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Carbon Paste Electrodes in Potentiometry: The State of the Art and Applications in Modern Electroanalysis (A Review)

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Abstract: The development of chemical sensors has received widespread attention during the past two decades because of their extensive use in environmental monitoring and clinical analysis via rapid, accurate, reproducible, and low-cost methods. The data reported in literature demonstrate that carbon paste electrodes (CPEs) are very suitable for a variety of applications and many works have thus been devoted to developing new ion-selective electrodes based on carbon paste as the electrode material of choice. Chemically modified CPEs have frequently been employed as potentiometric sensors in trace analysis for metal ions, organic pollutants and biological substances. Most of these electrodes are operated via the ion-exchange process of the active component incorporated into the carbon paste matrix. This review article concentrates on such achievements in the context of the general development across the field.

Keywords: Potentiometry; Ion-selective electrodes; Carbon paste; Applications; Review.

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Introduction

A number of instrumental techniques such as UV-visible and infrared spectrophotometry, atomic absorption spectrophotometry, flame photometry, fluorimetry, mass spectrometry, chromatography, etc. are available at the disposal of analytical chemists. These methods provide reproducible results with a high sensitivity and good selectivity. However, all these analytical techniques require sophisticated instruments and chemical manipulation of sample before measurement which may be time consuming and inconvenient. Chemical sensors have no such requirements. These provide accurate, reproducible, fast and often selective determination methods of various chemical species. Additionally, the technique could be non-destructive, adaptable to small sample volumes and to on-line monitoring due to these merits. The utility of chemical sensors is being increasingly realized in medicinal, industrial, agricultural, and environmental fields. Monitoring of detrimental metal ions, anions and organic compounds in the environment is one of the most important tasks of modern analytical chemistry. Electrochemical methods are especially suitable for large scale environmental monitoring of electrochemically active pollutants because they are inexpensive, extremely sensitive, and applicable as an independent alternative to so-far prevalent spectrometric and separation techniques [1].

In general, electrochemical methods are based on the transformation of chemical information into an analytical and electrochemically measurable signal. Any sensor used in such determinations contains two basic functional units; one receptor part, which transforms the chemical information into a form of energy and one transducer part which transforms the energy, bearing chemical information, into a useful signal. A broad range of electrochemical techniques can be used for this purpose. Some of the most commonly used are voltammetry, amperometry, impedometry, conductimetry, and potentiometry, when the last named is based on the measurement of a potential under zero-current flow. The potential measured may then be used to quantify the concentration of some components occurring in a gas or a solution. The signal is measured as the potential difference between the indicator (electrode of the first kind, ion-selective electrode, metal-metal oxide electrode) and the reference electrode (e.g. SCE) with known and constant potential. The majority of ion-selective electrodes (ISEs) employ polymeric membranes as the material of choice for construction of the sensing proper. A suitable internal solution and the optimal properties of such a membrane are then the crucial factors for electrodes of this kind.

In recent years, scientists pay attention to new electrode materials characterized by broader potential window, higher signal-to-noise ratio, mechanical stability enabling their application in flowing systems, and resistance toward passivation. The last requirement is especially important because electrode fouling is probably the biggest obstacle to more frequent applications of electroanalytical methods in environmental analysis. Carbon paste electrodes (CPEs) have attracted attention as ion-selective electrodes mainly due to their advantages over membrane electrodes such as chemical inertness, robustness, renewability, stable response, low ohmic resistance, no need for internal solution and suitability for a variety of sensing and detection applications [2-6]. Moreover, CPEs belong to nontoxic and environmentally friendly electrodes. In their case, problems with passivation are simply eliminated by a simple and quick renewal of their surface.

Up until now, carbon paste electrodes and their utilization in analytical electrochemistry are documented in more than 2000 original papers with 100-150 contributions appearing annually in the last 5 years [5,7]. Bare or modified CPE are used as electrodes or sensors for analysis in environmental applications, in the DNA hybridization studies, for *in-vivo* measurements, as biosensors with immobilized enzymes in various medical applications, or in pharmaceutical analysis as summarized recently [7]. In this article, special attention will be paid to various possibilities of traditional (equilibrium) potentiometry with carbon paste as ion-selective electrodes, CP-ISEs.

Ongoing Development in Potentiometry, Including Ion-Selective Electrodes

Potentiometric measurements involve the determination of the potential difference between either an indicator or a reference electrode or two reference electrodes separated by a permselective membrane, when there is no significant current flowing between them. Most common are ion-selective electrodes based on thin films or selective membranes as recognition elements for pH, F^-, I^-, CN^-, Na^+, K^+, Ca^{2+}, NH_4^+, Pb^{2+}, Cd^{2+}, Cu^{2+}, *etc.* or even gases (*i.e.* CO_2, NH_3). The potential differences between these indicator and reference electrodes are proportional to the logarithm of the ion activity or gas fugacity (or concentration), as described by the Nernst-Donnan equation. This is only the case when: (*i*) the membrane or layer selectivity is infinite or if there is a constant or low enough concentration of interfering ions; and, (*ii*) potential differences at various phase boundaries are either negligible or constant, except at the membrane-sample solution boundary.

Potentiometric sensors based on liquid or polymer membrane materials are an established technology that successfully spearheaded the integration of sensing devices in the clinical laboratory for the automated testing of physiological samples for key electrolytes such as potassium, sodium, calcium, chloride and pH [8]. Various practical applications of ISEs with recently improved lower detection limits are actually being developed. Their utility for trace metal analysis in drinking water has been documented by obtaining good agreement with results from inductively coupled plasma mass spectrometry (ICPMS) measurements (since the ISE response depends on free ionic activities and ICPMS does not distinguish between the different forms of the analyte, a direct comparison is only possible when the analyte during potentiometric measurements is in its free form) [9].

The performance of potentiometric sensors has been dramatically improved during the last decade. New applications include the study of host-guest equilibria in lipophilic organic phases and trace analysis in environmental samples [9]. One emerging new field is potentiometric bioanalysis using nanoparticle (NP) labels or nanopores, which could eventually provide an inexpensive and highly sensitive technology. The low limits of detection (LODs) and miniaturization possibilities achieved so far by ISEs are opening up interesting application fields: in most of the reported works, NPs were used as labels for the analysis of proteins or DNA sequences, exploiting their direct or indirect electrochemical determination (see [10] and refs. therein). Recent improvements in the LODs of ISEs based on polymeric membranes containing selective receptors (ionophores) yielded sensors for the direct measurement in the sub-nanomolar concentration range [10]. This accomplishment was made possible by minimizing passive zero-current ion fluxes from the membrane into the sample solution. It is now possible to use miniaturized ISEs for detecting the fM amounts of ions in micro-volume samples since there has been no deterioration expected in the signal or even LOD as the sample volume is reduced.

Among the above mentioned detection systems, CPEs, CMCPEs, and CP-biosensors (*i.e.*, bare and chemically / biologically modified carbon paste electrodes) take important position in the form of ion-selective electrodes, CP-ISEs, applicable in determinations of inorganic and organic species. Typically, they are applied in both direct potentiometry and potentiometric titrations; the latter utilizing often the ion-pair formation principles. (Note: modern potentiometric measurements with carbon paste-based electrodes comprise also some chronopotentiometric techniques such as PSA or CCSA [1,5]. Due to rather different principal background and the corresponding instrumentation, they are not considered hereafter.)

Carbon Pastes and Their Main Characteristics

Carbon paste, which is a mixture of graphite powder and a suitable liquid binder, represents one of the most frequent laboratory-made electrode materials and apparently is the most flexible substrate for chemical and biological modifications [5]. Among the rest, the carbon paste mixtures were prepared from acetylene black, glassy carbon microparticles with an organic pasting liquid, pulverized diamond, fullerenes (C_{60}), and the most frequent choices in the carbon paste configuration - various types carbon nanotubes [11-13].

Because of the presence of binder, in common mixtures represented by highly lipophilic liquids [5], carbon pastes have typically hydrophobic surface which, in aqueous solutions, repel hydrophilic species involved in the electrode transformations of numerous redox systems. The result is specific reaction kinetics at CPEs which further depends upon the actual carbon paste composition and the quality of both main components. Typical compositions of common carbon paste mixtures are being quoted to be approximately 1.0 g graphite powder – 0.5 – 1.0 mL liquid binder [5]. The huge number of CPEs used worldwide belongs to pastes with insulating liquids (paraffin oil, silicon oil, bromonaphthalene, tricresylphosphate and others). The basic requirements for a pasting liquid are its practical insolubility in the solution under measurement, a low vapor pressure to ensure both mechanical stability and long lifetime, and further, in the case of voltammetric and amperometric applications, its electrochemical inactivity in the potential window of interest.

Preparation of carbon paste electrodes where ionic liquids (ILs) are used as a binder has been reported in several studies [14-16]. Room temperature ionic liquids (RTILs) have attracted considerable attention due to their unique physical and chemical properties, such as negligible vapor pressure, high thermal and chemical stability, high conductivity, the ability to dissolve a wide range of organic and inorganic molecules [17,18], wide electrochemical potential window, the ability to facilitate direct electron-transfer reactions, good biocompatibility [18], etc. Especially, they can be used both as electrolyte and solvent [18]. These properties attract intense interest in the fields of electrochemistry and analytical electrochemistry [19]. However, one major concern was the high background current which limits the analytical utility of these IL-based pastes.

The heterogeneous character of CPE, the specific influence of the liquid binder, the variability of the used carbon material, and the various proportional compositions require a broad and reliable spectrum of characterization methods.

The topic of characterization measurements with CPEs and related sensors has been reviewed [20] together with numerous practical hints with regard to how to select the proper carbon paste components and how to test the freshly made carbon paste mixtures. The modification of carbon pastes represents a unique approach, when the electrode is modified simultaneously on the surface and in the bulk. Among numerous specifics of carbon pastes, the rather individual behavior of the corresponding mixtures - differing from paste to paste and from laboratory to laboratory - is often emphasized. On one hand, one can appreciate the advantage to control the desired properties of a particular mixture; on the other hand, it can be a certain limitation, with respect to the choice of a CPE for routine analysis, where commercially available electrodes with unambiguously defined behavior are usually preferred [21].

