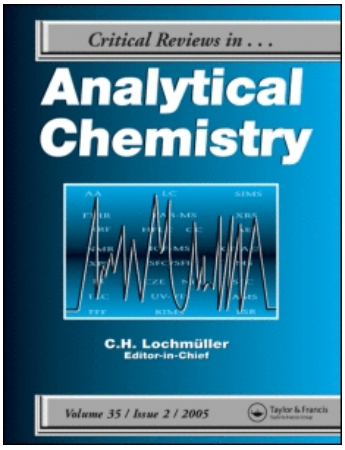

Critical Reviews in Analytical Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713400837

Ion-Selective Membrane Electrodes in Pharmaceutical Analysis

Raluca-Ioana Stefan[a]; George Emil Baiulescu[a]; Hassan Y. Aboul-enien[b]
[a] Department of Analytical Chemistry, Faculty of Chemistry, University of Bucharest, Bucharest-3, Romania [b] Bioanalytical and Drug Development Laboratory, Biological and Medical Research Department (MBC-03), King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia

To cite this Article Stefan, Raluca-Ioana , Baiulescu, George Emil and Aboul-enien, Hassan Y.(1997) 'Ion-Selective Membrane Electrodes in Pharmaceutical Analysis', Critical Reviews in Analytical Chemistry, 27: 4, 307 — 321
To link to this Article: DOI: 10.1080/10408349708050589
URL: http://dx.doi.org/10.1080/10408349708050589

Critical Reviews in Analytical Chemistry, 27(4):307–321 (1997)

Ion-Selective Membrane Electrodes in Pharmaceutical Analysis

*Raluca-Ioana Stefan,[1] George-Emil Baiulescu,[1] and Hassan Y. Aboul-Enein[2]**

[1]Department of Analytical Chemistry, Faculty of Chemistry, University of Bucharest, Blvd. Republicii #13, 70346, Bucharest–3, Romania; [2]Bioanalytical and Drug Development Laboratory, Biological and Medical Research Department (MBC–03), King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia

* Author to whom correspondence should be addressed; Fax: ++966-1-442-7858; email: enein@kfshrc.edu.sa

ABSTRACT: The improving of knowledge about the ion-selective electrodes membrane configuration and mechanism of potential development rendered the quality of analytical information obtained by ion-selective membrane electrodes utilization to increase. Some important ion-selective membrane electrodes described for the pharmaceutical analyses are presented. Also, one of the most recently introduced important class of membrane electrodes, namely, the enantioselective-membrane electrodes class, is presented briefly.

KEY WORDS: ion-selective membrane electrodes, membrane configuration, membrane potential, enantioselective membrane electrodes, drugs, dissolution, apparent first-order dissolution and disintegration rate constants.

I. INTRODUCTION

Ion-selective membrane electrodes assure the reliability of analytical information in drug assay due to the possibility to determine directly, without any prior separation, the activity of ions in solution. For pharmaceutical analysis the best electrodes are based on ion-pair complexes. The main problem in the electrodes construction is the choice of the best counter ion and the best matrix of the membrane. Literature data[1] confirm that under the same conditions for ions with equivalent size and structure, the obtained experimental data are quite different. The tendency was to modify other experimental conditions such as solvents,[2] plasticizers, and functionalization of polyvinyl chloride (PVC)[3] that considerably affect the slopes.[3–5]

Due to the accuracy of the analytical information assured by using the ion-selective membrane electrodes, they can be used successfully for both *in vitro* and *in vivo* assay of pharmaceutical products,[6] as well as in clinical analysis.[7,8] The reliability of the method that uses ion-selective membrane electrodes make it suitable for automation. Solich and co-workers[6] proposed an automated flow-injection method that use a diflunisal ion sensor for assay, content uniformity test, and dissolution studies of formulations. The rapidity of analysis increases by using the flow system, to 40 measurements per hour, with a precision of 0.5 to 1.8% relative standard deviation. The data

1040-8347/97/$.50

obtained at the dissolution test can be used for the apparent first-order dissolution and disintegration rate constants determination.[9]

Ion-selective membrane electrodes miniaturization can be used for *in vivo* assay of drugs. The geometry and the size of the sensor affect its selectivity due to the antigen-antibody reaction.[10] Another essential problem of ion-selective membrane electrodes used *in vivo* measurements is the assurance of their biocompatibility. This is achieved by using membrane biocompatible materials.[11] However, the biocompatible material used as matrix must assure the best response of ion-selective electrodes. The correlation between the kind of biocompatible material and the electrode response must be taken into account when constructing ion-selective membrane electrodes for *in vivo* measurements. The pharmaceutical industry should consider the use of the electrochemical sensors and biosensors as reliable and feasible alternatives for drug analysis for the following reasons:

1. The sensor is, in most cases, specific for the drug of interest.
2. The linearity of the calibration curve is relatively large, generally covering a 10^{-2} to 10^{-5} *M* range. Detection limits of 10^{-6} or 10^{-7} *M* are also reported for some drug-sensitive sensors. With previous preconcentration of the sample, the detection limits of potentiometric techniques using membrane sensors may equal or surpass those of some expensive and sophisticated techniques such as radioimmunoassay, gas-liquid chromatography, high-performance liquid chromatography, and chemical ionization mass spectrometry.
3. With some exceptions, the electrochemical sensors have fast response times, usually within 30 s, depending on the analyte concentration. Among the exceptions are enzyme electrodes as well as microbial and plant-tissue electrodes. There is, as yet, no general theoretical formulation for the steady-state and time-dependent behaviour of these electrodes in terms of geometric and kinetic parameters.
4. Many sensors are amenable to miniaturization (e.g., for ease of intravascular insertion) and can be constructed of material that is physiologically compatible, non-toxic, and easily sterilized. A new type of ion-selective device, called the ion-selective field effect transistor (ISFET), promises to be adequate for biomedical analysis *in vivo*.
5. The time and cost of one determination with selective membrane sensors are substantially reduced.

II. ION-SELECTIVE MEMBRANE ELECTRODES DESIGN

The number of ion-selective electrodes with PVC-matrix membrane is increased when compared with liquid membranes[12–14] reported. This is due to the potential for the use of the ion-selective electrodes with plastic membrane microsensors and its application for *in vivo* measurements. The selection of the suitable counter ion is the most crucial step in electrode design. Stefan[15] showed that lauryl sulfate is a counter ion of choice that assures the best response and selectivity to ion-selective membrane electrodes proposed for a lot of drug assays.

