Chapter 1

Introduction

Analytical chemistry deals with methods for determining the chemical composition of the samples of matter. A qualitative method yields information about the atomic or molecular species or the functional group that exist in the sample; a quantitative method, in contrast, provides numerical information as to the relative amount of one or more of these components. Chemical analysis is the resolution of a chemical compound into its proximate or ultimate parts; the determination of its elements or the foreign substances it may contain. This definition outlines the broad scope of analytical chemistry. There is an escalating need and desire for us to monitor all aspects of our environment in real time and it has been brought about by our increasing concern with pollution, our health and safety. There is always a desire to determine contaminants and analytes at lower and lower levels and one could say that the aim of all modern analytical chemistry is to lower the detection limits and to improve the accuracy and precision of those methods. There are a number of methods available for the determination of chemical composition of the various species such as titrimetry, absorption/emission spectroscopy, thermal methods etc. Electroanalytical method is yet another technique developed for trace level analysis. Of the different electroanalytical techniques, development of sensors is a promising field and getting wider attention now a days. Sensors can be categorized into

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two general groups. They are physical sensors, which are sensitive to such physical responses as temperature, pressure, magnetic field and force and these do not have a chemical interface. Then there are the chemical sensors which rely on a particular chemical reaction for their response.

Chemical analysis has especially become important in industrial processes, hospitals, geological surveys etc; appropriate choice of the method of chemical analysis is very important. Important factors which must be taken into account when selecting an appropriate method for analysis include, the nature of information sought, size of sample available, proportion of constituent to be determined and purpose for which analytical data is required. Chemical analysis may be proximate analysis, partial analysis, trace constituent analysis and complete analysis with respect to the information which is furnished. On the basis of sample size, analytical methods are classified as macro, meso, micro, submicro and ultramicro.

1.1 Common techniques

The main techniques employed in quantitative analysis are based upon quantitative performance of suitable chemical reactions, appropriate electrical measurements and measurement of certain optical properties. In some cases a combination of optical or electrical measurements and quantitative chemical reaction may be used.

The quantitative execution of chemical reactions is the basis of traditional or classical methods of chemical analysis: gravimetry, titrimetry and volumetry. In gravimetry the substance being determined is converted into an insoluble precipitate which is collected and weighed; in the special case of electrogravimetry, electrolysis is carried out and the material
deposited on one of the electrodes is weighed. Volumetry and titrimetry involves measuring the volume of gas or solution involved in a chemical reaction\(^4\). The need for trace level analysis led to the development of chromatography, spectrophotometry and electroanalysis. Chromatography is a separation process employed for the separation of mixtures of substances. It is widely used for the identification of components of mixtures. It is often possible to make quantitative determination particularly when using gas chromatography and high performance liquid chromatography. In spectrophotometric analysis, a source of radiation is used that extends to the ultraviolet region of the spectrum. The fundamental law that governs spectrophotometry is the Beer's law. Atomic absorption spectroscopy (AAS), atomic fluorescence spectroscopy (AFS), flame emission spectroscopy (FES) and inductively coupled plasma (ICP) make use of absorption/emission spectroscopy\(^5\). Electroanalytical technique has become relevant due to its lower detection limits. Electroanalysis is often compared with atomic absorption spectroscopy (AAS) or its modern version, inductively coupled plasma (ICP). Unlike AAS and ICP, the electrochemical approach when applied to solution samples, will give a rapid answer without digestion, as to the labile fraction of a given element in a particular oxidation state and the experiment can be performed on-site in the field.

Electroanalysis can be defined as the application of electrochemistry to solve real life problems\(^6\). The principal criterion of an electroanalytical technique is that the species which is desired to be measured should react directly (or indirectly through coupled reaction) at, or be adsorbed onto the electrode. Electroanalytical measurements can only be carried out in situations in which the medium between the two electrodes making up the
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Electrical circuits be sufficiently conducting. Electroanalytical measurements offer a number of important potential benefits:

(i) selectivity and specificity
(ii) selectivity resulting from choice of material
(iii) high sensitivity and low detection limits
(iv) possibility of giving results in real time or close to real time
(v) application as miniaturized sensors in situations where other sensors may not be usable.

1.2 Types of electroanalysis

There are essentially three types of electro analytical measurements that can be performed:

(i) Conductimetry: The concentration of charge is obtained through measurement of solution resistance. The method is therefore not species selective. It is useful in situations where it is necessary to ascertain whether the total ion concentration is below a certain permissible maximum level or for use as an on-line detector after separation of a mixture of ions by ion chromatography.

(ii) Potentiometry: It is the procedure of using a single measurement of electrode potential to determine the concentration of an ionic species in solution. The electrode whose potential is dependent upon the concentration of the ion to be determined is termed as the indicator electrode and the case where the ion to be determined is directly involved in the reaction, it is an electrode of the first kind. When the concentration of the ion to be
determined is not directly concerned in the electrode reaction, it is an electrode of the second kind. The measurement is made at effectively zero current. The current paths between the electrodes can be highly resistive. By judicious choice of electrode material, the selectivity of the response to one particular ion can be increased, in some cases with very minimal interference in the measured potential from other ions. Such electrodes are known as ion selective electrodes. Detection limits of the order of 100 nanomolecules per litre of the total concentration of the ion present in a particular oxidation state can be achieved. It is possible to measure 100 picomolar differences in concentration.

