Analytical Chemistry is the study of the chemical composition of natural and artificial materials. It is a sub discipline of chemistry that has the broad mission of understanding the chemical composition of all matter and developing the tools to elucidate such compositions. This differs from other sub disciplines of chemistry in that it is not intended to understand the physical basis for the observed chemistry as with physical chemistry and it is not intended to control or direct chemistry as is often the case in organic chemistry and it is not necessarily intended to provide engineering tactics as are often used in material science. Analytical chemistry generally does not attempt to use chemistry or understand its basis; however, these are common outgrowths of analytical chemistry research. It has a significant overlap with other branches of chemistry, especially those that are focused on a certain broad class of chemicals, such as organic chemistry, inorganic chemistry or biochemistry, as opposed to a particular way of understanding chemistry, such as theoretical chemistry. Analytical chemistry is particularly concerned with the questions of "what chemicals are present, what are their characteristics and in what quantities are they present?" These questions are often involved in questions that are more dynamic such as what chemical reaction an enzyme catalyzes or how fast it does it, or even more dynamic such as what is the transition state of the reaction. Although analytical chemistry addresses these types of questions, it stops after they are answered. The next logical steps of understanding what it
means, how it fits into a larger system, how can this result be generalized into theory or how it can be used are not analytical chemistry. Since analytical chemistry is based on firm experimental evidence and limits itself to some fairly simple questions to the general public it is most closely associated with hard numbers such as how much lead is in drinking water.

Chemical Analysis may be defined as the application of a process or a series of processes in order to identify and/or quantify a substance, the components of a solution or mixture or the determination of structures of chemical compounds. Chemical analysis generally consists of a chain of procedures to quantify and / or identify one or several components in a sample of matter. The needs for improved analytical methods are increasing, especially for compounds with known or possible effects on human health due to increasing number of environmental pollutants, drugs and their metabolites, and additives used in the food industry.

With increasing demands for pure water, better food control and cleaner atmospheres, the analytical chemist has a greater and greater role to play within modern society. From the study of raw materials such as crude oil and minerals to the finest quality scents and perfumes, the analytical chemist is called upon to play a part in determining composition, purity and quality. Manufacturing industries rely upon both quantitative and qualitative chemical analysis to ensure their raw meet certain specifications and to check the quality of final product. These needs place high demands on the analytical methods employed, which must be efficient, accurate and predominantly automated. Recent advances in instrumentation and the range of detectors available enable analytical scientists to measure and identify target analytes at lower and lower concentrations. Thus the scope of analytical chemistry is
very broad and embraces a wide range of manual, chemical and instrumental
techniques and procedures. The objective and purpose of the analysis has to
be sensibly assessed before selecting an appropriate procedure.

1.1 Different Methods of Analytical Techniques

A qualitative method in analytical chemistry yields information about
the identity of atomic or molecular species or the functional groups in the
sample. Whereas a quantitative method in contrast provides numerical
information as to the relative amount of one or more of these constituents. The main techniques employed in quantitative analysis are based on

(i) The quantitative performance of suitable chemical reactions and
either measuring the amount of reagent needed to complete the
reaction product obtained.

(ii) Appropriate electrical measurements

(iii) The measurement of certain spectroscopic properties

(iv) The characteristic movement of a substance through a defined
medium under controlled conditions.

The quantitative execution of chemical reactions is the basis of the
traditional or classical methods of chemical analysis: gravimetry, titrimetry and
volumetry. In gravimetric analysis the substance being determined is converted
into an insoluble precipitate which is collected and weighed. In
electrogravimetry, electrolysis is carried out and the material deposited on one
of the electrodes is weighed. Some common techniques record a parameter as a
function of temperature or time. Thermogravimetry records the change in
weight, differential thermal analysis record the difference in temperature
between the test substance and an inert reference material. Differential
scanning calorimetry records the energy needed to establish a zero temperature difference between a test substance and a reference material.

The titrimetric analysis is carried out by determining the volume of a solution of accurately known concentration which is required to react quantitatively with a measured volume of a solution of the substance to be determined. Volumetry measures the volume of a gas evolved or absorbed in a chemical reaction.

Spectroscopic methods of analysis depend on measuring the amount of radiant energy of a particular wavelength absorbed by the sample, or measuring the amount of radiant energy of a particular wavelength emitted by the sample. Atomic absorption spectroscopy (AAS), atomic fluorescence spectroscopy (AFS), flame emission spectroscopy (FES) and inductively coupled plasma (ICP) make use of absorption/emission spectroscopy\(^4\). Chromatography encompasses a diverse and important group of methods that permit the scientist to separate closely related components of complex mixtures when many of these separations are impossible by other means\(^5\).

Electroanalytical chemistry encompasses a group of quantitative analytical methods that are based upon the electrical properties of a solution of the analyte when it is made a part of an electrochemical cell\(^6\). These techniques are capable of producing exceptionally low detection limits and a wealth of characterization information describing electrochemically addressable systems. Electrochemical techniques are powerful and versatile analytical techniques that offer high sensitivity, accuracy, and precision as well as a large linear dynamic range. Electroanalytical measurements offer a number of important benefits\(^7\):
(a) selectivity and specificity
(b) selectivity resulting from the choice of electrode material
(c) high sensitivity and low detection limit
(d) possibility of furnishing results in real time or close to real time
(e) application as miniaturized sensors where other sensors may not be useful

Electrochemical measurements are two-dimensional, with the potential being related to qualitative properties (with thermodynamic or kinetic control) and the current related to quantitative properties (controlled either by mass transport process or reaction rates). Thus, compounds can be selectively detected by electrochemical methods. The principal criterion for electroanalytical measurements 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 electrical circuit is sufficiently conducting.

1.2 Classification of Electroanalytical Techniques

Electroanalytical Techniques can be in general classified into three types. They are:

(1) Conductimetry
(2) Potentiometry
(3) Amperometry and voltammetry
1.2.1 Conductimetry:

Here the concentration of charge is obtained through measurement of solution resistance. This is therefore not species selective. It is useful when the total ion concentration is below a certain permissible maximum level or for use as an on-line detector after separation of mixture of ions by ion chromatography. Conductimetry measures the conductance of a solution, using inert electrodes, alternating current, and an electrical null circuit, thereby ensures no net current flow and no electrolysis. The concentration of ions in the solution is estimated from the conductance.

1.2.2 Potentiometry:

In potentiometry the measuring set up always consists of two electrodes: the measuring electrode, also known as the indicator electrode, and the reference electrode. Both electrodes are half-cells. When placed in a solution together they produce a certain potential. The equilibrium potential of an indicator electrode is measured against a selected reference electrode using a high impedance voltmeter, i.e. effectively at zero current. Thus the current path between the two electrodes can be highly resistive. Potential-determining transitions always occur at the phase boundaries, e.g. between the solution and the electrode surface. 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 are of the order of 100 nanomoles per litre of the total concentration of the ion present in a particular oxidation state, although down to 10 picomolar differences in concentration can be measured.
1.2.3 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. Depending on the potential that is applied, the magnitude of the current is directly proportional to the concentration. In amperometric titrations, the titrant undergoes reaction at the indicator electrode to produce a current which is proportional to the concentration of the electroactive substance. Detection limits in the micromolar region can be obtained.

The common characteristic of all voltammetric techniques is that they involve the application of a potential \( E \) to an electrode and the monitoring of the resulting current \( i \) flowing through the electrochemical cell. In many cases the applied potential is varied or the current is monitored over a period of time \( t \). Thus, all voltammetric techniques can be described as some function of \( E, i, \) and \( t \). They are considered active techniques (as opposed to passive techniques such as potentiometry) because the applied potential forces a change in the concentration of an electroactive species at the electrode surface by electrochemically reducing or oxidizing it. The analytical advantages of the various voltammetric techniques include excellent sensitivity with a very large useful linear concentration range for both inorganic and organic species \((10^{-12} \text{ to } 10^{-1} \text{ M})\).

1.3 Sensors

A sensor can be defined as something which senses a particular analyte or a substance. It is a device which measures a physical quantity and converts it into a signal which can be read by an observer or by an instrument. Sensors are designed to detect and respond to an analyte in the gaseous, liquid or solid
Sensors can be broadly classified into physical sensor and chemical sensor.

Physical sensors are sensitive to such physical responses as temperature, pressure, magnetic field, force and these do not have a chemical interface. Chemical sensors rely on a particular chemical reaction for their response.

