Recent Advances on Potentiometric Membrane Sensors for Pharmaceutical Analysis

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Abstract: Prime concerns with modern developments are attributed to high level undetected but important biological substances or even toxicants cycled often among individual and populations; which in turn agonizes environmental monitoring, trace-gas detection, water treatment facilities, *in vivo* detection in biological fluids and other accomplishments. For the detection of such analytes, several analytical devices combined with biological component have been designed with a physiochemical detector component. Here, we essentially focus on drug-based potentiometric membrane sensors known as ion selective electrodes (ISEs). The functionality of ion-selective membrane is quite intricate, challenging, and our undertsanding is yet to be thrived with more interventions. ISEs have applied explications to enormous variety of analytical inquires as well as informative tools for probing host-guest chemistry. However, expansion of ISEs based applications is aimed to improve the system performance, acquiring enhanced understanding of their response mechanism, and finding new chemical or physical configurations mainly for human welfare. The major strength of ISEs is the precised analytical information, assured by using the ion-selective membrane electrodes used successfully for both *in vitro* and *in vivo* assays of pharmaceutical products as well as in clinical analyses. In this review, we attempt to provide a brief prologue to the applicability and advantages of potentiometric sensors in the analysis of pharmaceutically active compounds emphasizing their employment at molecular level for *in situ* selection of biologically important analytes.

Keywords: Ion-selective electrodes, potentiometry, biosensors, ionophore, pharmaceutical analysis.

INTRODUCTION

The primary objective of medicinal chemistry is the design and discovery of new compounds that are suitable for use as drugs. The discovery of a new drug requires not only its design and synthesis but also the development of testing methods and procedures. The drive to improve the efficiency of the drug discovery process has created the need for efficient methods for screening compounds for biological activity. Therefore, the arena of pharmaceuticals has grown into a billion dollar business and the pharmaceutical industry has continued to be one of the leaders in pioneering new analytical methods. Within the realm of pharmaceutical drug analysis modern and important techniques that have emerged in the last three decades include HPLC, capillary electrophoresis, high fixed resolution and solid NMR, electrospray MS and computer automation. However, most of these methods suffer from either wide spread availability of instrumentation, prohibitive cost or technical difficulty. Practical demands for monitoring the main component concentration in pharmaceutical dosage forms and the necessity of determining drugs in biological fluids stimulate research into the development of rapid analytical methods.

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Knowledge and understanding gained through advances in ion-selective electrodes can be leveraged in pharmaceutical research. Therefore, in molecular recognition of drugs ion selective sensors are very important and they have superseded and outclassed the other techniques with many analytical aspects including the high reliability that is given by high precision, high reproducibility, rapidity and due to fact that electrochemical sensors can be used directly for measurement of compounds in solution without any prior separation of substances that has to be analyzed. Over the last two decades, ISEs in drug analysis have acquired increasing prominence [1-4]. This technique also offers lots of promise as an analytical tool in pharmaceutical quality control and coupled with the reliability of the analytical information leads to attractive approach for the assay of pharmaceutical products. Recent years have seen an upsurge of interest in the application of ion selective electrodes in the field of pharmaceutical analysis. One of the very common existing principles for the construction of ion selective membranes, sensitive to various drugs compounds is the addition of a lipophilic ion-pair complex into a highly plasticized membrane. The methods for determining drug cations are mostly based on ISE involving associates between the cations and large ions such as TPB, tris(octylhydroxy)benzenesulfonate (TOBS), molybdophosphate (MPA), and diphenylhydroxyacetate (DHAA). The anions of drugs are determined using electrode-active substances with counter ions represented by cations of

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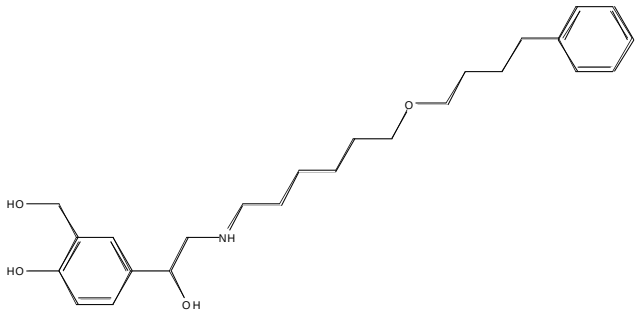
tertiary ammonium bases. Therefore, considerable attention has been paid to research in this field.

SENSORS FOR DRUGS

New developments in the design and application of various drug membrane sensors are continuously being reported. The potentiometric characteristics of the various ion-selective electrodes for drugs are discussed below.

1.1. Alcohols Based Potentiometric Sensors

Alcohols are basically used in chemical and pharmaceutical industries. Salmeterol is a long-acting beta2-adrenergic receptor agonist drug that is currently prescribed for the treatment of asthma and chronic obstructive pulmonary disease (COPD) Tohamy *et al.* [5] developed a polymeric membrane sensor for investigating its electrochemical response characteristics and finally for potentiometric determination of salmeterol. The construction of the sensor was based on the incorporation of salmeterol-phosphomolybdate ion-pair in a poly (vinyl chloride) matrix. Linear response was obtained at a pH of 3-9 over the concentration range of 1×10^{-6} - 1×10^{-3} M with a slope 52.11 ± 0.5 mV/decade. The direct potentiometric determination of salmeterol in pure forms using salmeterol-phosphomolybdate sensor gave average recovery % of 99.46 ± 0.4. The proposed sensor was also applied successfully to the determination of the drug in pharmaceutical preparations.



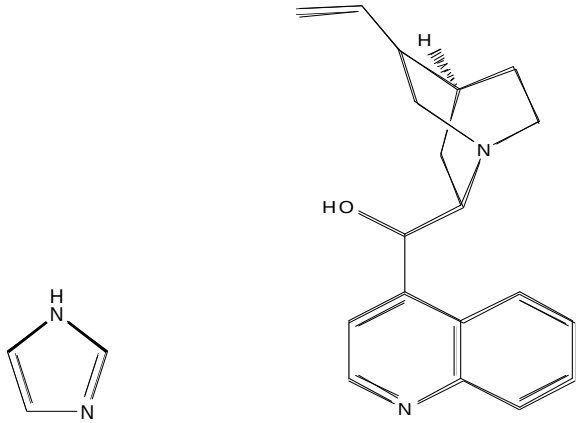
Salmaterol

1.2. Alkaloids Based Potentiometric Sensors

Polymeric sensors have been developed for the determination of various alkaloids. A PVC based membrane sensor based on 4-methyl-2,6-diphenylthiopyrylium perchlorate (MPPP) was developed by Ganjali *et al.* [6]. The proposed membrane electrode responded to the imidazole in a wide concentration range 1.0×10^{-5} to 10×10^{-1} M, with a sub-Nernstian slope of +36.2 ± 0.2 mV per decade of activity of imidazole. The detection limit of the sensor was 2.0×10^{-6} M and the sensitivity of the electrode was high enough to permit the detection of as little as 0.15 μg/mL of imidazole without any significant interference from high levels of other components such as common cations and anions and specially, amino acids. The electrode showed a relatively fast response time in whole concentration range (<30s) and finally was used for fast direct potentiometric monitoring of imidazole in synthetic serum samples.

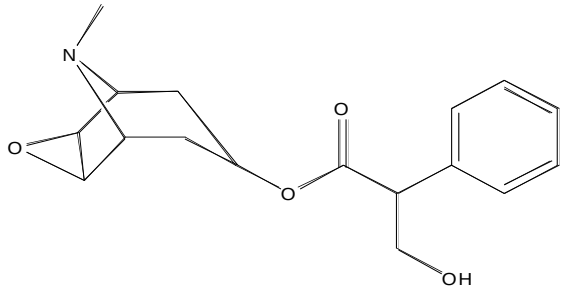
Yuan *et al.* [7] developed a sensing method for the determination of cinchonine based on the sensitive mass response of PQC and the selective adsorption of cinchonine on PVC membrane containing ion-pair complex. The proposed sensors showed wider working pH range, higher sensitivity and selectivity. The sensor was linear over concentration range of 5×10^{-8}-2.1×10^{-4}M with a detection limit of 4×10^{-8}M at pH 7.1, and recoveries 97.7-108.6%. Results from real samples were found to be satisfactory.

Mostafa *et al.* [8] reported the construction of PVC based membrane sensor based on a ion pair complex with phosphotungstate for the determination of scopolamine. The sensor shows a near- Nernstian response for 1.0×10^{-2} – 1.0×10^{-6} M. The direct determination of scopolamine in some formulations (injection and eye drop) gave favorable results comparable to those obtained by the United States Pharmacopeia.



Imidazole

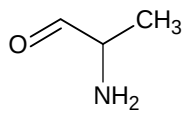
Cinchonine



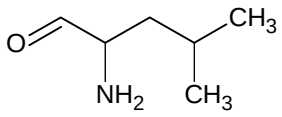
Scopolamine

1.3. Amino Acids Based Potentiometric Sensors

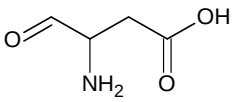
A cysteine selective electrode as detection system was developed for determination of this amino acid in pharmaceuticals. Several electrodes were constructed for this purpose by Sales *et al.* [9], having PVC membranes with different ionic exchangers and mediator solvents. Better working characteristics were attained with membranes comprising o-nitrophenyl octyl ether as mediator solvent and a tetraphenylborate based ionic-sensor. The developed sensor showed linearity ranges from 5.0×10^{-5} to 5.0×10^{-3} M, with slopes of 76.44 ± 0.6 mV decade^{-1} and $R^2 > 0.9935$. Analysis of real samples were performed and considered accurate, with a relative error to an independent method of +2.7%.



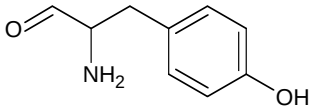
Alanine



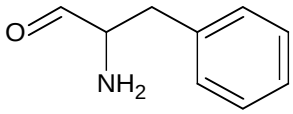
Leucine



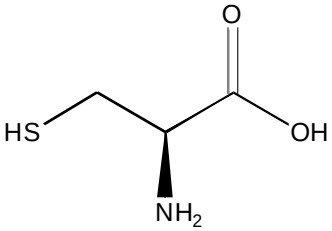
Aspartic acid



Tyrosine



Phenylalanine



Cysteine

1.4. Antidepressants Based Potentiometric Sensors

Potentiometric based ion selective electrodes were used for the determination of a wide variety of antidepressant drugs.