Due to numerous advantageous properties and characteristics [5], CPEs are widely used mainly for voltammetric measurements; however, carbon paste-based sensors are also applicable in amperometry, coulometry, and potentiometry. In contrast to the relatively complicated modifications of solid substrates, carbon pastes can be modified simply to obtain quantitatively new sensors with desired, often predefined, properties [5]. Recently, a review was published [22] in the form of a retrospective compilation presenting the field by means of various facts, data, surveys, and summaries that illustrate individual achievements and milestones.

Carbon paste mixtures are divided into two basic categories unmodified and chemically (biologically) modified carbon pastes. Regarding biologically modified variants, the most frequent term for their reference is carbon paste biosensors. Also, three major groups of substances, comprising *1)* organic derivatives, including environmental pollutants, *2)* biologically important compounds, and *3)* pharmaceuticals plus narcotics represent the remaining two thirds of the analytes sharing the database of electroanalysis with CPEs, CMCPEs, and CP-biosensors.

The reason why CPEs are so popular can be seen mainly in the fact that carbon pastes are easily obtainable at minimal costs and are especially suitable for preparing an electrode material with desired composition, and hence, with pre-determined properties. Such a position is undoubtedly the result of optimal constellation of physicochemical and electrochemical properties of this carbon-like substrate, which soon obtained a high reputation among both theoretical and practical electrochemists, as well as elsewhere, beyond the boundary of electrochemical sciences. Electrodes made in this way are usually thought to be used as highly selective sensors for both inorganic and organic electrochemistry [5].

Carbon Paste-Based Ion-Selective Electrodes

In comparison with ion-selective electrodes based on polymeric membranes, the CMCPEs possess advantages of much lower ohmic resistance, very stable response, easy renewal of its surface, and ease of preparation. An important advantage for CPEs is that they do not need an internal solution, which in some cases represent a problem of being reactive toward the metal of the internal reference system. Modified carbon pastes are very useful materials for fabricating electrometric sensors for analytical determination various agents [7,22-25].

Determination of Anions

Most of the reported potentiometric carbon paste electrodes were cation-selective and only few papers have been reported about anion-selective electrodes [3,4,26-34].

Iodide. Various PVC membrane-selective electrodes have been used for determination of iodide, such as electrode based on ion exchangers [35], silver(I) thiourea complexes [36], bis(benzoin)semiethylenediamine complex of mercury(II) [37] and Schiff-base complexes of cobalt(II) [38].

An iodide-selective carbon paste electrode based on a synthesized Schiff-base complex of Fe(III) [26] and cetyltrimethylammonium iodide ion-pair (CTMAI) have been described [27]. The versatility of the CTMAI-modified CPE [27] has been examined for the determination of iodide content in *Flaxedil* (gallamine triethiodide, pharmaceutical preparation [28,29]). A sparingly soluble complex of cetyltrimethylammonium iodide was instantaneously formed upon the addition of a cetyltrimethylammonium bromide (CTMABr) solution to a solution of potassium iodide. The dry powder of the formed ion pair was used to construct of iodide ion-selective carbon paste electrode (composition of the complex CTMA-I is 1:1). CTMAI-modified CPE was prepared by thoroughly mixing weighed amounts of CTMAI, high-purity graphite, dibutyl sebasate and paraffin oil until obtained a uniformly wetted paste. The electrode shows a linear response for iodide ion over the concentration range of 4×10^{-5} M to 0.1 M with a lower detection limit of 4×10^{-5} M at 25 ^{o}C. The electrode has a Nerstain slope of 55.0 ± 0.4 mV per decade and a fast potential response of 45 s, which is constant over a pH range of 5.0 – 9.0. Selectivity coefficient data of the CTMAI-CPE for some common ions (SCN^-, NO_3^-, Cl^-, Br^-, F^-, ClO_4^-, SO_4^{2-}, $Cr_2O_7^{2-}$, IO_4^-, PO_4^{3-}, AcO^-)

show negligible interference, and the electrode has high selectivity towards the iodide ion. The selectivity coefficient was calculated from the following equation:

$$(E_1 - E_2)/S = \log a_I - \log K_{I,J}^{pot} (a_j)^{1/y}$$

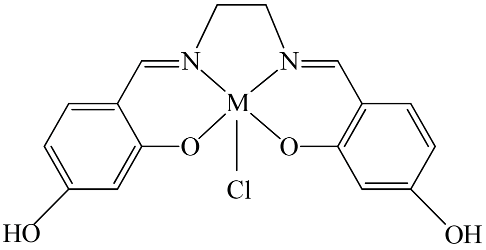
where E_1 and E_2 are the potential readings observed after 1 min of exposing the sensor to the same concentration of iodide ion and interfering ions alternatively; a_I and a_j are activities or concentrations of the iodide ion and interfering ions, y is the change of the interfering ion, and S the slope of calibration graph (mV/concentration decade). An average recovery of 101.83% with a relative standard deviation of 1.53% has been achieved for the determination of iodide in *Flaxedil* ampoules. The electrode has been successfully utilized for the determination of iodide in saline water and as end-point indicator electrode for the determination of $Hg(II)$ and phenylmercury(I) in their aqueous solutions using potentiometric titration with a potassium iodide standard solution [27].

Bromide. Since the halide ion selective electrodes possess a wide variety of applications especially in clinical chemistry, in the past decade, a relatively large number of carrier-based ion-selective polymeric membranes for chloride and iodide ions have been reported in the literature (see [30] and refs. therein).

However, despite the urgent need for selective determination of bromide ion in different industrial, environmental and clinical samples, there are only a limited number of previous reports on the carrier-based ion-selective membrane sensors for bromide ion (again, see [30] and the respective refs.). Shamsipur *et al.* employed a hexa-coordinated mercury(II) complex of a pyridine containing proton transfer compound {$(pyda.H)_2[Hg(pydc)Cl]_2$ x $2H_2O$}n (where pyda = 2,6-pyridinediamine and $pydc.H_2$ = 2,6-pyridinedicarboxilic acid) as an ion-carrier to construct a highly selective CMCPE for potentiometric determination of Br^- ion. The electrode has a linear dynamic range between 3.0×10^{-2} and 1.0×10^{-5} mol/L with a near-Nernstian slope of 61.0 ± 0.9 mV per decade and a detection limit of 4.0×10^{-6} M (0.32 ppm). The potentiometric response is independent of the pH of the solution in the pH range 4.0 – 8.3. The electrode possesses the advantages of low resistance, fast response and good over a variety of other anions. It was applied as an indicator electrode in potentiometric titration of bromide ions and for the recovery of Br^- from tap water [30].

Sulfate. The quick determination of trace quantities of sulfate ion by simple methods such as potentiometric using ISEs is important in chemical, industrial, environmental and pharmaceutical samples [39]. However, because of high hydrophilic characteristic of SO_4^{2-}, construction of suitable ISEs for sulfate ion have been difficult [40-42]. Most of the reported solid state and ionophore-free ion exchanger sulfate-selective electrodes have not been satisfactory due to the lack of adequate selectivity [43]. Only carrier based sulfate-selective electrode with relatively good selectivity and sensitivity were reported [39,44]. However, all of these electrodes were based on PVC polymeric liquid membrane electrodes.

Soleymanpour *et al*. [31] employed Schiff base complex of $Cr(III)$ {*N*,*N*'-ethylene-bis(5-hydroxysalicylideneiminato) chromium(III) chloride} (see Scheme 1) as an ion carrier to construct a modified carbon paste electrode for the potentiometric determination of SO_4^{2-} which displayed good response characteristics to sulfate ion.



Scheme 1: Structure of metal Schiff base complexes.

The modified CPE showed good response characteristics to SO_4^{2-} ion [31]. The electrode exhibits a Nernstian slope of 28.9 ± 0.4 mV per decade for SO_4^{2-} ion over a wide concentration range from $1.5 \times 10^{-6} – 4.8 \times 10^{-2}$ M, with a detection limit of 9.0×10^{-7} M. The CPE electrode manifested advantages of relatively fast response time, suitable reproducibility and life time and, most important, good potentiometric selectivity relative to a wide variety of other common inorganic anions. These characteristics are comparable to the previously reported PVC membrane sulfate-ion selective electrodes. The potentiometric response of the electrode is independent of the pH of the test solution in the pH range 4.0 – 9.0. The chemically modified carbon paste electrode based on Cr(III) / Schiff-base complex can be used as a useful analytical tool and interesting alternative for the determination of otherwise not easily quantifiable sulfate ion in different samples.

The electrode permits the direct measurement of sulfate ion in different real samples such as tablet and water without prior separation steps: it was used as an indicator electrode in potentiometric titration of sulfate with Ba^{2+} ion, the determination of zinc in zinc sulfate tablet and also determination of sulfate content of a mineral water sample [31].

Heteropoly Anions. Salts of some heteropoly anions (mostly 12-tungstophosphates) can be incorporated as electroactive ion-exchangers into membranes of ion-selective electrodes used in direct potentiometric determination of various cations and, in addition, the solutions of these salts can also be used as anionic titrants in potentiometric ion-pair formation-based titrations. Applications have been described in the determination of salts of various alkaloids, antibiotics, vitamines, cationic and non-ionic surfactants, etc. (see [3] and refs. therein].

Vytřas *et al.* investigated the possibility of the use of heteropoly anions formed by addition of phosphate in the solutions of either molybdate or tungstate in the determination of phosphorus using carbon paste electrodes as potentiometric indicators. The heteropoly anions are titrated on the ion-pairing principle using a titrant containing a lipophilic counter-ion {1-(ethoxycarbonyl)pentadecyltrimethylammonium bromide (Septonex)}, the titration being monitored by carbon paste electrode. Calibration plots of the titrant end-point consumption *vs.* concentration are not linear, but allow one to evaluate the content of phosphorus. Similar procedures, when optimized, could be elaborated for determination of numerous other elements forming heteropoly anions [3].

Arsenic(V) is able to form 12-heteropoly anions of general formula $\left[AsM_{12}O_{40}\right]^{3-}$ where *M* represents either $Mo(VI)$ or $W(VI)$. Especially, molybdo-heteropoly anions are of some importance in analytical chemistry of arsenic(V) [32]. Determination of arsenate based on its conversion to molybdo-arsenate heteropoly anions followed using potentiometric titration has been described by Vytřas *et al.* [32]. The titration has been realized on the ion-pairing principle using cetylpyridinium chloride (or an analogous titrant containing a lipophilic cation), and monitored by a carbon paste electrode. The method could be applied in the analyses of samples with a low arsenic content (amounts ~10 µg As in 50 cm^3 could be titrated). This method is very useful in cases of colored or turbid samples, where spectrophotometric methods are inapplicable [32].