A chemical sensor is a device which responds to a particular analyte in a selective way through a chemical reaction and can be used for the qualitative or quantitative determination of the analyte\(^\text{10}\). A useful definition for a chemical sensor is a small device that as the result of a chemical interaction or process between the analyte and the sensor device, transforms chemical or biochemical information of a quantitative or qualitative type into an analytically useful signal. The role of the chemical sensor is to provide information about the chemical state of the process and one can say that the chemical sensor is the "eye" of the process control system. Chemical sensors can also provide essential information about the chemical state of our environment. There are two parts to a chemical sensor - a region where selective chemistry takes place and the transducer.

### 1.4 Types of Chemical Sensors

Chemical sensors are categorized into the following groups depending on the transducer type

1. Electrochemical
2. Optical
3. Mass sensitive
4. Heat sensitive
1.4.1 Electrochemical Sensors

These include potentiometric sensors (ion selective electrodes, ion selective field effect transistors) and voltammetric/amperometric sensors including solid electrolyte gas sensors. Electrochemical sensors can be applied for solid, liquid, or gaseous analytes with the latter two most common.

1.4.2 Optical Sensors

In optical sensors there is a spectroscopic measurement associated with the chemical reaction. Optical sensors are often referred to as 'optodes' and the use of optical fibres is a common feature. Absorbance, reflectance, and luminescence measurements are used in the different types of optical sensors.

1.4.3 Mass Sensitive Sensors

These make use of the piezoelectric effect and include devices such as the surface acoustic wave sensor and are particularly useful as gas sensors. They rely on a change in mass on the surface of an oscillating crystal which shifts the frequency of oscillation. The extent of the frequency shift is a measure of the amount of material adsorbed on the surface.

1.4.4 Heat Sensitive Sensors

The heat of a chemical reaction involving the analyte is monitored with a transducer such as a thermistor or a platinum thermometer. They are often called calorimetric sensors.

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 important applications in the fields of clinical, industrial, environmental and agricultural analyses\(^\text{12}\).

1.5 Potentiometric Sensors

Potentiometric sensors come under the class of electrochemical sensors. They 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 the solution. The charge separation formed across the interface gives rise to an electrical potential difference. In potentiometric sensors, a local equilibrium is established at the sensor interface, where either the electrode or membrane potential is measured, and information about the composition of a sample is obtained from the potential difference between two electrodes. Potentiometric sensors have found the most widespread practical applicability since the early 1930s, due to their simplicity, familiarity and cost. There are three basic types of potentiometric sensors or devices: ion selective electrodes (ISEs), coated wire electrodes (CWEs) and ion selective field effect transistors (ISFETs).

1.5.1 Ion Selective Electrodes (ISEs)

The ion selective electrode is an indicator electrode capable of selectively measuring the activity of a particular ionic species. In the classic configuration, such electrodes are mainly membrane-based devices, consisting of permselective ion-conducting materials, which separate the sample from the inside of the electrode. One electrode is the working electrode whose potential is determined by its environment. The second electrode is a reference electrode whose potential is fixed by a solution containing the ion of interest at a constant activity. Since the potential of the reference electrode is constant, the value of the
potential difference (cell potential) can be related to the concentration of the dissolved ion. It is related to processes taking place at the membrane interface\textsuperscript{13,14}. 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. In contrast to metal electrodes, an ISE does not measure a redox potential. If the ion to be measured is contained in the sample solution then this ion can penetrate the membrane. This alters the electrochemical properties of the membrane and causes a change in potential. One hundred percent selectivity for exactly one type of ion is only possible on rare occasions. Most ion-selective electrodes have only a particular sensitivity for a special type of ion, but also often react with ions with similar chemical properties or a similar structure.

1.5.2 Coated-Wire Electrodes (CWEs)

CWEs were first introduced in the mid of 1970's by Freiser\textsuperscript{15,16}. In the classical CWE design, a conductor is directly coated with an appropriate ion-selective polymer membrane usually poly (vinyl chloride), poly (vinyl benzyl chloride) or poly (acrylic acid) to form an electrode system that is sensitive to electrolyte concentrations. The CWE response\textsuperscript{17} 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 benefits during miniaturization, for example. This is particularly useful for the in vitro and in vivo biomedical and clinical monitoring of different kind of analytes.
1.5.3 Ion Selective Field Effect Transistors (ISFETs)

Ion selective field effect transistors work as an extension of CWE. ISFET incorporate the ion sensing membrane directly on the gate area of a field effect transistor (FET). The FET is a solid state device that exhibits high input impedance and low output impedance and therefore is capable of monitoring charge buildup on the ion sensing membrane. The construction is based on the technology used to fabricate microelectronic chips\textsuperscript{18-19}, and the great contribution is that it is possible to prepare small multisensor systems with multiple gates, for sensing several ions simultaneously, while their small size permits the in vivo determination of analytes.

There are generally four categories of membranes of ion selective electrode potentiometric sensors. These are:

1.5.1.1 Glass Membrane

The most widely used glass electrode is the pH electrode, which has been used for several decades. Glass membranes have a very high electrical resistance in the MΩ range; however they must conduct ionic charge to some extent in order to be able to make measurements with them. Its success is attributed to a series of undisputed advantages, such as simplicity, rapidity, non destructiveness, low cost, applicability to a wide concentration range and, particularly, to its extremely high selectivity for hydrogen ions. Nevertheless, measurements of pH can also be performed using other types of potentiometric sensors. Application of glass electrodes for other monovalent cations, including sodium, lithium\textsuperscript{20,21}, ammonium and potassium sensors based on new glass compositions, have also been reported\textsuperscript{22}. 
1.5.1.2 *Sparingly Soluble Inorganic Salt Membranes*

This type consists of a section of a single crystal of an inorganic salt such as LaF₃ or a pressed powdered disc of an inorganic salt or mixtures of salts such as Ag₂S/AgCl. Such membranes are selective for ions such as F⁻, S²⁻, and Cl⁻. Three types of sensor membranes employing sparingly soluble inorganic salts are known. They are

(i) Single crystal membranes.
(ii) Pressed powder membranes.
(iii) Membranes where the powdered salt is held together by an inert binder. (usually a polymer.)

1.5.1.3 *Polymer-immobilized Ionophore Membranes*

In these, an ion-selective complexing agent or ion-exchanger is immobilized in a plastic matrix such as poly (vinyl chloride).

1.5.1.4 *Gel-immobilized and Chemically Bonded Enzyme Membranes*

These membranes use the highly specific reactions catalyzed by enzymes. The enzyme is incorporated into a matrix or bonded onto a solid substrate surface.

According to the nature of the substances affecting ion exchange in the membrane²³⁻²⁵, ion selective electrodes can also be classified as (a) ion selective electrodes with solid membranes and (b) ion selective electrodes with liquid membranes.

In ion selective electrodes with solid membranes, the membrane can be either 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.

In the second case, the electrode membrane is represented by a water immiscible liquid, in which is dissolved a 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.

1.6 Potentiometric Ion Selective Electrodes

Ion selective sensors including ion selective membrane electrodes have been becoming one of the effective and powerful means for analytical scientists in the determination of drug substances and are playing an important role in pharmaceutical analysis due to offering advantages of simplicity, rapidity and accuracy over more established pharmaceutical analysis methods. Moreover the interest in developing small sensing devices for biomedical use is growing rapidly. The key problem associated with development of small or miniaturized ion selective sensors used for in vivo assay of drugs and for the determination of drug in a flow system is how to eliminate an internal reference electrode together with the corresponding inner filing electrolyte in the conventional polymeric membrane ion-selective electrodes. The response of most ion-selective electrodes (ISEs) has been described on the basis of the Nicolskii-Eisenman selectivity formalism.

The different independent achievements in the mid-1960s marked the starting point of modern potentiometry. In 1967, Ross described the first membrane electrode based on a liquid ion exchanger. James Ross and Martin Frant of Orion Research are the founding fathers of ISEs. Bloch and
co-workers introduced the first ionophore-based solvent polymeric membrane based on PVC, a matrix still widely used today. At about the same time, Stefanac and Simon discovered that antibiotics inducing selective ion transport through biological membranes also generate a selective potentiometric response in liquid membranes.