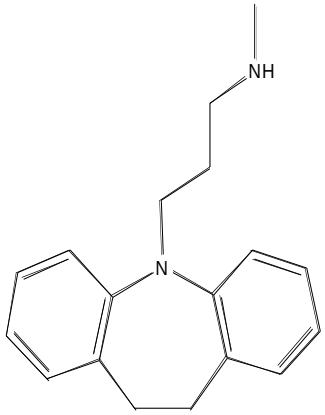
Citalopram is an antidepressant drug used to treat depression associated with mood disorders. A citalopram-tetraphenyl borate ion-pair based poly (vinyl chloride) (PVC) membrane sensor was developed for the citalopram determination [10]. The electrode with a membrane composition of 30% PVC, 66% dibutyl phthalate (DBP), and 4% ion-pair, illustrated a fast (~5 s), stable and Nernstian response (58.6 ± 0.3 mV/decade) across a relatively wide citalopram concentration range 1×10^{-5} to 1×10^{-2}M and in the pH range of 3.0-5.5. Validation of the method showed suitability of the sensors for the quality control analysis of citalopram hydrobromide in pharmaceutical formulation and urine.

Gupta *et al.* [11] reported a membrane electrode for desipramine hydrochloride based on the use of tetraphenylborate ion-pair complex as an electroactive material with detection limit of 2.2×10^{-6} - 1.0×10^{-2} M.

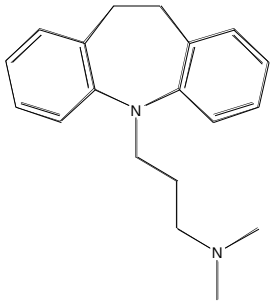
Hussien *et al.* [12] developed a fluoxetine (FX) ion selective liquid membrane and coated wire graphite electrodes from PVC containing FX-tetraphenylborate (FX-TPB) as the sensing element in the presence of DOP as the plasticizing solvent mediator. The two electrodes showed nearly Nernestian response over the concentration range 2×10^{-5}-1×10^{-2}mol/L of the drug with slopes of 58.5 and 55.5mV/decade for the liquid membrane and the coated wire graphite electrodes, respectively. The electrodes exhibited good selectivity for the FX with respect to a large number of inorganic cations and organic substances of biological fluids. The anti-depressant fluoxetine was determined successfully in pure solutions and in capsules or in biological fluids.

Doxepin is a psychotropic agent with tricyclic antidepressant and anxiolytic properties. The construction and general characteristics of potentiometric doxepin liquid membrane, based on the use of the doxepin-picrate, doxepin-picrolonate and doxepin-tetraphenylborate ion-pair complexes in nitrobenzene solvent was developed by Hopkala *et al.* [13]. The electrodes exhibited near Nernstian response in different concentration ranges, depending on the nature of the use counter ion. The liquid electrode based on doxepin-tetraphenylborate as an ion exchanger was proposed for use in determination of doxepin hydrochloride. The potentiometric titrations with sodium tetraphenylborate was used to determine doxepin hydrochloride in substance and capsules (10 mg, 25 mg) with satisfactory results.

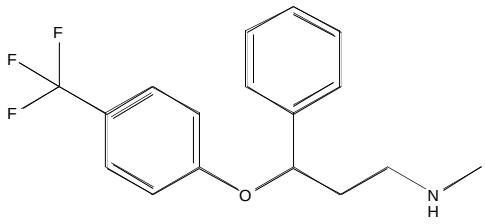
Hassan *et al.* [14] described potentiometric sensors for trifluoperazine hydrochloride (TFPH). The sensing membranes incorporated trifluoperazine cation and phosphotungstic acid (PTA) or phosphomolybdic acid (PMA) or sodium tetraphenyl borate (NaTPB) as electroactive materials in poly(vinyl chloride) matrix membrane. The sensor had a Nerstian slope of 28.43 and 32.11 mV /decade, respectively with a linear concentration range between 1×10^{-5} -1×10^{-2}M.



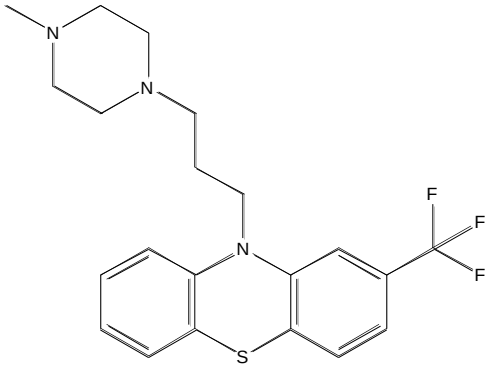
Desipramine



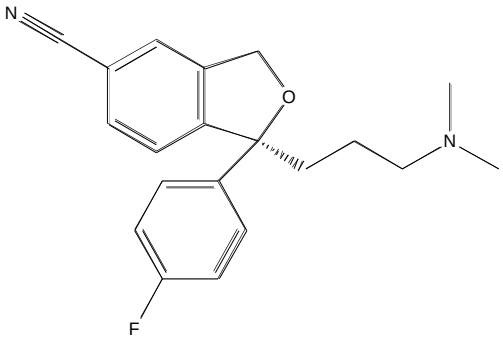
Imipramine



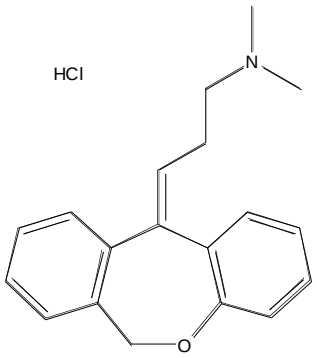
Fluoxetin



Trifluoperazine



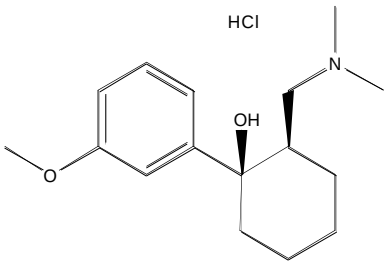
Citalopram



Doxepin

1.4.1. Analgesics Based Potentiometric Sensors

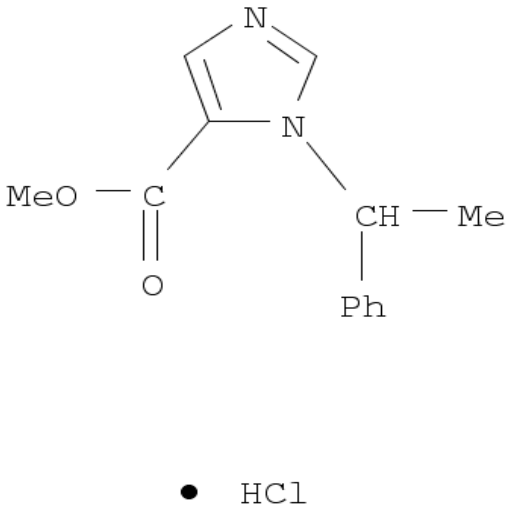
Tramadol, a 4-phenyl-piperidine analogue of codeine, is usually marketed as the hydrochloride salt and is a centrally acting analgesic, used for treating moderate to severe pain. A potentiometric liquid membrane sensors for simple and fast determination of tramadol hydrochloride in pharmaceutical formulation and urine was constructed by Ganjali *et al.* [15]. For the membrane preparation, tramadol-tetraphenyl borate complexes were employed as electroactive material in the membrane. The wide linear range (10^{-5}-10^{-1} M), low detection limit (3 μg /ml), and fast response time (10 s) are the characterizations of the proposed sensors. Validation of the method shows suitability of the sensors for applies in the quality control analysis of tramadol hydrochloride in pharmaceutical formulation and urine. The proposed sensor was found to be simple, accurate and precise which could be used as a detector for HPLC.



Tramadol

1.5. Anesthetics Based Potentiometric Sensors

Metomidate hydrochloride is used as a sedative and anaesthetic drug. A liquid membrane electrode based on metomidate - dipicrylamine ion-pair complex, dissolved in nitrobenzene as solvent was developed by Stefan *et al.* [16]. The linear response ranged from 10^{-2} - 10^{-6} M metomidate solution, with a slope of 55.98 mV/decade (pH range 1.75 to 4.50) The detection limit was 3.31×10^{-9} M. The electrode showed stability, good reproducibility and fast response. These characteristics of the electrode made it useful for the determination of metomidate in pharmaceutical samples.



Metomidate hydrochloride

1.6. Vitamins Based Potentiometric Sensors

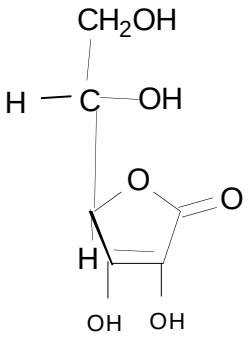
Various membrane electrodes have been used successfully for the determination of vitamins by potentiometric techniques.

A new solid-contact ion-selective electrode was developed for determining choline and derivatives in aqueous solutions by Ampurdanés *et al.* [17]. The electrode displayed a nearly Nernstian slope (57.3 ± 1.0 mV/decade) and very stable behaviour ($\Delta E/\Delta t$ = 224 μV h^{-1}) throughout the dynamic range (10^{-5} to 10^{-1} M). The limit of detection of $10^{-6.4}$ M and the high selectivities obtained enabled choline and derivatives to be determined in biological samples.

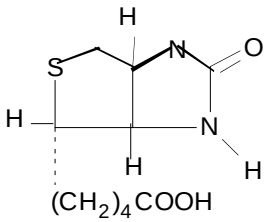
The construction, evaluation and analytical application of potentiometric sensors sensitive to vitamin B_1 and vitamin

B_6 was reported by Pires *et al.* [18]. The solid contact electrodes were produced using β-cyclodextrins as ionophores in a carboxylated poly(vinyl chloride) support matrix. Near Nernstian slopes (mV/decade) of 51.7 ± 0.8, 60.6 ± 0.6 and 61.1 ± 1.4, within the intervals (M) of 1.0×10^{-4} to 1.0×10^{-1}, 5.8×10^{-5} to 1.0×10^{-1} and 4.3×10^{-5} to 1.0×10^{-1} were obtained, for thiamine and pyridoxine I and II prepared membranes, respectively. A pH operational range of 6.5-8.5 for thiamine and 2-4.5 for pyridoxine electrodes was found. Analysis of vitamins B_1 and B_6 in complex multivitamin drugs was achieved with recoveries within the intervals of 95.1-99.6% for thiamine and 95.1-102% for pyridoxine.

