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Drug Analysis: A Perspective of Potentiometric Sensors

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Abstract: The remarkable specificity of biological recognition processes has led to the development of highly selective bio-sensing devices. Electrochemical biosensors hold a leading position among the bio-probes currently available and hold great promise for the task of pharmaceutical analysis. They are inherently sensitive and selective towards electro-active species, fast and accurate, compact, portable and inexpensive. Among them potentiometric sensors are very attractive strategy that can be used for the direct measurement of ions, gases and bio-molecules in complex samples. In this report, an attempt has been made to provide a brief insight to the applicability and advantages of potentiometric sensors in analysis of pharmaceutically active compounds.

Key words: Membrane sensors · Potentiometry · Biosensors · Ionophore · Drugs analysis

INTRODUCTION

The largest group among potentiometric sensors is represented by ion-selective electrodes (ISEs), the oldest and most widely used among them being a pH-sensitive glass electrode. Now-a-days there exists a large variety of commercially available ISEs that may be helpful in direct determination of ion concentration in liquid samples of different nature. Measurements with ISEs are performed with reference to some stable and well defined reference electrode contacting the sample solution through a liquid junction. In ISEs the signal is generated by charge separation at the interface between ion-selective membrane and the solution due to selective partitioning of ionic species between these two phases. In classical ISEs the arrangement is symmetrical which means that the membrane separates two solutions, the test solution and the inner solution with constant concentration of ionic species. The electrical contact to an ISE is provided by a reference electrode (usually Ag/AgCl) in contact with the internal solution that contains chloride ions at constant concentration. Potentiometric sensors operate at thermodynamic equilibrium conditions. Thus, in practical potentiometric sensing, the potential measurement needs to be made under zero-current conditions.

An important requirement for the preparation of an ion selective sensor is that the electro active material (ionophore), which is used in the membranes, should exhibit high lipophilicity and strong affinity for a particular ion to be determined and poor affinity for others. Ionophores for use in sensors should have rapid exchange kinetics and adequate complex formation constants in the membrane. Also, they should be well soluble in the membrane matrix and have a sufficient lipophilicity to prevent leaching from the membrane into the sample solution. In addition, the selectivity of the neutral carrier-based ISEs is known to be governing by stability constant of the neutral carrier-ion complex and its partition constant between the membrane and sample solution. A significant number of ionophores including crown ethers, cryptands, aza-crowns, thiocrowns and thia compounds have already been exploited for fabrication of poly(vinyl chloride) (PVC) membrane electrodes for series of alkali, alkaline earth, transition and heavy metal ions. Now-a-days developments in pharmaceutical analysis with ion-selective electrodes have enabled the direct and selective measurement of the activity of various organic cations or anions of pharmaceutical interest, in most instances without prior separation of the active substance from the formulation matrix. Significant technological advances have been envisaged during last decade to facilitate the pharmaceutical applications of these devices. Various reports have been published which highlights the important contribution of ion-selective sensors for quantification of drugs [1-4]. This report highlights some of the important potentiometric sensors which have been used in pharmaceutical analysis.

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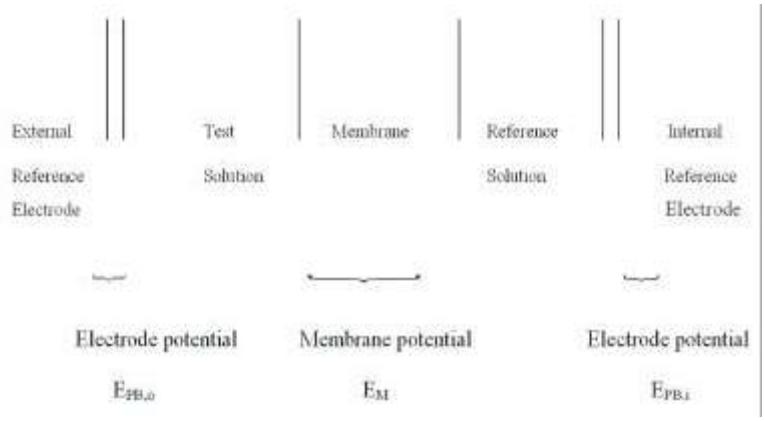
Principle of Ion-selective Membrane: Ion-selective electrodes are typically investigated under zero current condition by following cell set up.



The electromotive force (emf) across this cell is the sum of all individual potential contributions. Many of these are sample-independent and the measured emf can usually be described as

$$\text{emf} = E_{\text{const}} + E_J + E_M \quad (1)$$

Liquid junction potential originates E_J from the different mobility of ionic species in the sample solution and in the bridge electrolyte of the reference electrode if ion-selective electrodes can be kept constant by employing concentrated bridge electrolytes with similar mobilities of cations and anions (e.g. 1M KCl, NH_4NO_3, or LiOAc).

The utility of membrane electrodes depends upon the determination of *membrane potentials* E_M, which is ideally a function of the sample ion activity [5]. So we will only focus on the membrane potential E_M of electrode.

Since the membrane is usually interposed between the sample and an inner reference electrolyte, it is commonly divided into three separate potential contributions, namely the phase boundary potentials at both interfaces and the diffusion potential within the ion-selective membrane.

$$E_M = E_{PB} + E_{Diff} \quad (2)$$

The potential at the membrane/inner filling solution interface can be assumed to be independent of the sample, whereas the diffusion potential within the membrane may become significant if considerable concentration gradients of ions with different mobilities arise in the membrane. If no concentration gradients occur within the membrane, diffusion potential E_{Diff} is zero. This is often the case for membranes that show theoretical Nernstian response. Phase boundary potential E_{PB} arises from a charge separation caused by the non-uniform distribution of ionic species between the organic membrane and the aqueous phase. The phase boundary potential can be derived from basic thermodynamic considerations of chemical and electrical potential contributions. The electrochemical potential, $\bar{\mu}$ for species A in aqueous phase could be written as follows.

$$\bar{\mu}_{A(aq)} = \mu^{o}{}_{A(aq)} + 2.303RT \log a_{A(aq)} + Z_A F \phi_{(aq)} \quad (3)$$