Liquid membrane electrode ISE, based on water immiscible liquid substances impregnated in a polymeric membrane, are widely used for direct potentiometric measurements of several polyvalent cations as well as certain anions. The polymeric membrane is used to separate the test solution from the inner compartment containing a solution of the target ion. The membrane-active recognition can be by a liquid ion exchanger or by a neutral macrocyclic compound having molecule-sized dimensions containing cavities to surround the target ions. The construction of a hydrogen ion selective potentiometric electrode based on a tridodecylamine ionophore dispersed in a poly (vinylchloride) membrane, or poly(l-aminoanthracene) films has been described. 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. Rodwedder et al. and Fatibello and co-workers have shown the use of coated graphite epoxy ion selective electrodes for determination of cations using ion-pair formation with tricaprylmethylammonium cation in a PVC matrix. Using a similar system with incorporation of saccharinate anion and toluidine, Rover et al. have described the construction of a tubular ion selective electrode useful for determination of saccharin. Alfaya et al. described a more sensitive system for saccharin determination using a thin film of silsesquioxane 3-n-propylpyridinium chloride polymer coated on a
graphite rod. The successful use of thin film electrodes modified, by nickel(II) hexacyanoferrate, for potassium determination has been described by Stradiotto and co-workers\textsuperscript{50}.

1.7 Solid State Ion Selective Electrodes

Solid electrodes began to be used in electroanalysis about forty years ago\textsuperscript{51}. Solid-state electrodes are miniaturized version of an electrochemical sensor. Solid state membrane electrodes are preferred over liquid membrane electrodes because they can easily be used in all kinds of media which are suitable for environmental analysis, food analysis, clinical analysis as well as for in vivo analysis.

Carbon materials in the form of graphite, glassy carbon, carbon fibres etc are important solid state electrodes for several reasons. This is because carbon has rich surface chemistry, which can be explored to influence reactivity. Also the adsorption on carbon surfaces can be used to enhance analytical utility. Adams, the inventor of CPEs\textsuperscript{52}, and his research group were the first who published an extensive study on carbon pastes comprising numerous test measurements\textsuperscript{53,54}. Carbon paste electrodes (CPEs) belong to a special group of solid state ion selective 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\textsuperscript{55}. The biggest disadvantage of CPEs, which limits their applicability in practical analysis, is that the success in working with carbon-paste based electrodes depends on the experience of the user\textsuperscript{56}.

Mixtures containing merely two main components ie, carbon powder and the liquid binder are commonly classified as unmodified carbon pastes.
The modified graphite paste electrodes represent a class of electrodes with high reliability of the construction and with high potential in accommodation of molecules of different sizes. The base of modified carbon paste is usually a mixture of powered graphite and non electrolytic binder and modifying agent. The composition of modified carbon paste will influence the response characteristics of the designed electrode. Carbon paste based biosensors contain enzyme (or its carrier) together with appropriate mediator. The main advantages of CPEs is that it does not require any internal solution or internal reference electrode. Also the surface of the electrode can be renewed easily.

Thus it is possible to conclude that potentiometric sensors have been important since 1930, when the commercialization of a glass electrode resulted in the foundation of one of the most successful analytical instrument companies (Beckman Instruments). History also shows that, since 1960, when ion-selective electrodes revolutionized the approach to the difficult analysis of inorganic ions, up to now, the growth of patents for different formulations of glass, for different membrane types and for diverse shapes and sizes of electrodes testify to interest in the area. Therefore, there are many commercially available ion-sensing potentiometric devices. These systems tend to be low in cost, simple to use, easily automated for rapid sampling, with low interferences from the matrix, and can be applied to small volumes. These advantages make potentiometric sensors an ideal choice for both clinical and industrial measurements where speed, simplicity, and accuracy are essential.

1.8 Performance Factors of a Potentiometric Ion Selective Electrode

1.8.1 Slope of the Electrode

The slope, S (also called response of the electrode), is the main characteristic of the potentiometric electrodes. The ideal value of the slope is
given by Nernst: $59.16/z \text{ mV/decade of concentration}$, where $z$ is the charge of the ion that has to be determined. This value can be computed from the Nernst equation.

$$E = E^0 \pm \frac{RT}{zF} \log a,$$

where $E$ is the potential of the electrode, $E^0$ is the standard electrode potential, $R = 8.31 \text{ J/mol K}$, $F = 96500 \text{ C}$, $T = 298 \text{ K}$, and $a$ is the activity of the ion. From this equation, the slope of the potentiometric electrode is given by: $S = \frac{RT}{zF}$

Nernstian response implies ideal sensitivity, but not necessarily ideal selectivity since interfering ions may also give Nernstian response when present as the sole potential determining species. The slope is dependent on the stability of the compound formed at the membrane-solution interface. The slope depends on some parameters which characterize the matrix such as polarity of the plasticizer, oil or solvent. The slope of the potentiometric electrodes can be improved by choosing a suitable selector that forms a compound with higher stability or by changing the composition of the matrix.

1.8.2 Limit of Detection

The value of the limit of detection can be deduced from the calibration graph as the concentration defined by the intersection of the extrapolated two linear regions of the curve. Experimental conditions such as composition of the test solution, history of the electrode and stirring rate should be recorded.

1.8.3 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\textsuperscript{61}.

1.8.4 Influence of pH

The pH can influence the formation of protonated and unprotonated species of the same substance. The pH plays a very important role in the response of the potentiometric sensors. Special care must be accorded to the buffering of solutions, because a small difference in pH may cause a significant change in the potential, and that will result in an error in the measurement.

1.8.5 Response Time

IUPAC defined the response time as the time which elapses between the instant when the electrodes of the potentiometric cells are brought into contact with the sample solution (or at which the activity of the ion of interest in solution is changed) 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 the accuracy\textsuperscript{62}. The response time is influenced by the membrane-solution interface processes. The response time increases with decreasing the concentration of the molecule that has to be assayed.

1.8.6 Selectivity

Selectivity is one of the basic characteristics of the electrochemical sensors. It depends on the composition of the membrane (active sites as well as matrix), ratio between the activities of the main ion and interfering ion in the solution, complexity of the matrix of the sample that is analysed, current applied, and the pH of the solution. This property of electrochemical sensors
restricts their utilization for the assay of an ion from a complex matrix. IUPAC defined the interfering substance as any substance, other than the ion being determined, whose presence in the sample solution affects the measured emf of a cell. The degree of selectivity of an electrochemical sensor is given by the value of potentiometric selectivity coefficient.

1.8.7 Life Time or Shelf Life

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 ⁶³. 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.

1.9 Electroanalytical Techniques for Drugs

Electrochemical techniques are well suited for the determination of drugs in various samples, that is, raw material, pharmaceutical dosage forms even those involving a complex matrix such as syrups, tablets, creams, suppositories, or ointments or else in biological fluids. The principal advantage of the modern electrochemical methods is that the excipients do not interfere, and generally the separation and extraction procedure is not necessary. Thus, sample preparation usually consists of dissolving out the active ingredient from the pharmaceutical dosage form with a suitable solvent and performing direct analysis on an aliquot portion of this solution. In addition to the analytical aspect, electrochemistry allows the establishment of the electrochemical behaviour of a given drug through mechanistic studies. This is of particular interest knowledge of the drug. Electrochemical techniques are most suitable to investigate the redox properties of a new drug; this can give insights into its metabolic fate.
Progress in the pharmaceutical industry results in the creation of a great number of drugs including substances of various structures and compositions, differing in their pharmacological action and therapeutic properties. This situation poses a problem of controlling not only the quality of drugs but the content of drugs (and their metabolites) in various media as well, including biological liquids of the human and animal organism, food products, waste waters of pharmaceutical plants, etc. Applications of potentiometry techniques in pharmaceutical analysis and clinical chemistry have been reviewed by Vytras and Granzhan et al. There is a constant increase in the number of electrodes capable of selectively identifying various drugs. The potentiometric determination of drugs can be based on either direct potentiometry or potentiometric titration. The detection is performed with the aid of transducers, sensitive to either inorganic or organic ions, including biosensors. However, the present study is mainly concentrated on the potentiometric methods of drug analysis using ISEs.

The methods for determining drug cations are mostly based on ISE involving associates between the cations and large ions such as tetraphenyl borate (TPB), tris (octylhydroxy) benzenesulfonate (TOBS), molybdophosphate (MPA), and diphenylhydroxyacetate (DHAA). The anions of drugs are determined using electroactive substances with counterions represented by cations of tertiary ammonium bases. For example, benzyldimethylcetylammonium is used for determining antibiotics of the penicillin group and tetraoctylammonium (TOA) is employed for the analysis of 5,5-diethylbarbiturates. In the initial stage of development of drug ionometry, the investigations had a purely applied character. At present, most works are devoted to establishing the factors providing desired modification of the
properties of ion-selective membranes. In this context, interesting results were reported on the effects of the ion association and the character of a plasticizing solvent on the selective properties of counter electrodes for the organic cations of drugs.