Because many of the pharmaceutical products are administered as hydrochloride salts, great importance was given for the chloride-selective membrane electrode design.[16,17] The electrodes proposed for the chloride ion determination show a good response (around 55 mV per decade), and a good selectivity over many other anions present.

Suzuki and co-workers[18] proposed an electrode based on PVC (29%) and tricresyl

phosphate plasticizer (71%) for several pharmaceuticals (e.g., chlorpromazine, trihexyphenidyl, imipramine, dibucaine, papaverine, propanolol, tetracaine, trazodone as hydrochlorides) assay. The ion-selective membrane electrodes proposed assure near-Nernstian response. The results obtained for the active substance assay agreed well with those from a reference method, having relative standard deviation less than 1%. Due to the reliability of the analytical information, the electrode can be used successfully as detector for flow-injection analysis.

The ion-selective membrane electrodes based on polypyrrole films are obtained by electrochemical deposition on glassy carbon from aqueous solution of requested salts.[19] Great attention is given to the anion-selective membrane electrodes design, because their use for organic anions assay assure the best reliability of the analytical information. One of the most used designs for anion-selective electrodes is the electroactive material deposition on wire.[20]

The geometry and diameter size of the ion-selective membrane electrodes affect their response characteristics, especially when they are used as microsensors for *in vivo* measurements. The use of scanning electron microscopy (SEM) established that the best geometry for nanometer-sized electrodes is the conical one,[10] but at a very low size the ion-selective membrane electrodes cannot possess a perfect geometry. Improving of the reliability of nanometer-sized ion-selective membrane electrodes construction is still a real problem.

III. ION-SELECTIVE ELECTRODES: MEMBRANE CONFIGURATION

Using surface studies it was demonstrated that the processes that are given the membrane potential are chemosorbtion ones.[21,22] There are two types of equilibria that affect the ion-selective membrane electrodes function: extraction–reextraction and complexion-de-complexion. The extraction–reextraction equilibrium influence was established by Dumkiewicz.[23]

The establishment of the membrane configuration was possible by studies of the electrochemical characteristics of the membrane[24] as well as the membrane-solution interface.[25] All studies demonstrated the sandwich structure of membrane.[26] There are five zones: two zones are impregnated with filling solution, the middle zone is free of solution, and both end zones represent interfaces between solution and membrane. As a result of this sandwich structure of the membrane, it is possible to understand the complexity of the formula used to establish the membrane potential that contains a constant term and a variable one.

IV. ION-SELECTIVE ELECTRODES: THE MECHANISM OF MEMBRANE POTENTIAL DEVELOPMENT

To establish the mechanism of membrane potential development means to have knowledge about the main equilibrium and carrier mechanism that are taking place at the solution-membrane interface. The main equilibrium that affect the membrane potential is the complexation–decomplexation one,[27] through the stability constant of ion-pair complexes. To establish the carrier mechanism in the ion-selective electrodes membranes methods based on Boltzmann statistics are used,[28] on studying the selectivity coefficients as function of cationic or anionic additive concentration,[29] and on voltametric techniques.[30] To determine the electron transfer kinetics at modified carbon electrode surface voltametric techniques are used.[31]

The selectivity of ion-selective membrane electrodes is due to the competitive equilibrium that take place at the membrane-solution interface as well as to the stability

constants of ion-pair complexes between counter ion and the ions containing in the solution. A new method that involves conditioning the electrode membrane in discriminated ion solution before measurements is reported by Bakker[32] for potentiometric selectivity coefficients determination.[32] The main advantage of this method is that it is generally applicable, independent of the nature of primary or interfering ions. Selectivity coefficients have been found to be generally much smaller than those previously reported with classical methods, revealing the underlying ion-exchange selectivity of the membrane.

V. DRUG-TYPE SUBSTANCES

A. L-Ascorbic Acid

A copper (II) ion-selective electrode (Orion 94–29–00), the membrane of which must be polished with a special polishing strip (Orion 94–82–01) before each utilization is recommended for L-ascorbic acid assay by potentiometric titration, at microamount levels.[33] The reproducibility is assured by the RSD that does not exceed 0.07%. Due to its selectivity over the other components in the pharmaceutical preparations, the copper (II) ion-selective membrane electrode can be used successfully for L-ascorbic acid assay from pharmaceutical products.

B. Cholanic Acids

Campanella and co-workers[34] proposed an ion-selective field effect transistor (ISFET) device for cholanic acids assay in commercial drugs. The ISFET device is based on a PVC-sebacate membrane, containing benzyldimethylcetylammoniumcholate as counter ion. The response characteristics of ISFET device makes it suitable for assay of some cholanic acids (e.g., cheno and ursodeoxycholic acid) from pharmaceutical products and for critical micellar concentration (CMC) values assay of cholate, deoxycholate, and chenodeoxycholate.

C. Iopanoic Acid

An iopanoate-selective electrode with a liquid membrane is reported for iopanoic acid assay.[35] The counter ion selected for the electroactive material is tetraoctylammonium ion, the ion-pair complex being solved in β-nitrocumene. The electrode exhibits a rapid and slightly sub-Nernstian response (53 mV per decade) to iopanoate concentration ranging from 5×10^{-5} to 5×10^{-3} mol/l, at pH = 12. Due to the response characteristics and selectivity over the compression compounds, the ion-selective membrane electrode can be used for iopanoic acid assay directly from tablets by means of the calibration curve technique.

D. Aspirin

For the aspirin assay, an ion-selective electrode with a pseudoliquid membrane prepared from Aliquat 336S, PVC, dibutyl phthalate, and tributyl phosphate[36] is recommended. The low detection limit (50 μ*M*), the near-Nernstian response, as well as the large pH range (5–11) renders the proposed ion-selective membrane electrode used successfully for aspirin assay in pharmaceuticals with use of the addition of the sample to the standard method.