Other Anions. Potentiometric carbon paste electrode has been applied for the determination of chromium(VI) [33], perchlorate and fluoroborate ion [4].

A trace level of $Cr_2O_7^{2-}$ was determined in 2.0 mol L^{-1} H_2SO_4 (at 20 °C) with a carbon paste electrode (mixture of liquid paraffin and spectroscopically pure graphite, without ionophore) by using a potentiometric method with the linear range within $2.2 \times 10^{-7} - 3.2 \times 10^{-6}$ mol L^{-1}, response slope at 130 – 180 mV decade^{-1}, and a detection limit at 3×10^{-8} mol L^{-1} [33]. The respective interferences by some common ions were brought under study. An evaluation was made of the recovery of $Cr_2O_7^{2-}$, with an average value of 99.7% [33].

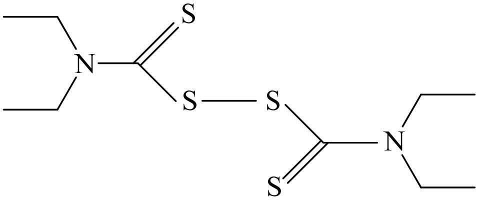
Perchlorate and tetrafluoroborate ion-selective carbon paste electrodes based on different modified pasting liquids were prepared and their basic characteristics were tested in the direct potentiometric measurements [4]. Although the slopes of calibration plots, detection limits as well as selectivity coefficients were similar to those obtained with commercial liquid/plastic membrane type ion-selective electrodes, the carbon pastes offered some advantages as more rapid response and very low ohmic resistance. The electrodes were applied in ion-pair formation-based potentiometric titrations of perchlorate, fluoroborate and iodide ions with cetylpyridinium chloride (CPC) [4]. Further, the perchlorate selective CPEs were successfully applied for the direct potentiometric determination of the ClO_4^- content in organotin compounds of the $Bu_3SnClO_4 \cdot H_2O$ and $Bu_2Sn(ClO_4)_2$ type (Bu = butyl). The ion-pair formation procedure with 0.01 M CPC was utilized in titrimetric determination of perchlorate in solid samples of explosives and in aqueous extracts of rocket propellants [4]. This type of potentiometric CPEs can advantageously be used to monitor the titration based on ion-pairing principles [34].

Detection of Metals

The quest for techniques for analyzing heavy metals, which combine high sensitivity, accuracy and precision with speciation capabilities, has become of utmost importance due to the health threat that some of the heavy metals pose even at very low levels. Electrochemical methods, such as voltammetric or potentiometric stripping analysis that are widely used in water analysis [45], can frequently meet these criteria. Moreover, the analysis of ultralow levels of analytes has frequently been improved using chemically modified electrodes. Although different approaches for electrode modification, including adsorption, covalent attachment, and coating the surface with thin polymeric films have been developed, improving and developing of new approaches still remains an important research topic.

Copper and Mercury. Copper is a natural element that is an essential micronutrient to ensure the well being of all aerobic life forms. It plays a vital role in the development and performance of the human nervous and cardiovascular systems, as well as the skin, bone, immune and reproductive systems, including gene transcription. Copper can also inhibit the growth of microbes, thus providing a measure of protection against harmful germs and bacteria in many environments. It is an essential element that is present in all organisms, but it is toxic at high concentration. Mercury is a heavy metal that causes serious hazardous effects to biota and human health. Although many of its uses have been forbidden, this toxic element is employed in agricultural, industrial and clinical fields. Consequently, there is strong need to develop more accurate, precise and selective methods for mercury determinations to control its level in natural waterways, potable waters, soils, air, industrial wastes and a wide variety of chemical and biochemical samples. Both metals have important industrial uses, even though their toxicity is well recognized. Accordingly, the importance of controlling the levels of these pollutants in natural waterways, potable waters, soils, air and industrial wastes has generated much interest in the development of novel sensors for their detection.

Recently, several copper(II) and mercury(II) ion-selective electrodes have been reported. For copper(II) determinations, ISEs with a solid membrane based on copper sulphide, tungsten oxide, pyrimidine thione derivatives, thiosalicylic acid derivatives, copper complexes and electrodes with liquid membrane have been described (see [46] and refs. therein). For mercury(II) analyses, electrodes with a solid membrane based on triiodomercurate, chalcogenide and ISEs with a liquid membrane (see [46] and refs. therein) have been published, but there are fewer papers, than for copper. Gismera *et al.* [46] have described the construction, potentiometric characterisation, and analytical application of a carbon paste modified electrode based on tetraethyl thiuram disulfide (TETDS) as a potentiometric sensor in copper and mercury determinations (see Scheme 2).



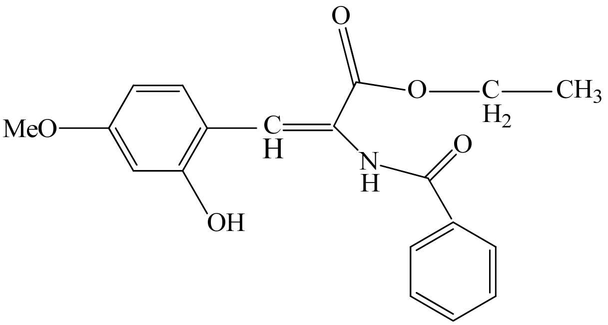
Scheme 2: Structure of TETDS used in the onstruction of the CMCPE.

The electrode presents wide linearity ranges and low detection limits for both metals. The potentiometric carbon paste sensor shows better selectivity to mercury ions than to copper ions. However, the copper response CMCPE has a minor dependence on the pH a shorter response time. Otherwise, the proposed CMCPE exhibits a similar detection limit, shorter response time (10 times better) and a wider pH range where the potentiometric response do not depend on pH than the published copper ISE with liquid membrane (PVC) and TETDS as ionophore [47]. The electrode is successfully used for metal determination in lubricant oil wastes and as an indicator electrode in the potentiometric titration of humic acids in order to obtain information about the complexing properties of these acids.

Tetrazolium–triiodomercurate-modified carbon paste electrode has been examined for the sensitive and selective determination of mercury [48]. The electrode shows a stable, near-Nernstian response for 1×10^{-3} to 6×10^{-6} M $\left[HgI_3\right]^-$ at 25 °C over the pH range of 4.0 – 9.0, with an anionic slope of 55.5 ± 0.4 mV. The lower detection limit is 4×10^{-6} M with a fast response time of 30 – 50 s. Selectivity coefficients of a number of interfering anions (SCN^-, CN^-, NO_3^-, Cl^-, I^-, $S_2O_3^{2-}$, IO_3^-, $H_2PO_4^-$, $[MoP_4]^{2-}$, HCO_3^-) and iodo complexes of some metal ions $\left(Cd^{2+}, Pb^{2+}, Cu^{2+}, Zn^{2+}, Bi^{3+}, Sb^{3+}, Ag^+, Th^+\right)$ have been estimated. The interference from many of the investigated ions is negligible. The determination of 1 – 200 µg/mL of mercury in aqueous solutions shows an average recovery of 98.5% and a mean relative standard deviation of 1.6% at 50.0 µg/mL. The electrode has been applied for the direct potentiometric determination of mercury in wastewater samples, amalgam and dental alloys and the results were compared with those obtained using cold vapor atomic absorption spectrometry (CVAAS).

The electrode in conjunction with an $Ag/AgCl$ reference electrode has also been examined as an end point indicator electrode for some potentiometric reactions. Potentiometric titration of mercury and phenylmercury acetate with standard potassium iodide has been monitored using the triiodomercurate–carbon paste electrode as an end point indicator electrode.

A modified carbon paste electrode based on a ligand of ethyl-2-(benzoylamino)-3-(2-hydroxy-4-methoxyphenyl)-2-propenoate (EBHMP, Scheme 3) as a suitable carrier for Hg^{2+} ion has been investigated by Mashhadizadeh *et al.* [49].

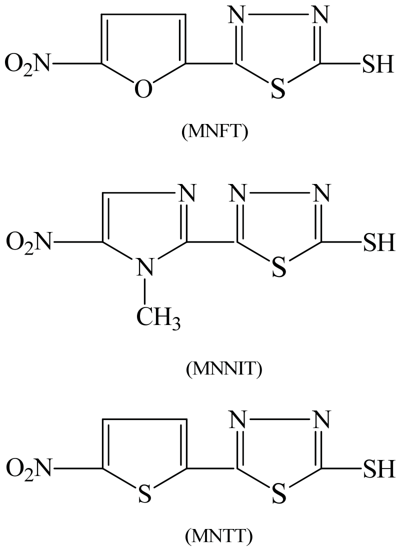


Scheme 3: Ethyl-2-(benzoylamino)-3-(2-hydroxy-4-methoxyphenyl)-2-propenoate.

The electrode exhibits a slope of 48.5 × 1.0 mV per decade for Hg^{2+} ion over a wide concentration range from $3.0 \times 10^{-7} - 3.1 \times 10^{-2}$ M. The lower detection limits are 1.0×10^{-7} M Hg^{2+}. The electrode has a fast response time (around 5 s) and shows a good selectivity toward Hg^{2+} ion in comparison to other common cations. The potentiometric responses are independent of the pH of the test solution in the pH range 1.0 – 4.0. The electrode was used as an indicator electrode in potentiometric titration of mercuric ion with standard solution of EDTA. The direct determination of mercury in spiked wastewater and a sample of dental amalgam gave results that compete favorably with those obtained by the cold vapor atomic absorption spectrometric method [49].