If the ion to be determined forms more stable associates than does the interfering ion, the potentiometric selectivity was increased by introducing a considerable amount of a well dissociated ion exchanger salt with a highly hydrophobic cation into the membrane. The counterions in the electroactive substances are mostly represented by heteropolycomplexes between cations of the drugs analyzed and anions of molybdophosphoric (PMo$_{12}$O$_{40}^{3-}$), molybdosilic (SiMo$_{12}$O$_{40}^{4-}$), and molybdotungstogallic (GaMo$_{2}$W$_{10}$O$_{40}^{5-}$) acids. Study of the electrode characteristics depending on the nature of the central atom of a heteropolyanion showed that an increase in the negative charge of the heteropolyanion leads to decreasing sensitivity and selectivity of the electrodes and increasing potential drift. Optimum electrode characteristics were observed for the electrodes based on molybdophosphoric acid. The determination of drugs by the method of direct potentiometry with ISE offers a rapid and simple procedure satisfying all requirements of pharmaceutical analyses.

1.10 A Brief Review on Potentiometric Sensors for Drugs

The control of drug quality is a branch of analytical chemistry that has a wide impact on public health. So the development of reliable, quick and accurate methods for the determination of the active ingredients is welcomed. In recent years, ion selective membrane electrodes have been used more and more in drug quality control, but no pharmacopoeias yet introduced their use for assays, though this will probably be done in the next few years. An
important advantage of ion selective membrane electrodes is that they can in principle, be designed for any ionic species, even for organic ions with complicated structures and high molecular weight\textsuperscript{77-79}. Ion selective electrodes, including ion selective membrane electrodes have been becoming one of the effective and powerful means for analytical scientists in the determination of drug substance and are playing an increasing role in pharmaceutical analysis\textsuperscript{80-82}, due to offering advantages of simplicity, rapidity and accuracy over more established pharmaceutical analysis methods. Most of the ISEs sensitive to medically important ionic compounds such as sulpha drugs\textsuperscript{83}, vitamins\textsuperscript{84} and alkaloids\textsuperscript{85} belong to the class of ion-pair based liquid membrane electrodes.

A liquid membrane electrode based on an amiodarone-dipicrylamine ion-pair complex was developed by Aboul-Enien \textit{et al.} The electrode exhibited a Nernstian slope of 57.3 mV/decade with a detection limit of $4 \times 10^{-9}$ M. The electrode was used for the determination of amiodarone in pharmaceutical dosage forms such as tablets\textsuperscript{86}.

S.S.M.Hassan and his group reported four novel potentiometric sensors for the selective determination of cinnarizine. These sensors are based on the use of the ion-association complexes of the cinnarizininium cation with tetraphenylborate, flavianate, reineckate and 12-molybdatophosphate counter anions as ion exchange sites in a plasticized PVC matrix. These sensors proved useful for determining cinnarizine in various dosage forms, monitoring tablet dissolution rates and testing tablet uniformity\textsuperscript{87}.

Hassan Y. Aboul-Enein and his co-workers reported the construction and the performance characteristics of an ion-selective PVC membrane electrode for flurbiprofen. The sensor exhibited a near-Nernstian response in
the concentration range $1 \times 10^{-2} - 7 \times 10^{-5}$M. The active component flurbiprofen in pharmaceutical preparations were determined using the proposed electrode\textsuperscript{88}.

A mexiletine-sensitive membrane electrode based on crown ether and ion exchanger was described by T. Katsu \textit{et al}. The electrode exhibited high selectivity against many inorganic cations. The sensor was used to determine mexiletine content in saliva\textsuperscript{89}.

M. A. Ahmed and M.M. Elbeshlawy proposed five novel polyvinyl chloride matrix membrane sensors for the selective determination of sulbutamine. These sensors were based on molybdate, tetraphenylborate, reineckate, phosphotungstate and phosphomolybdate, as possible ion-pairing agents. These sensors display rapid near Nernstian stable response over a relatively wide concentration range of sulbutamine, with calibration slopes 28 - 32.6mV/decade over a reasonable pH range 2 - 6. The proposed sensors proved to have a good selectivity for salbutamine over some inorganic and organic cations. The five potentiometric sensors were applied successfully in the determination of the drug in a pharmaceutical preparation (arcalion-200) using both direct potentiometry and potentiometric titration\textsuperscript{90}.

The construction and evaluation of tripelennamine conventionally shaped ion selective electrodes and tubular detectors for the determination of this compound in pharmaceutical formulations are described. The electrodes showed a linear response in a concentration range of about $4 \times 10^{-5}$M - $1 \times 10^{-1}$M and a slope near the theoretical value. The electrodes were applied to
different pharmaceutical formulations such as creams, gels and syrups and good results were obtained\textsuperscript{91}.

Kiyoyuki \textit{et al} were successful in developing a cocaine selective membrane electrode with the use of sodium tetrakis [3,5-bis (trifluoromethyl) phenyl]borate as an ion-exchanger. The lower limit of detection was $4 \times 10^{-5}$M cocaine. Interference by other drugs (morphine and codeine) and a stimulant (methamphetamine) was negligible. This electrode was successfully applied for the determination of cocaine in a drug mixture containing cocaine and morphine, which is widely used to suppress acute pain in cancer patients\textsuperscript{92}.

The construction and electrochemical response characteristics of poly (vinyl chloride) matrix membrane sensors fluorouracil are described by Hassan \textit{et al}. The membranes incorporate ion association complexes of fluorouracil anion with bathophenanthroline- nickel (II), bathophenanthroline -iron (II) and phenanthroline-iron (II) as electroactive materials. These sensors exhibited fast response time, low determination limit ($1 \times 10^{-5}$M), good stability (4 - 8 weeks) and reasonable selectivity. The sensors were used for direct potentiometry and potentiometric titration for the determination of fluorouracil in some pharmaceutical preparations\textsuperscript{93}.

R. I. Stefan reported the construction and performance characteristics of two ion-selective membrane electrodes based on ion pair complexes between lauryl sulphate and moclobemide (I) and disopyramide. The electrodes presented a wide linear range and also showed high selectivity to moclobemide and disopyramide in the presence of other foreign ions\textsuperscript{94}. 
S. Khalill and N. Borham reported the construction and performance characteristics of ion selective membrane electrodes for phenothiazine drugs based on their ion pair complexes with tetraphenylborate and dinonylnaphthalenesulfonate in a poly (vinyl chloride) matrix. The electrodes showed a near Nernstian response over various ranges depending on the nature of the phenothiazine drug. The reported sensors were used to determine the phenothiazine drugs in pharmaceutical preparations with satisfactory results\textsuperscript{95}.

A novel ion selective electrode was reported for the determination of ranitidine by Hassen \textit{et al.} The potentiometric technique was based on direct measurements of the drug cation with novel PVC matrix membrane sensors incorporating ranitidine-reineckate, tungstophosphate and tungstosilicate ion association complexes as electroactive compounds with 2-nitrophenyl ether as plasticizing solvent mediator. The sensors were used for the determination of ranitidine in a variety of pharmaceutical dosage forms\textsuperscript{96}.

Salem \textit{et al} reported two novel, simple, low cost and sensitive ion-selective electrodes for the determination of some 1,4-benzodiazepines in their pharmaceutical preparations as well as in biological fluids. Sodium tetraphenyl borate and phosphotungstic acid were used for the formation of ion pairs with the drugs. The electrodes were used for determining trace amounts of bromazepam, clonazepam and diazepam in their pharmaceutical preparations as well as in biological fluids\textsuperscript{97}.

Naader Alizadeh and Rasoul Mehdipour developed an ion selective membrane electrode for the drug ketamine hydrochloride using a modified PVC membrane which has ionic end groups as ion exchanger sites and was
plasticized with ortho nitrophenyloctyl ether (o-NPOE) as plasticizer. This drug electrode showed excellent Nernstian responses (59 mV per decade) in the concentration range $1 \times 10^{-5} - 1 \times 10^{-2}$ M with a detection limit of $5 \times 10^{-6}$ M. The electrode was applied for determination of ketamine hydrochloride in pharmaceutical preparations using direct potentiometry.  

Newly developed solid contact ion selective electrodes have been proposed for determining diazepam, bromazepam and clonazepam 1,4-benzodiazepines in pure forms and in pharmaceutical preparations. The electrodes are based on polyvinyl chloride membranes doped with drug-tetraphenyl borate (TPB) or drug-phosphotungstic acid (PTA) ion. Successful application of developed electrodes for drugs determinations in pharmaceutical preparations was obtained.