(iii) Amperometry and Voltammetry: In amperometry, a fixed potential is applied to the electrode, which causes the species to be determined to react and a current to pass. If this potential is conveniently chosen, then the magnitude of current is directly proportional to the concentration. Detection limits in the micromolar region can be obtained.

Voltammetry is concerned with the study of current-voltage-time relationships during electrolysis carried out in a cell. The technique commonly involves studying the influence of changes in applied voltage on the current flowing in the cell, but in some circumstances, the variation of current with time may be investigated. Using this technique several species which react at different applied potentials can be determined almost simultaneously in the same experiment without the need of any previous separation step. Very low detection limits of down to
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Picomolar concentrations can be reached using state-of-the-art instrumentation and preconcentration of the analyte on the electrode surface.

1.3 Electrochemical sensors

An overview of development of analytical chemistry demonstrates that electrochemical sensors represent the most rapidly growing class of chemical sensors. A chemical sensor can be defined as a device that provides continuous information about its environment. Ideally, a chemical sensor provides a certain type of response directly related to the quantity of a specific chemical species. All chemical sensors consist of a transducer, which transforms the response into a detectable signal on modern instrumentation and a chemically selective layer, which isolates the response of the analyte from its immediate environment. They can be classified according to the property to be determined as: electrical, optical, mass and thermal sensors and they are designed to detect an analyte in the gaseous, liquid or solid state.

Compared to optical, mass and thermal sensors, electrochemical sensors are especially attractive because of their remarkable detectability, experimental simplicity and low cost. They have a leading position among the presently available sensors that have reached the commercial stage and which have found a vast range of applications in the fields of clinical, industrial, environmental and agricultural analyses.

Potentiometric sensors are a type of electrochemical sensors. Potentiometric sensors have found the most widespread practical applicability since the early 1930s due to their simplicity, familiarity and
cost. There are three types of potentiometric devices: ion selective electrodes (ISEs), coated wire electrodes (CWEs) and field effect transistors (FETs).

1.4 ISEs

ISEs are classified as potentiometric sensors since some selective chemistry takes place at the surface of the electrode producing an interfacial potential. Species recognition is achieved with a potentiometric chemical sensor through a chemical equilibrium reaction at the sensor surface. Thus the surface must contain a component which will react chemically and reversibly with the analyte. This is achieved by using ion selective membranes which make up the sensor surface.

Most analytical sensors are electrodes of the 2\textsuperscript{nd} kind. As with all electrodes that are not metal - metal ion electrode of the 1\textsuperscript{st} kind [$\text{M/M+}$], speed of response and reversibility is of critical importance for accuracy and reproducibility of measurements. In fact the issue of reversibility and consideration of all electrochemical systems as equilibrium processes was one of the major contributions of Nernst. The Nernst equation describes that a change in potential of an electrochemical system is linear to change in the ion activity (in logarithmic units) of the selected analyte ion.

The development of ion selective electrodes during the last 20 years has quickly been followed by many applications in addition to those in inorganic analysis. The field of applications was broadened by the introduction of liquid ion - exchanger membranes, membranes containing electroneutral macrocyclic compounds, enzyme electrodes and gas sensors\textsuperscript{11-14}. Such new electrode materials facilitated the development of
potentiometric sensors for most of the important inorganic ions and several types of organic compounds, many of which are of ionic character\textsuperscript{15}.

1.5 Classification

There are 4 categories of membranes used in potentiometric chemical sensors.

1) \textit{Glass membranes}: These are selective for ions such as $\text{H}^+$, $\text{Na}^+$ and $\text{NH}_4^+$. Glass membranes have a very high electrical resistance in the $\Omega$ range; however they must conduct ionic charge to some extent in order to be able to make measurements with them. When a glass membrane is put in water, a charge separation process occurs across the glass / $\text{H}_2\text{O}$ interface giving rise to an electrical potential difference; the magnitude of which depends on the position of the equilibrium which in turn depends on the number of hydrogen ions in the aqueous solution originally.

2) \textit{Sparingly soluble inorganic salt membrane}: This type consists of a section of a single crystal of an inorganic salt such as $\text{LaF}_3$ or a pressed powdered disc of an inorganic salt or mixtures of salts such as $\text{Ag}_2\text{S}/\text{AgCl}$. Such membranes are selective for ions such as $\text{F}^-$, $\text{S}^2-$ and $\text{Cl}^-$. Three types of sensor membranes employing sparingly soluble inorganic salts are known. They are

a) Single crystal membranes.

b) Pressed powder membranes.

c) Membranes where the powdered salt is held together by an inert binder. (usually a polymer.)
3) **Polymer immobilized ionophore membranes**: In these an ion-selective complexing agent or an ion exchanger is immobilized in a plastic matrix such as poly (vinyl chloride).

Ion selective electrodes are classified according to the physical state of the substances forming the electrode membrane, or possibly according to the nature of the substances affecting ion exchange in the membrane\textsuperscript{16-18}.

(i) **Ion selective electrodes with solid membranes**: The membrane can either be homogeneous (a single crystal, a crystalline substance or a glass which is considered to be a solid with regard to the immobility of the anionic groups) or heterogeneous where a crystalline substance is built into a matrix made from a suitable polymer.

(ii) **Ion selective electrodes with liquid membranes**: In this case the electrode membrane is represented by a water immiscible liquid, in which a dissolved substance capable of exchanging the ion in the solution for which the electrode is selective. This substance is either an associate of this ion with an oppositely charged ion, soluble in the membrane or it is a complex of the ion for which the electrode is selective.