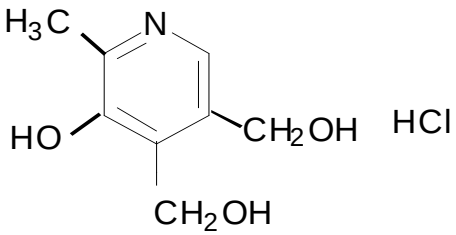
Ahmad *et al.* [19] developed five polyvinyl chloride (PVC) matrix membrane sensors for the selective determination of sulbutiamine (SBA) cation. These sensors are based on molybdate, tetraphenylborate, reineckate, phosphotungstate and phosphomolybdate, as possible ion-pairing agents. These sensors displayed rapid near-Nernstian stable response over a relatively wide concentration range 1 x 10^{-2}-1 x 10^{-6} M of sulbutiamine, with calibration slopes 28-32.6 mV decade^{-1} over a reasonable pH range 2-6. The proposed sensors proved to have a good selectivity for SBA over some inorganic and organic cations. The five potentiometric sensors were applied successfully in the determination of SBA in a pharmaceutical preparation (arcalion-200).



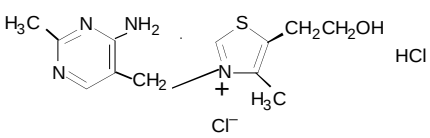
Ascorbic acid



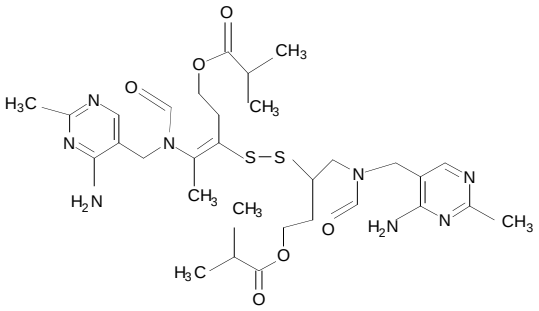
Biotin



Pyridoxine hydrochloride



Thiamine hydrochloride



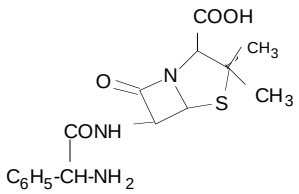
Sulbutiamine

1.7. Antibiotics Based Potentiometric Sensors

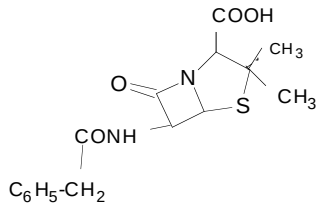
The sensors of antibiotics have been categorized as follows:

1.7.1. Penicillins Based Potentiometric Sensors

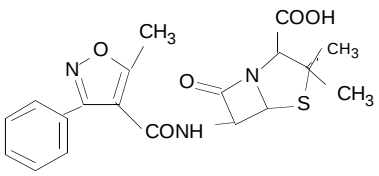
Arrays of potentiometric sensors with plasticized polymer membranes based on tetraalkylammonium organic ion exchanges with anions of penicillin class antibiotics (benzylpenicillin, ampicillin, oxacillin, and amoxicillin) was developed by Kulapina *et al.* [20] for the individual determination of antibiotics in model mixtures and pharmaceutical preparations. The average slope of the electrode function was $54 < Sav < 61$, the nonselectivity factor was $2.8 < F < 74.6$, and the reproducibility factor was $31.9 < K < 61.2$. Artificial neural networks were further applied to the treatment of analytical signals from the multisensor system in the concentration range $2.5 \times 10^{-4} \times 10^{-1}$ M. The average error of the individual determination of penicillin class antibiotics was 5–7%.



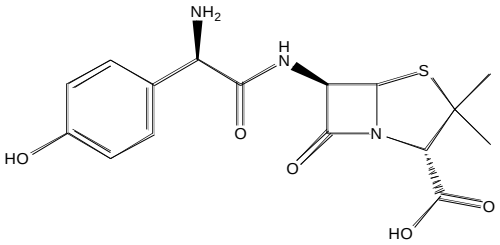
Ampicillin



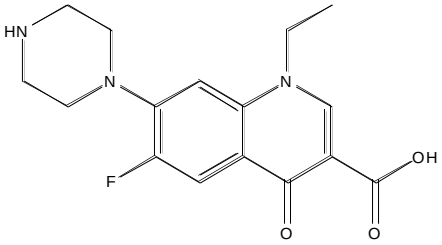
Benzyl penicillin



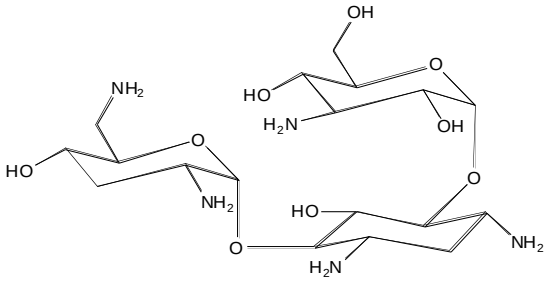
Oxacillin



Amoxycillin



Norfloxacin



Tobramycin

1.7.2. Others Related Antibiotics Based Potentiometric Sensors

Norfloxacin is a synthetic chemotherapeutic agent occasionally used to treat common as well as complicated urinary tract infections. The potentiometric membrane sensor method is used for the determination of norfloxacin based antibiotics [21]. The sensor exhibited near-Nernstian response in steady state evaluations, and detection limits ranged from 0.40 to 1.0 μgmL^{-1}. Good selectivity was observed over several potential interferents. In flowing media, the sensors exhibit fast response, a sensitivity of 68.2 mV per decade, a linear range from 79 μM to 2.5 mM, a detection limit of 20 μgmL^{-1}, and a stable baseline. The sensors were successfully applied to field monitoring of norfloxacin in fish samples, biological samples, and pharmaceutical products.

The construction and electrochemical response characteristics of β-cyclodextrin-based sensor for determination of the amino glycosidic antibiotic, tobramycin, was described by Amira *et al.* [22]. The membrane incorporated carboxylated poly (vinyl chloride) as matrix polymer, tetrakis-fluorophenyl borate as fixed anionic site and nitrophenyloctylether as plasticizer. The uptake of aminoglycosidic drug was applied to determine permeability changes in the Gram-negative bacteria *Escherichia coli* as test organism and ethylenediamine tetraacetic acid as model permeabilizer. The sensor showed linear response over concentration range of 10^{-2} to 10^{-5} M tobramycin with cationic slope of mV per concentration decade and accuracy of 99.8 ± 2.14%. The proposed method was successfully applied to the determination of tobramycin uptake, by 100 μl *E. coli* suspension in presence of up to 10 μg ml^{-1} of EDTA solution, with average recovery of 99.3 ± 2.77%.

1.7.3. Tetracyclins Based Potentiometric Sensors

Tetracycline (TC), the 2-(amino-hydroxy-methylidene)-4-dimethylamino-6,10,11,12a-tetrahydroxy-6-methyl-4,4a,5,5a- tetrahydrotetracene-1,3,12-trione, is one of the most used compounds for the treatment of bacterial infections in human and veterinary medicine due to its broad spectrum of activity against gram-positive and gram-negative bacteria. In the same manner its semi-synthetic derivatives such as chlortetracycline (CTC), oxytetracycline (OTC) and doxycycline (DC) prevent the docking of amino-acylated tRNA to bacteria ribosomes, thus exerting a bacteriostatic effect by impairing the synthesis of new proteins.

An internal solid contact sensor for the determination of doxycycline hydrochloride (DC) was developed based on a conducting polypyrrole (PPy) film immobilized on a glassy carbon electrode surface casted by a plasticized polyvinyl chloride (PVC) membrane containing an ion-pair compound of DC with tetraphenylborate (TPB) and dibutylphthalate (DBP) as plasticizer [23]. Under the condition of pH 2.8, the sensor showed a near-Nernstian response over the range of DC concentration of 1.0×10^{-2}–1.0×10^{-5} mol l^{-1} with the slope (at 25°C) of 54.4 mV per decade. The detection limit obtained was 4.0×10^{-6} mol l^{-1}. The sensor was successfully applied to determination of DC in pharmaceutical formulation.

The construction and performance of plastic membrane (PME) oxytetracycline hydrochloride (OTC)-selective electrodes, based on three types of ion-pairs, OTC–tetraphenylborate (TPB), OTC–phosphotungstate (PT) and OTC–silicotungstate (SiT), as the electroactive substance in a plasticized PVC membrane with dibutylphthalate (DBP), were described by Sun *et al.* [24]. Furthermore, internal solid contact sensors (ISCS) OTC-selective sensors, based on a conducting polypyrrole (PPy) film immobilized on a platinum or glassy carbon electrode surface casted by a plasticized PVC membrane were constructed and evaluated. An ISCS (Pt/PPy/PVC (OTC–TPB)) showed an excellent Nernstian response over the linear concentration range of 4.0×10^{-7}–5.0×10^{-2} M with the slope of 60.6 mV per decade (at 25°C). The limit of detection was 1.0×10^{-7} M of OTC (0.03 ppm). The response time was <25 s. The sensor was successfully used for the analysis of OTC in pharmaceutical formulation by using direct potentiometry.

Cunha *et al.* [25] constructed and evaluated the performance of PVC membranes ion-selective electrodes for the determination of tetracycline type antibiotics. Electrodes with the best responses were based on plastic membranes containing 31% (w/w) PVC, 68% (w/w) of dibutylphthalate as plasticizer and 1% (w/w) of *β*-cyclodextrin as ionophore.

The electrodes were responsive over 6 months to tetracycline, oxytetracycline, doxycycline and chlortetracycline in glycine buffer solution (pH 2), in the dynamic range 2×10^{-5}–10^{-2} mol L^{-1} with a constant slope of about 55 mV/dec.

Goreiti *et al.* [26] described the construction and evaluation of different tetracycline (TC)-selective electrodes with poly(vinyl chloride) or ethylene(vinyl acetate) membranes comprising *o*-nitrophenyl octyl ether or bis(2-ethylhexyl)sebacate as mediator solvents and tetracycline tetrakis(4-clorophenyl)borate as ion exchanger. The best performance was recorded for the poly(vinyl chloride) membranes with bis(2-ethylhexyl)sebacate. Using solutions with adjusted ionic strength, this type of electrode presented a slope of 57.4 mV decade^{-1} and a reproducibility of ±0.3 mV day^{-1}, for an analytical range from 1.2×10^{-4} to 1.0×10^{-2} M. The pH working range was 2.0–3.8.

PVC membrane electrodes selective for hydrochlorides of tetracycline (TC), doxycycline (DC) and oxytetracycline (OTC) were prepared by Shoukry *et al.* [27]. The electrodes showed a linear response with Nernstian slope over the range of 1.6×10^{-5}–$10^{-2}M$, 7.9×10^{-5}–$1.9 \times 10^{-3}M$, and 6.3×10^{-5}–$6.3 \times 10^{-3}M$ for TC, DC, and OTC, respectively. The electrodes exhibited good selectivity for the investigated antibiotics with respect to a large number of inorganic cations and organic substances of biological importance. TC, DC, and OTC are determined successfully in pure solutions and in some pharmaceutical preparations using the standard additions method.