Takashi Katsu and Yuki Mori fabricated a disopyramide-sensitive membrane electrode. Sodium tetrakis [3,5-bis (2-methoxyhexafluoro-2-propyl) phenyl]borate was incorporated as the ion exchanger and 2-fluoro-2′-nitrodiphenyl ether was used as the solvent mediator in a poly(vinyl chloride) membrane matrix.

Hisham E. Abdellatef and coworkers were successful in reporting the construction of a plasticized poly (vinyl chloride) matrix type famotidine ion selective membrane electrode and its use in the potentiometric determination of famotidine in pharmaceutical preparations. It is based on the use of the ion associate species, formed by famotidine cation and tetraphenyl borate (TPB) counter ion. The electrode exhibited a linear response for $1 \times 10^{-3} - 1 \times 10^{-5}$ M of famotidine solutions over the pH range 1 - 5.
A PVC membrane electrode was reported for the stimulant phenetermine by Takashi Katsu and his group using the ion exchanger sodium tetrakis [3,5-bis(2-methoxyhexafluoro-2-propyl)phenyl] borate. The electrode showed high selectivity to the stimulant in presence of other analogous compounds. This electrode was applied to the determination of phenetermine in ion exchange resin complexes containing this stimulant\textsuperscript{102}.

The construction and general performance characteristics of potentiometric plastic membrane sensors for piroxicam and tenoxicam drug-anions are described by Khalil and group. The electroactive materials are based on ion pair complexes with aliquot 336S cation. The selectivity of the electrodes to a number of organic and non organic anions is reported. The electrodes exhibit useful analytical characteristics for the determination of the active ingredients in their respective pharmaceutical tablet formulations without any prior separation with good reproducibility\textsuperscript{103}.

Hassan \textit{et al} reported the construction and characterization of five poly (vinyl chloride) matrix membrane sensors responsive to some β -blockers (atenolol, bisoprolol, metoprolol, propranolol and timolol). The sensors are based on the use of the ion association complexes of the β -blocker cations with tungstophosphate anion as electroactive materials. The performance characteristics of these sensors, evaluated according to IUPAC recommendations, reveal fast, stable and near Nernstian response for $1 \times 10^{-2}$ - $2 \times 10^{-7}$ M of different β-blockers over the pH range 2 - 9. The sensors were used for direct potentiometry of β-blockers in some pharmaceutical preparations\textsuperscript{104}.

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An internal solid contact sensor was developed for the determination of
doxycycline hydrochloride by Sun et al. This was based on a conducting
copolymer (PPy) film immobilized on a glassy carbon electrode surface
casted by a plasticized polyvinyl chloride membrane containing an ion pair
compound of doxycycline hydrochloride with tetraphenylborate (TPB) and
dibutylphthalate (DBP) as plasticizer. The detection limit obtained was \(4.0 \times 10^{-6}\) M. The sensor was successfully applied to determination of doxycycline
hydrochloride in pharmaceutical formulation\(^{105}\).

S. Khalil and group were successful in reporting an ion selective
electrode for prazosin based on prazosinium - phosphotungstate ion associate.
The electrode exhibited a linear response with an approximate Nernstian
slope over the range of \(2.7 \times 10^{-6} - 1 \times 10^{-2}\) M. The working pH of the
electrode ranged from 1.5 to 6.4 and exhibited very good selectivity for the
prazosin with respect to a large number of inorganic cations and organic
substances of biological importance\(^{106}\).

A coated-wire benazepril-selective electrode based on incorporation
of the benazepril - tetraphenylborate ion pair in a poly (vinylchloride)
coating membrane was constructed by S. Khalil and S. Abd El-Aliem. The
influences of membrane composition, temperature, pH of the test solution,
and foreign ions on the electrode performance were investigated. The
electrode was successfully used for potentiometric determination of
benazepril hydrochloride both in pure solutions and in pharmaceutical
preparations\(^{107}\).

Shamsipur et al developed a new cimetidine ion selective electrode,
characterized and used in pharmaceutical analysis as well as its recovery
from urine samples. The electrode incorporated PVC membrane with
cimetidine-phosphotungstate ion pair complex. The electrode exhibited a
Nernstian response for cimetidine in the concentration range $1.0 \times 10^{-5} - 1.0 \times 10^{-2}$ M with a slope of 58 mV per decade. The limit of detection was $5.0 \times 10^{-6}$ M$^{108}$.

The construction and electrochemical response characteristics of four
poly (vinyl chloride), membrane sensors for determination of fluphenazine
hydrochloride and nortriptyline hydrochloride are described by El-Ragehy et al. 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 (KtpCIPB). The proposed sensors were used for the
direct potentiometric determination of fluphenazine and nortriptyline
hydrochlorides in their pure forms and pharmaceutical dosage forms$^{109}$.

Hassan et al reported the fabrication of metformin ion selective
electrodes based on metformin – reineckate and metformin - tungstosilicate ion
pairs as electroactive species with dioctylphthalate and o-nitrophenyloctylether
as plasticizers, respectively. These sensors give rapid Nernstian response for
$1 \times 10^{-1} - 1 \times 10^{-5}$ M metformin in the pH range 5-11$^{110}$.

S. Khalil and M.A. EL-Ries reported a new prenalterol ion selective
PVC membrane electrode based on the ion pair complex of prenalterol with
sodium tetraphenylborate and its performance characteristics were studied.
The electrode exhibited a linear response with a good Nernstian slope over a
relatively wide range of concentration. The electrode showed very good
selectivity for the drug with respect to a large number of inorganic and
organic cations. The standard addition method and potentiometric titration
were used to determine prenalterol in pure solutions and in pharmaceutical formulations\textsuperscript{111}.

Reproterol hydrochloride selective PVC membranes based on ion associates of reproterolium-phosphotungstate, reproterolium-phosphomolybdate or a mixture of both were prepared by Shoukry and group. The electrodes displayed a linear response over the concentration range of $6.3 \times 10^{-6} - 1.0 \times 10^{-1}$ mol dm$^{-3}$ of reproterol. The electrodes showed good selectivity to the reproterolium ion with respect to many inorganic cations, sugars and amino acids\textsuperscript{112}.

Two novel potentiometric membranes sensors responsive to the drug ibuprofen have been developed by Hassan and co-workers. The sensors showed a near Nernstian response of -53 and -55 mV/decade over a wide concentration range. Both the sensors were used for the quantification and quality control assessment of ibuprofen in pharmaceutical preparations\textsuperscript{113}.

Gamal Abdel El-Hafeez Mostafa reported a novel PVC membrane electrode for the determination of scopolamine ion based on the formation of an ion association complex of scopolamine with phosphotungstate counter anion as an electroactive material dispersed in a PVC matrix. The sensor showed a fast stable near Nernstian response over a wide concentration range within a pH range of 3 - 7\textsuperscript{114}.

Ribeiro and coworkers developed a simple, precise, rapid and low cost potentiometric method for captopril determination in pure form and in pharmaceutical preparations. No interferences were observed in the presence of common components of the tablets as lactose, microcrystalline cellulose, croscarmellose sodium, starch and magnesium stearate. The analytical results
obtained by applying the proposed method compared very favourably with those obtained by the United States Pharmacopoeia Standard procedure\textsuperscript{115}.

A plastic membrane electrode for the determination of methacycline hydrochloride was fabricated by Hassan \textit{et al} based on the use of methacycline-tetraphenylborate as the electroactive substance, and dioctylphthalate as the plasticizing agent. The electrode was successfully applied to determination of methacycline hydrochloride in tablet by direct potentiometric method. The result obtained with the electrode was in good agreement with the value obtained by using the official method\textsuperscript{116}.

Zhi-Hua-Liu and co-workers reported a novel PVC membrane electrode for the drug pethidine with dibutyl phthalate as plasticizer based on pethidine-silicotungstate as the electroactive material. The membrane electrode was highly stable and had a longer life time compared to the earlier reported electrode. The electrode was successfully applied to determination of pethidine hydrochloride in tablet and injections\textsuperscript{117}.

H.Y. Aboul-Enein and Xian Xiang Sun developed novel ion selective PVC membrane electrode for determination of propranolol. Silicotungstic acid was used as the counter ion and diisononyl phthalate was used as the plasticizer. The electrode exhibited excellent potential response properties, showing a Nernstian response in the concentration of $3.0 \times 10^{-6} - 2.6 \times 10^{-2}$ M with the slope of 54.7 mV per decade. The electrode was successfully used for the analysis of propranolol in pharmaceutical formulation\textsuperscript{118}.