Selective sensors have been used for analytical determination of a wide variety of ions since the 1900s.

4) **Gel-immobilized and chemically bonded enzyme membranes**: These membranes use the highly specific reactions catalysed by enzymes. The enzyme is incorporated into a matrix or bonded onto to a solid substrate surface.
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1.6 Potentiometric sensors

Potentiometric chemical sensors make use of the development of an electrical potential at the surface of a solid material when it is placed in a solution containing ions which can exchange with the surface. The magnitude of the potential is related to the number of ions in solution. There occurs a charge separation across the interface which gives rise to an electrical potential difference. In potentiometry, it is said that the measurement of cell potential is made under a zero current condition.

Ion-selective electrodes (ISEs) are the chemical sensors with longest history and probably the most frequent routine application. James Ross and Martin Frant of Orion Research are the founding fathers of ISEs. The calcium and fluoride ISEs they developed in the mid 1960s were the big bang that started a new era in potentiometric analysis.

The common glass electrode for pH measurement is an example of a potentiometric sensor and has been known for more than 80 years, well before the development of the so called new breed of ion selective electrodes such as the fluorides in 1960s. The membrane in a pH electrode is essentially a sodium silicate glass made by fusing a mixture of Al₂O₃, Na₂O and SiO₂. Increasing the amount of Al₂O₃ in the glass leads to an increasing response to other monovalent cations such as Na⁺, K⁺ and Li⁺. The selectivity of glass electrodes to alkali metal ions was systematically studied by Eisenman et al. In all cases however, the glass membrane also responds to pH.

Liquid membrane containing a dissolved ion exchanger was first used by Sollner and Shean. In 1961, the first ISE with precipitate containing heterogeneous membranes were prepared by Pungor and Hallos-Rokosinyi. Compact ion exchange membranes were obtained by Frant and Ross.
Concepts from medicine and physiology also spurred the development of ISEs. In 1964, Cyril Moore and Besston C Pressman observed that neutral macro cyclic antibiotics induce ion permeation in mitochondria, leading to the development of neutral carrier electrodes. Wilhem Simon an eminent organic chemist, used extracts of poisonous mushrooms containing the dipsipetide valinomycin dissolved in a liquid ion exchanger membrane. Although the response was slow, an electrode that measured the $K^+$ in the presence of a 5000 fold excess of $Na^+$ was soon developed and patented. His studies on the structure selectivity relationships of many synthetic ionophores, plasticizers and additives allowed him to fabricate ISEs\textsuperscript{29}.

In 1966, it was discovered that a slice of a single crystal of lanthanum fluoride attached to the end of an electrode barrel could be used to sense the fluoride ion in aqueous solution\textsuperscript{30}. In 1967, a liquid membrane ion selective electrode was produced for the first time, which provided the means for direct determination of the activity of calcium ions in solution. This was of great importance in the biological and chemical sciences because of the importance of calcium in biological fluids\textsuperscript{31}. The most significant advance in liquid membrane electrodes, other than the original discovery occurred in 1970 when it was shown that organic liquid of the liquid membrane ion selective electrode could be immobilized into poly (vinyl chloride) to produce a polymer film with sensing properties for calcium, as good as, if not better than, the liquid membrane itself. The use of PVC to make sensor membranes originated from the laboratory of Prof. J.D.R. Thomas\textsuperscript{32}.

In an effort to miniaturize the sensor and to avoid using internal filling solution, the coated wire electrode was developed in 1971. The response of coated wire electrode is similar to that of classical ISE, with
regard to detectability and range of concentration. The great advantage is that
the design eliminates the need for an internal reference electrode, resulting in
the benefits during miniaturization. This is particularly useful for the in vivo
and in vitro biomedical and clinical monitoring of different kind of
analytes. Pungor and his co-workers developed an iodide ion selective
electrode by incorporating finely dispersed silver iodide into a silicone
rubber monomer and then carrying out polymerization. An enzyme ISE
for amygdalin has also been proposed. The electrode contains a cyanide
solid state electrode coated with an acryl-amide gel containing β-
glucosidase. Ruzika et al introduced liquid state electrode based on
carbon in 1970. In 1973, Mesaric and Dahmen developed sensors using
spectral grade graphite powder, nujol and metal salts of low solubility in a
plastic body. In 1980, Heineman et al, first described the use of polymer
film chemically modified carbon paste electrode.

Carbon paste electrodes (CPEs) belong to a group of heterogenous
carbon electrodes. CPEs are represented by carbon paste, ie, a mixture
prepared from graphite powder and a suitable liquid binder packed into a
suitably designed electrode body. Due to numerous advantages, properties
and characteristics, these electrodes are widely used for potentiometry,
voltammetry, amperometry and coulometry. Adams, the inventor of CPEs
and his research group were the first to publish an extensive study on carbon
pastes comprising numerous test measurements. Their investigations
have been primarily focused on the characterization of CPEs with respect to
their applicability in anodic and cathodic voltammetry. A study of Farsang
can be regarded as a pioneering attempt to optimize the carbon paste
composition via the chemical structure of the binder by observing the
behaviour of several CPEs prepared from silicone oils with different molecular weight. Lindquist\textsuperscript{53} carried out a systematical comparison of the properties of carbon pastes when investigating mainly the effect of liquid binders with respect to their content in the paste mixture.