Similarly, the electrochemical potential for the analyte ion (A) in contacting organic phase is

$$\bar{\mu}_{A(aq)} = \mu_{A(aq)} + Z_A F \phi_{(aq)}$$

$$\bar{\mu}_{A(org)} = \mu_{A(org)} + Z_A F \phi_{(org)} \quad (4)$$

Where μ is the chemical potential and $\mu°$ is chemical potential under standard conditions, z_A is valency of analyte ion A and a_A is the activity of the uncomplexed ion A, ϕ is the electric potential and R, T and F are the universal gas constant, absolute temperature and Faraday constant. It is assumed that the interfacial ion transfer and complexation processes are relatively fast and therefore, equilibrium holds at the interface so that the electrochemical potential for both phases are equal. This leads to a simple expression for the phase boundary potential, *i.e.*

$$\bar{\mu}_{A(aq)} = \bar{\mu}_{A(org)} \quad (5)$$

Thus, equation (5) indicates that the phase boundary potential is a simple function of sample ion activity ($a_{A(aq)}$) particularly if $a_{A(org)}$ is not significantly altered by the sample. The complexation of analyte ion A with the ionophore inside the organic membrane phase influences free analyte activity $a_{A(org)}$ and therefore, also the phase boundary potential [6]. However, due to the strong complexation with the ionophore, concentration of the free ion in the organic membrane is small relative to that of the complexed ions. Consequently, the concentration of the complex is approximately equal to that of the anionic sites provided by the anion discriminator and remains unaltered if an excess of ionophore is added. This is so because, in order to maintain electroneutrality of the membrane, only as many cations could enter the membrane phase as are the anionic sites provided by the anion excluder. By combining equations (2) and (5).

$$E_M = E_{constt} + E_{PB} \quad (6)$$

Since $a_{A(org)}$ remains constant under the experimental conditions, it can be put together with all other sample-independent potential contributions, *i.e.* it could be included in a single term (E°). Thus, equation (6) is reduced to a well-known Nernst equation.

$$E_M = E^o + \frac{2.303RT}{Z_A F}\log a_{A(aq)} \quad (7)$$

Thus, it is clear from equation (7) that the cell potential is directly proportional to the concentration or activity of the sample ions in aqueous solution under investigation. At 25°C, the value of 2.303 RT/ z_AF is $0.059/z_A$ volts. The membrane is said to exhibit Nernstian response if the slope of a plot between cell potential and log activity comes out to be $0.059/z_A$ volts. These plots are then called Nernst plot and slope as Nernstian slope.

Construction and Performance of Various Ion-Selective Sensors for Drugs: From the past two decades various potentiometric sensors for drugs have been reported. The potentiometric characteristics of the various ion-selective electrodes for drugs are discussed below.

There have been reports on polymeric sensors for determination of various alkaloids like berberine, cocaine, heroin, codeine, ethaverine, nicotine. Watanabe and coworkers reported a improved cocaine membrane selective electrode [7] with the use of sodium tetrakis [3,5-bis(trifluoromethyl)phenyl] borate as an ion-exchanger and tetrakis (2-ethylhexyl)pyromellitate (TEHPY) as a solvent mediator. The use of TEHPY suppressed the responses to lipophilic quaternary ammonium ions and strengthened the response to cocaine. The electrode exhibited a near-Nernstian response over a concentration range of 10^{-2} to 10^{-6} M cocaine with a slope of 56 mV per decade.

Recently Abbas and coworkers reported novel potentiometric membrane ion-selective electrodes for determination of papaverine hydrochloride [8]. They are based on the formation of the ion-association complexes of papaverine (PA) with tetraphenylborate (TPB)(I) or tetrathiocyanate (TTC)(II) counter anions as electro-active material dispersed in a PVC matrix. The sensors exhibited fast, stable, near Nernstian response for 1×10^{-2} -6×10^{-5} M and 1×10^{-2} -1×10^{-5} M for PA-TPB and PA-TTC, respectively with a cationic slope of 56.5±0.5 mV/decade for both sensors, respectively. The direct determination of PA in some formulations (Vasorin injection) gave results that compare favorably with those obtained using the British Pharmacopoeia method. Katsu and coworkers [9] reinvestigated the response characteristics of a caffeine electrode, taking into consideration the pKa value and constructed a new electrode with a combination of the lipophilic cation-exchanger, tetrakis [3,5-bis(2-methoxyhexafluoro-2-propyl)phenyl] borate (HFPB) and the solvent mediator with high degree of dielectric constant, 2-fluoro-2'-nitrodiphenylether (FNDPE). This electrode showed a pH-dependent response to caffeinium ion and gave a detection limit of 50 μM with a slope of 55 mV per concentration decade at pH 2. The electrode was applied for the determination of caffeine in some central stimulants.

There have been reports for the selective determination of different amino acids like alanine, leucine, aspartic acid, L-tyrosine and L-phenylalanine. In all cases, short linear ranges and poor selectivities were observed.

Shvedene and coworkers reported ion-selective electrodes based on *p*-1-adamantylcalix [8] arene ionophores for the determination of amino compounds as well as amino acids [10]. The electrodes were based on lipophilic ion-associate tetraphenylborate. All membranes exhibited extremely short response time (5-10 s) in wide pH and analyte concentration ranges. Volf *et al*. reported novel potentiometric sensor for determination of cysteine based on substituted poly(diphenylporphyrins and metalloporphyrins) [11]. A remarkable selectivity for cysteine 1×10^{-2} M has been found. The comparison of polymeric films with monomeric porphyrin units showed the higher binding efficiency of the polymeric films.