Furthermore, a chemically modified carbon paste electrode based on *N,N′*-disalicylidenehexameythylenediaminate $Cu(II)$ complex (*i.e.*, CuSALHMN) has been utilized for determination of Cu^{2+} in real samples [50]. The electroanalytical performance of this electrode was investigated and characterized with the aid of potentiometric measurements. As found out, the sensor developed has exhibited a good linear response of 31.2 ± 1.0 mV per decade over the concentration range of $4.1 \times 10^{-7} - 0.01$ mol l^{-1}. The respective method has offered a very low limit of detection of about 6×10^{-8} mol l^{-1} (*i.e.*, 3.9 ppb Cu), with response time less than 12 s. In addition, the electrode has revealed a very good selectivity with respect to alkali, alkaline earth, and some transition metal ions when used in the pH range of 4.0–6.5. Finally, this CMCPE was successfully applied as an indicator electrode for potentiometric titration of the Cu^{2+} ions with EDTA and for direct detection of copper in multivitamin tablets and tap water [50].

Metal nanoparticles play an important role in modern bioanalytical chemistry due to their usefulness for the preparation of sensors giving rise to improved responses from biological compounds with respect to those observed at conventional metal surfaces. Gold nanoparticles display electronic, chemical and physical properties that may be employed in optical and electronic devices, catalysis, and sensor technology [51]. In particular, gold nanoparticles have demonstrated to be very appropriate for the development of modified electrodes. Gold nanoparticles allow the construction of electrode nanoarrays in one or several dimensions. Colloidal gold-modified electrodes have been prepared using glassy carbon [52], metal Au [53] and carbon paste [54] as electrode substrates. Three mercapto compounds [2-mercapto-5-(1-methyl-5-nitroimidazole-2-yl)-1,3,4-thiadiazole] (MMNIT), [2-mercapto-5-(5-nitrofuran-2-yl)-1,3,4-thiadiazole] (MNFT) and [2-mercapto-5-(5-nitrothiophen-2-yl)-1,3,4-thidiazole] (MNTT) were used for self-assembled-gold nanoparticle (SAGNP) modified carbon paste electrodes (Scheme 4) [55].


(MNFT)

(MNNIT)

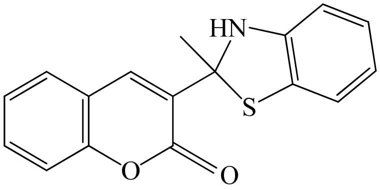
(MNTT)

Scheme 4: Structures of mercapto compounds used as ionophore in the proposed electrodes.

The electrodes were applied as indicator electrodes to the potentiometric determination of $Cu(II)$ ion, exhibiting a Nernstian slope of 31.0 ± 0.5 mV per decade for $Cu(II)$ ion over a wide concentration range of $7.9 \times 10^{-9} - 3.2 \times 10^{-2}$, $7.9 \times 10^{-9} - 7.9 \times 10^{-4}$, and $2.8 \times 10^{-8} - 7.9 \times 10^{-3}$ M for MMNIT, MNFT and, MNTT, respectively.

The detection limits of electrodes were 3.5 (± 0.2) × 10^{-9}, 4.1 × 10^{-9}, and 4.1 × 10^{-8} mol L^{-1} of Cu(II) ion, respectively. The potentiometric responses of electrodes based on MMNIT, MNFT, and MNTT are independent of the pH of test solution in the pH range 2.0 – 5.5, 2.5 – 7.0, and 2.0 – 6.5, respectively. They have quick response with response time of about 5 s. Again, the electrodes show fairly good selectivity over some alkali, alkaline earth, transition, and heavy metal ions and they were successfully employed to detect $Cu(II)$ ion in hair and water samples [55].

Onward, nanocomposite based carbon paste ion-selective electrode for analysis of copper was investigated [56]. Different amounts of the ionophore (3-(2-methyl-2,3-dihydrobenzothiazol-2-yl)-2H-chromen- 2-one, L (Schema 5) acts as a suitable ion carrier in fabrication of Cu^{2+} carbon paste electrode) along with appropriate amount of graphite powder, nanosilica and MWCNTs were mixed for construction CPE. The sensing material used in this sensor was a coumarin derivative.

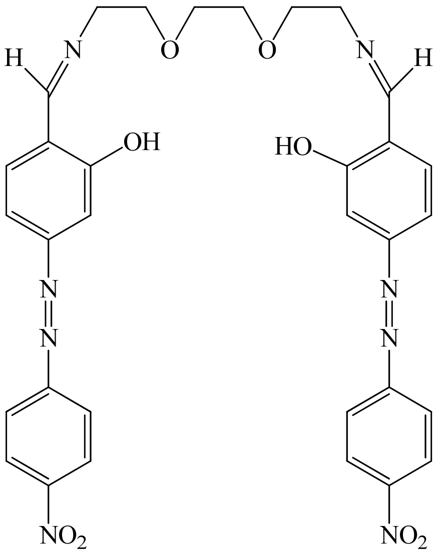


Scheme 5: Chemical structure of L.

Conductomeric study in acetonitrile solution showed a selective interaction between sensing material and copper ions in comparison with other common metal ions. MWCNT in the composition of the carbon paste improves the conductivity of the sensor, and increases the transduction of the chemical signal to electrical signal. If the conductivity of the carbon paste electrode increases, the dynamic working range of the sensor also improves. Nanosilica in the composition of the carbon paste can also improve the response of the electrode. Nanosilica is a filler compound which has highly specific surface area that helps extraction of the ions into the surface of the CPE. In addition, using nanosilica in the carbon paste enhances the mechanical properties of the electrode [56]. The electrode showed a stable potential response to Cu^{2+} ions with Nernstian slope of 29.3 ± 0.5 mV per decade over a wide linear concentration range of 10^{-6} – 10^{-1} mol L^{-1}. The electrode has short response time of 15 s and could be used for a period of six weeks for detecting copper ion in waste water samples.

Silver. Electrodes consisting of silver chloride, silver chloride-silver sulphide, silver bromide-silver sulphide or silver iodide-silver sulphide with carbon-nujol or carbon-paraffin wax have been investigated by Mesaric and Dahmen [57]. The electrodes have low ohmic resistance, showing a rapid response (within 2-5 mV) for halide, X-, and Ag(I) ions down to 5 × 10^{-5} M Cl^-, 1 × 10^{-5} M Br^- and 5 × 10^{-7} M I^-, with the respective electrode(s). The ion-selective carbon-paste electrodes are suitable for determination of halide ions as well as silver ion in aqueous solutions by direct potentiometric measurement and potentiometric titration [57].

Mashhadizadeh *et al*. used a Schiff base of [bis 5-(4-nitrophenyl azo)salisylaldimine] 1,8-diamino, 3,6-dioxo octan (BNSAO, Scheme 6) as a carrier in construction of a modified carbon paste electrode for silver ion [58].



Scheme 6: Chemical structure of BNSAO.

The influences of the membrane compositions on the potential response of the Ag^+ sensors were investigated. The electrode exhibits a Nernstian slope of 58.4 ± 0.3 mV per decade for Ag^+ ion over a wide concentration range from 3.1 × 10^{-2} to 9.0 × 10^{-7} M. The CPE has limit of detection of 6.3 × 10^{-7} M and a fast response time (~5 s) . The sensor shows a fairly good selectivity toward Ag^+ ion in comparison to other common cations. The potentiometric response is independent of the pH of the test solution in the range of pH 3.5 – 7.0.

The proposed electrode was used as indicator electrode in potentiometric titration of silver ion with standard solution of potassium iodide. The direct determination of silver in spiked wastewater and radiology film gave results that compare favorably with those obtained by the atomic absorption spectrometric method.

Artificial neural network (silver, mercury and copper). In recent years, artificial neural network (ANN) as a powerful non-parametric non-linear modeling technique has attracted increasing interest (see [59] and refs. therein). The strength of modeling with layered, feed-forward ANNs lies in the flexibility of the distributed soft model defined by the weight of the network. The multilayer feed forward neural network trained with back-propagation learning algorithm becomes an increasingly popular technique (see [59] and refs. therein). The application of ANN to non-linear calibration of ion selective array and multi-metal analysis utilizing optical sensors, quantitative structure-activity relationship, optimization of experimental conditions, and modeling of reaction kinetic data have been reported (see [59] and refs. therein).

Shamsipur *et al*. [59] used a three-layer ANN with back-propagation of error algorithm for modeling the relationship between potential and concentration through a multicomponent potentiometric titration of Ag^{+}, Cu^{2+} and Hg^{2+} with thiocyanate as a titrant using an unmodified carbon paste electrode as the indicator electrode. This modeling could process the non-linear relationship between the potential at a given volume of the titrant and precisely predict the concentration of the three cations in synthetic, unknown sample solutions [59]. In the paper the network architecture and parameters were optimized to give low prediction errors. For all cations, high correlation coefficients ($r > 0.990$) were obtained.

Other Metals (Co, V, Sb, Tb). Cobalt is a biologically essential trace element. Although cobalt is required only in min amounts for maintaining normal health, a lower or higher concentration of it may lead to deficiency or toxicity states, respectively, resulting in impairment or abnormalities of health. There have been several reports on cobalt-selective electrodes that make use of chelates as sensor materials in PVC membranes (see [60] and refs. therein). A modified CPE based on a cyclam (1,4,8,11-tetraazacyclotetradecane) as a modifier was investigated for the determination of $Co(II)$ ions [60]. Cyclam as a modifier for the carbon paste electrode, occupies an intermediate position between crown ethers and cryptands. The former shows rapid cyclization coordination for guest cations, while the latter forms rigid and encapsulated complexes. The existence of four nitrogen atoms in the structure of the ligand as well as its sufficiently high rigidity and lipophilicity was expected to increase both the selectivity and stability of its transition and heavy metals ions complexes over alkali and alkaline earth cations [60]. The utilized CMCPE shows a Nernstian slope 28.4 mV per decade over a concentration range $5.0 \times 10^{-6} - 1.0 \times 10^{-1}$ M of Co^{2+} ions with detection limit 2.5×10^{-6} M. The sensors exhibits good selectivities for Co^{2+} over a wide variety other cations. It can be used as an indicator electrode in potentiometric titration of cobalt(II) ions, as well as in direct determination of Co(II) ions in wastewater of acidic electroplating baths.