Various online monitoring systems have benefited from the inherent specificity, wide scope, dynamic behaviour and simplicity of potentiometric sensors\textsuperscript{54}. They have become widely used as detectors in high speed automated flow analyzers such as air segmented\textsuperscript{55,56} and flow injection systems\textsuperscript{57}. In addition, the coupling of modern ion chromatography with potentiometric detection has been with significant success\textsuperscript{58}. Miniaturization of ISE has also permitted their use as on-column detectors for capillary electrophoresis\textsuperscript{59}.

Rohwedder \textit{et al}\textsuperscript{60} and Fatibello and co-workers\textsuperscript{61-64} have shown the use of coated graphite epoxy ISE for determination of cations using ion pair formation with tricaprylmethylammonium cation in a PVC matrix. Rover \textit{et al} have described the construction of tubular ISE useful for the determination of saccharin\textsuperscript{65}. The construction and application of ISEs applied for the determination of pharmaceutical compounds such as acetyl salicylic acid and vitamin B6 have also been described\textsuperscript{66}.

1.7 Performance factors

Some critical issues that will arise with all ion selective sensors are detection limits, linear measurement range and selectivity over interfering ions. In addition, the operational pH, temperature and pressure limits of the sensor greatly determine its use in real world industrial and laboratory
Applications. Another very important criterion for utility of any given sensor is the expected life time under constant use.

1.7.1 Slope (Response) of the electrode

The slope also called the response of the electrode is the main characteristic of the potentiometric sensors. The value of the slope is given by Nernst: \( \frac{59.16}{z} \text{ mV decade}^{-1} \) of concentration, where \( z \) is the charge of the ion that has to be determined. The value can be deducted from Nernst equation. Nernstian response implies ideal sensitivity. The slope is dependent upon the stability of the compound formed at membrane solution interface.

1.7.2 Linear concentration range

The linear concentration range represents the range of concentration of a substance (or ion) over which sensitivity of the electrode is constant within a specified variation usually \( \pm 5\% \). The reproducibility of the linear range is connected with the working conditions of the electrode such as pH, composition of the solution, history and pre conditioning of the electrode and temperature.

1.7.3 pH range

The pH plays a very important role in the response of the potentiometric sensors. It can influence the formation of protonated and unprotonated species of the same substance, it can favour the redox processes at the electrode or the electrode can become pH selective under certain conditions.
1.7.4 Response time

IUPAC defined the response time as the time which elapses between the instant when the electrodes are brought into contact with a sample solution and the first instant at which the slope of the working electrode becomes equal to a limiting value selected on the basis of the experimental conditions and/or requirements concerning accuracy\textsuperscript{71}. For ISE the response time depends on concentration as well as on the stability of the compound formed between the ion that has to be determined and the ligand at the membrane solution interface.

1.7.5 Selectivity

Selectivity is one of the basic characteristics of the electrochemical sensors. It depends on the composition of the membrane, ratio between the activities of the main and interfering ion in solution, complexity of the matrix sample that is analyzed, current applied and pH of the solution. The selectivity of an ion pair based sensor depends on the physico-chemical characteristics of the ion exchange process at the sensor – sample solution interface and the mobility of the respective ions in the sensor\textsuperscript{72}.

1.7.6 Shelf life or Life time

Life time may be defined as the storage or operational time for the sensitivity of the sensor to decrease by a factor of 10\% to 50\%, within the concentration range\textsuperscript{73}. The lifetime of a sensor refers to the period of time during which the sensor can be used for the determination of the analyte and it is determined by the stability of the selective material.
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1.8 A brief review on potentiometric sensors for drugs

Quality assurance plays a central role in determining the safety and efficiency of medicines. Highly specific and sensitive analytical techniques hold the key to the design, development, standardization and quality control of medicinal products. Modern physical methods of analysis are extremely sensitive, providing precise and detailed information from small samples of material. They are for the most part rapidly applied and in general are readily amenable for automation.

ISEs have found many successful applications in pharmaceutical analysis mainly because of their low cost, ease of use and maintenance and the simplicity and the speed of assay procedures. It is usually possible to develop procedures for the determination of drugs in pharmaceutical preparations that need only a pre-dilution step with a suitable buffer (eg; injection preparations) or dissolution of tablets in the measuring solvent. Turbidity due to tablet matrix is not usually a problem so that even the filtration step can be avoided.

The vast majority of solvent polymeric ISEs for organic ions that have been reported so far are ionophore free ion-exchanger electrodes but a considerable number of ionophore based ISEs for organic analytes have also been described. Cationic organic analytes that have been measured with ionophore based ISEs are 1-phenyl ethyl amine, ephedrine, norephedrine, amphetamine, dopamine, amino acid amides, benzyl amine, mexiletine, local anesthetics (procaine, prilocaine, lidocaine, bupivacaine, lignocaine), imipramine, desipramine, trimipramine diquat and paraquat (herbicides), guanidine, metformin, phenformin, creatinine, protamine and the condensates of a Girard reagent with glucose or other aldehydes. Anionic
analytes that were detected with ionophore based ISEs are acetate, nucleotides, heparin salicylate, phthalate, maleate and a number of other carboxylates.

While a number of these ISEs were used to measure analytes in relatively uncomplicated samples such as drug capsules and tablets, a few of them were also tested for use in more complex matrices. Examples are the measurement of acetate in vinegar, salicylate in urine and blood serum, phenyl pyruvate in urine, benzoate in blood serum, glucose in human blood upon reaction of the analyte with a Girard reagent and protamine and heparin in blood samples.