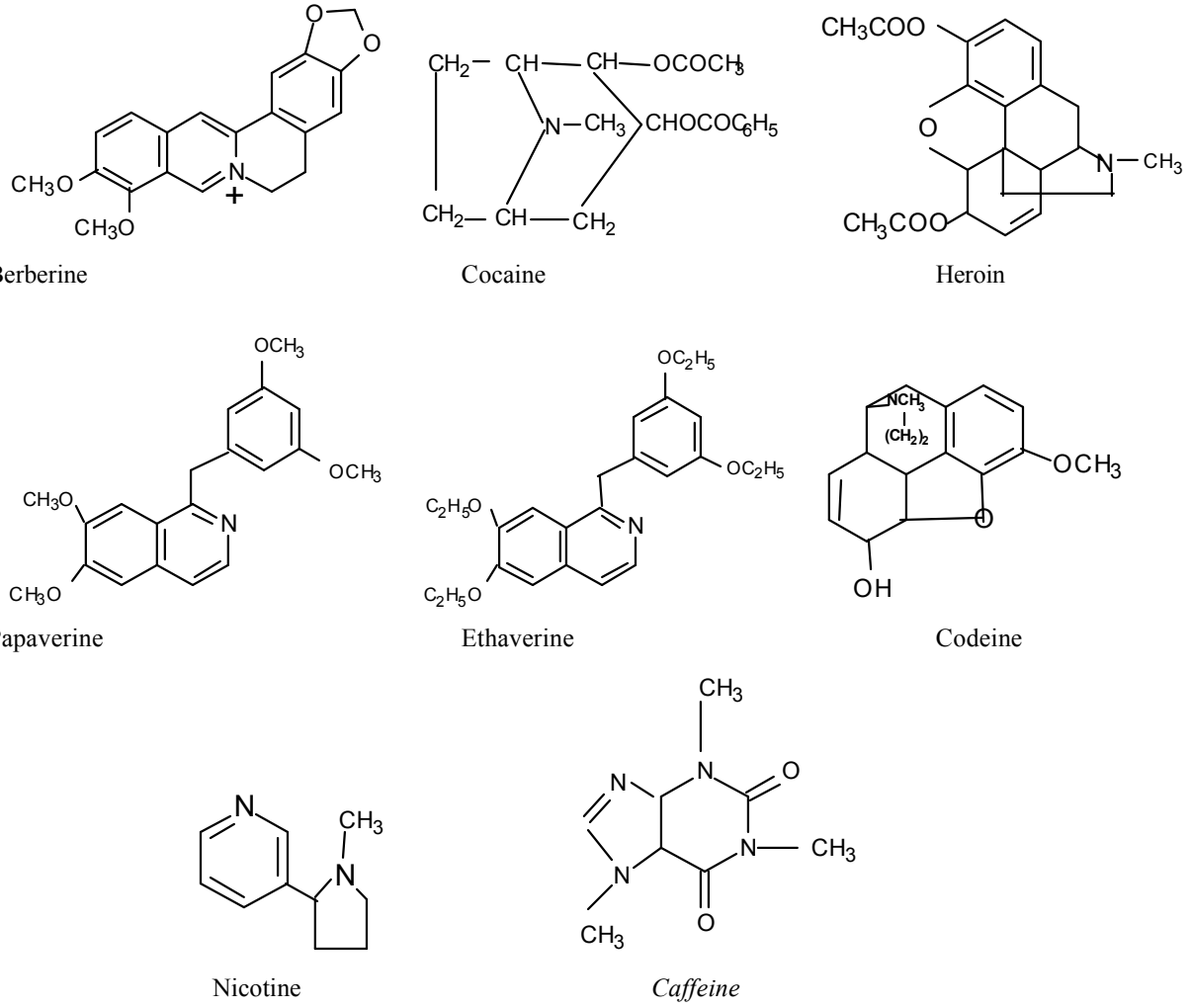


Fig. 1: Structures of various alkaloids

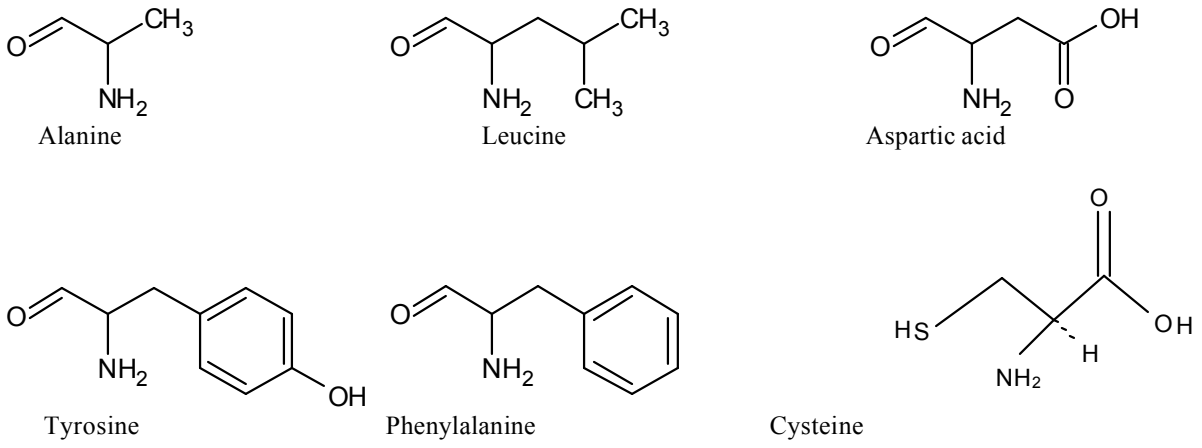


Fig. 2: Structures of various amino acids

The variety of antidepressants drugs were determined by potentiometric membrane electrodes like amitryptyline, imipramine, chlorpromazine and propranolol. Erdem and co-workers reported ion-selective membrane electrodes for phenylpiperazine antidepressant, nefazodone (NFN), based on its ion-pair complexes with phosphotungstate (PT), tetraphenylborate (TPB), tungstosilicate (TS) and reineckate (RN) in a poly(vinylchloride) (PVC) matrix [12]. The best ion-selective electrode for determination of NFN contains NFN-PT as the active material. This electrode exhibited a Nernstian response (62.6±0.4 mV per decade) in the range 1.5×10^{-5}-1.0×10^{-2} M.

El-Ragehy and coworkers described potentiometric membrane sensors for determination of fluphenazine hydrochloride and nortriptyline hydrochloride [13]. The method is based on the formation of the ion-pair complexes between the two drugs cations and sodium tetraphenylborate (NaTPB) or tetrakis (4-chlorophenyl) borate (KtpClPB). 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 54.3 mV/decade, respectively. The direct potentiometric determination of fluphenazine and nortriptyline hydrochloride 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%, respectively.

Khalil *et al*. reported potentiometric membrane sensors for determination of triiodide [14] consisting of triiodide-fluphenazine (FP) and triiodide-trifluoperazine (TFP) ion pair complexes dispersed in PVC matrix plasticized with *o*-nitrophenyl octyl ether with unique selectivity toward I_3^- ions. The optimized membranes demonstrate Nernstian response for triiodide ions over a wide linear range from 1.0×10^{-2} to 5.0×10^{-6} M at 25°C. The sensors were successfully used as indicator electrode in the potentiometric titration of triiodide ions and ascorbic acid.

Rizk *et al*. reported two novel polymeric membrane sensors for the analysis of Pb(II) based on two therapeutic drugs, thiopental (TP) and phenytoin (PT) as two ionophores and potassium tetrakis(*p*-chlorophenyl)borate (KT*p*ClPB) as a lipophilic additive, in plasticized PVC membranes [15]. The sensors showed a Nernstian response for Pb(II) ions over the wide concentration ranges of 1×10^{-2} - 7×10^{-6} M and 1×10^{-2} - 8×10^{-6} M for the sensors based on thiopental and phenytoin, respectively.

There are various anesthetics (procaine, tetracaine, benzocaine, oxybuprocaine etc.) or amide type (lidocaine, dibucaine, mepivacaine, bupivacaine etc.) determined by potentiometric sensors. These drugs exist in both positively charged and uncharged forms under normal *in vivo* condition. Most of them displayed linear responses with near-Nernstian slopes in working concentration ranges up to 1.0×10^{-4}- 1.0×10^{-2} M.