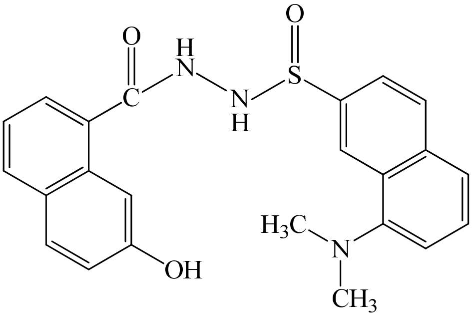
Abundant references concerning the determination of vanadium with EDTA is available in literature. Many efforts have been performed in order to develop direct procedures for the determination of vanadium(V) with EDTA – $V(V)$ has tendency to form polymerized species strictly dependent on pH. Quintar *et al*. studied a chemically modified electrode as a potentiometric sensor for the end-point detection in the automatic titration of vanadium(V) with EDTA [61]. The electrode was constructed with a paste prepared by mixing spectral-grade graphite powder, Nujol oil and *N*-2-naphthoyl-*N*-*p*-tolylhydroxamic acid (NTHA). Interference ions were separated by applying a liquid–liquid extraction procedure. The CMCPE did not require any special conditioning before using. It could be continuously used, at least two months without removing the paste. Automatic potentiometric titration curves were obtained for $V(V)$ within 5×10^{-5} to 2×10^{-3} M with acceptable accuracy and precision. The method was applied to determine $V(V)$ in alloys for hip prothesis [61].

Antimony is ubiquitously present in the environment as a result of natural processes and human activities. It exists mainly as $Sb(III)$ and $Sb(V)$ in environmental, biological and geochemical samples. According to European community standard [62], the maximum admissible concentration of antimony in surface and drinking water is 10 μg/L. In addition to its industrial application, the derivatives of antimony are utilized in therapeutic agents against several major tropical parasitic diseases. As the toxicity and physiological behavior of antimony, has paid for more accurate, precise and selective methods for the determination of antimony. Most of electrochemical methods reported for selective determination of antimony are mainly voltammetry (see [63] and refs. therein). Mostafa [63] has described the construction, potentiometric characterization and analytical application of a modified carbon paste electrode selective for antimony based on the use of TIA-CP (tetraiodoantimonate anion with cetylpyridinium counter cation) and TIA-TPT (tetraiodoantimonate anion with triphenyl tetrazolium counter cation) ion association complex as electroactive material.

The two sensors exhibits fast, stable and near-Nernstian for the mono charged TIA anion over the concentration range 1×10^{-6} to 1×10^{-3} M at 25 °C in the pH range 4 – 10 with anionic slope of 58.0 ± 0.5 and 55.0 ± 0.7 per concentration decade for TIA-CP and TIA-TPT, respectively. The lower detection limits are 4 and 5×10^{-6} M and response time are 20 and 30 s in the same order of both electrodes.

Selectivity coefficients for antimony relative to a number of different cations and anions were also investigated. There is negligible interference from many inorganic cation and anion except for Hg^{2+}, Cd^{2+}, and Bi^{3+}; however, their effect were eliminated by EDTA. The determination of 1.0 – 120.0 µg/mL of antimony in aqueous solutions shows an average recovery of 99.0 and 97.5% with relative standard deviation of 2.0% for both electrodes at 40 µg/mL. The determination of antimony in wastewater and some antibilharzial compounds using the investigated electrodes gave results that compare favorably with those obtained by the atomic absorption spectrometric method. Precipitation titrations involving cetylpyridinium chloride as titrant are monitored with both electrodes with inflection point of 180 and 100 mV for TIA-CP and TIA-TPT, respectively [63].

Terbium and other Lanthanides, considered only lightly toxic, are used for gasoline-cracking catalysts, carbon arcs, and in movie projectors. Spectrophotometry, spectrofluorimetry, ICP-MS and inductively coupled plasma atomic emission spectroscopy (ICP-AES) are the main methods for the low-level monitoring of terbium ions in solutions. Owing to a strong interaction between *N*'-(2-naphthoyl)-8-(dimethylamino)naphthalene-2-sulfonohydrazide (L; Scheme 7) with Tb^{3+} ions, L was used as the ionophore in a composite carbon paste electrode [64].



Scheme 7: Chemical structure of L.

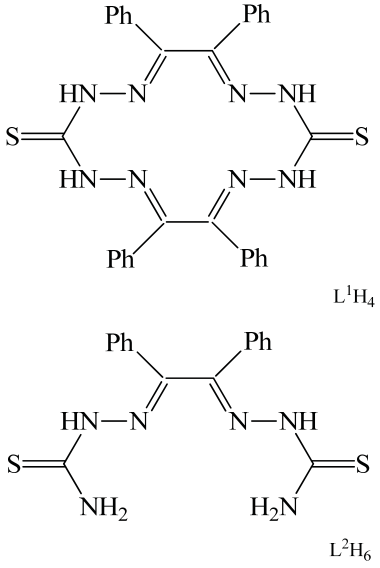
The electrodes were made based on a nano-composite including multi-walled carbon nanotube, graphite, and room temperature ionic liquid, 1-n-butyl-3-methylimidazolium tetrafluoroborate, *[BMIM]BF$_4$*. Ionic liquids are salts with relatively low melting points that encompass a subcategory namely room temperature ionic liquids that are such compound being liquid in room temperature. Good solvating properties, high conductivity, non-volatility, low toxicity, good electrochemical and chemical stability, low vapor pressure, low toxicity, low melting temperature, high ionic conductivity are properties of ILs [65,66] that make them good candidates for being used as binders in CPEs. Carbon nanotubes (CNTs), on the other hand, enjoy interesting physicochemical properties, including ordered structures with a high aspect ratios, ultra-light weights, high mechanical strengths, high electrical conductivities, high thermal conductivities, metallic or semi-metallic behaviors and high surface areas [67,68], the combination of which makes them unique materials that can find a variety of applications. The nanocomposite carbon paste electrode showed improved sensitivity, selectivity, response time, response stability and lifetime in comparison with typical Tb^{3+} carbon paste sensor based L [64]. The best results were observed for nanocomposite sensors with electrode composition of 15% L + 15% *[BMIM]BF$_4$* + 60% graphite powder + 10% MWCNT. The electrode exhibited a Nernstian response (19.9 ± 0.2 mV per dec.) in the range of $7.5 \times 10^{-8} – 1.0 \times 10^{-2}$ mol L^{-1} with a LOD of 6.0×10^{-8} mol L^{-1} and in the pH range of 3-8.

Analysis of Acids

Humic Acids. Humic substances (HS’s) are naturally occurring, bio-organic, and heterogeneous organic materials and contain a wide variety of oxygen-containing functional groups, such as carboxyl $(COOH)$, carbonyl $(C=O)$, and hydroxyl (OH), which are capable of complexing metal ions. These substances are the most important complexing ligands for metal ions in natural waters, soils, and sediments and control the chemistry and determine the fate of the metal ions in natural environmental systems (see [69] and refs. therein). HS’s from various sources have been shown to react with heavy or polluting metal ions such as $Cu(II)$ and $Pb(II)$ (see [69] and refs. therein).

Gismera *et al*. [70] applied carbon paste ion-selective electrodes, based on complexes of copper, for potentiometric titrations of humic acids (HAs) with copper(II). The authors investigated the behavior of potentiometric carbon paste modified electrodes based on several copper complexes with two derivatives of thiocarbazide and thiosemicarbazide: 3,4,10,11-

tetraphenyl-1,2,5,8,9,12,13-octaaza-cyclotetra-deca-7,14-dithizone-2,4,9,11-tetraene $\left(L^1H_4\right)$ and benzilbisthio-semicarbazone $\left(L^2H_6\right)$ Scheme 8).


L^1H_4

L^2H_6

Scheme 8: Structure of ligands.

These ligands, as a result of their structure, bind metal cations with varying ionic strength [70] and they are suitable as electroactive materials for use in ion-selective electrodes. The calibration graphs were linear for a wide concentration range ($1.0 \times 10^{-5} - 1.0 \times 10^{-2}$ M). The limits of detection for $Cu-L^1$ (1:1) and (1:2) complexes were pCu = 5.2 and 4.8, whereas for $Cu-L^2$ (1:1) and (1:2) complexes were pCu = 5.6 and 4.8, respectively. The response times for these electrodes were fast and stable potentials were obtained within 2 – 18 s for concentrations higher than 1×10^{-4} M. The electrodes are very useful for the determination of complexation characteristic of natural ligands with copper.

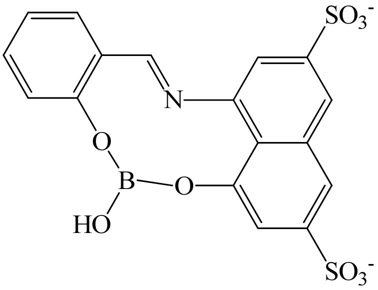
A mercury(II) ion selective carbon paste electrode based on dithiosalicylic acid (DTSA) have been utilized for potentiometric measurement of mercury(II) ions in solution and potentiometric titrations of humic acids [71]. Although dithiosalicylic acid has been used in a copper ion selective electrode [72] the sulfur atoms in the molecule display greater affinity for mercury than copper ions [46].

The mercury ion-selective carbon paste electrode based on DTSA exhibits wide linearity range of response and high selectivity for mercury ions. Also the DTSA sensor presents a detection limit lower than others mercury ISEs previously reported in the bibliography (1.8×10^{-8} M). These good analytical characteristics allow this CMCPE to be successfully used as indicator electrode in humic acids titrations to investigate their complexing properties. The methodology can be used to study adequately the binding to medium and weak sites present in HA macromolecules. These binding sites are present in HA molecule in the higher concentration and therefore they are the most interesting in environmental studies because they control the metal fixation.

Thioglycolic Acid. Thioglycolic acid (TGA) and its salts are frequently used in hair-waving, depilatory products and also in the preparation of culture media. Several complexes of transition metals have been applied as catalysts in oxidation of TGA (see [73] and refs. therein). Phthalocyanine complexes of transition metals are known as redox mediators in the electrochemical oxidation of thiols (see [73] and refs. therein). Cobalt phthalocyanine (CoPc) and its derivatives have been shown to act as effective electrocatalysts towards a wide range of redox systems. Electrodes modified with this compound have shown great promise for the electrocatalytic determination of many important compounds such as herbicides, thiols, hydrazine, carbohydrates, aliphatic amines and phenols, mainly with regard to their catalytic activity toward oxygen reduction or the possibility for decreasing the required potential of various reactions (again, see [73] and refs. therein). The voltammetric behavior of thioglycolic acid has been studied at a carbon paste electrode modified with cobalt phthalocyanine [73]. Further, this CoPc-modified carbon paste electrode has been successfully applied as a sensitive potentiometric sensor for the determination of TGA in hair-treatment ointment and culture media. The detection limit of sub-micromolar was obtained for the potentiometric determination of TGA. A high sensitivity and a low detection limit, together with the very easy preparation of the electrode, makes the whole system useful for constructing simple devices for the determination of TGA [73].