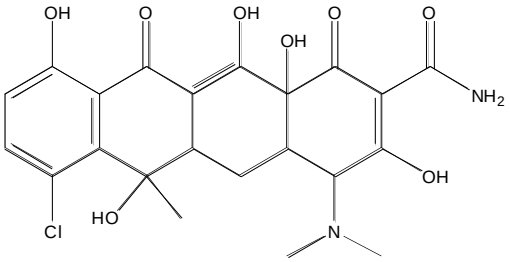
Sun *et al*. described an internal solid contact sensor for the determination of methacycline hydrochloride [28] based on conducting poly(pyrrole) as solid contact material and methacycline phosphotungstate as an ion-exchanger. The sensor worked in the concentration range of 6.4×10^{-6} – 3.0×10^{-6} M with Near -Nernstian slope of 52.4 mV/decade. Recently, Rachidi and Elharti reported a potentiometric membrane electrode sensitive to macrolide antibiotic azithromycin [29]. The sensor exhibited good linear response over the concentration range 1.0×10^{-2} -7.0×10^{-6} M with Nernstian slope.

Pandey and coworkers [30] reported oxytetracycline hydrochloride (OTC)-selective electrodes, based on three types of ion-pairs, OTC–tetraphenylborate (TPB), OTC–phosphotungstate (PT) and OTC–silicotungstate (SiT), as the electroactive substance in plasticized PVC membranes. The electrodes showed an excellent Nernstian response over the linear concentration range of 4.0×10^{-7} –5.0×10^{-2}M and a limit of detection was 1.0×10^{-7} M of OTC.

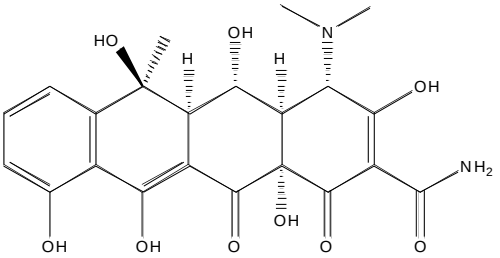
1.8. Phenothiazine Derivatives Based Potentiometric Sensors

Among the phenothiazine drugs, Chlorpromazine remains the most widely used drug and continues to serve as a standard antipsychotic drug.

New chlorpromazine selective electrodes with a tubular arrangement were proposed by Goreti *et al.* [31]. Selective membranes were of poly(vinyl chloride) (PVC) with the tetraphenylborate chlorpromazine (TPB·CPZ) ion-exchanger dissolved in *o*-nitrophenyl octyl ether (*o*NPOE). Analytical features of the electrodes were evaluated on a single-channel flow assembly having 500 µl injection volumes and flow-rates of 4.5 ml min^{-1}. For a carrier solution of 3.3×10^{-3} M in sodium sulphate, Nernstian response was observed over the concentration range 1.0×10^{-5} to 1.0×10^{-2} M. Average slopes were about 59 mV decade^{-1} and squared correlation coefficients were >0.9984. The electrode displayed a good selectivity for CPZ, and were successfully applied to the analysis of pharmaceutical preparations. The proposed method offers the advantage of simplicity, accuracy, applicability to coloured and turbid samples, and automation feasibility.

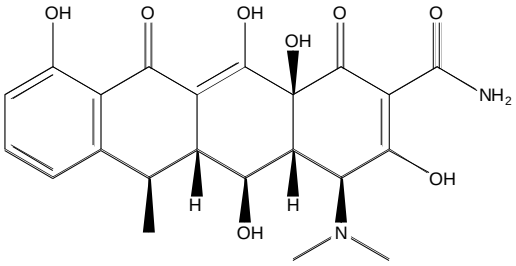


Chlortetracycline



Oxytetracycline

H_2O

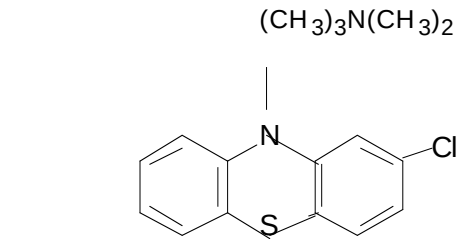


Doxycycline

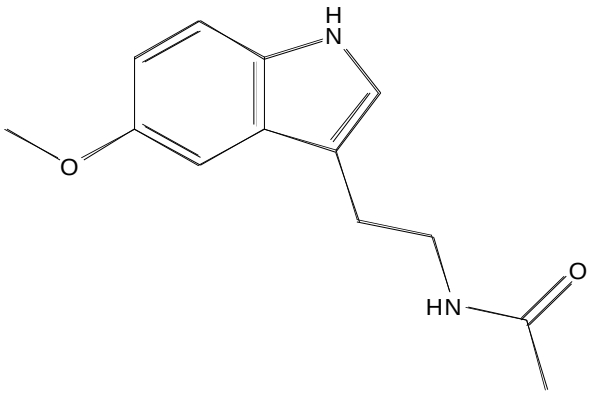
Simple, selective and accurate sensors were developed for the determination of melatonin and oxomemazine in biological samples (urine) and in pharmaceutical preparations by Saber [32]. Potentiometric measurements were based on bismus tetraiodate-drug ion-pair as novel electroactive materials incorporating a plasticized PVC membrane with *o*-nitrophenyl octyl ether or dioctyl phthalate. It exhibited fast and stable Nernstian response for melatonin and oxomemazine over the concentration range of 1.0×10^{-6}–1.0×10^{-2} M and 1.0×10^{-5}–1.0×10^{-2} M, pH range of 3.0–6.5 and 3.5–6.0 for melatonin and oxomemazine sensors, respectively. The sensors showed reasonable selectivity towards investigated drugs in presence of many cations.

Pioglitazone is a prescription drug of thiazolidinedione group with hypoglycemic action. Faridbod *et al.* [33], developed a pioglitazone potentiometric sensor based on the ion pair reagent pioglitazone-tetraphenyl borate in PVC membranes. A wide linear range of 10^{-5}-10^{-2} mol L^{-1}, low detection limit of 6.0×10^{-6} mol L^{-1}, and fast response time of ~20 s are characterizations of the proposed sensors. Validation of the method shows suitability of the sensor for application in the quality control analysis of pioglitazone hydrochloride in pure and pharmaceutical formulation.

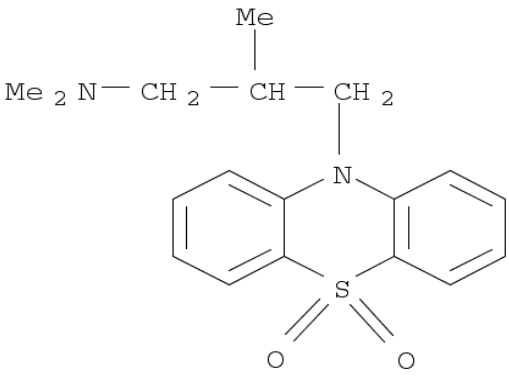
In 1999, Khalil *et al*. also reported ion-selective membrane electrodes for phenothiazine drugs based on their complexes with tetraphenylborate and dinonylnapthalenesulfonate [34]. The electrodes showed better performance as compared to previously reported.



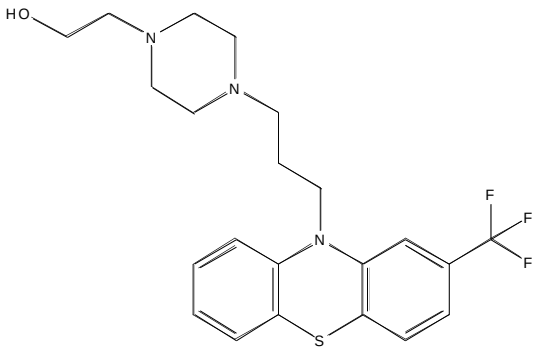
Chlorpromazine



Melatonin



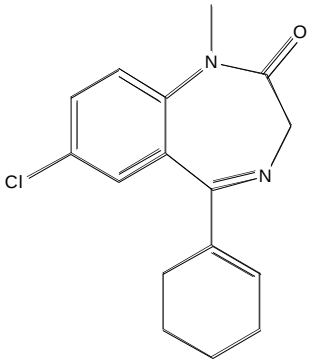
Oxomemazine



Fluphenazine

1.9. Muscle Relaxants Based Potentiometric Sensors

Tetrazepam is a benzodiazepine derivative with anticonvulsant, anxiolytic, hypnotic and muscle relaxant properties. The construction and performance characteristics of two types of tetrazepam selective electrodes were developed by Tohamy *et al*. [35] viz. plastic membrane I and coated wire II based on the incorporation of tetrazepam with phosphomolybdic acid. The electrodes showed a Nernstain response with a mean calibration graph slope of 58.88±0.5 and 59.18±0.1 mV $decade^{-1}$ at 25°C for electrode I and II respectively, over tetrazepam concentration range from 5×10^{-3}-1×10^{-6} M and 1×10^{-2}-1×10^{-6}M, and with detection limit 5.0×10^{-7} M and 4.8 $\times10^{-7}$M for electrode I and II respectively. The results obtained by the proposed electrodes were also applied successfully to the determination of the drug in pharmaceutical preparations and biological fluids.



Tetrazepam

1.10. Non-steroidal Anti-Inflammatory Drugs (NSIADS) Based Potentiometric Sensors

Bunaciu *et al.* reported the development and performance characteristics of an ion selective membrane electrode for flurbiprofen [36]. The electrode which is based on Aliquot 336S (tricaprylmethylammonium chloride) cation shows near Nernstian response in the concentration range 1.0×10^{-2} –7×10^{-5} M. This electrode was used to determine the active component and dissolution profile in pharmaceutical preparations.

In 2003, two potentiometric sensors based on PVC and polyurethane matrix contaning 5,10,15,20-tetraphenylporphyrinato (TPP) indium(III) have also been reported [37]. Khormosh *et al.* [38] reported the indomethacin selective sensor based on rhodamine B-indomethacinate ion pair (IP) as a membrane electroactive component. The sensor shows linear response in concentration range up to $1.0 \times 10^{-4} - 5.0 \times 10^{-2}$ M. The electrode was successfully used for the direct determination of indomethacin in pharmaceutical preparations.

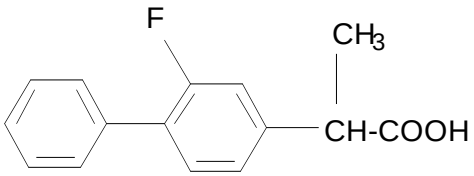
The construction and general performance characteristics of potentiometric plastic-membrane sensors for piroxicam and tenoxicam drug-anions was described [39]. The electroactive materials was based on ion pair complexes with aliquot 336S cation. Both electrodes showed near Nernstian response over the range 10^{-2}-10^{-5}mol/l, with a detection limit of about $2.4x10^{-6}$mol/l for piroxicam and $6x10^{-6}$mol/l for tenoxicam. The electrodes proved useful in the determination of the active ingredient in their respective pharmaceutical preparations.