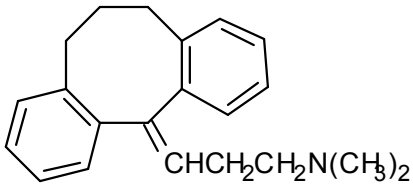
Alizadeh *et al*. reported ion-selective membrane electrode to the drug ketamine hydrochloride [16] using a modified PVC membrane which has ionic end-groups as ion-exchanger sites and which was cast using plasticized with *o*-nitrophenyloctyl ether (*o*-NPOE) as plasticizer. This electrode show excellent Nernstian responses (59 mV/decade) in the concentration range 1×10^{-5}-1×10^{-2} M with a detection limit of 5×10^{-6} M. The electrode was applied for determination of ketamine hydrochloride in pharmaceutical preparations using direct potentiometry. The sensor has also been used to study the interaction of bovine serum albumin (BSA) with ketamine in buffer solution.

There have been reports for the determination of vitamins such as ascorbic acid (vitamin C) biotin (vitamin H), pyridoxine hydrochloride (vitamin B_6) and thiamine hydrochloride (vitamin B_1) by potentiometric techniques with various membrane electrodes. In 1999, Ahmed *et al*. reported ion selective electrode for determination of a thiamine derivative sulbutiamine [17]. The membrane electrodes were based on molybdate, tetraphenylborate, reineckate, phosphotungstate, phosphomolybdate as ion-pairing agents.

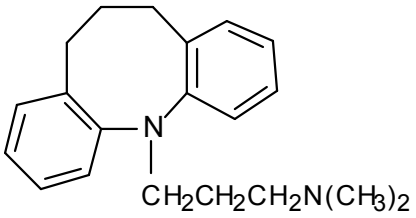
Mostafa *et al*. described two novel potentiometric membrane electrodes responsive to the pyridoxine hydrochloride vitamin B_6 [18]. These sensors were based on the use of the ion-association complexes of the pyridoxine cation with molybdophosphate and tungstophosphate counter anions as ion pairs in a plasticized PVC matrix. The electrodes showed a stable, near-Nernstian response for 6.0×10^{-5}–1×10^{-2} M with a cationic slope of 54.0±0.5 and 54.5±0.4 mV/decade for pyridoxine-molybdophosphate and pyridoxine-tungstophosphate, respectively.

Polymeric membranes sensors have been developed for determination of different classes of antibiotics.

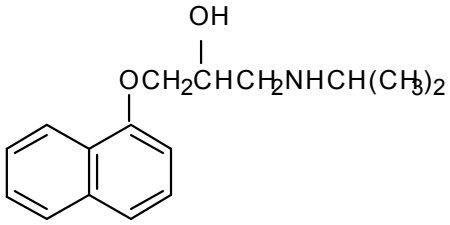
There has been report of ion-selective electrodes sensitive to penicillins (ampicillin, benzyl penicillin, oxacillin, penicilin V) which were based on the use of quaternary ammonium, phosphonium, or arsonium ions as the exchange sites. In the subsequent years Kulapina *et al.* [19] reported improved ion-selective electrodes with plasticized membranes based on ion pairs formed by tetradecylammonium and benzylpenicillin, ampicillin, or oxacillin were proposed. The procedures were also developed for determining various penicillins in pharmaceutical forms and biological fluids.



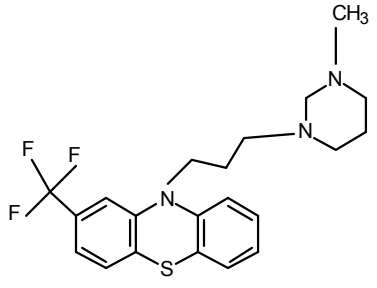
Amitriptyline



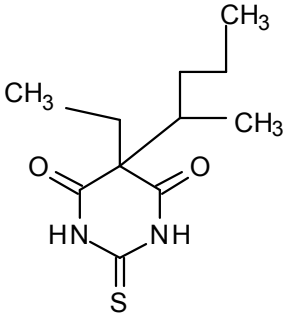
Propranol



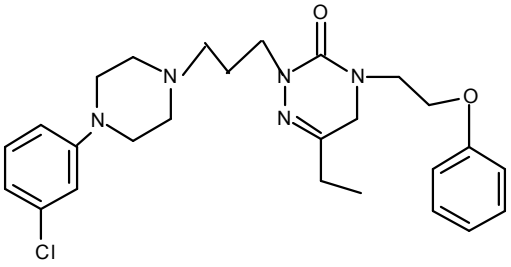
Imipramine



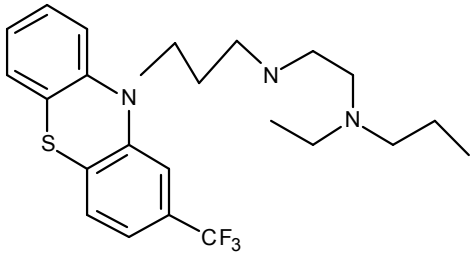
Trifluoperazine hydrochloride



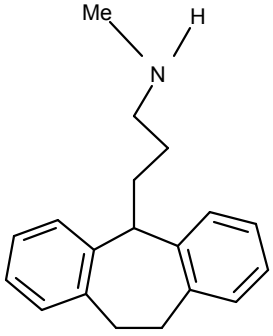
Thiopental



Nefazodone

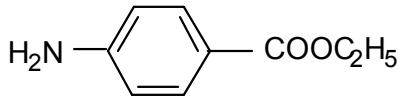


Fluphenazine hydrochloride

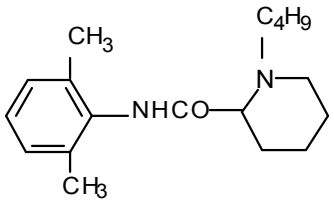


Nortriptyline hydrochloride

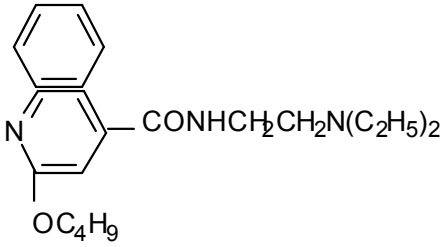
Fig. 3: Structures of various antidepressants