Magda et al. were successful in developing two new potentiometric methods for the determination of famotidine. The famotidine selective membrane sensor was based on the use of the ion association formed between famotidine and tetraphenyl borate. The sensor exhibited a linear response in the range $10^{-3} - 10^{-5}$ M.

Amodiaquine polymeric membrane sensors were developed by Kauffmann et al. The sensing components were composed of the ion association formed between the drug and sodium tetraphenyl borate or tetrakis (4-chlorophenyl) borate. The sensors gave a near Nernstian response over the pH range 3.7 and 5.5. The sensors were successfully applied for the determination of amodiaquine in pharmaceutical dosage forms.

A conventional polymer membrane, graphite coated and carbon paste electrode for triprolidine was prepared by S.I.M. Zayed. The sensors incorporated triprolidine-sodium tetraphenyl borate ion pair as the electro active material. It exhibited a fairly wide pH range of 4.70 - 8.75. The sensors showed very good selectivity for triprolidine.
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A mexiletine selective membrane electrode based on the crown ether 4', 4", (5')-di-tert-butyldicyclohexano-18-crown-6 showing the highest sensitivity and a detection limit of 30 µM has been reported. The sensor was successfully employed for the determination of mexiletine in saliva.

Khalil et al were successful in fabricating a membrane sensor for phenothiazine. The electroactive materials were either phenothiazine drug - tetraphenyl borate or phenothiazine drug - naphthalene sulphonate ion pairs. The electrodes exhibited useful analytical characteristics for the direct or indirect determination of phenothiazine drugs in pure form or in pharmaceutical preparations.

The ion pair complexes formed between fluphenazine hydrochloride and nortriptyline hydrochloride with sodium tetraphenyl borate or tetrakis (4-chlorophenyl) borate were used for the fabrication of the sensors for these drugs. These sensors gave Nernstian slopes over the concentration range $10^{-2}$ to $10^{-5}$ M. These sensors were used for the determination of the corresponding drugs in pharmaceutical dosage forms and in presence of their degradates.

Liquid membrane ion selective electrodes with the ion association complexes of novocaine with tetraphenyl borate or dipicrylamines were proposed for use in the determination of novocaine by Cosofret et al. The developed sensors gave a linear response in the range $10^{-1}$ - $10^{-5}$ M.

The scopolamine sensor developed by G.A.E. Mostafa was based on the ion association of the drug with phosphotungstic acid. The sensor gave a stable near Nernstian response for $10^{-2}$ - $10^{-6}$ M scopolamine over the pH range 3-7. The direct determination of scopolamine in some formulations...
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gave results that compare favourably with those obtained by the USP method\textsuperscript{100}.

Two novel potentiometric PVC membrane sensors responsive to pyridoxine hydrochloride were reported. These sensors have the ion associations of the drug formed with molybdophosphoric acid or tungstophosphoric acid as the electroactive material. The developed sensors had a lower detection limit of $4 \times 10^{-5}$ M and a fast response time of nearly 35 - 45s and was selective to pyridoxine over a number of interfering ions. The determination of pyridoxine in some pharmaceutical preparations using the proposed sensors gave satisfactory results comparable with BP method\textsuperscript{101}.

Rizk et al developed polyurethane sensors for thiopental on solid graphite support. The electroactive materials of thiopental with Cu (II) and Co (II) bathophenanthroline were dispersed in a polyurethane matrix. The sensors showed a fast response time, low detection limit and a long life time. The sensors were used for the direct potentiometry of thiopental in pharmaceutical formulation and human serum\textsuperscript{102}.

A ketoconazole membrane sensor was developed based on an ion association of ketoconazole with sodium tetraphenyl borate. The sensor gave a Nernstian slope within the concentration range $10^{-3}$ – $10^{-6}$ M. The developed sensor was used to evaluate the equilibrium constants of $\alpha$ and $\beta$ cyclodextrin ketoconazole complexes in addition to its use in the determination of ketoconazole in pharmaceutical preparations and biological fluids\textsuperscript{103}.

Wen and co-workers reported a pethidine selective membrane sensor based on the ion association of the drug with silicotungstic acid. The
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electrode had a detection limit as low as $9.91 \times 10^{-7}$ mol/dm$^3$. The sensor could be used for the determination of pethidine in tablets and injections$^{104}$.

Enein and his co-workers used the ion association formed with silicotungstic acid for the determination of propranolol in pharmaceutical formulations. It had a short conditioning time of three hours and a fast response time$^{105}$.

A potentiometric sensor immobilized in a graphite matrix for the determination of diclofenac was reported by Pezza and his group. Studies on the determination of diclofenac in pharmaceutical formulations, especially tablet dosage formulations and injectable ampoules were carried out to illustrate the feasibility of the proposed sensor$^{106}$.

S. S. M. Hassan and his group explored the use of 5,10,15,20-tetraphenylporphyrinato indium (III) as ionophore in fabrication of a sensor for ibuprofen in a PVC and polyurethane matrix. The sensors were found to be useful for the quantification and quality control assessment of ibuprofen in pharmaceutical preparations$^{107}$.

Enein and his group studied the response of a PVC membrane sensor for methacycline based on methacycline - tetraphenyl borate as the electroactive material. The membrane could be used for the determination of methacycline in tablets and the results agreed well with pharmacopoeia method$^{108}$.

