (1) sample[a]	Drug recovery (%)[b]	
	Sensor I	Sensor II
1 : 0.5	101.47±0.53	101.27±0.91
1 : 1	100.55±0.62	99.78±0.86
1 : 2	100.65±0.48	100.71±0.97
1 : 5	101.24±0.58	99.95±0.79
Mean recovery±S.D.	100.98±0.45	100.43±0.69

a) The drug solutions were always 10^{-3} M. *b*) Average of five determinations.

Table 4. Determination of Tiapride Hydrochloride in Spiked Human Plasma by the Proposed Sensors

Concentration (M)	Recovery %[a] of tiapride	
	Tia-TPB	Tia-R
1×10^{-3}	100.33±0.52	100.12±0.97
1×10^{-4}	101.36±0.27	98.71±0.81

a) Average of four determinations.

that there is no significant difference between the proposed and the reported method in term of accuracy and precision (Table 5).

Validation of the proposed potentiometric methods for determining tiapride was made by measuring the range, lower limit of detection (LOD), accuracy (recovery), precision (R.S.D.), between day-variability, and linearity and sensitivity (slope) (Table 1).

Table 5. Statistical Analysis of the Results Obtained by the Proposed and the Reported Methods[24] for the Analysis of Tiapride

Parameter	Tia-TPB	Tia-R	Reported spectrophotometric method[28]
Mean	99.95	99.92	99.53
R.S.D.	0.678	1.157	1.040
N	6	6	6
Student's *t*-test (2.23)	1.660	1.472	—
F-test (5.05)	2.350	1.238	—

The values between parentheses are the corresponding theoretical values of t and F at the 95% confidence level.

These data render the proposed potentiometric method applicable as stability indicating one for quality control of drug formulations.

CONCLUSION

Tia-TPB and Tia-R electrodes are sufficiently simple and selective for the quantitative determination of tiapride at a wide concentration range (1×10^{-5}–1×10^{-2} M) in pure, pharmaceutical formulations and in plasma. The method is a stability indicating one as the degradate is not interfering in the determination of the drug.

The use of the proposed sensors offers the advantages of fast response, elimination of drug pretreatment or separation steps, low detection limit and direct determination of drug in turbid and colored solutions. They can therefore be used for routine analysis of the drug in quality control laboratories.

REFERENCES

1) The British pharmacopoeia, ''Her Majesty's Stationary Office,'' London, U. K., 2001, p. 1611.
2) Martindale ''The Extra Pharmacopoeia,'' 31 ed. The Pharmaceutical Press, London, 1996, p. 735, 740.
3) Wu B., Lu M., Wang Y., Fang X., *Yaowu Fenxi Zazhi*, **5**(1) 55, 20–25 (1985).
4) Wu B., Lu M., Wang Y., Fang X., *Yaoxue Tangbao*, Apr. (19) 4, 58–61 (1984).
5) Norman T.R., James R.H., Gregorry M. S., *J. Chromatogr. Biomed. Appl.*, **48** (375), 197–201 (1986).
6) Duan G., Lu M., Wu B., *Yaoxue-Xuebao*, **21** (12), 917–921 (1986).
7) Chiba R., Ogasawara A., Kubo T., Yamozaki,

Y., Umino M., Ishizuka Y., *Analytical Saenies.*, **19**(5), 785–792 (2003).
8) Jin S.-E., Ban E., Kim Y.-B., Kim C.-K., *J. Pharm. Biomed. Anal.*, **35**(4) 929–936 (2004).
9) Kamizono A., Inotsume N., Miyamoto K., Ueda K., Miyakawa T., Arimoto H., Nakano M., *J. Chromatogr. Biomed. Appl.*, **105** (567) 113–120 (1991).
10) de la Torre C. Sanchez, Martinez M.A., Almarza E., *J. Forensic Sci. Int.,* **155** (2–3) 193–204 (2005).
11) Buna M., Aaron J. J., Prognon P., Mahuzier G., *Analyst*, **121** (11) 1551–1556 (1996).
12) Li J., Zhao F., Ju H., *J. Chromatog.*, B **835** (1–2) 84–89 (2006).
13) Aly F. A., Alarfaj N. A., Alwarthan A. A., *Talanta*, **54** (4) 715–725 (2001).
14) Plossl F., Giera M., Bracher F., *J. Chromatogr.*, **A. 1135** (11) 19–26 (2006).
15) Kissinger P. ''Laboratory Techniques in Electrochemical Chemistry,'' Marcel Dekker, New York, 1991, Chap. 4.
16) Diamond D., ''Principles of Chemical and Biological Sensors, in Chemical Analysis,'' Vol. 150, Wiley, 1998, Chap. 2.
17) Lima J., Montenegro M., *Mikrochim. Acta*, **131**, 187 (1999).
18) Hassan S. S. M., Abdel-Aziz R. M., Abbas A. B., *Anal. Chim. Acta*, **321**, 47 (1996).
19) Hassan S. S., Amer M. M., Abdel-Fatah S. A., El-Kossasy A. M., *Talanta*, **46**, 1395 (1998).
20) British Pharmacopoeia ''Her Majesty Stationary Office,'' London, 2001 Appendix 1 DA 119.
21) Metwally F. H., Abdlkaway M., Abdelwahab N. S., *J. AOAC* (under publication).
22) IUPAC Analytical Chemistry Division Commission on Analytical Nomenclature, *Pure Appl. Chem.*, **72**, 1852–1856 (2000).
23) Ma T. S., Hassan S. S., ''Organic Analysis Using Ion Selective Electrodes,'' Vol. 1 and 2, Academic Press, London, 1982.
24) Conway B. E., ''Ion Selective Electrodes,'' Ottawa Press, Ottawa, 1995.
25) Zyka, J. ''Instrumentation in Analytical Chemistry,'' Vol. 2, Ellis Horwood, Chichester, UK, 1994.
26) Freiser H., ''Ion Selective Electrodes'', *Anal. Chem.*, 8 (1978).
27) The European Pharmacopoeia, ''Councel of Europe Strasbourg,'' the fourth ed., 2002, p. 2032.
28) Memphis Co. for Pharm. and Chemical Ind. Cairo, Egypt. by personal communication.