Boric Acid. Boron is an essential element for the plants and fruits and its deficiency can cause damages during growth, but in particular affects adversely form and color. The basic importance of the boron in animals and human beings has not been identified; nevertheless the excess of Boron can affect seriously the human beings health. Boron has been mainly determined by atomic absorption / emission, gamma radiation method [74,75].

It has been shown that a carbon paste electrode modified with a β-Cyclodextrine-Azomethine-H inclusion complex was useful for the potentiometric determination of H_3BO_3 in aqueous solution where Azomethine-H plays the role of recognition agent for H_3BO_3 (Scheme 9) [76].



Scheme 9: Structural formula of Az-Boron complex

However, after the first determination, the amount of Azomethine-H on the electrode surface diminished to about 80% of the initial value. In order to improve the electrode time-life two polymers: glutaraldehyde and Nafion were used to avoid the loss of the recognition agent [76].

Biologically and Pharmaceutically Important Compounds (BIC and PIC)

As already mentioned, ion-selective electrodes are widely used for the direct potentiometric determination of ion activities or ion concentrations in different samples. Particularly, the feasibility, their use in continuous, as well as *in-situ* applications may impose a strong competition on the currently established methods like official chromatographic methods.

Under a variety of membrane types, solvent polymeric membranes have proved to be especially suited for clinical analysis since they can easily be manufactured in different sizes and shapes and are less affected by the response of biological substrates such as protein, enzyme, antibody. The membranes were made from liquid and plasticized polyvinylchloride and are based on a water-insoluble ion-pair complex acting as ion-exchanger. Some problems have been encountered with membranes; *e.g.*, the requirement of extensive pre-conditioning treatment, care in storage, and sensitivity to some hydrophobic counter ions, and a relative short lifetime. The biosensors based on carbon paste electrodes have been extensively used to investigate biomolecules, pharmaceutical compounds, or drugs [77-81].

The development of surface-confined DNA modified carbon paste electrodes has drawn much attention for the important applications in the preparation of biosensors and in the studies of the interactions between DNA and other molecules [77-81]. The text below aims to confirm usefulness of carbon paste electrodes in the sphere of vital importance.

Selected BIC

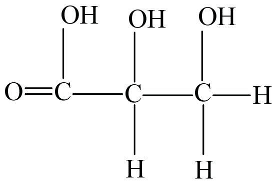
Ascorbic acid (*Vitamin C*) plays an important role in body health, as it is necessary for the formation of collagen, assists in the absorption of iron by promoting its reduction to the ferrous state and luck of it, provokes increased susceptibility to many kinds of infections, and slows down the rate at which wounds and fractures heal [82]. Moreover, the concentration of ascorbic acid in foodstuffs, beverages and pharmaceuticals can be an index of quality, since it varies during production and storage stages [82]. The indirect potentiometric determination of ascorbic acid by using electrodes selective to chloramine-T, triphenyltetrazolium, dichromate, triiodide, etc. has been proposed (see [83] and refs. therein). Other approaches include non-specific electrodes such as, pressed-pellet potentiometric electrode based on derivatives of cobalt(II) phthalocyanine doped with iodine, carbon electrode coated with an electrodeposited cobalt chelate of a tetra-*N*-methylpyridoporphyrazino cobalt derivative, graphite/epoxy electrode covered with a poly(ethylene-co-vinyl acetate) matrix doped with copper(II) ions, copper-based mercury film electrode, chemically-prepared tubular silver electrode, iron(II) phthalocyanine-modified carbon-paste electrode and a ferrocene-modified platinum electrode (see [83] and refs. therein).

A chemically modified electrode constructed by incorporating iron(II) phthalocyanine [Fe(II)Pc] into carbon-paste matrix has been successfully applied as a sensitive potentiometric sensor for fast and accurate determination of ascorbic acid (AA) in some commercial vitamin products [84]. The resulting electrode exhibits catalytic properties for the electrooxidation of AA, and lowers the overpotential for the oxidation of this compound. The faster rate of electron transfer results in a near-Nernstian behavior of the modified electrode, and makes it a suitable potentiometric sensor for AA detection. A linear response in concentration range from 10^{-6} to 10^{-2} M AA (0.18 – 1800 μg/mL) was obtained with a detection limit of 5.0×10^{-7} M for the potentiometric detection of ascorbic acid. The modified electrode was used for the determination of ascorbic acid in vitamin preparations.

The recovery was 97.2 – 102.4% for the vitamin added to the preparations with the RSD less than ±5%. The modified electrode exhibited a fast response time ($t_R < 10$ s), had good stability, and an extended life-time [84].

Leng *et al.* [85] have employed a chemically modified electrode by di-iso-octyl phthalate for the potentiometric measurement of ascorbic acid in the solution of 0.10 mol/L $NaOH$ – 0.1 mol/L $NaCl$, with the linear range $7.0 \times 10^{-7} - 4.0 \times 10^{-5}$ M, average response slope 95 mV/decade and detection limit 1×10^{-7} mol/L.

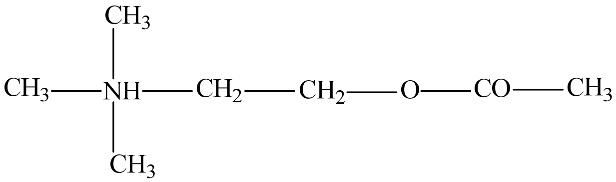
Glyceric acid (2,3-dihydroxypropionic acid, Scheme 10) exists in two configurations, D- and L- enantiomers in mammalian metabolism.



Scheme 10: Glyceric acid.

The presence of one of these enantiomers in blood or urine in abnormal concentration causes a different type of illness. Enantiomers may originate from different metabolic pathway, due to enzymes deficiencies. Enantioanalysis of chiral substances of clinical importance is a vital subject for the biomedical applications and early discovery of illnesses. Enantioselective, potentiometric membrane electrodes (EPMEs) based on chiral selectors has been developed for enantiomeric assay [86]. The authors have utilized EPMEs for the direct enantioanalysis of L- and D- glyceric acids. The EPMEs are based on three maltodextrins varied by different values of dextrose equivalence (DE), and the same amount of graphite powder mixed with paraffin oil. The enantioselective, potentiometric membranes electrodes have been excellent for the real time enantioselective analyses of glyceric acid in biological fluids (*e.g.*, serum or urine samples). One of the main advantages of this method was that the serum and urine samples had not needed any pre-treatment before the assay of any of the enantiomers [86].

Acetylcholine (Ach, Scheme 11) has an important function in the cholinergic system where it acts as a transmitter of impulses on the cholinergic synapses. Acetylcholinesterase (AchE) promotes the hydrolysis of the neutral neurotransmitter Ach, while organophosphorous and carbamate pesticides [87] inhibit the action of AchE.



$$CH_3-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{NH}}-CH_2-CH_2-O-CO-CH_3$$

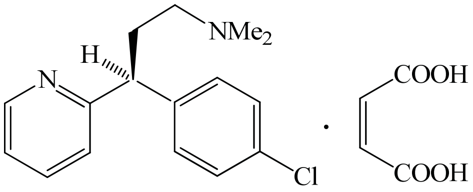
Scheme 11: Acetylcholine.

This inhibition leads to an accumulation of Ach that potentially causes paralysis of the living organism leading to death. Therefore, AchE or Ach determination is very important. The techniques most commonly used for the determination AchE or Ach are spectrophotometry, high-performance liquid chromatography, gas chromatography (GC) using a flame ionization detection, GC with mass spectrometry (GC-MS), amperometric and potentiometric sensors (see [88] and refs. therein). Most of the potentiometric AchE-based Ach sensors involve pH detection. A disadvantage of these sensors is their response to pH changes of the analyte solutions. Barsoum *et al*. [88] developed a sensitive potentiometrical method for the quantitative analysis of Ach in pure and biological samples, as well as in the homogenates of cotton leaf worm ”*Spodoptera littoralis*”. The method is based on the construction of an Ach sensor using carbon paste containing 1–10 % (w/w) 2,3,6-trimethyl o-β-cyclodextrin doped as an ionophore with tricresyl phosphate (TCP) (a plasticizer) and potassium tetrakis-*p*-chlorophenyl borate (TCB). The increase in the potentiometric response of the carbon paste electrode CPE toward Ach is characterized by a slope of 57.4 ± 0.5 mV per decade in the range of $1.0 \times 10^{-5} - 1.0 \times 10^{-3}$ M Ach solution. The sensor is widely applicable to the detection of biologically, pharmacologically and clinically important analytes [88].

Cysteine (α-amino acid, $HO_2CCH(NH_2)CH_2SH$) has been determined using a chemically modified carbon paste electrode constructed by incorporating N,N'-bis(salicylidene)-1,2-phenylenediaminocobalt(II) into carbon-paste matrix as a sensitive electrochemical sensor [89]. The resultant electrode exhibits catalytic properties for the electrooxidation of cysteine and lowers the overpotential for the oxidation of this compound. The faster rate of electron transfer results in a near-Nernstian behavior of the modified electrode and makes it a suitable potentiometric and voltammetric sensor for the fast and easy determination of cysteine. A linear response in concentration range from 2.0×10^{-6} M to 1.0×10^{-2} M was obtained with a detection limit of 1.0×10^{-6} M for the potentiometric detection of cysteine.

Selected PIC

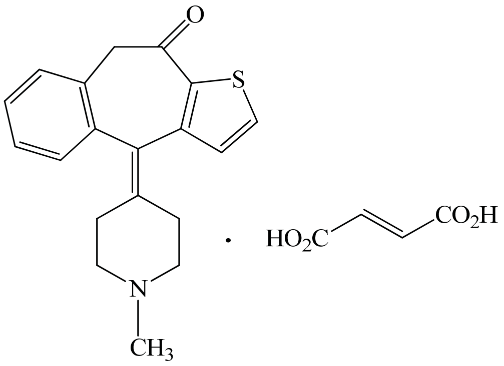
Chlorpheniramine Maleate, (±)-3-(4-chlorophenyl)-*N,N*-dimethyl-3-(2-pyridyl) propylamine (Scheme 12), is an antihistamine (H1-receptor antagonist) that competitively inhibit histamine at H1 receptor sites. It does not inactivate or prevent the release of histamine, but can prevent histamine's action on the cell. Besides its antihistaminic activity, this agent has varying degrees of anticholinergic and CNS activity (sedation) [90].