E. Primary Amines

Due to the fact that a lot of active substances have a primary amine structure, it is important to find counter ions that can assure the best response characteristics. For

this purpose, Zhang and Yu[37] used eight macrocyclic polyether derivatives of *o*-phenantroline enclosed in PVC matrix membranes. The response characteristics (Nernstian, or near-Nernstian responses, low limits of detection, large pH ranges) as well as the selectivity of primary amines-selective membrane electrodes made them suitable for primary amines determination in pharmaceutical product.

F. Amiodarone

The assay of amiodarone in its pharmaceutical formulations (tablets and ampoules) is proposed by using an amiodarone-selective membrane electrode based on a liquid membrane that contains the amiodarone-dipicrylamine ion pair complex in nitrobenzene as solvent.[38] The near-Nernstian slope (57.3 ± 0.4 mV per decade), on the 10^{-2} to 10^{-5} mol/l concentration range and the low limit of detection (4.1×10^{-9} mol/l) made the ion-selective membrane electrodes suitable for amiodarone assay as raw material and from pharmaceutical products. The membrane electrode is selective over a lot of ions (vitamin B_1, vitamin B_6) and tablets compression compounds. The RSD values for amiodarone assay as raw material and from its tablets and ampoules dosage forms is less than 1%. The electrode can be used successfully for the dissolution model determination, as well as for the apparent first-order dissolution and disintegration rate constants determination for the tablet formulations.

G. Ampicilin

Ampicilin ion-selective membrane electrodes of both conventional and coated-wire type were prepared and their performance characteristics were investigated. The electrodes were based on incorporation of ampicillinium phosphotungstate in a PVC membrane plasticized with dioctyl phthalate.[39] A linear response was obtained for the 0.16 to 40 m*M*/l concentration range, the range of pH was 3 to 11. The selectivity of the membrane electrodes proved useful in ampicilin assay as raw material and from pharmaceutical products.

H. Amitriptyline

The amitriptyline assay is reported by using an ion-selective membrane electrode based on ammonium Reineckate (1:1)–water-insoluble drug–Reineckate ion pair complex.[40] The slope of 60 mV per decade and the lower detection limit of 9.8×10^{-6} mol/l as well as the ion-selective membrane electrodes selectivity over a lot of organic and inorganic ions made it suitable and reliable for amitriptyline assay as raw material and in pharmaceutical products (RSD < 1%).

I. Atropine

A flow injection system that used ion-selective membrane electrodes as detection systems is described for atropine and scopolamine assay. The preparation of the flow through tubular atropine and scopolamine electrodes and assemblage of the integrated microconduit potentiometric analytical system with tubular ion-selective electrodes, microvalve, chemfold, electrostatic and pulse inhibitors are made.[41]

The near-Nernstian slopes obtained for atropine (59.2 mV per decade) and scopolamine (58.0 mV per decade), as well as the low detection limits of 10^{-6} mol/l magnitude level, and ion-selective membrane electrodes selectivity coefficients over a lot of inorganic cations allowed them to be used successfully at a rate of 120 samples per hour, for the simultaneous determination of atropine and scopolamine. The reproducibility being confirmed by the RSD of 0.1 mV/day.

J. Benzoate

An electrode without an internal reference solution was prepared with a PVC membrane, based on *bis*(triphenyl phosphoranylidene) ammonium benzoate, dissolved in 2-nitrophenyl octyl ether as mediator solvent and 4-octylphenol as additive, and recommended to be used for benzoate assay in several medicinal syrups by direct potentiometry.[42] The electrode slope is near-Nernstian (54.7 ± 0.5 mV per decade), and the reproducibility is at (2 mV/day level. The electrode shows a good selectivity especially over iodide and nitrate ions.

K. Buformin

Two PVC matrix membrane buformin-selective electrodes based on tetraphenyl borate and 5-nitrobarbituric acid as counter ions are described for buformin assay as raw material and in pharmaceutical products.[43] The best response characteristics were obtained when dioctyl phthalate was used as plasticizer: slopes had 60.0 ± 0.2 mV per decade value, and the limit of detection is of 10^{-4} mol/l magnitude.

L. Ciprofloxacin

A ciprofloxacin-selective, PVC-coated wire membrane electrode based on quinoline–4-ones is used for ciprofloxacin assay.[44] The near-Nernstian response was obtained for the 0.1 to 10 m*M* concentration range and 4.5 to 7.0 pH range.

M. Chlorpromazine

The chlorpromazine assay as raw material and from pharmaceutical products is recommended by using a chlorpromazine-selective membrane electrode.[45] The more reliable method that utilizing the proposed membrane electrode is the direct potentiometric assay.

N. Chlortetracycline

The best electrode for chlortetracycline assay was established by Pueglin and coworkers, which were based on tungstosilicate counter ion.[46]

O. Diltiazem

The diltiazem-tetraphenyl borate ion-pair complex was described as an electroactive material for ion-selective membrane electrode. The electrode showed a low limit of detection (10^{-6} mol/l in magnitude), near-Nernstian response, and a large pH range: 2.5 to 7.0.[47] It was useful for diltiazem determination in pharmaceutical products.

P. Dimedrol

Forelov and Talokneva[48] constructed ion-selective membrane electrodes for dimedrol assay using molybdophosphate, tungstophosphate, molybdosilicate, tungstosilicate, tetrphenylborate as counter ions.[48] The recommended method obtained the most reliable analytical information by direct potentiometric assay.

Q. Disopyramide

Two disopyramide-selective membrane electrodes are proposed. The liquid membranes contains as counter ions dipicrylamine,[49] and lauryl sulfate.[15] The response of membrane electrodes are near-Nernstian, and the detection limit is of low magnitude (10^{-8} mol/l). By using lauryl sulfate as counter ion, the selectivity over the ephedrine ion improved.

The reliability of the disopyramide assay as raw material, and from tablets and ampoules formulations, by potentiometric titration is demonstrated by the RSD values that are less than 0.5%. The ion-selective membrane electrodes has been used successfully for obtaining the dissolution model of tablets as well as for apparent first-order dissolution and disintegration rate constants determination.

R. Ephedrine

Ephedrine assay can be made using ion-selective membrane electrodes based on picrate,[50] tetrakis-(4-chlorophenyl) borate,[51] 5-nitrobarbiturate,[52] and tetraphenylborate.[53] All proposed ion-selective membrane electrodes show near-Nernstian responses, low limits of detection, and large pH ranges. The RSD is less than 2% for the ephedrine assay as raw material and from pharmaceutical preparations (syrup and tablets).