Recently Khormosh *et al*. [40] reported PVC based ion-selective membrane electrodes for the ketoprofen and piroxicam. Ion-pairs of these drugs with Rhodamine G were used as electroactive materials for fabrication of sensors. The sensors show linear response in concentration range up to $1.0 \times 10^{-4} - 1.0 \times 10^{-1}$ M and $1.0 \times 10^{-4} - 5.0 \times 10^{-2}$ M, respectively. The electrodes were successfully used for the determination of ketoprofen and piroxicam in commercial pharmaceutical preparations.

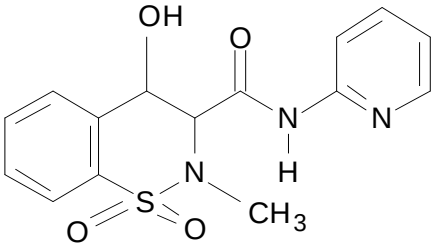
Diclofenac is a non-steroidal anti-inflammatory agent (NSAID) with antipyretic and analgesic actions. In 2003, Hasan *et al.* [41] developed a novel potentiometric PVC membrane sensor for determination of diclofenac in pharmaceutical preparations. The sensor was based on the use of the 2,4,6-tri(2-pyridyl)-s-triazine iron(II) diclofenac complex [diclofenac-TPTZ-Fe(II)] as an electroactive material in a plasticized PVC membrane matrix. The sensor exhibited fast, stable and near Nernstian response for diclofenac over the concentration range 10^{-2}-10^{-6} M and pH 5.5-9.5. Application to quality control analysis of diclofenac in various dosage forms showed an average recovery of 99% with a mean standard deviation of 0.2%.

Similar novel diclofenac ion-selective electrode was prepared characterized and used in pharmaceutical analysis by Shamsipur *et al.* [42]. The diclofenac complex with hexadecylpyridinium bromide was obtained by soaking the PVC-membranes in a 1×10^{-2} M diclofenac solution. Among four different solvent mediators tested, dibutyl phthalate (DBP) exhibited a proper behavior including Nernstian slope of the calibration curve, fast response time and good reproducibility of the emf values. The electrode exhibited a Nernstian slope of -59 ± 1 mV decade^{-1} for diclofenac in the concentration range 1.0×10^{-5} to 1.0×10^{-2} M with a limit of detection of 4.0×10^{-6} M. The membrane sensor was successfully applied to the determination of diclofenac in its tablets as well as for its recovery from blood serum and urine samples.

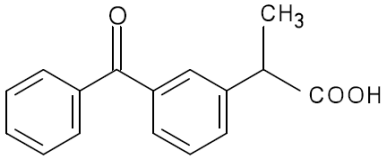
More recently, in 2007, Maleki *et al.* [43] developed a PVC membrane sensor for diclofenac based on its ion pair complex with silver. The optimized membrane demonstrates Nernstian response (-58.9 ± 0.2 mV/decade) for diclofenac anions over a wide linear range from 5.2×10^{-5} to 1.1×10^{-2} M at 25 ± 1°C. It was successfully used for determination of diclofenac in pharmaceuticals and also in potentiometric study of interaction of diclofenac with bovine serum albumin.



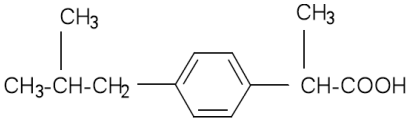
Flurbiprofen



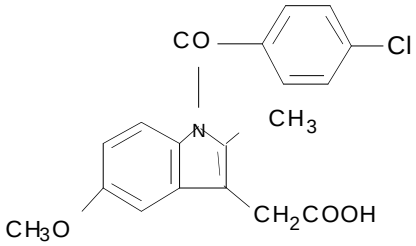
Tenoxicam



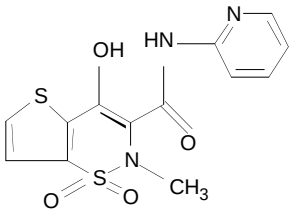
Ketoprofen



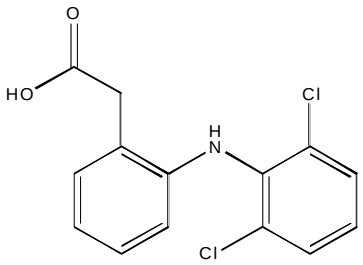
Ibuprofen



Indomethacin



Piroxicam



Diclofenac

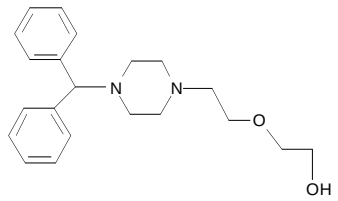
1.11. Antihistamines Based Potentiometric Sensors

In recent years, polymeric membrane electrodes have been reported for the determination of antihistamines like hydroxyzine and cetrizine dihydrochloride, triprolidine hydrochloride. Bouklouze *et al.* [44] described PVC based electrode for hydroxyzine.

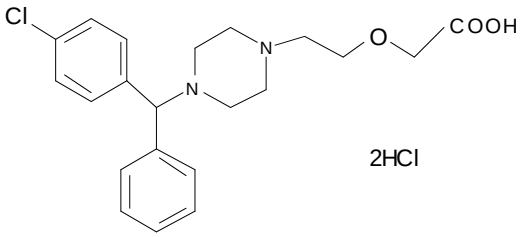
The electrode was based on silicotungstate ion pair that showed a Nernstian response in the concentration range of 6.0×10^{-7} -1.0×10^{-2} M. The sensor was successfully used to determine hydroxyzine in pharmaceuticals. New ion-selective PVC membrane electrodes of both conventional and coated graphite type sensitive to cetrizine [45] and based on tetraphenylborate have been reported. Both electrodes exhibited slope of 66.8 mV decade^{-1} activity with concentration range up to 3.1×10^{-5} – 3.1×10^{-3} M. Three types of membrane electrodes were reported for the determination of triprolidine [46]. The electrodes showed a good selectivity and were used to determine triprolidine in pharmaceutical preparations and urine samples.

Ranitidine is a histamine H_2-receptor antagonist that inhibits stomach acid production. It is commonly used in treatment of peptic ulcer disease (PUD) and gastroesophageal reflux disease (GERD). Hasan *et al.* [47] developed a new, simple and convenient potentiometric method for the determination of ranitidine. The potentiometric technique is based on direct measurements of the drug cation with novel PVC matrix membrane sensors incorporating ranitidine-reineckate, tungstophosphate and tungstosilicate ion association complexes as electroactive compounds with 2-nitrophenyl phenyl ether as plasticizing solvent mediator. These sensors exhibited rapid near-Nernstian stable responses for 10^{-2}-10^{-6} M ranitidine over the pH range 4-8, and was used in a flow-through sandwich cell for flow injection determination of the drug.

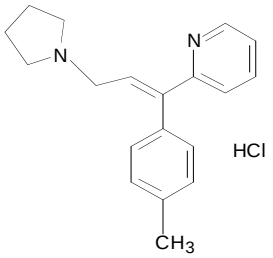
Cinnarizine is an antihistamine which is mainly used for the control of nausea and vomiting due to motion sickness. The construction and general performance characteristics of four novel potentiometric PVC membrane sensors responsive to the cinnarizinium cation was described [48]. These sensors were based on the use of the ion-association complexes of the cinnarizinium cation with tetraphenylborate, flavianate, reineckate and 12-molybdatophosphate counter anions as ion exchange sites in a plasticized PVC matrix. These sensors exhibited fast, stable and near-Nernstian response for the doubly charged cinnarizinium cation over the concentration range 10^{-2} to 10^{-6} M and pH 2-3. The sensors proved useful for determining cinnarizine in various dosage forms, monitoring tablet dissolution rates and testing tablet uniformity.



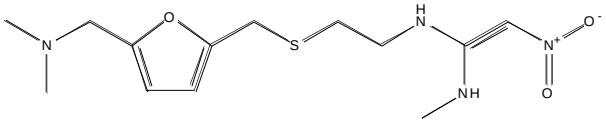
Hydroxyzine



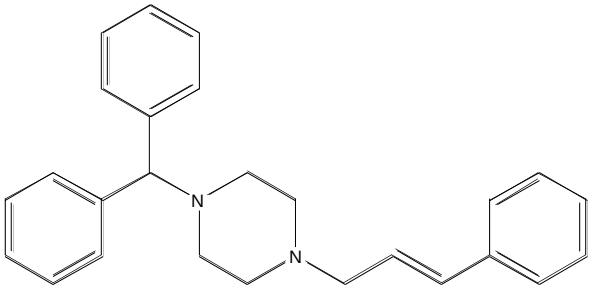
Cetrizine dihydrochloride



Triprolidine



Ranitidine hydrochloride



Cinnarizine

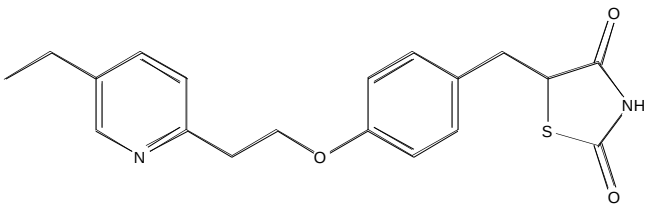
1.12. Thiazolidinedione Based Potentiometric Sensors

Pioglitazone is a prescription drug of the class thiazolidinedione (TZD) with hypoglycemic (antihyperglycemic, antidiabetic) action.

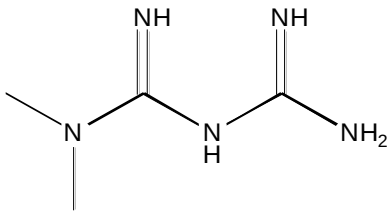
The construction and electrochemical response characteristics of poly(vinyl chloride) membrane sensors for pioglitazone HCl (PG) was described by Mostafa and Al-Majed [49]. The sensing membranes incorporated ion association complexes of pioglitazone cation and sodium tetraphenylborate (NaTPB) (sensor 1) or phosphomolybdic

acid (PMA) (sensor 2) or phosphotungstic acid (PTA) (sensor 3) as electroactive materials. The sensors displayed a fast, stable and near-Nernstian response over a relative wide pioglitazone concentration range (1×10^{-2} to 10^{-6} M), with cationic slopes of 55.0 ± 0.5, 58.0 ± 0.5 and 53.0 ± 0.5 mV per concentration decade over a pH range of 1.0-5.0. The sensors showed good discrimination of pioglitazone from several inorganic and organic compounds. The proposed sensors were applied for direct determination of pioglitazone in some pharmaceutical preparations.