Scheme 12: Chemical structure of chlorpheniramine maleate.

A few reports on potentiometric determination of *Chlorpheniramine Maleate* based on polymeric membranes, coated wire and carbon paste electrodes have been reported [91-93]. An optimized mixture of graphite, insoluble mixture of two ion-exchangers, chlorpheniramine-silicotungstate (CPM-ST) and chlorpheniramine-tetraphenylborate (CPM-TPB) as electroactive materials with plasticizing solvent mediator tris(2-ethylhexyl) phosphate (DOPh) and NaTPB as a lipophilic additive was prepared and used in construction of a chemically modified carbon paste electrode (CPM-CMCPE) that is tested as a potentiometric sensor for determination of chlorpheniramine ion [93]. The results [93] show that the sensor developed for chlorpheniramine ion has a wide concentration range, low limit of detection, good Nernstain slope, and high selectivity over a wide variety of other cations and compared with electrodes already reported [91,92]. The modified carbon paste electrode was applied to potentiometric determination of CPM in its pharmaceutical preparations and biological fluids (serum and urine) with average recoveries of 97.5–102 % and relative standard deviations of ±0.32 – ±1.97%.

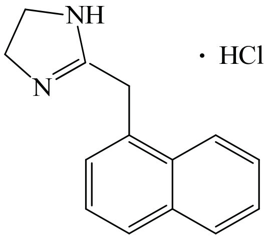
Ketotifen Fumarate (KTF, Scheme 13; 4-(1-methylpiperidin-4-ylidene)-4,9-dihydro-10*H*-benzo[4,5]cyclohepta[1,2-b]thiophen-10-one-hydrogen(*E*)-butenediene) is a widely accepted substance prescribed as an antiasthmatic / antianaphylactic drug, and alleviating also some allergic disorders via a combination of several actions.



Scheme 13: Structural formula of ketotifen fumarate

Ketotifen is a relatively selective, non-competitive antagonist of histamine H1 receptors and is a mast cell stabilizer, inhibiting the release of inflammatory mediators from mast cells [94]. Ketotifen fumarate was determined using spectrophotometric, chromatographic and electroanalytical methods (see [95] and refs. therein). Frag *et al*. [95] employed CPE for the potentiometric determination of Ketotifen fumarate in the pure form and in its pharmaceutical preparations and biological fluid (urine) using direct potentiometric, calibration and standard addition methods. The performance characteristics of the sensor were evaluated according to IUPAC recommendations which reveal a fast, stable and linear response for KTF over the concentration range of 10^{-7} to 10^{-2} mol/L. The electrode shows Nernstian slope value of 52.51 ± 0.20 mV per decade at 30 °C. The potential is nearly stable over the pH range 3.0 – 6.0. Selectivity coefficient values towards different inorganic cations, sugars and amino acids reflect high selectivity of the prepared electrodes. The direct potentiometric determination of KTF using the sensor gave recoveries % of 98.97 ± 0.53 with RSD = ±1.4 %. Validation of the method shows suitability of the CPE for use in quality control assessment of KTF. The respective results were in good agreement with those obtained by using the reported spectrophotometric method (see [95] and refs. therein).

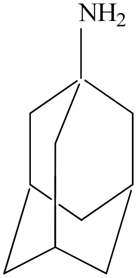
Naphazoline hydrochloride, 2-(1-naphthylmethyl)-2-imidazoline monohydrochloride (NPZ, Scheme 14) acts as an ocular vasoconstrictor where it constricts the vascular system of the conjunctiva. It is presumed that this effect is due to the direct stimulation action of the drug upon the alpha adrenergic receptors in the arterioles of the conjunctiva, giving rise to the decrease of the conjunctival congestion. Otherwise, naphazoline belongs to the imidazoline class of sympathomimetics.



Scheme 14: Structure of naphazoline hydrochloride

Frag *et al.* [96] performed a screen-printed and carbon paste sensors for rapid and sensitive quantification of NPZ in both pure and pharmaceutical preparations under batch conditions. The influence of the electrode composition, conditioning time of the electrode and pH of the test solution, on the electrode performance were investigated. The drug electrode showed Nernstain responses in the concentration range from 1.0×10^{-6} to 1.0×10^{-2} M with slopes of 57.5 ± 1.3 and 55.9 ± 1.6 mV per decade for SPE and CPE, respectively, and was found to be very precise and usable within the pH range 3 – 8. These sensors exhibited a fast response time (about 3 s for both SPE and CPE, respectively), a low detection limit (3.5×10^{-6} and 1.5×10^{-6} M for SPE and CPE, respectively), a long lifetime (3 and 2 months for SPE and CPE, respectively), a good selectivity and stability. The percentage recovery values for the assay of NPZ in tablets (relative standard deviations ≤ 0.3% for n = 4) were compared well with those obtained by the official method [96].

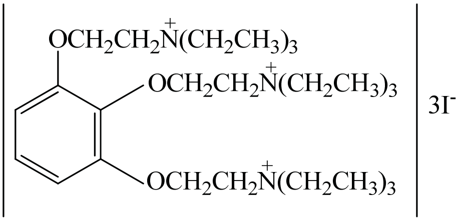
Amantadine (Scheme 15) is a tricyclic aminohydrocarbon with antiviral directed uniquely the influenza-A virus. It has also been approved for the treatment of Parkinson's disease [97]. According to the literature, potentiometric ion-selective electrodes have been made for the determination of amantadine in pharmaceutical preparations and urine samples; a carbon-paste electrode is also reported in which ion-pairs with amantadine have been used to modify the electrode (see [98] and refs. therein).



Scheme 15: Amantadine.

The lack of selectivity and high limits of detection are among the disadvantages of the made sensors. Jalali *et al*. [98] applied a simple potentiometric method for the determination of trace amounts of amantadine using a β-cyclodextrin modified carbon paste electrode. The electrode shows sub-Nernstian response of 51.0 ± 1.0 mV per decade for amantadine in the concentration range of $6.3 \times 10^{-10} - 7.1 \times 10^{-7}$ M. The electrode could be used more than three months. Blood-serum samples spiked with trace amounts of amantadine were used as real samples as well as tablets of amantadine with a relative error of 2%.

Gallamine Triethiodide {2,2',2''-(benzene-1,2,3-triyltrioxy)tris-(tetraethylammonium) triiodide} is a widely used muscle-relaxant medication; Scheme 16) [27].



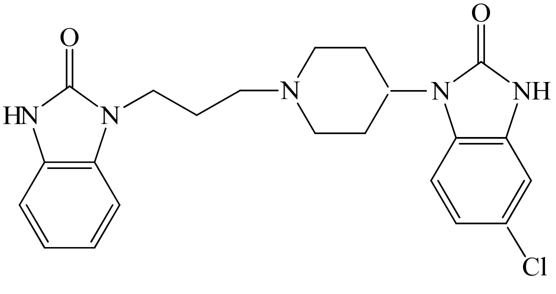
Scheme 16: Structural formula of gallamine triethiodide.

Most of the methods cited in literature for its determinations involve high-performance liquid chromatography (HPLC) and thin-layer chromatography (see [27] and refs. therein). Despite the sensitivity of chromatographic methods is quite reasonable, however, the analysis time usually needed to perform efficient separation is rather not a short time compared with the direct potentiometric measurements method. PVC membrane electrodes selective to some muscle relaxants including gallamine using dipicrylaminate and tetraphenylborate as counter ions have been described [99]. Abbas *et al*. [100] applied a gallamine-modified carbon paste electrode based on the use of gallamine-tetraphenylborate (GAL-TPB) as electroactive material and dioctylphthalate (DOP) as plasticizer for quantitative determination of gallamine content in its pharmaceutical preparation, gallamine ampoule. The electrode shows a stable, potentiometric response for gallamine in the concentration range $2.0 \times 10^{-6} - 1.0 \times 10^{-3}$ M at 25 °C independent of pH in the range 5 – 8. This method is considered to be fast compared with chromatographic methods and does not use any hazardous mercury or mercuric salts, like the case in adsorptive voltammetric methods using HMDE or the British pharmacopoeia method used for gallamine determination.

Potentiometric titration of gallamine with sodium tetraphenylborate and phosphotungstic acid as a titrant has been monitored with the modified carbon paste electrode as an end-point indicator electrode [100].

Dicyclomine Hydrochloride, 2-(diethylamino)ethylbicyclohexyl-1-carboxylate hydrochloride (DcCl) is an antispasmodic and anticholinergic drug, a mediation that reduces the effect of acetylcholine on smooth muscles. Dicyclomine is used to treat or prevent spasms in the muscles of the gastrointestinal tract in the irritable bowel syndrome. Mostly, dicyclomine hydrochloride has been determined by spectrophotometry, gas chromatography, NMR (see [101] and refs. therein). A modified carbon paste electrode has been applied to the potentiometric determination of dicyclominium ion in its pure state and in pharmaceutical preparations as well as in biological fluids using standard additional method [101]. The electrode is based on a mixture of two ion-exchangers as electroactive materials: dicyclominium-phosphomolybdate (Dc-PM) and dicyclominium-tetraphenylborate (Dc-TPB), dissolved in dioctyl phthalate (DOP) as pasting liquid (a plasticizer). The modified electrode showed a near-Nernstian slope of 58 ± 2 mV over the concentration range of $1.2 \times 10^{-5} - 1.6 \times 10^{-2}$ M, with an average recovery of 97 – 102% and a RSD of 0.09 – 1.00. The electrode exhibits good selectivity for DcCl with respect to a large number of inorganic cations, sugars, amino acids and organic substances of biological fluids [101].

Domperidone, {5-chloro-1-[1-[3-(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl) propyl]-4-piperidinyl]-1,3-dihydro-2H-benzimidazole-2-one}, DOM (Scheme 17) is a dopamine antagonist used as an antiemetic agent for the short-term treatment of nausea and vomiting of various etiologies.