Khalil Farhadi and Ramin Maleki reported a triiodide ion selective electrode based on clotrimazole-triiodide ion as the membrane carrier. The electrode showed a linear range within $10^{-3}$ to $10^{-6}$M with a slope of
-68.9 mV/decade and detection limit of $5 \times 10^{-6}$ M. The electrode was used for the indirect potentiometric determination of clotrimazole in pharmaceutical preparations\textsuperscript{119}.

G.A.E. Mostafa discussed the construction and characteristic performance of a metoclopramide - polyvinyl chloride membrane sensor. The sensor was based on the use of metoclopramide-tetraiodomercurate ion pair as electroactive material in PVC matrix in presence of dioctylphthalate as solvent mediator. The membrane sensor showed a stable, near Nernstian response over the concentration range $1 \times 10^{-2} - 6 \times 10^{-5}$ M of metoclopramide in the pH range 3 - 7 with cationic slope of 53.0 mV/decade. The determination of metoclopramide in tablets, injection, and syrup gave results that compare favorably with those obtained by the British pharmacopoeia method\textsuperscript{120}.

The construction and performance characteristics of ion selective membrane electrodes for a newly found phenylpiperazine antidepressant, Nefazodone, based on its ion pair complexes with phosphotungstate, tetraphenylborate, tungstosilicate and reineckate in a poly (vinyl chloride) matrix were described by Erdem \textit{et al.} The selectivity of these electrodes to Nefazodone in the presence of a number of sugar molecules, cations and drugs was reported. The potentiometric standard addition method was used to determine the drug in pure solution\textsuperscript{121}.

G. A. E. Mostafa described the construction and general performance characteristics of two novel potentiometric PVC membrane sensors responsive to the pyridoxine hydrochloride known as vitamin B6. These sensors are 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 $6 \times 10^{-5} - 1 \times 10^{-2}$M vitamin B6 over the pH range 2 - 4 with a cationic slope of 54.0 and 54.5 mV per concentration decade for pyridoxine-molybdophosphate and pyridoxine-tungstophosphate, respectively\textsuperscript{122}.

Kauffmann \textit{et al} described the construction and electrochemical response characteristics of two types of poly (vinyl chloride) membrane sensors for the determination of amodiaquine hydrochloride. The sensing membrane comprised an ion pair formed between the cationic drug and sodium tetraphenyl borate or potassium tetrakis(4-chlorophenyl) borate in a plasticized PVC matrix. Eight PVC membrane ionselective electrodes were fabricated and studied. The sensors displayed a fast, stable and near Nernstian response over a relative wide amodiaquine concentration range ($3.2 \times 10^{-6}$ to $2.0 \times 10^{-2}$M), with slopes comprised between 28.5 and 31.4 mVdec$^{-1}$ in a pH range between 3.7 and 5.5\textsuperscript{123}.

Mojtaba Shamsipur and group reported the preparation and characterization of a novel diclofenac ion selective electrode. The electrode exhibited a Nernstian slope for diclofenac in the concentration range $1.0 \times 10^{-5}$ to $1.0 \times 10^{-2}$M with a limit of detection of $4.0 \times 10^{-6}$M. The electrode displayed a good selectivity for diclofenac with respect to a number of common inorganic and organic species. The membrane sensor was successfully applied to the determination of diclofenac in its tablets as well as for its recovery from blood serum and urine samples\textsuperscript{124}. 

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Four glutathione selective electrodes were reported by Shehata et al with different ion exchangers in different polymeric matrices. The proposed sensors were successfully used for the determination of glutathione in capsules and also in plasma\textsuperscript{125}.

Khadiga M. Kelani reported the construction and electrochemical response characteristics of 4 polymeric membrane sensors for potentiometric determination of zolpidem hemitartrate. A linear response was obtained over the concentration range of $1 \times 10^{-5} - 1 \times 10^{-2}$ M with a cationic slope of 29 mV per concentration decade. The 4 proposed sensors were also applied successfully to the determination of the drug in tablets and in biological fluids\textsuperscript{126}.

Joanna Drozd and Hanna Hopkala described sensitive and reasonably selective poly (vinyl chloride) membrane electrodes for cyproheptadine. They are based on the use of cyproheptadine-tetrakis (4-chlorophenyl)borate and cyproheptadine-dipicrylamine as a novel electroactive compounds. The electrodes were used in the potentiometric determination of cyproheptadine in bulk substance and tablets. The results were in good agreement with those obtained by UV spectrophotometric method\textsuperscript{127}.

Pezza and group reported the characteristics, performance and application of a potentiometric sensor immobilized in graphite matrix for diclofenac ion. This electrode responds to diclofenac over the range $5.0 \times 10^{-5}$ to $1.0 \times 10^{-2}$ mol l\textsuperscript{-1} at pH 6.5 - 9.0 and a detection limit of $3.2 \times 10^{-5}$ mol l\textsuperscript{-1}. The proposed sensor displayed good selectivity for diclofenac in the presence of several substances, especially concerning carboxylate and inorganic
anions. It was used to determine diclofenac in pharmaceutical preparations by means of the standard addition method\textsuperscript{128}.

Moghimi \textit{et al} reported a potentiometric sensor for the selective determination of picrate ion immobilized in a graphite matrix. The electrode showed easy construction, fast response time (about 25 s), low cost, and excellent response stability (lifetime > 6 months, in continuous use). The proposed sensor showed high selectivity towards picrate ion over many hydrophilic and lipophilic anions. 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 picrates\textsuperscript{129}.

The construction and performance characteristics of a potentiometric sensor for p-amino benzoate ion immobilized in graphite matrix were reported by Pezza \textit{et al}. The proposed sensor displayed good selectivity for p-aminobenzoate in the presence of several substances, especially, concerning carboxylate and inorganic anions. It was used to determine p-aminobenzoate in pharmaceutical formulations by means of the standard additions method\textsuperscript{130}.

El-Shahawi \textit{et al} described the construction and performance characteristics of ion selective membrane electrodes for sildenafil citrate. The proposed sensors were based on the formation of the complex ion associates of the drug with sodium tetraphenylborate and phosphomolybdic acid as ionophores in poly vinyl chloride membrane. The sensors showed a linear and stable potential response with near Nernstian slope of 55.5 and 53.5 mV per decade over a wide range of concentration $10^{-2}$ to $10^{-5}$ M sildenafil with
good reproducibility. The selectivity coefficients indicated good selectivity for the drug over a large number of nitrogenous compounds and some inorganic cations. The proposed sensors were tested for the analysis of sildenafil citrate in pure form, pharmaceutical preparations and blood serum\textsuperscript{131}.

Hassan \textit{et al} reported the construction and characterization of potentiometric membrane sensors for quantification of diclofenac. The membranes of the sensors incorporate iron (II) - phthalocyanine as a molecular recognition reagent, dibutylsebacate solvent mediator, tridodecylmethylammonium chloride as membrane additive in poly(vinyl chloride) matrix. The sensors displayed a wide linear range and pH range of 5.5 - 9.0\textsuperscript{132}.

New PVC membrane electrodes selective for the determination of hyoscyamine ion (Hy\textsuperscript{+}) based on hyoscyamine tetraphenylborate (Hy-TPB) or hyoscyamine phosphotungstate (Hy-PT) ion exchangers as electroactive materials were described by Badawy and group. The electrodes gave near Nernstian slopes of 56.5 and 57.8 mV/decade for Hy-TPB and Hy-PT respectively. The electrodes have been applied to the potentiometric determination of hyoscyamine in pure solution and in pharmaceutical preparations under batch and FIA conditions and as end point indicator electrode for the determination of hyoscyanine using potentiometric titration\textsuperscript{133}.

Y.M. Issa and S.I.M Zayed reported a new oxymetazoline ion selective electrode based on the ion associate of oxymetazoline with phosphotungstic acid. The electrode exhibited a linear response with a calibration slope of
57.16 mV/decade. The proposed sensor showed high selectivity for oxymetazoline ion with respect to a large number of inorganic cations and compounds\textsuperscript{134}.

Rizk \textit{et al} developed polyurethane sensors for thiopental on solid graphite support. The sensors were based on the electroactive materials of thiopental with Cu (II) and Co (II) bathophenanthroline 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{135}.