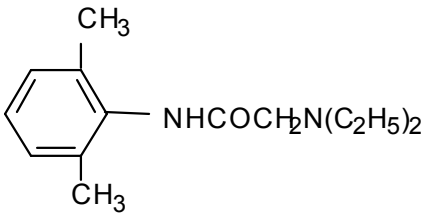
Benzocaine



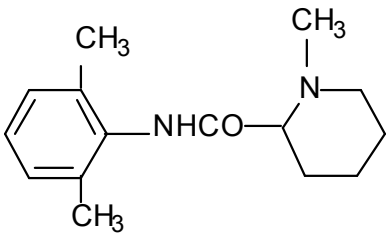
Bupivacaine



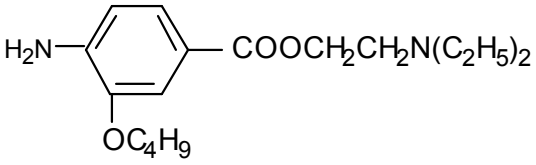
Dibucaine



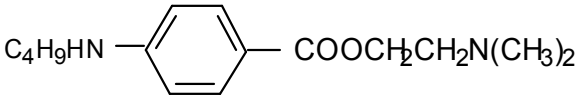
Lidocaine



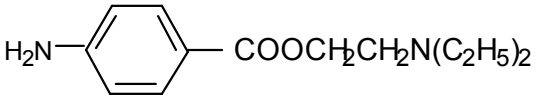
Mepivacaine



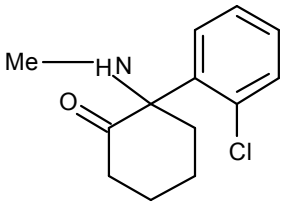
Oxybuprocaine



Tetracaine

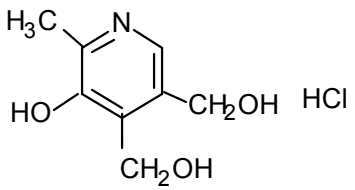


Procaine

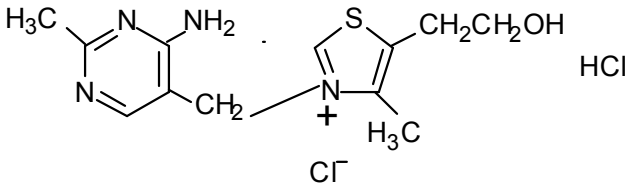


Ketamine hydrochloride

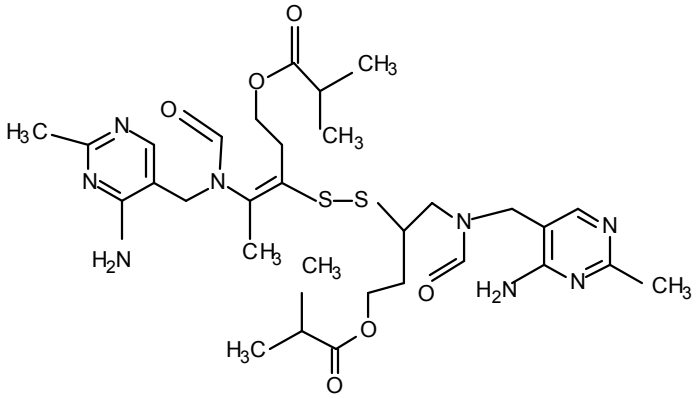
Fig. 4: Structures of various anesthetics



Pyridoxine hydrochloride

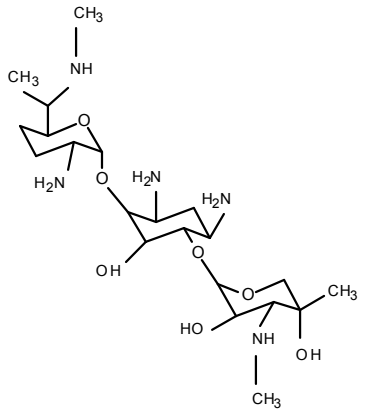


Thiamine hydrochloride

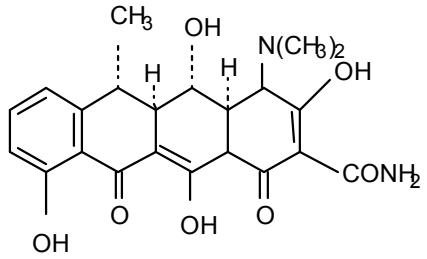


Sulbutiamine

Fig. 5: Structures of various vitamins

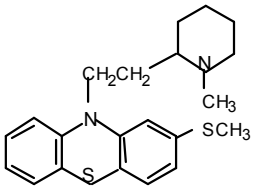


Gentamycin

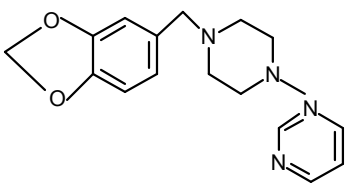


Doxyciline

Fig. 7 Structures of Gentamycins and related antibiotics



Chlorpromazine



Thioridazine

Piribedil

Fig. 9: Structures of various phenothiazine derivatives

Shvedene and co-workers also reported ion-selective electrodes for antibiotics from the penicillin series [20], with membranes based on three different classes of ionophores (anion exchangers, aza compounds and metal phthalocyanines). The proposed ISEs were suitable for the quantitative determination of benzylpenicillin, oxacillin and ampicillin in pharmaceutical preparations.

A variety of gentamycins were quantified by potentiometric membrane sensors. Kulapina and co-workers reported ion-selective electrodes with plasticized membranes based on ion pairs of gentamycin and kanamycin [21] with tetraphenylborate and acid chrome black. The electrodes exhibited excellent Nernstain response. The electrodes were successfully used for determination of aminoglycoside antibiotics in pharmaceutical dosage forms, serum and saliva from patients with infectious pathologies.

Recently, ion-selective electrode for the determination of macrolide antibiotic azithromycin [22] has also been reported. The electrode was constructed by incorporating the azithromycin-tetraiodomercurate ion pair complex into PVC matrix. The sensor exhibited good linear response over the concentration range 1.0×10^{-2} -7.0×10^{-6} M with Nernstian slope.

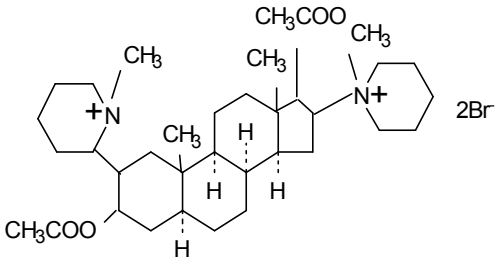
Phenothiazine derivatives are compounds with well known neuroleptic activity. Some of the most widely used antipsychotic drug thioridazine was determined by potentiometric electrodes. Issa and coworkers reported PVC based membrane sensor for antipsychotic drug piribedil [23] doped with piribedil-tetraphenylborate (PD-TPB) as electroactive component. The sensor displayed a linear response over the concentration range 2.0×10^{-5} M with Nernstain slope 30mV/decade. Piribedil was determined in tablets as well as in biological fluids with this sensor.