S. Flecainide

Two liquid membrane electrodes were prepared based on ion pair complexes of flecainide with dipicrylamine (I) and lauryl sulphate (II).[54] The utilization range is 10^{-2} to 10^{-5} mol/l flecainide solution for both electrodes, with a slope of 51.3 mV per decade (I) and 54.0 mV per decade (II), respectively. The detection limits are 8.3×10^{-7} mol/l (I) and 1×10^{-9} mol/l (II), respectively. The compression compounds of tablets do not interfere. Electrodes can be used to test the uniformity of flecainide tablets and to determine the purity of flecainide acetate-raw material, with an RSD less than 0.50%. They can also be used to determine the dissolution profile, and the apparent first-order rate constants for disintegration and dissolution processes of tablets.

T. Flurbiprofen

The ion-selective membrane electrode used for flurbiprofen assay is based on Aliquat 336S as counter ion.[55] The slope is near-Nernstian (55.4 ± 0.7 mV per decade), and the detection limit is 4.1×10^{-5} mol/l. The electrode is selective over a lot of inorganic and organic anions. The flurbiprofen can be assayed by direct potentiometric method, as raw material, and from tablets with an RSD < 2%.

U. Heparin

Tridodecylmethylammonium ion is proposed as counter ion for heparin-selective membrane electrode construction.[56,57] The biomedical utility of the sensor is demonstrated by measuring its response in whole blood from patients undergoing open heart surgery before and after heparin therapy and correlating such response to conventional blood clotting time measurements.

V. Imipramine

For imipramine assay, picrate,[58] tetraphenylborate,[58] and dinonylnaphthalene sulfonate[59] are used as counter ions membranes with PVC matrix as well as liquid membranes. The electrodes proved near-Nernstian responses and low limits of detection and imipramie can be analyzed successfully by potentiometric titration with a RSD less than 1.5%.

W. Labetalol

Labetalol assay is made by using a labetalol PVC matrix selective membrane electrode based on tetraphenylborate as counter ion.[60] The slope of the membrane electrode is 55 mV per decade, and the

detection limit is of 10^{-6} mol/l magnitude. It can be used for labetalol determination as raw material and from pharmaceutical products.

X. Lithium

A voltammetric assay of lithium is proposed using an ion-selective membrane electrode.[61] The membrane is liquid one; with nitrobenzene, *o*-nitrophenyloctyl ether (*o*-NPOE), and *o*-nitrophenylphenyl ether (*o*-NPPE) used as solvents. The selectivity over various inorganic anions was demonstrated.

Y. Metformin

A plastic membrane electrode based on metformin tetraphenylborate ion pair complex is reported for metformin assay.[62] The electrode shows a near-Nernstian response on the 0.2 m*M* to 0.1 *M* concentration range. It is used successfully for metformin assay as raw material and in pharmaceutical products.

Z. Metomidate

A liquid membrane ion-selective electrode based on dipicrylamine as counter ion is proposed for metomidate assay.[63] The slope is near-Nernstian: 55.98 mV per decade, on the 10^{-2} to 10^{-6} mol/l concentration range. The detection limit is: 3.3×10^{-9} mol/l and the pH range is: 1.75 to 4.50. Selectivity is good over many inorganic and organic cations.

AA. Mexiletine

A liquid membrane mexiletine-selective electrode based on mexiletine-disopyramide ion pair complex is used for mexiletine assay as raw material and from pharmaceutical products, with a RSD < 1.5%.[64] The response of the electrode is of 51.5 (0.7 mV per decade and its limit of detection is 2.1×10^{-6} mol/l. It is selective over many organic (vitamin B_6 and polyvinylpyrolidone) and inorganic cations.

BB. Mianserin

A near-Nernstian slope (56.5 ± 0.7 mV per decade) was obtained by using a mianserin-selective membrane electrode based on mianserin dinonylnaphthalene sulfonate as counter ion.[65] The selectivity and the detection limit (1.5×10^{-6} mol/l) made mianserin-selective membrane electrode useful for mianserin assay as raw material and in pharmaceutical products, with a RSD > 1.5%. It can also be used successfully for dissolution model determination as well as for apparent first-order rate constants of dissolution and disintegration processes determination.

CC. Moclobemide

Two liquid membrane electrodes based on dipicrylamine[66] and lauryl sulfate[15] as counter ions are proposed for moclobemide assay as raw materials and in pharmaceutical products with a RSD less than 1%.

The slope of liquid membrane electrode increases by using lauryl sulfate as counter ion, to 53.5 mV per decade, and the detection limit is low: 1.1×10^{-10} mol/l. The selectivity over several organic cations is increasing by using lauryl sulfate as counter ion.

DD. Norfloxacin

A PVC matrix ion-selective membrane electrode is proposed for norfloxacin assay.[67] It proved a near-Nernstian response and a

low detection limit (10^{-6} mol/l in magnitude). The RSD < 1% obtained at the norfloxacin assay as raw material and in pharmaceutical products demonstrated the good reliability of the analytical information.

EE. Pentoxyverine

Three counter ions: picrate, picrolonate, and tetraphenylborate are proposed for PVC matrix and liquid membrane electrodes.[68] These electrodes show near-Nernstian response values in different concentration ranges, on 3.3 to 7.8 pH range, and used successfully for pentoxyverine assay as raw material and in pharmaceutical products.

FF. Procaine

A procaine flavianate ion pair complex for procaine-selective membrane electrode is constructed.[69] The membrane is a solid one, with PVC matrix. A slope of 56.0 mV per decade and a detection limit of 5.07×10^{-6} mol/l were obtained. The reliability of analytical information obtained by ion-selective membrane electrodes utilization allowed the electrode to be used in flow injection analysis (FIA) for procaine assay.

GG. Procainamide

A procainamide-selective membrane electrode was constructed and applied for the determination of procainamide concentration in blood serum.[70] The detection limit is 1.5 μg/ml; however, determination down to 0.5 μg/ml was possible with an appropriate calibration. The method is simple, rapid, economical, and unaffected by common cations present in the blood. It is therefore useful for therapeutic drug monitoring in a clinical setting.