Metformin is an oral anti-diabetic drug in the biguanide class. It is the first-line drug of choice for the treatment of type 2 diabetes, particularly in overweight and obese people and those with normal kidney function. In 1999, Hasan *et al.* [50] developed a PVC membrane for the determination of metformin in pharmaceutical preparations. The sensors were prepared by incorporating metformin-reineckate, and metformin-tungstosilicate ion-pairs as electroactive species with dioctylphthalate and o-nitrophenyloctylether as plasticizers, respectively. A membrane consisting of carboxylated PVC plasticized with dibutylsebacate was also prepared and tested. These sensors gave rapid Nernstian response for 10^{-1}-10^{-5}M metformin at pH range 5-11. The metformin-tungstosilicate based sensor was used in a flow-through sandwich cell for flow injection potentiometric determination of metformin. Results obtained by these techniques were comparable with data obtained using the British Pharmacopoeia method.



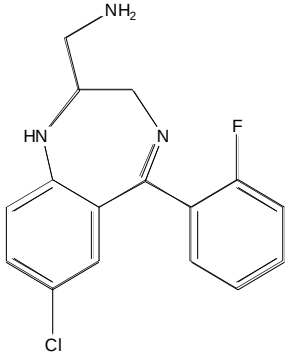
Pioglitazone



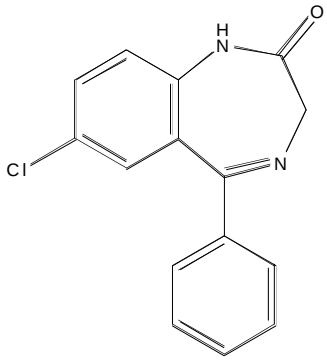
Metformin

1.13. Benzodiazepine Based Potentiometric Sensors

In 2008, Aamorin *et al.* [51] described the implementation of benzodiazepine ion-selective electrodes for pharmaceutical formulations control. The solid-contact electrodes for midazolam and diazepam were based on polymeric membranes incorporating respectively β-cyclodextrin and (2-hydroxiproyl)-γ-cyclodextrin as ionophores, 2-fluorophenyl 2-nitrophenyl ether as plasticizer and potassium tetrakis (p-chlorophenyl) borate as ionic additive. For conventionally shaped midazolam electrode a slope of 61.9 ± 1.3 mV dec^{-1}, a LLLR of 5.7 ± 2.7 × 10^{-4} g L^{-1} and pH range of 2.6-5.4 was obtained, while the corresponding values for diazepam electrodes were of 67.6 ± 3.0 mV dec^{-1}, 4.9 ± 1.5 × 10^{-2} g L^{-1} and 1.9-2.7 pH units, respectively. Membrane optimization was based on the molar ratio between the ionophore and additive for midazolam and on inclusion cavity of cyclodextrin for diazepam.



Midazolam



Diazepam

1.13.1. Phenothiazines Based Potentiometric Sensors

Fluphenazine is a typical antipsychotic drug used for the treatment of psychoses such as schizophrenia and acute manic phases of bipolar disorder. It belongs to the piperazine class of phenothiazines. The construction and electrochemical response characteristics of poly(vinyl chloride) (PVC), membrane sensors for determination of fluphenazine hydrochloride and nortriptyline hydrochloride was described by Ragehy *et al.* [52]. The method was based on the formation of the ion-pair complexes between the two drugs cations and sodium tetraphenylborate (NaTPB) or tetrakis (4-chlorophenyl) borate (KtpClPB). Four poly(vinyl chloride) sensors were fabricated. For fluphenazine HCl sensors 1 and 3 were prepared using NaTPB and KtpClPB, respectively. For nortriptyline HCl sensors 2 and 4 were prepared using NaTPB and KtpClPB, respectively. They showed linear responses for both drugs over the concentration ranges of 10^{-3}-10^{-5}, 10^{-2}-10^{-5}, 10^{-3}-10^{-5} and 10^{-2}-10^{-5}M with cationic slopes of 58.9, 52.5, 59.3 and 54.3mV per concentration decade, for sensors 1-4, respectively. The direct potentiometric determination of fluphenazine and nortriptyline hydrochlorides in their pure forms using the proposed sensors gave recoveries of 98.8±0.9, 99.0±0.9, 98.7±0.8 and 99.4±0.8% for sensors 1-4, respectively. This was compared reasonably with the data obtained using the British Pharmacopoeial method (1993). Sensors 1-4 were also used for determination of both drugs in their pharmaceutical dosage forms and in the presence of their degradates.

1.13.2. Miscellaneous Potentiometric Sensors

PVC based sensors based on lipophilic derivatives of tetraphenyl borate for the determination of quinine in soft drinks has been reported by Zareh *et al.* [53]. The electrode showed a Nernstian response over the range 0.01-10 mM quinine with a detection limit of 6.3 μM. The determination of quinine in soft drinks was performed successfully in the presence of ascorbic, citric and benzoic acids and colored matter.

Pseudoephedrine is a sympathomimetic drug of the phenethylamine and amphetamine chemical classes. It is used as a nasal/sinus decongestant and stimulant, or as a wakefulness-promoting agent. An ion-selective electrode (ISE) was developed for the rapid determination of pseudoephedrine hydrochloride (PSEHCl) in pharmaceutical preparations [54]. The electrode incorporates a PVC membrane with a pseudoephedrine-phosphotungstate ion pair complex. The sensor exhibited a Nernstian response for pseudoephedrine hydrochloride ions over a relatively wide concentration range (1.0×10^{-1} to 1.0×10^{-5} mol L^{-1}) with a slope of 56.2 ± 0.5 mV per decade at 25°C. The membrane sensor was successfully applied to determination of PSEHCl in its tablets and syrup.

Mostafa *et al.* [55] reported *s*-benzylthiuronium (*s*-BT)-PVC membrane sensor responsive for cetylpyridinium chloride based on *s*-BT-tetraphenylborate.

New PVC based membrane sensitive for some antiepileptic drugs such as lamotrigine, felbamate and primidone in their pharmaceutical preparations as well as in biological fluids have been developed [56]. The electrodes were based on poly(vinyl chloride) membranes doped with drug–tetraphenyl borate (TPB) or drug–phosphotungstic acid (PT) ion-pair complexes as molecular recognition materials. The novel electrodes displayed rapid Nernstian responses with detection limits of approximately 10^{-7} M. Calibration graphs were linear over the ranges 5.2×10^{-7}–1.0×10^{-3}, 1.5×10^{-6} 1.0×10^{-3}M, and 2.6×10^{-7}–1.0×10^{-3} M for drug-TPB and 5.8×10^{-7}–1.0×10^{-3}, 1.8×10^{-7}–1.0×10^{-3}, and 6.6×10^{-7}–1.0×10^{-3} M for drug-PT electrodes, with slopes ranging from 52.3 to 62.3 mV/decade, respectively.

Four PVC based membrane sensors for the determination of antispasmodic drug hyoscine butylbromide have been described by El-Saharty *et al.* [57]. The sensors are used for determination of hyoscine butylbromide in laboratory prepared mixtures, plasma and pharmaceutical preparations in combination with ketoprofen.

Three coated wire electrodes (CWEs) for the antispasmodic drugs; dicyclomine (Dc), mebeverine (Mv) and drotaverine (Dv) hydrochlorides were developed [58]. Each electrode based on ion-associate of a heteropoly anion with the drug cation incorporated in membrane sensor modified with graphite and deposited on silver internal solid contact. The practical utility of each electrode has been demonstrated by using it successfully in potentiometric determination of its respective drug in pharmaceutical preparations both in batch and flow injection conditions.

Disopyramide is a Class Ia antiarrhythmic (sodium channel blocker) used in the treatment of ventricular tachycardias. Disopyramide ion-selective poly(vinyl chloride) membrane electrodes were developed by Hopkala *et al.* [59] containing an ion-pair complex of disopyramide - tetrakis (4-chlorophenyl)borate as the electroactive material with 2-nitrophenyl octyl ether (electrode I) or bis(2-ethylhexyl)sebacate (electrode II) as the solvent mediators. The electrodes (I and II) showed a linear response for the disopyramide concentration range 3.0×10^{-4}-10^{-2} and 8.5×10^{-5}-10^{-2} mol · l^{-1} over a pH range of 3.75-8.30 with a cationic slope of 57.3 and 58.5 mV $decade^{-1}$, respectively. The response time varied from 20 s to 1 min depending on the disopyramide concentration. Electrode II was used for the potentiometric determination of the disopyramide phosphate substance and the content of capsules with average recovery and mean standard deviation (± SD) of 100.8 ± 0.34 and 100.1 ± 0.68 of the nominal values, which are comparable with those obtained by the U.S. Pharmacopoeia method.

A liquid membrane electrode based on disopyramide - dipicrylamine ion - pair complex, dissolved in nitrobenzene as solvent was proposed for the determination of disopyramide - an antiarrhythmic drug [60]. The linear response covered the range from 10^{-2} - 5×10^{-6} M disopyramide solution, with a slope of 51.0 mV/decade (pH range 3.0 to 7.0). The electrode shows a good stability, reproducibility and fast response. These characteristics of the electrode made it to be used for the determination of disopyramide in pharmaceutical formulations such as capsules and ampoules.

Terazosin is a selective alpha 1 antagonist used for treatment of symptoms of an enlarged prostate (BPH). It also acts to lower the blood pressure, and is therefore a drug of choice for men with hypertension and prostate enlargement. Kumar *et al.* [61] in 2005 developed a potentiometric sensor for the determination of terazosin in pure form and in dosage forms- Terazosin-silicotungstic acid ion-association is developed as an ionophore in the fabrication of the potentiometric sensor. The optimum concentration range of the developed method was 7×10^{-2} to 8×10^{-4} M of the drug. The system gave a perfectly Nernstian slope (59.3 mV per decade) in the pH 4.2 with hardly any interference from the common cations and anions. The method has been applied for the determination of the drug in two commercially available tablets and the results are highly precise and accurate.

Enalapril and ramipril are angiotensin converting enzyme (ACE) inhibitor used in the treatment of hypertension and some types of chronic heart failure The construction and general performance characteristics of potentiometric plastic-membrane sensors for enalapril and ramipril drug-anions, was described [62]. The electroactive materials are based on ion pair complexes between enalapril and ramipril anions, respectively, with Aliquot 336S cation. Both electrodes showed near Nernstian response over the range 1×10^{-2} - 10^{-5} mol/L, with a detection limit of about 2.4×10^{-6} mol/L for enalapril and 6×10^{-6} mol/L for ramipril. The electrodes proved useful in the determination of the active ingredient in their respective pharmaceutical preparations. The method is simple, rapid and does not require prior sample pre-treatment.