Aubeck *et al*. reported ion-selective membrane electrodes for the peripheral muscle relaxants. Ibrahim and coworkers reported four PVC membrane electrodes for the determination of mebeverine hydrochloride (MvCl) [24]. The membranes of these electrodes consist of mebeverinium-silicotungstate (Mv-ST), silicomolybdate (Mv-SM), phosphotungstate (Mv-PT), or phosphomolybdate (Mv-PM) ion-associations dispersed in PVC matrix with dibutyl phthalate plasticizer. The electrodes showed near-Nernstian response over the concentration range of 4.0×10^{-6}-1.0×10^{-2} M MvCl and were applied to the potentiometric determination of mebeverinium ion in pharmaceutical preparations, serum and urine. Bouklouze *et al*. reported three types of polymeric electrodes for determination of tizanidine [25]. The electrodes exhibited a Nernstian response in the concentration range 5×10^{-6}-1×10^{-2} M with a slope between 55 and 57 mV/ decade.

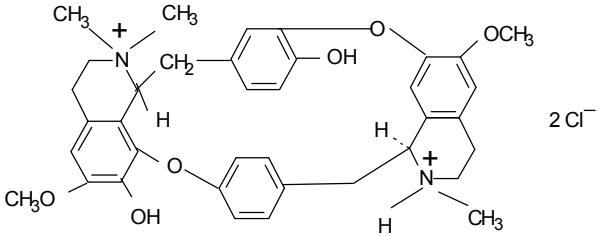
Khormosh and coworkers reported rapid and low-cost potentiometric method for diclofenac determination in urine samples and pharmaceuticals [26]. The electrode was constructed by incorporating the diclofenac ion pair complex with rhodamine 6G. The electrode exhibited a Nernstian slope of 59±2 mV/decade. In recent years, polymeric membrane electrodes have been reported for the determination of antihistamines like hydroxyzine and cetrizine dihydrochloride, triprolidine hydrochloride.

Shamsipur *et al*. described potentiometric membrane sensor for quantification of anti-histamine cimetidine [27]. The electrode incorporates PVC-membrane with cimetidine–phospohotungstate ion pair complex and exhibited a Nernstian response for cimetidine in the concentration range of 1.0×10^{-5}–1.0×10^{-2} M with a slope of 58±1 mV per decade. The limit of detection is 5.0×10^{-6} M. The electrode displays a good selectivity for cimetidine with respect to a number of common inorganic and organic species and can be used to determine cimetidine in its tablets as well as its recovery from a urine sample. Ghoreishi *et al.* reported ketotifen (KET)–selective electrode of both conventional polymer membrane and coated graphite types, based on incorporation of ketotifen-tetraphenyl borate (KETTPB) ion-pair [28]. The electrode showed a Nernstian response in the concentration range of 1.0×10^{-5} to 1.0×10^{-2} M and 5.0×10^{-6} to1.0×10^{-2} M with a slope of 57.5±1.07 and 59.0±0.9 mV/decade and lower limit of detection 1.0×10^{-5} M and 5.0×10^{-6} M for conventional and coated graphite types, respectively. The electrode was successfully used for determination of ketotifen both in pure solution and in pharmaceutical preparation.

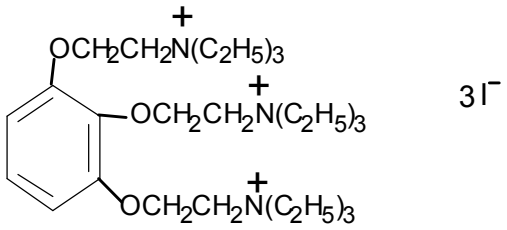
New ion-selective electrodes have been developed for determination of some antiepileptic drugs such as lamotrigine, felbamate and primidone in their pharmaceutical preparations as well as in biological fluids [29]. The electrodes were based on poly (vinyl chloride) membranes doped with drug–tetraphenyl 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.



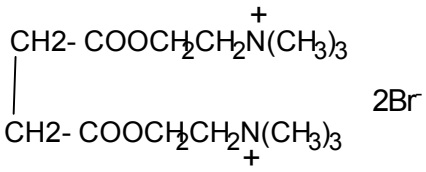
Pancuronium bromide



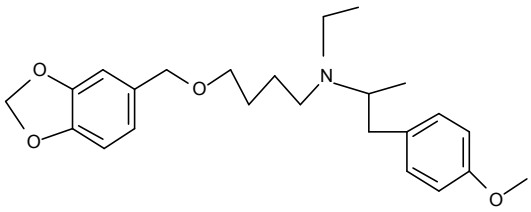
Tubocurarine chloride



Gallamine triethiodide



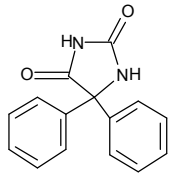
Succinylcholine bromide



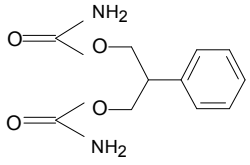
Mebeverine hydrochloride

Fig. 10: Structures of various muscle relaxants

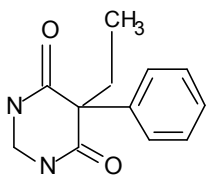
Recently El-Tohamy *et al*. described potentiometreic membrane electrode for determination of phenytoin sodium [30] based on two types of electrodes plastic membrane I and coated wire II. The electrodes were based on the incorporation of phenytoin sodium with tungstosiliic acid. The electrodes showed a Nernstian response with a mean calibration graph slope of 30.9±0.1 and 28.9±0.1 mV decade-1 at 25°C for electrode I and II respectively, over a phenytoin sodium concentration range of 510^{-3}-5×10^{-6} M and 1×10^{-3}- 1×10^{-6} M with a detection limit of 1.3×10^{-6} M and 2.5×10^{-7} M for electrode I and II, respectively. The results obtained by the proposed electrodes were also applied successfully for the determination of the drug in pharmaceutical preparations and biological fluids.