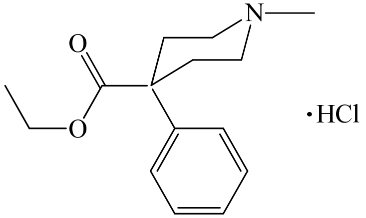


Scheme 17: Structure of domperidone.

Domperidone is indicated for treating symptoms associated with upper gastrointestinal motility disorders caused by chronic and sub acute gastritis.

It is a gastrointestinal emptying adjunct, a peristaltic stimulant, and also exhibits antiemetic properties. Domperidone is a drug that has a side effect of increasing milk production, probably by increasing prolactin production by the pituitary gland. Domperidone is excreted in breast milk, and no studies on its effects on breast feeding infants have been reported in the literature. Analytical methods reported for quantitative determination of domperidone include radioimmunoassay (RIA), spectrophotometry, high performance liquid chromatography, anodic differential pulse voltammetry, titrimetry, and potentiometry (see [102] and refs. therein). Kumar *et al*. [102] described a carbon paste potentiometric sensor for the selective, quantitative determination of domperidone. The investigated sensor includes DOM–PTA (phosphotungstic acid) ion pair as the electroactive material. The CPE showed a linear, stable, and near-Nernstian slope of 57.8 mV per decade over a relatively wide range of DOM concentration ($3.55 \times 10^{-6} – 1.0 \times 10^{-1}$ M). The CPE has been successfully applied for the determination of DOM in pure solutions and in pharmaceutical preparations, and the results obtained are in good agreement with those obtained by the official method. The sensors were also applied to the recovery of the drug from spiked urine samples [102].

Pethidine (Meperidine hydrochloride, Dolantin) {ethyl, 1-methyl-4-phenylpiperidine-4-carboxylate hydrochloride} (PD, Scheme 18) is a potent opiate analgesics, which has been employed in the treatment of a variety of medical conditions [103].

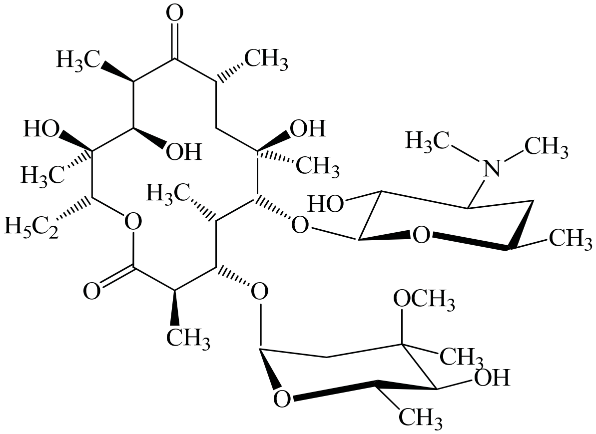


Scheme 18: Chemical structure of pethidine hydrochloride.

Pethidine is also prescribed as a substitute for heroin, and often used medically as postoperative analgesia. Therefore, determination of pethidine has important practical meanings. Many analytical techniques were reported to determine the pethidine, such as HPLC, GC-MS, spectrophotometry, or even potentiometry (see [104] and refs. therein). A pethidine-chemically modified carbon paste electrode (PD-CMCPE) was based on the use of pethidine-phosphotungstate (PD-PT) as electroactive materials and 2-nitrophenyl octyl ether (2-NPOE) as plasticizer having been proposed by Abu Shawish *et al*. [104].

The pethidine electrode showed Nernstian responses in the concentration range 2.1×10^{-6} – 0.01 mol l^{-1} with a LOD of 7.3×10^{-7} mol l^{-1} and usable within the pH range of 3.5–6.6, a fast response time (5-8 s) and good stability. The electrode can be recommended as a useful analytical tool and interesting alternative for the determination of PD ions in pharmaceutical preparations and urine samples [104].

Erythromycin (Scheme 19) is a macrolide antibiotic that has an antimicrobial spectrum (nearly all Gram-positive and Gram-negative bacteria) similar to penicillin and it is often used for people who have an allergy to penicillin-based medicaments. It is an important antibiotic currently used in clinical applications.



Scheme 19: Chemical structure of erythromycin.

Erythromycin is a complex 14-carbon lactone ring with two "deoxy sugars", which one of them has an amino group with *pKa* = 8.8. It is highly lipophilic and almost water-insoluble. Normally, the use of HPLC is a routine approach for measurement of erythromycin.

Recently, with a view to improve the response of CPEs, the paste is modified by nanomaterials [105]. Carbon nanotubes have very interesting physicochemical properties, such as an ordered structure with ultralight weight, metallic or semi-metallic behavior and a high aspect ratio, mechanical strength, electrical conductivity, thermal conductivity, surface area [105]. The combination of these characteristics makes CNTs unique materials with the potential for various applications. A carbon paste electrode with incorporated multi-walled carbon nanotubes and nanosilica has been successfully applied in the determination of erythromycin [106].

Conclusions

The development of selective sensors has received a great attention during the past three decades because of their potentially effective use in environmental screening and clinical analysis and thanks to some valuable features, such as rapid, accurate and low-cost procedures.

Arguably, carbon paste is the most useful material for laboratory preparation of various electrometric sensors. In the CPE configurations, a selective agent (modifier) is commonly incorporated into the surface via the mixtures with graphite powder and a pasting liquid, when one obtains chemically modified carbon paste electrodes, CMCPEs. For many years, most of applications of CMCPEs in electroanalysis fall mainly amongst voltammetric determinations; often, in combination with electrochemical stripping analysis (ESA).

As shown above, often identical configurations and analogical principles can be advantageously exploited for proposals, development, and applications of carbon paste-based ion-selective electrodes, CP-ISEs, that can be operated in traditional potentiometry, either in the form of direct measurements (with calibration) or in potentiometric titrations (including the fully automated procedures). Furthermore — as illustrated in this review as well —, the CP-ISEs may achieve the detection limits down to the nanomolar range without any accumulation step, with good selectivity, and with nearly no sample perturbation. Such dramatic improvements in the sensitivity of potentiometric measurements have made the modern ISEs, frequently designed as CP-ISES, very attractive for trace metal measurements and, in some extent, competitive to the latest types of working electrodes in ESA, or even to other trace-analysis instrumental techniques. For these reasons, the field of potential applicability may be the industry, hygienic labs, or even outdoor environment; simply saying – the quality control as well as the routine analysis.

In another specific area of applications, in pharmaceutical and clinical analysis, many methods with CP-ISEs can be used for quantitative analysis without a special pre-separation, which can be particularly beneficial in the case of drugs that are unstable during such separation. Generally, a high selectivity of CP-ISEs is also a notable advantage over other instrumental techniques, including HPLC, or capilllary (zonal) electrophoresis. Hereto, elimination of potential drift by stable internal reference electrode and possibility of using carbon paste electrodes in routine analysis where symmetrical ISEs are difficult to operate, give these electrodes an advantage for applications in environmental, biological and pharmaceutical determinations and quality control. There are many examples to confirm this statement; among others, the newly coming papers and other publications [107-111].

Acknowledgement

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Abbreviations & Symbols Used

AA	ascorbic acid
Ach	acetylcholine
AchE	acetylcholinesterase
ANN	artificial neural network
BIC	biologically important compound
[BMIM]BF$_4$	1-n-butyl-3-methylimidazolium tetrafluoroborate
BNSAO	[bis 5-(4-nitrophenyl azo)salisylaldimine] 1,8-diamino, 3,6-dioxo octan
CCSA	constant current stripping analysis
CMCPE	chemically modified carbon paste electrode
CNT	carbon nanotube
CoPc	cobalt phthalocyanine
CPC	cetylpyridinium chloride
CPE	carbon paste electrode
CPM-ST	chlorpheniramine-silicotungstate
CPM-TPB	chlorpheniramine-tetraphenylborate
CuSALHMN	N,N'-disalicyli-denehexameythylenediaminate Cu(II) complex
CTMAB	cetyltrimethylammonium bromide
CTMAI	cetyltrimethylammonium iodide
CVAAS	cold vapor atomic absorption spectrometry
DcCl	dicyclomine hydrochloride
Dc-PM	dicyclominium-phosphomolybdate
Dc-TPB	dicyclominium-tetraphenylborate
DE	dextrose equivalence
DOM	domperidone
DOM–PTA	(domperidone-phosphotungstic acid
DOP	dioctylphthalate
DOPh	tris(2-ethylhexyl) phosphate
DTSA	dithiosalicylic acid
EPME	enantioselective, potentiometric membrane electrodes
GAL-TPB	gallamine-tetraphenylborate
GC	gas chromatography
HA	humic acids
HPLC	high-performance liquid chromatography
HS	humic substances
ICP-AES	inductively coupled plasma atomic emission spectroscopy

ICPMS	inductively coupled plasma mass spectrometry
IL	ionic liquid
ISE	ion-selective electrode
L^1H_4	3,4,10,11-tetraphenyl-1,2,5,8,9,12,13-octaaza-cyclotetra-deca-7,14-dithizone-2,4,9,11-tetraene
L^2H_6	benzyl-bis-thiosemicarbazone
LOD	limit of detection
MMNIT	[2-mercapto-5-(1-methyl-5-nitroimidazole-2-yl)-1,3,4-thiadiazole]
MNFT	[2-mercapto-5-(5-nitrofuran-2-yl)-1,3,4-thiadiazole]
MNTT	[2-mercapto-5-(5-nitrothiophen-2-yl)-1,3,4-thidiazole]
MS	mass spectrometry
MWCNT	multi-walled carbon nanotubes
2-NPOE	2-nitrophenyl octyl ether
NPZ	naphazoline hydrochloride
NTHA	*N*-2-naphthoyl-*N*-*p*-ytollhydroxamic acid
PD	pethidine
PD-PT	pethidine-phosphotungstate
PIC	pharmaceutically important compound
PSA	potentiometric stripping analysis
RTIL	room temperature ionic liquid
SAGNP	self-assembled-gold nanoparticle
SPE	screen-printed electrode
TCB	tetrakis-*p*-chlorophenyl borate
TCP	tricresyl phosphate
TETDS	tetraethyl thiuramdisulfide
TGA	thioglycolic acid
TIA	tetraiodoantimonate
TPT	triphenyl tetrazolium

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