In the year 1998, Hassan *et al.* [63] developed a poly(vinyl chloride) matrix membrane sensors for

fluorouracil. Fluorouracil is a drug that is a pyrimidine analog which is used in the treatment of cancer. The membranes incorporate ion association complexes of fluorouracil anion with bathophenanthroline-nickel(II) [sensor 1], bathophenanthroline-iron(II) [sensor 2] and phenanthroline-iron(II) [sensor 3] as electroactive materials. These sensors show linear response for fluorouracil over the range 1.3-130 μg ml^{-1}, with anionic slopes of 29.0, 27.9 and 34.3 mV per concentration decade with sensors 1, 2 and 3, respectively. These sensors exhibit fast response time (1.0-1.5 min), low determination limit (1 x 10^{-5} M), good stability (4-8 weeks) and reasonable selectivity. The sensors were also used to follow the stability of the drug in the presence of its degradates, namely formaldehyde, fluoroacetate and urea.

Oxybutynin is an anticholinergic medication used to relieve urinary and bladder difficulties, including frequent urination and inability to control urination (urge incontinence), by decreasing muscle spasms of the bladder. Four polyvinyl chloride (PVC) matrix membrane electrodes responsive to 2 drugs affecting the urogenital system - oxybutynin hydrochloride (OX) and flavoxate hydrochloride (FX) - were developed, described, and characterized [64]. Fast and stable Nernstian responses in the range 1×10^{-2}-1×10^{-6} M for the 2 drugs over the pH range 5-8 revealed the performance characteristics of these electrodes, which were evaluated according to International Union of Pure and Applied Chemistry recommendations. The method was applied to FX and OX in their pharmaceutical formulations and in human plasma samples. The 4 proposed sensors were found to be specific for the drugs in the presence of up to 60% of their degradation products.

Glutathione (GSH) is a powerful antioxidant of biological systems. Therefore its determination is necessary. GSH-selective electrodes were developed with different techniques and in different polymeric matrixes. Precipitation based technique with bathophenanthroline- ferrous as cationic exchanger in PVC matrix while β-cyclodextrin based technique with either terakis(4-chlorophenylborate) or bathophenanthroline-ferrous as fixed anionic and cationic sites in PVC and polyurethane matrix has been reported by El-Kosasy *et al.* [65]. The construction and characterization of potentiometric membrane electrodes have been described for the quantification of benign prostatic hyperplasia (BPH) drug alfuzosin hydrochloride [66]. The membranes of these electrodes consist of alfuzosin hydrochloride-tetraphenyl borate, (Az-TPB), chlorophenyl borate (Az-ClPB), and phosphotungstate (Az3-PT) ion associations as molecular recognition reagent dispersed in PVC matrix. The sensors revealed a stable and linear response over the concentration ranges of 8.3×10^{-6} to 1.0×10^{-2} M, 3.8×10^{-6} to 1.0×10^{-2} M, 7.5×10^{-7} to 1.0×10^{-2} M AzCl with cationic slopes of 57.0, 56.0 and 58.5 mV/decades, respectively.

A polyion-senstive membrane electrode sensitive for pentosan polysulfate [67] has been reported in recent years. Gupta *et al.* [68] reported the construction of potentiometric membrane based on quaternary ammonium drugs viz. propantheline bromide and neostigmine bromide.

Liu *et al.* [69] reported development and applications of a membrane electrode based on pethidine-tetraphenylborate as ion-exchange site and sensitive for pethidine. A linear response for 1×10^{-5} to 1×10^{-5} concentration range was observed.

El-Sharty *et al.* [70] described poly(vinyl chloride) membrane electrode based on sodium phosphotungestate (Dro-PTA) or ammonium reineckate (Dro-R) and sensitive for drotaverine. The sensor showed a linear response for drotaverine over a concentration range of 10^{-5} to 10^{-2} M. The sensors were used for determination of drotaverine hydrochloride in tablets, in its mixture with caffeine, paracetamol and in plasma.

A novel coated-graphite selective sensor based on verapamil ion pair with phosphomolybdate (PM) for its flow injection potentiometric (FIP) determination has been described in the year 2008 [71]. The sensor was prepared by coating the membrane cock-tail containing PVC, plasticizer, and carrier on the surface of graphite rode. The sensor membrane containing 3.6% Ver-PM ion-pair and 62.0% dioctylphethalate (DOP) in PVC possesses the best response with quasi-Nemstian slope of 62.6 mV/decade over a wide concentration range of 6×10^{-6}- 1×10^{-2} M and a lower limit of detection (LDL) of 1.9×10^{-6} M. The developed sensor has been applied for FIP determination of verapamil hydrochloride in pure solution, pharmaceutical preparations and urine. The determination of verapamil assay in Verpamil tablets after shelf-storage for more than one year using the proposed sensor has been achieved.

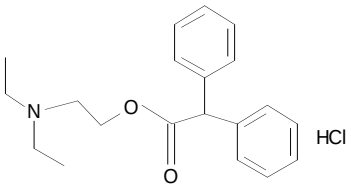
Potentiometric measurments for the determination of clopidogrel in pharmaceutical preparations by Saber *et al.* [72] are based on tetrakis (p-chlorophenyl) borate-clopidogrel ion-pair as an electroactive material incorporating a plasticized PVC membrane with o-nitrophenyl octyl ether or dioctyl phthalate. The sensor exhibits fast and stable Nernstian response for clopidogrel over the concentration range of $1.0 \times 10^{-5} \sim 1.0 \times 10^{-2}$ M and pH range of 1.5 - 4.0. Results with an average recovery of 100.6% and a mean standard deviation of 0.86% of the nominal were obtained. The sensor shows reasonable selectivity towards clopidogrel hydrogen sulphate in presence of many cations.

A novel plastic poly (vinyl chloride) membrane electrode based on bumetanide-tungstophosphate ion association as electroactive material for the determination of bumetanide in pure form, pharmaceutical formulations and biological fluids is developed by El-Tohemy [73], in which the plasticizer is di-butyl sebacate. The linear response covers the range of 1×10^{-6}-1×10^{-3}M drug concentration with a slope of 58.5 mV/decade. The practical pH range is 5-8. The proposed electrode has been successfully applied to determine bumetanide in pure form and the content uniformity for tablets. The results are correlated well with those obtained by the official USP 25, NF 20 method.

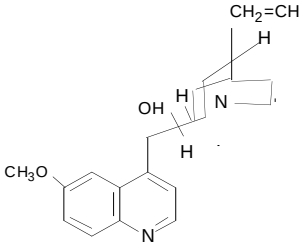
Mostafa in 2003 developed and studied the performance of metoclopramide (MCP)-polyvinyl chloride (PVC) membrane sensor [74]. The sensor is based on the use of MCP-tetraiodomercurate ion pair as electroactive material in PVC matrix in presence of dioctylphthalate (DOP) as solvent mediator. MCP membrane sensor shows a stable, near Nernstian response over the concentration range 1×10^{-2}-6×10^{-5} M of MCP at 25°C in the pH range 3-7 with cationic slope of 53.0±0.5. The detection limit of 4×10^{-5} M and the

response time of 30-60 s have been attained. The determination of MCP in Primperan tablets, injection, and syrup gave results that compare favorably with those obtained by the British pharmacopoeia method.

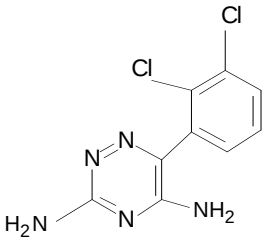
Beside these a variety of drugs viz. ketoconazole and anions [75-80], creatinine [81], thiopental [82], ketamine [83], diclofenac and warfarin drugs [84], fluphenazine hydrochloride and nortriptyline hydrochloride [85], tramadol [86], cimetidine [87], clotrimazole [88], piribedil [89], atenolol [90], mexiletine [91], 2-hydroxyglutaric acid [92], tripelenamine [93], tizanidine [94], paraquat [95], buformin [96], gabapentin [97], sildenafil citrate [98], pyrantel [99], diltiazem [100], etc. have been determined by ion selective electrodes.