HH. Propylhexedrine

The membrane electrode construction is based on the tetraphenylborate counter ion,[71] in a PVC matrix, with dioctyl phthalate as plasticizer. The near-Nernstian response was obtained in a pH range of 2.5 to 9.5. The electrode is reliably used for propylhexedrine assay.

II. Pyrantel

Four counter ions: tetraphenylborate, dipicrylaminate, reineckate, and tungstosilicate were chosen for the best ion-selective electrodes with PVC matrix membrane construction.[72]

The selectivity and the other response characteristics made them useful for pyrantel assay as raw material and in biological fluids.

JJ. Quinidine

The construction and evaluation of a quinidine-selective electrode based on tetrakis (4-chlorophenyl) borate as counter ion is proposed by Alçada et al.[73] The PVC matrix electrode show a near-Nernstian response (57.5 mV per decade). The quinidine assay is made by using the direct potentiometric method. RSD obtained is less than 2.5%.

KK. Tamoxifen

For tamoxifen assay two liquid ion-selective membrane electrodes are constructed.[74] As counter ions, dipicrylamine and lauryl sulfate are used. The best slope was obtained by dipicrylamine utilization as counter ion (54.6 ± 0.1 mV per decade). The detection limit is of 10^{-8} mol/l magnitude. Selectivity is improved by using lauryl sulfate counter ion.

The reliability of the analytical information, at the tamoxifen determination as raw material and in pharmaceutical products, by potentiometric titration, is demonstrated by RSD values (less than 0.1%). The proposed electrode can be used successfully for dissolution tests of tamoxifen tablets.

LL. Taxol

Two liquid membrane electrodes based on dipicrylamine and lauryl sulfate as counter ions are proposed.[75] By using lauryl sulfate as counter ion, the slope of taxol-selective membrane electrode increased at 57.2 ± 0.1 mV per decade, but the limit of detection is increased too, to the 10^{-7} mol/l magnitude. The selectivity over polyvinylpyrolidone also increased by using lauryl sulfate as counter ion. The RSD values less than 0.1% made the ion-selective membrane electrodes reliable for the taxol assay as raw material and from injection concentrate.

MM. Tetramisole

The tetramisole assay was made successfully using ion-selective membrane electrodes based on tetraphenylborate and 3 (phosphotungstate) as counter ions in PVC matrix membrane.[76] The slopes are near-Nernstian. For tetramisole assay the standard addition method and potentiometric titrations are recommended.

NN. Tizanidine

Three electrodes were proposed for tizanidine assay.[77] They are based on tungstophosphate, tungstosilicate, and tetraphenylborate as counter ions. They show good response characteristics, which made them suitable for tizanidine assay as raw material and in tablets.

OO. Trimethoprim

Trimethoprim-selective PVC membrane electrodes based on the ion pair complexes of trimethoprim cation with either ammonium Reineckate or sodium tetraphenylborate were prepared using dioctyl phthalate as the plasticizer.[78] The electrodes show linear response with near-Nernstian slope (57 and 58 mV per decade). The interferences are negligible for various species investigated.

The standard deviation ((1.5%) obtained for trimethoprim assay as raw material and in pharmaceutical products through direct potentiometric methods demonstrated the reliability of the method.

PP. Vitamin B_1

For vitamin B_1 an assay is proposed based on an ion-selective microelectrode using a liquid-liquid interface at the tip of a micropipette.[79] The stripping voltammetry demonstrated the determination of vitamin B_1 at 10^{-6} mol/l concentration level.

VI. ENANTIOSELECTIVE MEMBRANE ELECTRODES

Enantioselective analysis has become increasingly important in analysis, pharmaceuticals, agrochemicals, and flavoring agents. Many of the drugs marketed today are administered as racemic mixture despite the significant differences in pharmacological, pharmacodynamics, and pharmacokinetics of the individual enantiomers. Most often one enantiomer is many times more active, toxic, or totally inactive than its antipode.[80]

Accordingly, enantioselective analysis to evaluate the enantiomeric purity is becoming increasingly important in various fields dealing with pharmaceuticals, agrochemicals, among other agents. Chiral chromatography

has been a well-established and reliable technique used in this field;[80–82] however, it is expensive, not simple, and time consuming. Therefore, the last few years mark an increase in the development of enantioselective chemical sensors and biosensors capable for analysis of optical purity of pharmaceuticals through their capability for the chiral discrimination between the enantiomeric pair (R vs. S enantiomers or vice versa).

Lin et al.[83] described an enantiomer-selective chemical sensors and chiral ionophores that proved to be good counter ions for assay for only one enantiomer. Katoky et al.[84] also report the use of α-, β-, and γ-cyclodextrins as chiral selectors in sensors used for the potentiometric enantioselective analysis for alkyl and arylammonium ions of pharmaceutical significance based on the lipophilic properties of the cyclodextrins.

Kullick et al. described[85] a method for the detection of β-hydroxy acid esters and aromatic amino esters by development of enantioselective enzyme field effect transistors (En FETs). Lipase-esterase and α-chymatrypsin-esterase system were used for the analysis of these esters after their immobilization by co-crosslinking with glutaraldehyde, using human serum albumin as a coimmobilizer. The application of these biosensors in FIA proved useful in the analysis of these substances and monitoring the changes in and production of undesirable enantiomer.

VII. CONCLUSIONS

The ion-selective membrane electrodes can be used successfully for the assay of pharmaceutical products. They demonstrated the best reliability of the analytical information due to the possibility to determine directly and without any prior separation the active substance in the solution. The development of knowledge about membrane configuration, and mechanism of membrane potential development, increased the quality of analytical information obtained by using ion-selective membrane electrodes.

The development of enantioselective membrane electrodes are becoming increasingly important and gaining great momentum in the last few years in order to have a simple, inexpensive, and reliable method for enantiomeric purity determination of new pharmaceuticals marketed in optically active form (i.e., pure enantiomer).

The enantio-selective membrane electrodes offer an alternative, affordable method for the enantioselective analysis of enantiomeric drugs that is now required by all drug regulatory agencies.