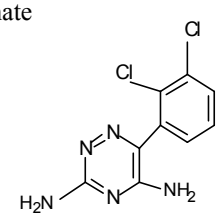
Phenytoin



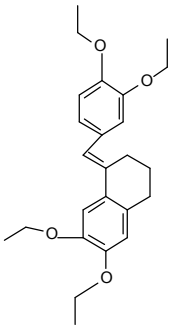
Felbamate



Primidone

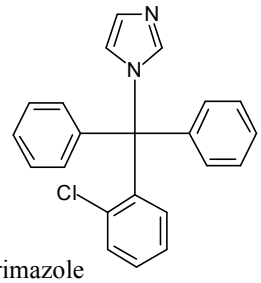


Lamotrigine

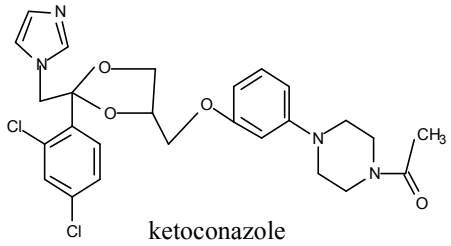


Drotaverine hydrochloride

Fig. 15: Structures of Anti- spasmodics



Clotrimazole



ketoconazole

Fig. 16: Structures of Anti-fungals

El-Sharty *et al*. [31] described poly(vinyl chloride) membrane sensors for the determination of anti-spasmodic drug drotaverine hydrochloride. The sensors were based on the use of the ion association complexes of drotaverine cation with sodium phosphotungestate and ammonium reineckate counter anions as ion exchange sites in the PVC matrix. The performance characteristics of these sensors, revealed a fast, stable and linear response for drotaverine over the concentration range 10^{-5} to 10^{-2} M with cationic slopes of 49.5 and 51.3 mV/decade. The sensors were used for determination of drotaverine hydrochloride in tablets, in its mixture with caffeine, paracetamol and in plasma.

The fabrication and analytical applications of two types of potentiometric sensors for the determination of antifungal drug ketoconazole (KET) have been reported [32]. The polymer membrane and carbon paste sensors were based on the use of KET-molybdophosphoric acid (MPA) ion pair as electro-active material. Both sensors showed a linear and near Nernstian slope of 57.8 mV/decade and 55.2 mV/decade for PVC membrane and carbon paste sensors, respectively over a relatively wide concentration range. The proposed sensors were successfully applied for the determination of KET in pharmaceutical formulations.

A novel clotrimazole ion selective membrane electrode has been reported [33]. The electrode incorporates PVC membrane with clotrimazole-phosphomolybdate ion pair complex. The electrode exhibited a Nernstian response for clotrimazole in the concentration range 1.3×10^{-5}-1.0×10^{-3} M with a slope of 59±2 mV decade^{-1}. The limit of detection is 1.0×10^{-5} M. The membrane sensor was successfully applied to the determination of clotrimazole in its tablets and creams as well as its recovery from a urine sample.

Miscellaneous Potentiometric Sensors: The construction and characterization of potentiometric membrane electrodes have been described for the quantification of benign prostatic hyperplasia (BPH) drug alfuzosin hydrochloride [34]. The membranes of these electrodes consist of alfuzosin hydrochloride-tetraphenyl borate, (Az-TPB), chlorophenyl borate (Az-ClPB) and phosphotungstate (Az_3-PT) ion associations as molecular recognition reagent dispersed in PVC matrix. The performance characteristics of these electrodes, revealed a fast, stable and linear response for alfuzosin 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.

Saber *et al*. [35] reported the potentiometric determination of anti-atherosclerosis drug clopidogrel. The measurments are based on tetrakis (p-chlorophenyl) borate-clopidogrel ion-pair as an electroactive material incorporated a plasticized PVC membrane with *o*-nitrophenyl octyl ether. The sensor exhibited fast and stable Nernstian response for clopidogrel over the concentration range of 1.0×10^{-5}-1.0×10^{-2}M. The sensor displayed reasonable selectivity towards clopidogrel hydrogen sulphate in presence of many cations, drug excipients and diluents.

Pandey and coworkers reported potentiometric sensing device for quantitative estimation of creatinine [36]. The polyaniline modified electrode is developed by electropolymerization of aniline based on sweeping the electrode potential with respect to Ag/AgCl in

non-aqueous medium. Five poly(vinyl chloride) matrix membrane sensors responsive to some β-blockers (atenolol, bisoprolol, metoprolol, propranolol and timolol) have been reported by Arvand and coworkers [37]. The sensors were based on the use of the ion-association complexes of the β-blocker cations with tungstophosphate anion as electro-active materials. The sensors were used for direct potentiometry of β-blockers in some pharmaceutical preparations.

Katsu and coworkers reported determination of anti-arrhythmic drug mexiletine**.** The electrode was based on crownether 4'4''(5'')-ditert-butylcyclohexano-18-crown-6 and ion exchanger sodiumtetrakis [3,5-bis(2-methoxy-hexafluoro-2-propyl)phenyl] borate [38]. The sensor showed detection limit up to 30 μM and 3 μM, respectively. The sensor showed good selectivity against inorganic cations and successfully applied for determination of the level of mexiletine in saliva.

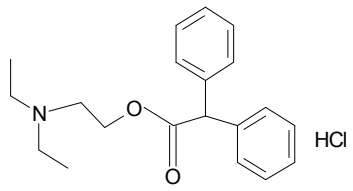
Saad *et al*. reported paraquat selective sensors based on sodiumtetrakis [3,5-bis(trifluoromethyl)phenyl] borate (NTB) and tetrakis (4-chlorophenylborate) (KtpClPB) as an ion-exchangers [39]. These sensors displayed distinct advantages for depicting resistance to fouling by surfactants as well as applied in various water samples. Othman and coworkers developed potentiometric sensors based on the formation of the complex ion-associates of sildenafil citrate with tetraphenyl borate (sc-TPB) and phosphomolybidic acid (sc-PMA) as ionophores in PVC matrix. Both sensors showed a linear and stable potential response with a near Nernstian slope of 55.5 and 53.5 mV/decade over a wide concentration range up to 10^{-2}-10^{-5} M with good reproducibility. The sensors were also applied for the analysis of this drug in pharmaceutical preparations and blood serum [40]. Peng *et al*. described membrane electrode based on fentanyl-phosphotungstate ion-association complex in PVC matrix [41]. The sensor showed linear response for 1.0×10^{-5}-1.0×10^{-2} M drug with a slope of 55.9 mV/decade. The electrode had been successfully applied to determine fentanyl citrate in injections.

Aubeck *et al*. reported the comparison of ion-selective poly(vinyl chloride) liquid membrane electrodes for the determination of pyrantel (PY) based on four different ion-pairing agents, *viz*., tetraphenylborate (TPB), dipicrylaminate (DIPIC), reineckate (REINE) and tungstosilicate (SIWO) [42]. The four electrodes showed similar detection limits of 1-2 μg ml^{-1} and nearly the same linear ranges of $1\times10^{-5}\geq10^{-2}$ mol l^{-1} for pyrantel in 100 nM sodium phosphate-buffered solutions of pH 7.0. Significant differences between the electrodes were observed in protein-containing solutions.