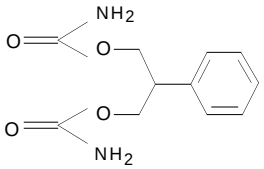
Adiphenine hydrochloride



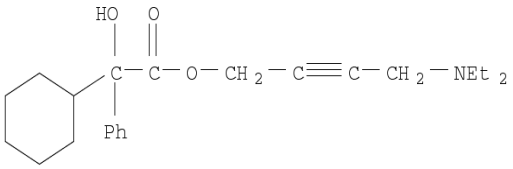
Quinine



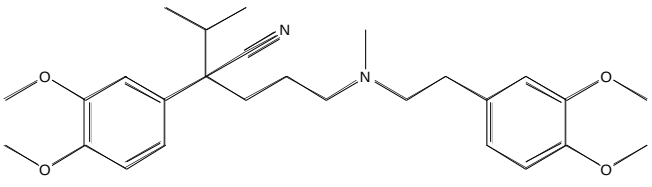
Lamotrigine



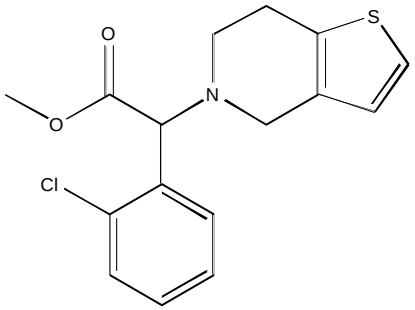
Felbamate



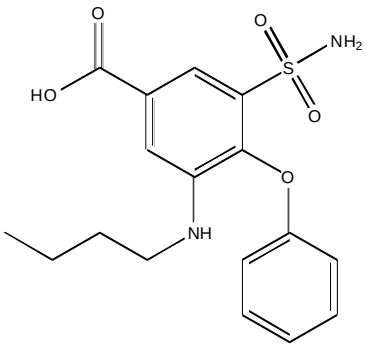
Oxybutynine



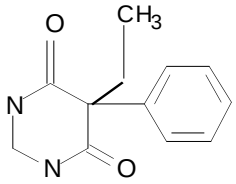
Verapamil



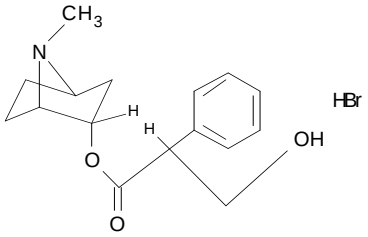
Clopidogrel



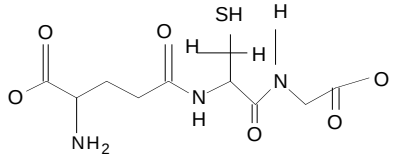
Bumetanide



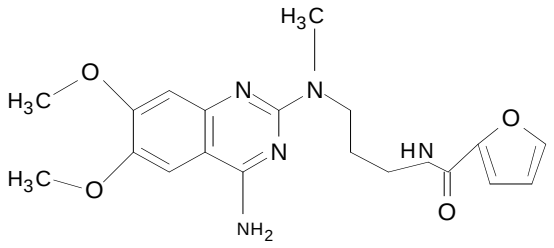
Primidone



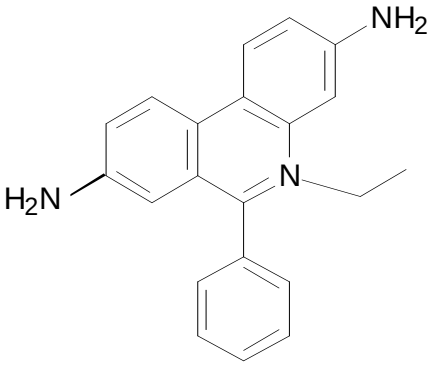
Hyoscine butylbromide



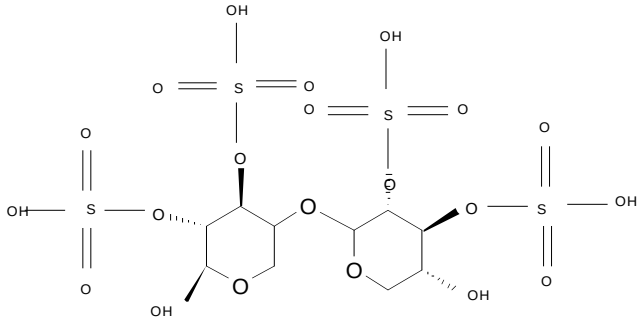
Glutathione



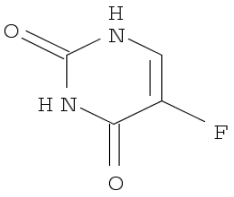
Alfuzosin



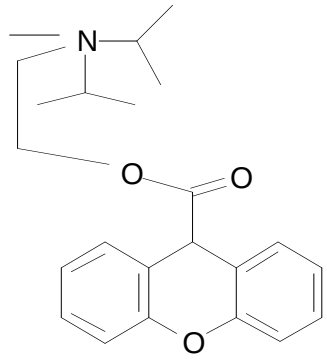
Neostigmine bromide



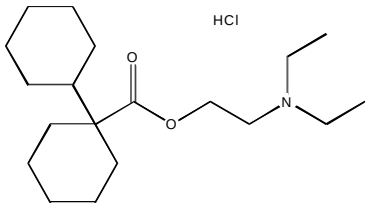
Pentosan sulphate



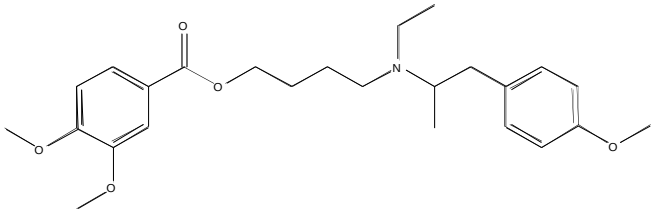
Fluorouacil



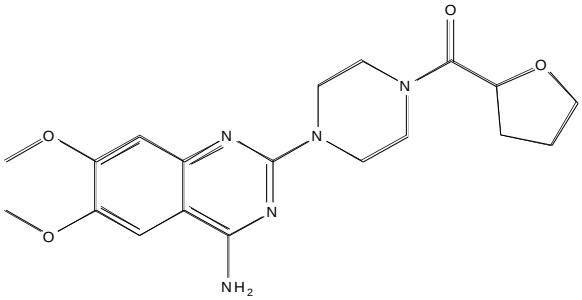
Propantheline bromide



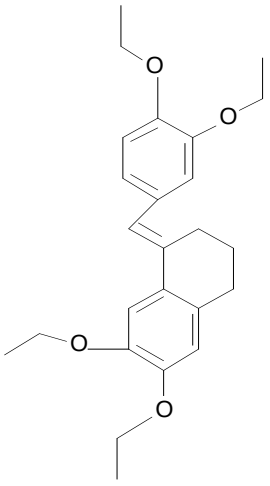
Dicyclomine



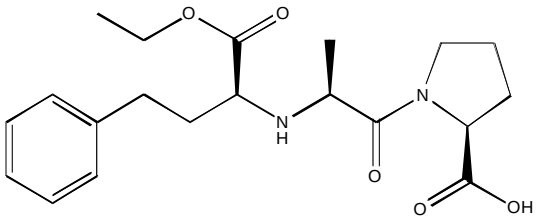
Mebeverine



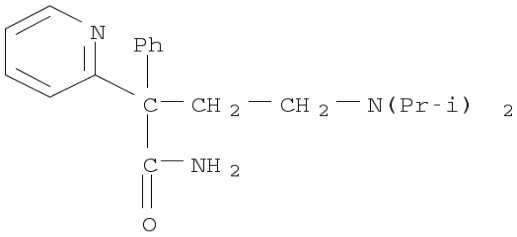
Terazosin



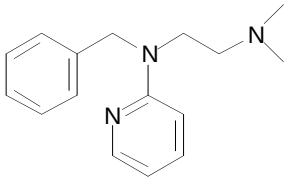
Drotaverine



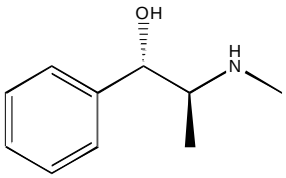
Enalapril



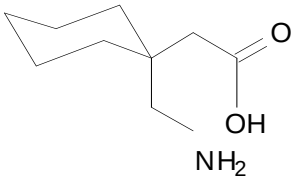
Disopyramide



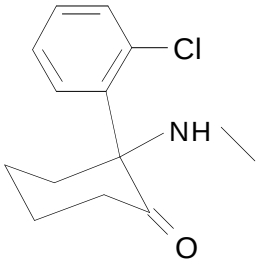
Tripelenamine



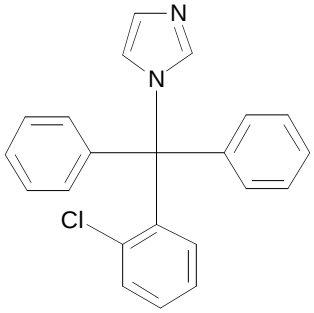
Pseudoephedrine



Gabapentin



Ketamine



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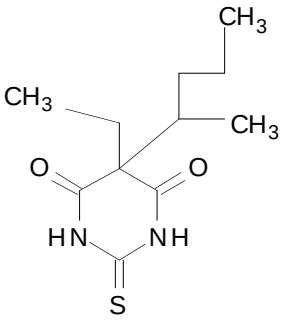

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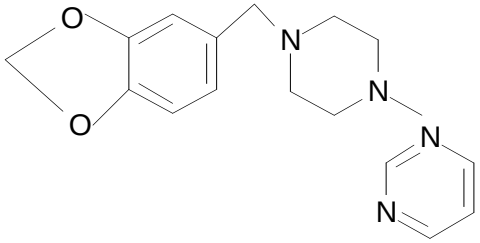

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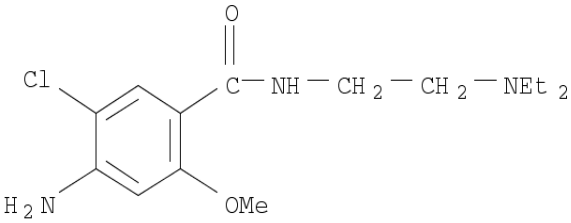

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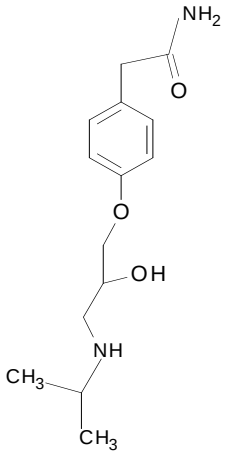

Atenolol

CONCLUSION

A review of some recent development of potentiometric membrane sensors for variety of drugs has been embraced. The field of pharmaceutical analysis includes a wide range of analytes, varying in structure from very simple components to complex biomolecules. Drugs have for many years, been

the most widely used form of therapeutic intervention. Drug ISEs have some valuable features that make them superior to other methods of drug analysis. These electrodes assure the reliability of analytical information in drug assay due to the possibility to determine directly, the activity of ions in solution, without any prior separation. Traditional ISE detection limits have been reasonably improved and measurement down to picomolar range is now possible.

FUTURE PROSPECTS

The last decade has been the rapid emergence of pharmaceutical industry. The scope of drug analysis includes the analytical investigation of bulk-drug materials, the intermediates in their synthesis, products of drug research, drug formulations, impurities and degradation products of drugs, biological samples containing the drugs and their metabolites with the aim of obtaining data that can contribute to the maximal efficacy, safety of drug therapy and the maximal economy of the production of drugs. To fulfill the above requirements, it became necessary to harmonize the demands and analytical strategies. As a consequence of the tendencies towards globalization and harmonization mentioned above and the necessity of increasing determination of drug and validation of the analytical methods has come to the forefront.

In the coming years the development of new membrane-based potentiometric devices will continue to play an important role in reducing the complexity and cost associated with direct chemical sensing. The next decade researches will likely focus on filling voids in existing membrane electrode technology. Advances in these and other areas, particularly the development of useful potentiometric biosensors, will require truly interdisciplinary research efforts. Another area likely to receive considerable attention will be that of miniaturized ion, gas, and bio-selective sensors. Small probes containing multiple sensing sites would be extremely useful as detectors for the simultaneous measurement of several species. At the same time, chemical approaches will need to be found that will render such in-dwelling probes more biocompatible without interfering with the membrane chemistry that is required to make accurate electrochemical measurements. Biocompatibility of implantable membrane sensors may be improved with innovative coatings or new blood-compatible polymer matrices. Thus, the advent of many new and exciting membrane electrodes appears imminent, awaiting the efforts of analytical chemists, electrochemists, immunologists, biochemists, material scientists working in concert toward this end. Emerging biosensor technologies such as lab-on-a-chip have revolutionized the integration approaches for a very flexible, innovative and user-friendly plat-form.

ACKNOWLEDGEMENT

The authors acknowledge Indian Institute of Technology Roorkee, Roorkee for supporting this work.

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Received: October 18, 2010 **Revised: December 5, 2010** **Accepted: December 16, 2010**