A novel potentiometric PVC membrane sensor for determination of diclofenac in pharmaceutical preparations has been developed by Hassan and group. The sensor is based on the use of the 2,4,6-tri(2-pyridyl)-s-triazine iron(II) diclofenac complex as an electroactive material in a plasticized PVC membrane matrix. No significant interferences were caused by inorganic and organic anions and various drug excipients and diluents\textsuperscript{136}.

Ibrahim \textit{et al} reported 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 proposed sensor exhibited high selectivity for dicyclomine ion with respect to a large number of inorganic cation, sugars, aminoacids and organic compounds\textsuperscript{137}.

Ghoreishi and group reported new naphazoline ion selective membrane electrodes of both conventional and coated graphite types prepared based on the ion-pair of naphazoline tetraphenylborate. The conventional type
electrode was fully characterized in terms of membrane composition, life span, pH, ionic strength and temperature\textsuperscript{138}.

Wang \textit{et al} developed a potentiometric PVC membrane sensor for determination of the drug tetracycline. The response time of the sensor was less than 2.0 min. In addition to high reproducibility and reversibility, the sensor also exhibited good selectivity over some common pharmaceutical species and some common organic and inorganic compounds\textsuperscript{139}.

A novel theophylline potentiometric sensor was prepared, characterized and used in pharmaceutical analysis by Mousavi \textit{et al}. The sensor was based on a PVC membrane containing dibutyl phthalate as plasticizer, 2,6-bis(phenyl)-4(phenyl)3H-thiopyran as ionophore and oleic acid as additive. A linear response in the range of $1.0 \times 10^{-6}$ to $1.0 \times 10^{-2}$ M of theophylline was established\textsuperscript{140}.

A novel plastic membrane electrode for the determination of diclofenac anion was described by Hassan \textit{et al}. The sensing membrane of the electrode consisted of diclofenac-nickel(II) bathophenanthroline as an ion-exchanger site in a poly(vinyl chloride) matrix plasticized with o-nitrophenyl phenyl ether. In borate buffer solutions of pH 8 - 12, the electrode exhibited a fast, stable and linear response for $1 \times 10^{-2}$ - $5 \times 10^{-5}$ M diclofenac solutions\textsuperscript{141}.

Mojtaba Shamsipur and Fahimeh Jalali proposed a novel clotrimazole ion selective electrode. The electrode incorporated PVC membrane with clotrimazole-phosphomolybdate ion pair complex. The electrode exhibited a Nernstian response for clotrimazole in the concentration range $1.38 \times 10^{-5}$ - $1.0 \times 10^{-3}$ M\textsuperscript{142}.
Chlordiazepoxide Hydrochloride electrodes were prepared by Issa et al using the ion associates of the drug with phosphomolybdic acid and phosphotungstic acid. The electrodes exhibited a mean slope of 59.4 and 60.8 mV/decades of chlordiazepoxide hydrochloride. The electrodes could be used within the concentration range $10^{-2}$ to $10^{-6}$ M$^{143}$.

Wassil et al reported the construction of PVC matrix type β-blockers (sotalol, carvedilol, and betaxolol) ion selective electrodes and their use for direct potentiometry of their respective species. The proposed sensors are based on the complex ion associates of β-blockers with tungstophosphate and ammonium reineckate ionophores in polyvinyl chloride membrane with dioctylphthalate plasticizer. The four electrodes showed stable potential response with near Nernstian slope within a range of concentration $1.0 \times 10^{-3}$ - $1.0 \times 10^{-1}$ M β-blockers$^{144}$.

A new triiodide ion selective PVC membrane sensor based on diprotonated ketoconazole-triiodide, as ion pair, was proposed Khalil Farhadi and group. The electrode has a linear dynamic range between $2.0 \times 10^{-3}$ and $7.0 \times 10^{-6}$ M with a detection limit of $3.0 \times 10^{-6}$ M. The potentiometric response is independent of the pH of the solution in the pH range 2 - 8.5. The proposed triiodide membrane sensor was used in development of a new, simple, fast, inexpensive and precise method for the determination of Ketoconazole in formulations$^{145}$.

Fuglein et al reported ion selective electrodes for the determination of the antibiotic drug chlortetracycline. The proposed electrode was based on chlortetracycline - tungstosilicate ion pair. The proposed sensor
exhibited high selectivity for chlortetracycline in presence of other interfering ions\textsuperscript{146}.

Xian Xiang Sun and Hassan Y. Aboul-enein reported an internal solid contact sensor for the determination of methacycline hydrochloride based on the use of conducting poly (pyrrole) as solid contact material and methacycline - phosphotungstate as the ion exchanger and dibutyl phthalate as the plasticizer. The determination of methacycline hydrochloride in tablets were carried out by direct potentiometry\textsuperscript{147}.

Two potentiometric sensors responsive to sildenafil citrate drug were described, characterized, compared and used for drug assessment by Hassan et al. The sensors are based on the use of the ion association complexes of cation with tungstophosphate and reineckate anions as electroactive materials in plasticized poly(vinyl chloride) membranes. The sensors display good selectivity for the drug over many nitrogeneous compounds, some inorganic cations and excipients and diluents commonly used in drug formulations. Validation of the assay methods with both sensors by measuring the lower detection limit, range, accuracy, precision and repeatability reveals good performance characteristics confirming applicability for continuous determination of sildenafil in pharmaceutical formulations and in spiked human serum\textsuperscript{148}.

Mojtaba Shamsipur and Fahimeh Jalali developed a novel atenolol ion selective electrode characterized, and used in pharmaceutical analysis. The electrode incorporates PVC membrane with atenolol tetrakis (p-chlorophenyl) borate ion pair complex. The electrode exhibited a Nernstian response for atenolol in the concentration range $3.0 \times 10^{-5}$ to $8.0 \times 10^{-2}$ M. The limit of detection was $1.0 \times 10^{-5}$M\textsuperscript{149}. 


Sergey V. Kharitonov reported the construction and electrochemical response characteristics of poly (vinyl chloride) matrix ion selective electrodes for papaverine hydrochloride. The membranes incorporate ion association complexes of papaverine with tetraphenylborate, picrate, tetraiodomercurate, Reinecke salt and heteropoly compounds of Keggin structure-molybdophosphoric acid, tungstophosphoric acid, molybdosiliconic acid, and tungstosiliconic acid as electroactive materials. These electrodes showed linear response for papaverine hydrochloride over the range from $1 \times 10^{-5}$ up to $5 \times 10^{-2}$ mol/l with cationic slopes from 42 up to 58 mV per concentration decade$^{150}$. 

A new polymeric membrane electrode has been developed by M. Rachidi and J. Elharti for the determination of azithromycin. The electrode was constructed by incorporating the azithromycin-tetraiodomercurate ion pair complex into a polyvinyl chloride matrix plasticized by nitrobenzene. This sensor exhibited good linear response over the concentration range $1.0 \times 10^{-2} - 7.0 \times 10^{-6}$M$^{151}$. 

Four poly (vinyl chloride) membrane sensors for the determination of hyoscine butylbromide were described and characterized by Saharty et al. The sensors were based on the use of the ion association complexes of hyoscine cation with ammonium reineckate counter anions as ion exchange sites in the PVC matrix. The membranes incorporate ion association complexes of hyoscine with dibutylsebacate, dioctylphthalate, nitrophenyl octyl ether and $\beta$-cyclodextrin The sensors were used for determination of hyoscine butylbromide in laboratory prepared mixtures, pharmaceutical formulations in combination with ketoprofen and in plasma$^{152}$. 

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Sadeghi *et al* reported a potentiometric sensor based on a molecularly imprinted polymer for recognition and determination of levamisole hydrochloride. The proposed sensor was highly responsive to levamisole in the presence of other similar structures like thiabendazole, (2-methylthio) benzothiazole or (2-amino) benzothiazole. The potentiometric selectivity coefficients of the proposed sensor were evaluated and it exhibited good selectivity to levamisole with respect to the electrode based on a non-imprinted polymer or the plasticized PVC membrane electrode based on levamisole hydrochloride-tetraphenyl borate.

Jalali *et al* reported a novel gabapentin ion selective electrode based on the ion association of the drug with phosphomolybdic acid. The electrode displayed a good selectivity for gabapentin with respect to a number of pharmaceuticals that may be taken with gabapentin simultaneously. The sensor can be used in a pH range of 1.8 - 3.2. The membrane sensor was successfully applied to the determination of gabapentin in its tablets as well as its recovery from blood serum samples.