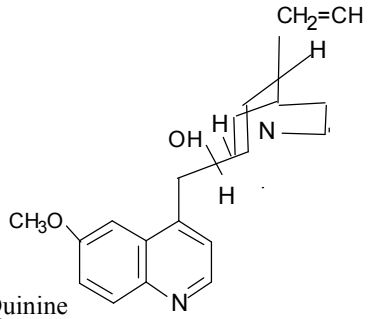
Ganjali and coworkers described potentiometric membrane electrode for determination of calcium channel blockers diltiazem [43]. The sensor comprised of diltiazem-tetraphenylborate (DTM-TPB) complexes as electroactive material and displayed wide linear range 1.0×10^{-5}-1.0×10^{-1} M and low detection limit (3.2 μg/ml). The sensor was successfully applied for determination of diltiazem hydrochloride in pharmaceutical formulations and urine. Recently Ganjali *et al*. described PVC membrane sensor for the decongestant drug phenylpropanolamine (PPA) [44]. The sensor was fabricated using phenylpropanolamine tetraphenylborate ion-pair as an electro-active material in the plasticized PVC membrane. This electrode illustrated a fast, stable and Nernstian response (55.9±0.4 mV/decade across a relatively wide phenylpropanolamine concentration range (1×10^{-5} to 1×10^{-2} M). The sensor has been successfully applied for the quality control analysis of phenylpropanolamine hydrochloride in pharmaceutical formulation and urine.

A new potentiometric sensor has been reported for anti-diuretic amiloride by Ensafi and coworkers [45]. The sensor having amiloride-sodium tetraphenyl phthalate (ion-pair) as an electroactive material and exhibits suitable response to amiloride in a concentration range of 1.0×10^{-2} - 1.0×10^{-6} mol L^{-1} with a limit of detection of 9.9×10^{-7} mol L^{-1}. The sensor was successfully applied to determination of amiloride in pharmaceutical samples with satisfactory results. Ganjali and coworkers reported potentiometric liquid membrane sensor for simple and fast determination of anti-parkinson's drug memantine in pharmaceutical formulation and urine [46]. Computational studies were performed electronically and geometrically on memantine and tetraphenylborate before and after complex formation. The sensor exhibited wide linear range (10^{-5}-10^{-2} mol L^{-1}), low detection limit (9.0×10^{-6} mol L^{-1}).

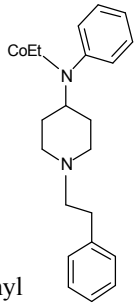
Belal *et al*. reported three polyvinylchloride (PVC) membrane sensors for the determination of orally active non-sulfhydryl angiotensin-converting enzyme (ACE) inhibitor moexipril hydrochloride [47]. The sensors are based on the use of the ion-association complexes of moexipril cation with either ammonium reineckate (sensor1) or tetraphenyl borate (sensor 2) or phosphotungistic acid (sensor 3) counter anions as ion exchange sites in the PVC matrix. The performance characteristics of these sensors reveal a fast, stable and linear response for moexipril over the concentration range of 10-6 to 10-2 M for the three sensors with cationic slopes of 29.1, 30.1 and 30.2 mV per concentration decade for the three sensors, respectively.



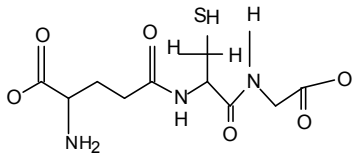
Adiphenine hydrochloride



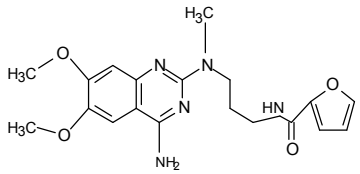
Quinine



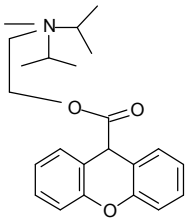
Fentanyl



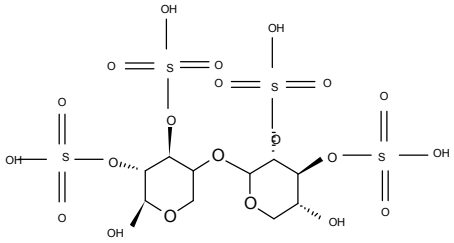
Glutathione



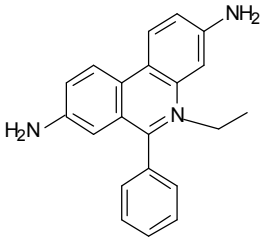
Alfuzosin



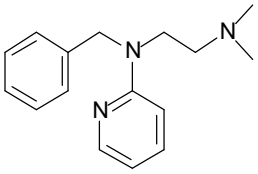
Propantheline bromide



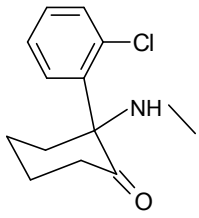
Pentosan sulphate



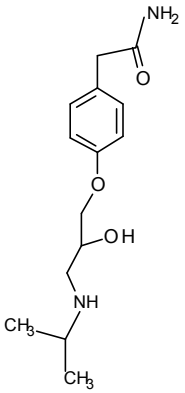
Neostigmine bromide



Tripelenamine



Ketamine



Atenolol

Fig. 16: Structures of some miscellaneous drugs

CONCLUSION

In recent years, the well-established field of potentiometric sensors has undergone a quiet revolution that did not go unnoticed in the general analytical chemistry community. This review is targeted at the general analytical chemist, in ion-selective electrode (ISE) development, for whom a variety of reviews and specialized articles have already appeared in recent years. This is compilation of the drug based potentiometric sensors and their future directions will be predicted.

Future Directions: The last few years have witnessed significant activity in understanding the principles of potentiometric sensors and in finding protocols and examples of successful improvements. Because of this, perhaps, a novice in the field may seem somewhat overwhelmed by the various choices. It will therefore be crucial to see a unified, simplified approach to producing potentiometric sensors with lower limit of detection, rapid response time, sufficient chemical ruggedness and long lifetime, so that they become widely accepted in a range of applications. Recent developments towards this goal have been very promising. Improvements will be made to enhance the sensitivity of such sensors. This will alleviate the need for robust, accurate reference electrodes, although the response will then be based on kinetic, rather than thermodynamic, principles. Advances in this direction have recently been realized with instrumentally controlled membranes in double- or triple-pulse experiments, where defined current and potential pulses are imposed on the measuring cell for accurate control.

ACKNOWLEDGEMENT

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