A new oxymetazoline ion selective PVC membrane electrode based on oxymetazoline - phosphotungstate ion association as the ionophore was reported. It had a fairly wide pH range of 1.0 - 9.4. The electrode was used for the determination of oxymetazoline in nasal drops$^{109}$.
Shamsipur's group developed a clotrimazole selective membrane sensor based on clotrimazole - phosphomolybdate ion pair complex. The electrode gave a Nernstian response and displayed a good selectivity for clotrimazole. The membrane sensor was successfully applied to the determination of clotrimazole in tablets and creams\textsuperscript{110}.

Ozsoz and his group published their results of polymeric membrane sensors for antidepressant nefazodone based on its ion pair complex with phosphotungstate, tetraphenyl borate, silicotungstate and reinckate. The best results were obtained with nefazodone - phosphotungstate and the sensor was used for the determination of the drug in pure solutions\textsuperscript{111}.

A potentiometric sensor immobilized in a graphite matrix for the determination of p-aminobenzoate in pharmaceutical formulations has been reported. It had a greater lifetime of over six months\textsuperscript{112}.

A clotrimazole - triiodide ion pair was used for the fabrication of triiodide selective sensor. The sensor gave a super Nernstian response. It was however used as an indicator electrode in the potentiometric titration of triiodide ions and indirect potentiometric determination of clotrimazole in pharmaceutical preparations\textsuperscript{113}.

G.A.E. Mostafa reported a metoclopramide selective membrane sensor incorporating metoclopramide - tetr.aiodomercurate as the ionophore. The membrane sensor showed a stable near Nernstian response. The determination of metoclopramide in tablets, injection and syrup using the sensor gave very good response\textsuperscript{114}.

The group of Salem developed solid contact ion selective electrodes for bromazepam, clonazepam and 1, 4-benzodizepines. The electrodes were
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based on PVC membranes doped with the drug - phosphotungstic acid ion pair complexes as electroactive materials. The electrodes were applied for the determination of the drugs in pharmaceutical preparations\textsuperscript{115}.

Construction and characterization of potentiometric membrane sensors for quantification of diclofenac and warfarin drugs have been described by S. S. M. Hassan \textit{et al}. The membrane sensors incorporated iron (II) phthalocyanin as a molecular recognition reagent. The sensor was applied to the determination of these drugs in dosage forms\textsuperscript{116}.

Shamsipur and co-workers reported a diclofenac selective membrane sensor having diclofenac - hexadecyl pyridinium bromide as the ionophore. The sensor was applied for the determination of diclofenac in tablets and also for its recovery from blood serum and urine samples\textsuperscript{117}.

Moghimi \textit{et al} reported a potentiometric sensor immobilized in a graphite matrix for the determination of picrate ion. The electrode was successfully applied to the potentiometric determination of picrate ions and indirect determination of some pharmaceuticals such as quinidine, through precipitation reaction with quinidines\textsuperscript{118}.

Ghoreshi and his group fabricated both conventional and coated graphite type electrodes for the determination of naphazoline based on naphazoline - tetraphenyl borate ion pair. Both the sensors gave Nernstian slopes and were used for the determination of naphazoline in pure state and in pharmaceutical preparations\textsuperscript{119}.

Pedreno \textit{et al} discussed several plasticized membranes for the determination of some multi drug resistance reversers. PVC membranes were doped with tetrabutyl ammonium tetraphenyl borate. The proposed sensor
was applied for the determination of chlorpromazine, clomipramine, imipramine, desipramine and verapamil in pharmaceutical preparations\textsuperscript{120}.

Ibrahim and his group discussed a carbon paste electrode for dicyclomine hydrochloride. The electrode was based on a mixture of two ion exchangers namely dicyclominium phosphomolybdate and dicyclominium tetraphenyl borate as the electroactive material. The sensors were applied for the determination of dicyclomine hydrochloride in tablets and biological fluids\textsuperscript{121}.

Badawy \textit{et al} fabricated a hydralazine ion selective PVC membrane electrode based on hydralazinium tetraphenyl borate as the electroactive material. The electrode was successfully applied for the determination of hydralazine in pure form and in pharmaceutical preparations\textsuperscript{122}.

The PVC membrane sensor for diphenhydramine reported by Badawy and his group used diphenhydramine - tetraphenyl borate ion pair. Diphenhydramine in pure solutions and in anti histamine syrups could be determined using the proposed sensor\textsuperscript{123}.

Cosofret \textit{et al} reported a membrane sensor for amantadine which was successfully used for the determination of the drug in pharmaceutical formulations\textsuperscript{124}.

Vire \textit{et al} conducted a comparative study of three polymeric membrane electrodes for tizanidine. The electrodes gave Nernstian response and were applied for the determination of tizanidine in tablet form\textsuperscript{125}.

Montenegro and his group fabricated quinidine ion selective electrode without inner reference solution based on quinidine tetrakis (4-
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chlorophenyl) borate as the ion exchanger. Quinidine in pharmaceutical preparations could be determined using the proposed sensor\textsuperscript{126}.

The group of Hampp reported ion selective PVC membrane sensor for muscle relaxants pancuronium, tubocurarinio, gallamine and succinyl choline based on two different counter ions dipicrylaminate and tetraphenyl borate\textsuperscript{127}.