REFERENCES

1. Cosofret, V. V.; Buck, R. P. Crit. Rev. Anal. Chem., *Recent advances in pharmaceutical analysis with potentiometric membrane sensors*. **1993**, 24, 1–58.
2. Jaramillo, A.; Lopez, S.; Justice, J. B., Jr.; Salamone, J. D.; Neill, D. B. Anal. Chim. Acta, *Choline-selective membrane electrodes*. **1983**, 146, 149–159.
3. Cobben, P. L. H. M.; Egberink, R. J. M.; Bomer, J.G.; Bergveld, P.; Reinhoudt, D. N. J Electroanal. Chem., *Chemically modified field effect transistors: the effect of ion-pair association on the membrne potentials*. **1994**, 368, 193–208.
4. Shin, K. K.; Chan, O. Y.; Pang, S. K. Anal. Chem., *Factors Affecting the electroanalytical behaviour of polypyrrole-modified electrodes bearing complexing ligands*. **1995**, 67, 2828–2834.
5. Mikhelson, K. N. Sens. and Actuat. B, *Ion-selective electrodes in PVC matrix*. **1994**, 18–19, 31–37.
6. Solich, P.; Macheras, P. E.; Koupparis, M. A. J. Pharm. Sci., *Construction of a diflunisal ion sensor and its use in automated flow-injection methods for assay, content uniformity, and dissolution studies of formulations*. **1995**, 84, 889–894.

7. Katsu, T.; Yamanak, K. Anal. Chim. Acta, *Potentiometric method for the determination of adenosine–5-triphosphate.* **1993**, 276, 373–376.

8. Aubeck, R.; Eppelsheim, C.; Bräuchle, C.; Hampp, N. Analyst, *Potentiometric thick-film sensor for the determination of the tumor marker bound sialic acid.* **1993**, 118, 1389–1392.

9. El-Yazigi, A. J. Pharm. Sci., *Disintegration-dissolution analysis of percent dissolved-time data.* **1981**, 70, 535–537.

10. Shao, Y.;Mirkin, M. V.; Fish, G.; Kokotov, S.; Palanker, D.; Lewis, A. Anal. Chem., *Nanometer-sized electrochemical sensors.* **1997**, 69, 1627–1634.

11. Benmakroha, Y.; Zhang, S.; Rolfe, P. Medical & Biological Engineering & Computing, *Haemocompatibility of invasive sensors.* **1995**, 33, 811–821.

12. Lewenstam, A. Scandinavian J. Clin.& Lab. Investigation-Suplement, *Design and pitfalls of ion selective electrodes.* **1994**, 217, 11–19.

13. Shankry, A. F. Sci. Pop.Univ. Pardubice, Ser. A, *Use of plastic membrane ion-selective electrodes for the analysis of drug substances.* **1995**, 1, 5–15.

14. Gilpin, R. K.;Pachla, L. A. Anal. Chem., *Pharmaceuticals and related drugs.* **1997**, 69, 145R–163R.

15. Stefan, R. I. Anal. Chim. Acta, *Lauryl sulphate as counter ion for construction of ion-selective membrane electrodes for moclobemide and disopyramide.* **1997**, (in press).

16. Kim, W.; Chung, S.; Park, S. B.; Lee, S. C.; Kim., C.; Sung, D. D. Anal. Chem., *Sol-gel method for the matrix of chloride-selective membranes doped with tridodecylmethylammonium chloride.* **1997**, 69, 95–98.

17. Xiao, K. P.; Bühlmann, Ph.; Nishizawa, S., Amemiya, S.; Umezawa, Y. Anal. Chem., *A chloride ion-selective solvent polymeric membrane electrode based on a hydrogen bond forming ionophore.* **1997**, 69, 1038–1044.

18. Suzuki, H.; Nakagawa, H.; Mifune, M.; Saito, Y. Chem. Pharm. Bull., *Widely applicable electrode sensitive to basic drugs based on poly(vinyl chloride) membrane plasticized with tricresyl phosphate.* **1993**, 41, 1123–1126.

19. Jovanovic, V. M.; Markicavic, Y.; Stankovic, S.; Stankovic, R.; Jovanic, M. S. Electroanalysis, *The behaviour of polypyrrole doped with different anions as an ion-selective electrode.* **1995**, 7, 574–578.

20. Jovanovic, V. M.; Jovanovic, M. S. J. Serb. Chem. Soc., *Deposited on wire anion-selective electrodes.* **1994**, 59, 265–289.

21. Pungor, E. Anal. Meth. Instr., *Ion-selective electrodes: surface studies.* **1993**, 1, 52–54.

22. Widmer, M. Anal. Meth. Instr., *Ion-selective electrodes and ion optodes.* **1993**, 1, 60–72.

23. Dumkiewicz, R. Analyst, *Mechanism of the origins of membrane potentials for pseudo-liquid poly(vinyl chloride) matrix membranes incorporating coordinatively solvated complexes.* **1993**, 118, 1533–1536.

24. Cosofret, V. V.;Lindner, E.; Buck, R. P.; Kusy, R. P.; Whitley, J. Q. Electroanalysis, *Electrochemical chracterization of aminated PVC-based ion-selective membranes.* **1993**, 5, 725–730.

25. Senda, M. Anal. Sci.Technol., *Voltammetry at liquid/liquid interface.* **1995**, 8, 95A–100A.

26. Stefan, R. I.; Aboul-Enein, H. Y. Instr. Sci. & Technol., *Ion-selective membrane electrodes: membrane configuration.* **1997**, 25, 169–173

27. Stefan, R. I., J. Chem. Inf. Comput. Sci., *Ion-selective membrane electrodes based on ion-pair complexes: correlation between slope of E vs pX dependence and stability of ion-pair complexes.* **1997**, in press

28. Starzak, M. E. J. Chem. Educ., *Illustrating chemical kinetic principles with ion motion in thin membranes.* **1997**, 74, 410–413.

29. Schaller, U.; Bakker, E.; Pretsch, E. Anal. Chem., *Carrier mechanism of acidic ionophores in solvent polymeric membrane ion-selective electrodes.* **1995**, 67, 3123–3132.

30. Buck, R. P.; Nahir, T. M.; Cosofret, V. V.; Lindner, E.; Erdösy, M. Anal. Proc. Including Anal. Comm., *Mechanism of transport in*

carrier-based ion-selective electrodes. **1994**, 31, 301–312.