Mojtaba Shamsipur and Fahimeh Jalali reported a PVC membrane sensor for the determination of ketoconazole in pharmaceutical preparations and biological samples. The membrane used in this electrode was made from liquid plasticized PVC and was based on a water insoluble ketoconazole-tetraphenyl borate ion pair as the ion exchanger.

V.D. Vaze and A.K. Srivastava developed a simple, rapid and sensitive sensor for the assay of pyridoxine hydrochloride. The method was based upon the use of calix-8-arene as a neutral carrier in the presence of phosphotungstic
acid as an ion extruder and di isooctyl phthalate as plasticizer. The sensor was found to have a short response time of 20 s to pyridoxine concentration\textsuperscript{156}.

M.N. Abbas and A.A. Radwan reported a novel potentiometric lipoate-selective sensor based on mercuric lipoate ion pair as a membrane carrier. The electrode was prepared by coating the membrane solution containing PVC, plasticizer, and carrier on the surface of graphite electrode. Fast and stable response, good reproducibility, long term stability, applicability over a pH range of 8.0 - 9.5 is demonstrated. The sensor has a response time of $\leq 12$ s and can be used for at least 6 weeks without any considerable divergence in its potential response. The proposed sensor has been applied for the direct and flow injection potentiometric determination of lipoic acid in pharmaceutical preparations and urine; and has been also utilized as an indicator electrode for the potentiometric titration of lipoic acid\textsuperscript{157}.

Ipratropium ion selective electrode has been constructed from poly (vinyl chloride) matrix membrane containing Ipratropium-tetraphenylborate as the electroactive component using 2-nitrophenyloctylether as plasticizer. The electrode exhibits near Nernstian response to Ipratropium bromide over the concentration range $1 \times 10^{-5}$ to $1 \times 10^{-2}$ M and detection limit $5.1 \times 10^{-6}$M. The electrode was successfully used as indicator electrode in the potentiometric titration of Ipratropium bromide versus sodium tetraphenylborate and in the determination of the drug in pharmaceutical formulations and spiked urine samples applying batch and flow injection techniques, with satisfactory results\textsuperscript{158}.

Shoukry \textit{et al} developed new chlorpromazinium plastic membrane electrodes of the conventional type based on incorporation of
chlorpromazinium-reineckate ion pair, chlorpromazinium-phosphotungstate or chlorpromazinium-phosphomolybdate ion associate into poly (vinyl chloride) membrane. The electrodes exhibited calibration graph slopes of 49.83, 52.87, and 61.30 mV/decade over life spans of 1, 5, and 3 days, respectively. All electrodes proved to be selective for chlorpromazine and have been applied to the assay of a pharmaceutical preparation

M. Arvand et al constructed an ion selective membrane electrode for the drug atenolol, based on incorporation of the atenolol phosphotungstate ion associate in a PVC coating membrane with acetophenone as plasticizer. The influence of the membrane composition, temperature, conditioning time of the electrode, pH of the test solution, and foreign ions on the electrode performance were investigated. The drug electrode showed Nernstian responses in the concentration range $5 \times 10^{-7}$ - $1 \times 10^{-2}$ M and was found to be very selective, precise and usable within the pH range 3 - 6.

Ali A. Ensafi and Ali R. Allafchian reported a new PVC membrane sensor for amiloride. The sensor was based on amiloride-sodium tetraphenyl phthalate ion pair as an electroactive material. The sensor was highly selective for amiloride over a large number of similar compounds. The sensor showing a fast response time of 6 s and was used over a period of 2 months with a good reproducibility. The sensor was successfully applied to determination of amiloride in pharmaceutical samples with satisfactory results.

A PVC membrane sensor for diclofenac was developed by Maleki et al based on its ion pair complex with silver. The electrode gave a Nernstian response for diclofenac anions over a wide linear range from $5.2 \times 10^{-5}$ to
1.1 × 10⁻² M at 25 ± 1 °C. The electrode was successfully used for
determination of diclofenac in pharmaceuticals and also in potentiometric
study of interaction of diclofenac with bovine serum albumin¹⁶².

Nesrin K. Ramadan and Hala E. Zaazaa developed five poly (vinyl
chloride) matrix membrane electrodes responsive to the β-blockers atenolol,
bisoprolol fumarate, timolol maleate, and levobunolol HCl. Ammonium
reineckate anion and tungstophosphate anion were used to form the ion
association with the drugs. The method was successively applied for the
determination of β-blockers in their pharmaceutical formulations¹⁶³.

Alizadeh et al reported a solid state valproate ion selective sensor based
on conducting polypyrrole films. The sensors showed a quasi Nernstian
behavior over 4 × 10⁻⁵ - 4 × 10⁻² M with a detection limit of 1 × 10⁻⁵M in an
aqueous solution. The response time of the electrode was about 20 s and the
electrode could be used at least for 4 months without any divergence. The
drug sensor was applied for determination of valproate ions in
pharmaceutical preparations by using titration potentiometry¹⁶⁴.

Rachidi et al developed a cetirizine selective membrane electrode based
on the ion association of the drug with sodium tetraphenyl borate anion. The
developed electrode showed a good Nernstian response in the concentration
range of 6.3 × 10⁻⁷ - 1.0 × 10⁻²M with a slope of 58.2 mV per decade and a
lower quantification limit of 3.16×10⁻⁷ M. Cetirizine selective electrode was
successfully applied for the determination of cetirizine in pharmaceutical
preparations using direct potentiometric method with high accuracy¹⁶⁵.

Kulapina et al reported the construction of ion selective electrodes with
plasticized membranes based on ion pairs of gentamycin and kanamycin with
tetraphenylborate and Acid Chrome Black Special. The developed electrodes were used for the rapid potentiometric determination of gentamycin and kanamycin in biological fluids and pharmaceuticals\(^\text{166}\).

Sayed S. Badway and group developed potentiometric membrane electrodes for the determination of Ranitidine Hydrochloride. These electrodes were based on the ion association of the drug formed with sodium tetraphenyl borate and phosphotungstate anions. The sensors showed fast and stable responses. The sensors were applied to the determination of the drug in pharmaceutical preparations\(^\text{167}\).

S. V. Kharitonov reported the construction and characterization of potentiometric ion selective electrodes based on different lipophilic derivatives of tetraphenylborate for the drug drotaverine hydrochloride. The electrodes were applied to the determination of drotaverine hydrochloride in different pharmaceutical forms by potentiometry and potentiometric precipitation titration\(^\text{168}\).

Ghani \textit{et al} reported new plastic membrane electrodes for dothiepin hydrochloride based on dothiepin phosphotungstate, dothiepin phosphomolybdate and a mixture of both. The selectivity of the electrodes towards many inorganic cations, sugars, and amino acids was also tested. The electrodes were applied to the potentiometric determination of the dothiepinium ion in its pure state and pharmaceutical preparations in batch and flow injection conditions\(^\text{169}\).

The construction and electrochemical response characteristics of a poly (vinyl chloride) membrane selective electrode for the determination of tiapride was described by Pedreno \textit{et al}. The sensing membrane comprised an
ion pair formed between the protonated drug and tetraphenylborate in a plasticized PVC matrix. The electrode has been applied to the determination of tiapride in human urine and iontophoresis solution\textsuperscript{170}.

Mostafa \textit{et al} reported the construction and characterization of two novel potentiometric membrane sensors for the drug acebutolol. The sensors were based on the use of ion association complexes of the drug formed with sodium tetraphenyl borate and phosphomolybdate anions in a PVC matrix. The sensors were applied to the determination of the drug in pharmaceutical preparations\textsuperscript{171}.

\subsection*{1.11 Scope of the Present Investigation}

Ion selective sensors have been becoming one of the effective and powerful means for analytical scientists in the determination of drug substances and are playing an increasing role in pharmaceutical analysis. Many methods have been employed in our laboratory for the quantitative analysis of drugs in pure form as well as in dosage forms\textsuperscript{172-179}. Apart from all the other methods developed, ISE's are cost effective, easy to prepare and can be rapidly manipulated. Thus it was aimed to develop potentiometric ion selective sensors for six drugs namely, Trimethoprim (TMP), Ketoconazole (KET), Lamivudine (LAM), Domperidon (DOM), Nimesulide (NIM) and Lomefloxacin (LOM). The sensors fabricated include both PVC membrane sensor as well as carbon paste sensor. A total of sixteen different sensors were developed. The response parameters of all the sensors have been studied and the sensors were applied to the determination of the drugs in pharmaceutical formulations and also in real samples like urine.