Enein and his co workers explored the response characteristics of an amiodarone selective membrane sensor based on amiodarone - dipicryl amine ion pair complex. It exhibited a detection limit of $4 \times 10^{-9}$ M. Though ephedrine and polyvinylprolidone interfered, it was found to be useful for the determination of amiodarone in dosage forms such as tablets and ampoules\textsuperscript{128}.

Khalil and Aliem successfully estimated the benazepril hydrochloride content in pure form and in pharmaceutical preparations. They employed a coated wire benazepril selective electrode based on the incorporation of benazepril - tetraphenyl borate ion pair in a PVC coated membrane. It had a wide usable pH range of 2.5 – 9.2\textsuperscript{129}.

The group of S.S.M. Hassan explored the response characteristics of PVC membrane sensors for some β-blockers such as atenolol, bisoprolol, metoprolol, propranolol and timolol. The electroactive materials for these sensors were the ion association complexes of the respective β-blockers with phosphotungstic acid. Validation of the method according to the quality assurance standards showed the suitability of the proposed sensors for use in the quality control assessment of these drugs. The determination of these β-
Kharitonov was successful in fabricating an ion selective membrane electrode based on tridecylmethyl ammonium chloride with ethylenediaminetetraacetate anion selective to bismuth (III). These electrodes were useful for direct potentiometric monitoring of bismuth (III) in stomach antiacids. The sensor exhibited a very good selectivity for [Bi (EDTA)] over a variety of complex metal ions with EDTA\textsuperscript{131}.

M. B. Saleh et al explored the possibility of using [4-(4'-nitrobenzyl)-1-phenyl-3,5-pyrazolidinedion] as an ionophore for the fabrication of PVC membrane sensor for the determination of cerium (III) ions. It had a fast response time of $< 10$ s. The proposed sensor was used successfully as an indicator electrode in potentiometric titration of phosphate, oxalate in aqueous media and carbonate, fluoride acetylsalicylate in some drugs\textsuperscript{132}.

A PVC membrane sensor selective to cimetidine with cimetidine-phosphotungstate ion pair complex as the ionophore has been reported. It gave a Nernstian slope and could be successfully applied to the determination of cimetidine in tablets and for its recovery from urine sample\textsuperscript{133}.

The construction and performance characteristics of four novel PVC membrane sensors responsive to cinnarizinium cation have been reported. These sensors were based on the use of ion association complexes of cinnarizinium cation with tetraphenyl borate, flavinate, reineckate and molybdophosphate counter anions as ion exchange sites in a plasticized PVC matrix. The sensors proved useful in determining cinnarizine in various dosage forms, in monitoring tablet dissolution rates and in testing tablet uniformity\textsuperscript{134}.
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In an attempt to detect illicit drugs and stimulants using ISEs, the group of Watanabe, fabricated a cocaine selective membrane electrode using sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate as ion exchanger. They used tetrakis(2-ethylhexyl)pyromellitate as solvent mediator to suppress the response to lipophilic quarternary ammonium ions and strengthened the response to cocaine. The electrode was applied for the determination of cocaine in a drug mixture containing cocaine and morphine which is widely used to suppress pain in cancer patients\textsuperscript{135}.

Drozd and Hopkala published their results of polymeric membrane electrodes for cyproheptadine hydrochloride. They are based on the use of cyproheptadine-tetrakis(4-chlorophenyl) borate and cyproheptadine-dipicrylamine as electroactive compound. The electrode was successfully applied for the determination of cyproheptadine in bulk substance and tablets\textsuperscript{136}.

A potentiometric sensor immobilized in a graphite matrix has been reported for the determination of diclofenac. The electrode gave a Nernstian slope and was used in the determination of diclofenac in pharmaceutical preparations\textsuperscript{137}.

Katsu and Mori discussed a disopyramide sensitive membrane electrode for determining free disopyramide levels in blood serum. The sensor incorporated sodium tetrakis[3,5-bis(2-methoxyhexafluoro-2-propyl)phenyl]borate as the ion exchanger. None of the similar antiarrhythmic drugs except bretylium interfered\textsuperscript{138}.

An internal solid contact sensor for the determination of doxycycline hydrochloride was developed based on a conducting polypyrrole film
immobilized on a glassy carbon electrode surface coated by a plasticized PVC membrane. The ion pair of the drug with tetraphenyl borate was used as the electroactive material. The sensor was successfully applied for the determination of the drug in pharmaceutical formulations\textsuperscript{139}.

The group of S. S. M. Hassan explored the response characteristics of PVC matrix membrane sensors for fluorouracil. The sensors incorporate ion association complexes of fluorouracil with bathophenanthroline nickel (II), bathophenanthroline iron (II) and phenanthroline iron (II) as electroactive materials. The sensors were used for the direct determination of fluorouracil in pharmaceutical preparations. They were also used to follow the stability of the drug in the presence of its degradates namely formaldehyde, fluoroacetate and urea\textsuperscript{140}.

A flurbiprofen sensor based on tricaprylmethyl ammonium chloride has been reported. The sensor was applied for the determination of dissolution profile of flurbiprofen\textsuperscript{141}.

Shehata \textit{et al} constructed four glutathione selective electrodes with different techniques and in different polymeric matrices. The developed sensors were used in the determination of glutathione in pharmaceutical preparations as well as for its recovery from plasma\textsuperscript{142}.