31. Chen, P.; Fryling, M. A.; McCreery, R. L. Anal. Chem., *Electron transfer kinetics at modified carbon electrode surface: the role of specific surface sites.* **1995**, 67, 3115–3122.

32. Bakker, E. Anal. Chem., *Determination of unbiased selectivity coefficients of neutral carrier-based cation-selective electrodes.* **1997**, 69, 1061–1069.

33. Campiglio, A. Analyst, *Ion-selective electrodes in the anlysis of drugs substances: potentiometric microtitration of L-ascorbic acid with copper (II) sulfate and its application to the anlysis of pharmaceutical preparations.* **1993**, 118, 545–547.

34. Campanella, L.; Battilotti, M.; Borracino, A.; Colapicchioni, C.; Sammartino, M. P.; Tomassetti, M. J. Pharm.& Biomed. Anal., *Cholanic acids determined in commercial drugs means of a new ISFET device.* **1993**, 11, 1207–1214.

35. Panagos, D. S.; Koupparis, M. A. Analyst, *Construction of an iopanoic acid ion-selective electrode and its application to pharmaceutical analysis.* **1995**, 120, 1643–1646.

36. Dumkievicz, R.; Sykut, K.; Kusak, A. Chem. Anal. (Warsaw), *Application of ion-selective electrode with a pseudoliquid potential creating phase of the salicylate function in the determination of aspirin in complex pharmaceutical preparations.* **1992**, 37, 35–42.

37. Zhang, Z. R.; Yu, R. Q. Anal. Chim. Acta, *Primary amine drug-sensitive poly(vinyl chloride) membrane electrodes based on synthetic macrocyclic polyether derivatives of o-phenanthroline.* **1994**, 285, 81–88.

38. Stefan, R. I.; Aboul-Enein, H. Y.; Baiulescu, G. E. Sens. and Actuat. B., *Amiodarone-selective membrane electrode.* **1996**, 37, 141–144.

39. Rizk, M. S.; Issa, Y. M.; Shoukry, A. F.; Abdel-Aal, M. M. Anal. Lett., *New ampicilin-selective plastic membrane and coated metal electrodes based on coated metal electrodes based on ampicillinium phosphotungstate ion-pair.* **1994**, 27, 1055–1065.

40. Elnemma, E. M.; El Zawawy, F. M.; Hassan, S. S. M. Mikrochim. Acta, *Determination of amitriptyline, imipramine and orphenadrine in antidepresant drugs by potentiometry, spectrophotometry and atomic absorption spectrometry.* **1993**, 110, 79–88.

41. Hongbo, C. Talanta, *Atropinium scopolaminium integrated microconduits in a potentiometric analytical system.* **1993**, 40, 1445–1448.

42. Lima, J. L. F. C.; Montenegro, M. C. B. S. M.; Sales, M.G. F. Mikrochim. Acta, *Benzoate ion-selective electrode with improved selectivity and reproducibility of benzoate determination in medicinal syrups.* **1996**, 124, 35–41.

43. Ahmed, M. A. Analyst (London), *Poly(vinyl chloride) matrix membranr electrodes for the selective determination of buformin.* **1994**, 119, 1367–1370.

44. Avsec, H.; Gomiscek, S. Anal. Chim. Acta, *Study of the prospects for a ciprofloxacin PVC-coated wire ion-selective electrode based on quinolin–4-ones.* **1992**, 268, 307–309.

45. Atta-Politou, J.; Macheras, P. E.; Koupparis, M. A. J.Toxicology-Clinical Toxicology, *The effect of polyethylene glycol on the charcoal adsorption of chlorpromazine studies by ion selective electrode potentiometry.* **1996**, 34, 307–316.

46. Pueglin, R.; Brauchle, Ch.; Hampp, N. Anal. Sci., *Ion-selective electrodes for the determination of the antibiotic drug chlortetracycline.* **1994**, 10, 959–962.

47. Leng, Z.; Hu, X.; Feng, P.; Bai, W. Fenxi-Yiqi, *Preparation and application of diltiazem-selective electrode.* **1993**, 3, 15–18.

48. Gorelov, I. P.; Toloknova, T. V. J. Anal. Chem., *Application of ion-selective electrodes to the determination of dimedrol.* **1995**, 50, 271–273.

49. Stefan, R. I.; Aboul-Enein, H. Y. Anal. Lett., *Disopyramide-selective membrane electrode.* **1996**, 29, 2333–2346.

50. Qu, A.; Sun, L.; Qu, Z. Yaowu-Fenxi-Zazhi, *Determination of ephedrine hydrochloride in expectorant syrup by using an ephedrine salt electrode.* **1993**, 13, 248–252.

51. Alçada, M. N. M. P.; Lima, J. L. F. C.; Montenegro, M. C. B. S. M. J. Pharm. Biomed. Anal., *PVC membrane electrode without inner reference solution for the direct determination of ephedrine in pharmaceutical preparations*. **1992**, 10, 757–761.

52. Chamorro, P. R., Diaz, R. C. Analyst (London), *Determination of ephedrine in pharmaceutical preparations with a double-membrane selective electrode based on ephedrine–5-nitrobarbiturate*. **1992**, 117, 1905–1907.

53. Chamorro, P. R.; Diaz, R. C. Talanta, *A double-membrane ephedrine-selective electrode based on ephedrine-tetraphenylborate in poly(vinyl chloride) resin*. **1993**, 40, 1461–1464.

54. Stefan, R. I.; Baiulescu, G. E.; Aboul-Enein, H. Y. Analusis, *Flecainide-selective membrane electrodes*. **1997**, 25, 39–42.

55. Bunaciu, A. A.; Grasu, A.; Aboul-Enein, H. Y. Anal. Chim. Acta, *Pharmaceutical applications of a flurbiprofen sensor*. **1995**, 311, 193–197.

56. Yang, V. C.; Ma, S. C.; Liu, D.; Brown, R. B.; Meyerhoff, M. E. ASAIO Journal, *A novel electrochemical heparin sensor*. **1993**, 39, M195-M201.

57. Ma, S. C.; Yang, V. C.; Fu, B.; Meyerhoff, M. E. Anal. Chem., *Electrochemical sensor for heparin: further characterizarion and bioanalytical applications*. **1993**, 65, 2078–2084.

58. Hopkal, H.; Misztal, G. Pharmazie, *Imipramine ion selective membrane electrodes and their pharmaceutical applications*. **1996**, 51, 96–99.

59. Stefan, R. I.; Baiulescu, G. E.; Ionescu, M. S.; Enachescu, I.; Bunaciu, A. A.; Cosofret, V. V. Rev. Chim.(Bucharest), *Ion-selective membrane electrode for imipramine. Its utilization to imipramine tablets determination*. **1994**, 45, 837–934.

60. Voulgaropoulos, A.; Sofoniou, M.; Kazakou, E. Electroanalysis, *Performance charcteristics of a labetalol-H^+-tetraphenylborate selective electrode*. **1993**, 5, 525–528.

61. Sawada, S.; Osakai, T.; Senda, M. Anal. Sci., *Voltammetric lithium ion-selective electrodes based on ion transfer at the oil/water interface facilitated by neutral ionophores*. **1995**, 11, 733–738.

62. Rizk, M. S.; Abdel-Fattah, H. M.; Issa, Y. M.; Atia, E. M. Anal. Lett., *New metformin selective plastic membrane electrode based on metformin tetraphenylborate*. **1993**, 26, 415–428.

63. Stefan, R. I. Aboul-Enein, H. Y. Anal. Lett., *Metomidate-sensing electrode and its pharmaceutical applications*. **1996**, 29, 35–42.

64. Stefan, R. I.; Ionescu, M. S. Anal. Lett., *Mexiletine-selective membrane electrode and its pharmaceutical applications*. **1995**, 28, 991–1004.

65. Bunaciu, A. A.; Ionescu, M. S.; Stefan, R. I.; Ioan, I.; Aboul-Enein, H. Y. Anal. Lett., *Mianserin ion-selective membrane electrode and its pharmceutical applications*. **1994**, 27, 1647–1658.

66. Stefan, R. I.; Baiulescu, G. E.; Aboul-Enein, H. Y. Talanta, *Moclobemide-selective membrane electrode and its pharmaceutical applications*. **1996**, 43, 1171–1175.

67. Guo, L.; Wang, Y.; Lin, J. Fenxi Huaxue, *Preparation and application of ion-selective electrode of norfloxacin*. **1996**, 24, 308–311.

68. Hopkala, H.; Przyborowski, L.; Flieger, J. Anal. Lett., *Selective liquid and poly(vinyl chloride) pentoxyverine membrane electrodes-their preparation and use for the potentiometric determination of pentoxyverine citrate*. **1994**, 27, 2223–2238.

69. Hamada, M. A.; Moody, G. J.; Thomas, J. D. R. Anal. Proc., *Poly(vinyl chloride) matrix membrane ion-selective electrode for the analysis of procaine drug*. **1993**, 30, 146–147.

70. Katsu, T.; Furuno, K.; Yamashita, S.; Gomita, Y. Anal. Chim. Acta, *Ion selective electrode for procainamide determination in blood serum*. **1995**, 312, 35–38.

71. Zareh, M.; El-Sheikh, R.; Issa, Y. M.; Shoukry, A. F. Anal. Lett., *Plastic membrane and coted-wire ion-selective electrodes for propylhexedrine*. **1992**, 25, 663–680.

72. Aubeck, R.; Hampp, N. Anal. Chim. Acta, *Ion-selective membrane electrodes for the determination of pyrantel with low protein interference*. **1992**, 256, 257–262.

73. Alçada, M. N. M. P., Lima, J. L. F. C.; Montenegro, M. C. B. S. M. Anal. Chim. Acta, *Quinidine ion-selective electrode for potentiometric determinations in pharmaceutical preparations*. **1993**, 283, 657–661.

74. Stefan, R. I.; Baiulescu, G. E.; Aboul-Enein, H. Y. Pharmazie, *Tamoxifen-selective membrane electrodes*. **1997**, 52, 780–783.

75. Stefan, R. I.; Aboul-Enein, H. Y. J. Anal. Chem., *Taxol-selective membrane electrodes*. **1997**, (in press).

76. Issa, Y. M.; Rizk, M. S.; Shoukry, A. F.; Abdel-Aziz, R.; Abdel-Fattah, H. M.; Attia, E. M. Talanta, *Construction and performance characteristics of new tetramisole-selective plastic membrane electrodes*. **1994**, 41, 135–141.

77. Bouklouze, A. A.; El-Jammal, A.; Vire, J. C.; Patriarche, G. J. Anal. Chim. Acta, *Comparative study of three polymeric membrane electrodes selective to tizanidine*. **1992**, 257, 41–48.

78. Ahmed, M. A.; Elbeshlawy, M. M. Anal. Lett., *Novel polymeric membrane electrodes for selective determination of trimethoprim*. **1995**, 28, 2123–2138.

79. Huang, B.; Yu, B.; Li, P.; Jiang, M.; Bi, Y.; Wu, S. Anal. Chim. Acta, *Vitamin B_1 ion-selective microelectrode based on a liquid-liquid interface at the tip of a micropipette*. **1995**, 312, 329–335.

80. Aboul-Enein, H. Y. and Wainer, I. W. *"The Impact of Stereochemistry on Drug Development and Use"* John Wiley & Sons Inc., New York, N. Y. **1997**.

81. Allenmark, S. *"Chromatographic Enantioseparation: methods and applications"* 2nd edition, Ellis Horwood Ltd., Chichester, West Sussex, England, **1991**.

82. Krustulovic, A. M. *"Chiral Separations by HPLC: applications to pharmaceutical compounds"* Ellis Horwood Ltd., Chichester, West Sussex, England, **1989**.

83. Liu, K.; Wang, P.; Wang, L.; Li, Y. Fenxi Huaxue, *Enantiomer-selective chemical sensors and chiral ionophores*. **1992**, 20, 728–734.

84. Kataky, R.; Parker, D.; Kelly, P. M. Scandinavian J. Clinic.&Lab. Investigation, *Potentiometric enantioselective sensors for alkyl, and arylammonium ions of pharmaceutical significance, based on lipophilic cyclodextrins*. **1995**, 55, 409–419.

85. Kullick, T.: Ulber, R.; Meyer, H. H.; Schefer, T.; Schüge I. K. Anal. Chim. Acta., *Biosensors for enantioselective analysis*. **1994**, 293, 271–276.