Alizadeh \textit{et al} developed an ion selective membrane electrode for ketamine hydrochloride which had ionic end groups as ion exchanger sites. The electrode gave a perfect Nemstian slope. In addition to its use in the determination of the drug from pharmaceutical preparations, it was also used to study the interaction of bovine serum albumin with ketamine\textsuperscript{143}.
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Sadeghi and his group constructed a potentiometric sensor based on a molecularly imprinted polymer for the recognition and determination of levamisole hydrochloride. It had a longer life span of four months and was used for the determination of levamisole in pure and tablet forms\textsuperscript{144}.

Hassan and his co-workers developed potentiometric, spectrofluorimetric and spectrophotometric methods for metformin determination. The ion association for the drug was obtained with reinckate and tungstosilicate\textsuperscript{145}.

Stefan employed lauryl sulphate as the counter ion for the construction of ion selective electrodes for moclobemide and disopyramide\textsuperscript{146}.

Katsu \textit{et al} fabricated a PVC membrane sensor responsive to a stimulant phentermine. They employed sodium tetrakis[3,5-bis(2-methoxyhexafluoro-2-propyl)phenyl]borate as the ion exchanger. This electrode was applied to determine phentermine in ion exchange complexes containing this stimulant\textsuperscript{147}.

Khalil \textit{et al} constructed a plasticized membrane electrode selective to prazosinium cation based on prazosinium phosphotungstate ion association. The sensor was found to be useful in determining the prazosin content in pure solution and in pharmaceutical preparations\textsuperscript{148}.

The prenalterol selective membrane sensor reported by the group of Khalil was based on an ion association of the drug with sodium tetraphenyl borate. The determination of prenalterol in pure form and in pharmaceutical formulations was achieved by the developed sensor\textsuperscript{149}. 

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The piroxicam and tenoxicam selective membrane sensor fabricated by Khalil and his group proved to be useful in the determination of the active ingredient in their respective pharmaceutical formulations. The electroactive materials were based on the ion pair complexes of the drug with aliquot 336S cation.

Shoukry and co workers developed PVC membrane sensors for the determination of reproterol hydrochloride based on ion associates of the drug with phosphotungstic acid, phosphomolybdic acid and a mixture of both; which proved to be useful for the determination of the drug in its pharmaceutical preparations.

The five different potentiometric sensors developed for sulbutiamine by Ahmed et al were useful for the determination of the drug in micro gram quantities. The ion pairs were based on phosphotungstic acid, molybdate, tetraphenyl borate, reinckate and phosphomolybdate.

Wang and his co workers immobilized heptakis(2,6-di-O-isobutyl)-β-cyclodextrin in a PVC matrix to fabricate a sensor selective to tetracycline.

Theophylline sensor reported by Shamsipur’s group was based on 2,6-bis(phenyl)-4-(phenyl)-3-H-thiopyran ionophore. The membrane sensor was successfully applied to the determination of theophylline in tablets.

Solid state valproate ion selective sensor based on conducting polypyrrole films was fabricated for the determination of valproate in pharmaceutical preparations. It had a long life span of 4 months.

Shahawi reported ion selective membrane electrodes for sildenafil citrate. The sensors were based on the formation of the complex ion associates of sildenafil citrate with tetraphenyl borate or phosphomolybdic...
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acid. The proposed sensors were tested for the analysis of sildenafil citrate in pure form, pharmaceutical preparations and blood serum\textsuperscript{156}.

The group of Sanchez Pedreno in 2007 reported the construction of a PVC membrane sensor for tiapride. The sensor incorporates an ion association of the drug with tetraphenyl borate. The sensor exhibited a fast, stable, Nernstian response over a wide concentration range $1 \times 10^{-5} - 1 \times 10^{-2}$ M with a slope of 57.2 mV/decade. The developed sensor was applied for the determination of tiapride in human urine and iontophoresis solution\textsuperscript{157}.

Zholt Khornosh and his co-workers in 2007 reported a diclofenac selective membrane sensor for the drug based on the ion associate of the drug with rhodamine B. The potentiometric response characteristics of the sensor based on the ion association in different plasticizers were extensively studied. The sensor exhibited a linear response within the diclofenac concentration range $1 \times 10^{-5} - 5 \times 10^{-2}$ M and a slope of 60 mV/decade\textsuperscript{158}.

H. Y. A. Enein et al were successful in developing a pethidine selective PVC membrane sensor based on the ion association of the drug with phosphomolybdate. It exhibited a near Nernstian response of 55.24 mV/decade over the concentration range $1 \times 10^{-5} - 1 \times 10^{-2}$ M. The useful pH range has been observed to be 2 - 7. The developed sensor has been found to be useful for the determination of the drug in pure form, pharmaceutical formulations and in biological fluids\textsuperscript{159}.

1.9 Scope of the present investigations

The quality of a drug is determined after establishing its authenticity by testing its purity and quality of the pure substance in the drug and its
formulations. A number of methods including physical, chemical, physico-chemical and biological ones are employed for determining the quality of the drugs. Among the physico-chemical methods, the electrochemical is the most widely used one. In continuation to the development of spectrophotometric\textsuperscript{160-164} and electrochemical methods\textsuperscript{165-168} for the determination of drugs in our laboratories, the present investigations involve the preparation of potentiometric sensors for drugs such as mebendazole, pefloxacin, ambroxol, sildenafil citrate, dextromethorphan and tetracycline. For all the sensors fabricated, the various analytical parameters studied include linear response range, calibration slope, detection limit, effect of pH, shelf life and selectivity. The developed sensors have been applied for the determination of the drugs in pharmaceutical formulations and in real samples.