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Electrochemical Detection for Flow-based System: A Review

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Abstract

Nowadays, a great deal of attention is given to the use of automatic systems coupled with various detection schemes. The most promising one is a flow-based system that increases the sample throughput while maintaining the reproducibility and repeatability of the method. This review focuses on electrochemical detection methods including amperometry, pulse amperometry, voltammetry, potentiometry, and miscellaneous detections for flow-based systems. Fundamental concepts and progress in the field of electrochemical detection with flow-based systems that have occurred within the past six years, including new methodologies and unique applications, are highlighted. The references cited herein were selected from the period between 2003 and 2009.

Key words Flow-based system, electrochemical detection, amperometry, pulse amperometry, voltammetry, potentiometry

1. Introduction

Recently, there has been an extensive development of automation in chemical analysis due to its versatility and applicability. Automation has been stimulated by the need of a rapid analysis in order to increase the numbers of sample throughput in clinical, pharmaceutical, and environmental chemistry, and by the demand for a continuous monitoring of different analytes in nature and industrial processes [1]. A significant number of these modern approaches of automated chemical analysis are based on flow-based analytical techniques. Flow analysis (FA) refers to all analytical techniques that are based on the introduction, processing, and detection of liquid samples in flowing media. The sample processing may involve sample transport, in-flow separation, chemical reaction, and heat treatment under hydrodynamically controlled conditions, among others. Therefore, the term flow analysis may be considered as equipment to controlled dispersion analysis. Flow analysis modes are classified according to (i) the basic character of the flow, which is either continuous or segmented, and (ii) the method of sample introduction, which can be continuous or intermittent [2].

Flow-injection analysis (FIA) was proposed by Ruzicka and Hansen in 1975 [3]. This technique is an important methodology in the area of non-segmented FA, in which the liquid analyte and/or reagent are injected into a non-segmented flowing stream of carrier solution, and the analyte, reagent, or a chemical reaction product is detected downstream. Injection refers to the formation of a well-defined zone of the analyte or reagent sample within the channel, where the zone disperses in a controlled manner on its way toward the detection cell. For the injection of a small volume of the sample as a narrow plug, mechanical injection valves and hydrodynamic injection techniques are employed. In both cases, volume- or time-based injections can be made either separately or in combination. The concentration profile of the analytes entering the detection cell depends on the mode of the sample introduction, flow parameters, and geometry of the FIA channel situated between the sampling point and the detection site. Therefore, a symmetric or asymmetric peak-shaped transient signal is obtained as the detection signal.

Ruzicka and Marshall [4] developed a new methodology called sequential injection analysis (SIA) in 1990. This approach to automated sample manipulation arose from a need to simplify manifolds and address the unique requirements of process analysis. In SIA, a selection valve and bi-directional pump is used to draw up small volumes of sample and reagents, and propel them through a coil to a detector. Again, the process causes mixing of the sample and reagent segments leading to chemical reactions that form detectable species before reaching the detector. Because SIA shares many characteristics with FIA, it is arguable that it is simply an extension of FIA. Nevertheless, more than 100 articles have been published on SIA since the first paper in 1990. Like FIA, it is fundamentally dependent on the dispersion of zones in a flowing stream but the concept in practice of SIA is different from FIA. The main benefits of SIA are a simpler hardware consisting of one pump, one valve, and one carrier stream. This method is also more efficient in reducing reagents and minimizing waste. It is a simple and universal manifold the ease with which different chemistries can be implemented in one manifold. Because of its advantages, SIA is ideally suited for

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multiple determinations and therefore for the manipulation of samples containing different chemical forms of species in the matrix. For all these reasons, many researchers have pointed out that SIA is a methodological innovation in various analytical fields.

In addition, batch injection (BIA), multicommuted flow injection analysis (MCFIA), all injection analysis (AIA), multisyringe flow injection analysis (MSFIA), and multipumping flow injection analysis (MPFIA), have been developed over the past few decades [5-8]. However, FIA and SIA are still the most widely used techniques because no complicated instruments or computers are required.

Various types of detection modes are applied to flow analytical techniques. Electrochemical detection is one of the most commonly utilized. The inherent features of electro-analytical techniques are the versatility of the detector design; electrochemical detection meets most of the requirements of flow analysis. The high sensitivity and wide linear dynamic concentration range of electrochemical detectors is often incidental to superb selectivity. In principle, the flow analytical manifold (the layout of the flow analytical technique) is simplified when a highly selective electrochemical detection mode is applied.

An electro-analytical detector uses the electrochemical properties including the reactivity at an electrode (amperometric or coulometric measurements), Nernstian potential, and conductivity to determine interested targets in a liquid stream. Perez-Olmos et al. [9] have reviewed published flow-based systems with electrochemical detections up to 2005, while Chailapakul et al. [10] have reviewed them up to 2006.

The aim of the present report is to extend the existing, recommended electrochemical detectors used in flow analytical techniques with a brief critical overview of the currently used electrochemical flow-through detectors.

2. Detection Modes

Electrochemical detection techniques are based on the measurement of the electrical properties of a sample solution. Typically, a flow system with electrochemical detection is accomplished based on a single-line configuration. This is because no reagent is required to develop the color. However, some systems, such as SIA or MSFIA, require a manifold in order to increase versatility. The flow-through cell is one of the most important parts in a flow system because it is where the electrodes are held. An electrochemical reaction occurs inside the flow cell, and then the electrochemical data such as the current or potential will be recorded. Various configurations of a commercial flow cell, such as wall-jet, thin-layer, and flow-through cell can be applied to this system [11]. The cost of an instrument can be minimized using a homemade version [12]. In the subsequent sections, we will review the use of various electrochemical techniques as detectors for flow-based systems.

2.1.1. Flow Analysis with Amperometric Detection

Amperometric detection is the most widely used and extensively reported electrochemical technique in flow analysis, high performance liquid chromatography, and capillary electrophoresis. This is due to the fact that it is easy to operate and because there are minimal background current contributions. In this technique, a constant potential is applied to the working electrode and the current is measured as a function of time. The redox reactions of the analytes at the working electrode surface are expedited by the applied potential, while the current output is proportional to the concentration of the analytes. Tunable selectivity is achieved by cautiously choosing the detection potential. The optimal potential is obtained by constructing hydrodynamic voltammograms.

The development of FIA and other related techniques with amperometry in recent years has brought several new achievements in the design of detection schemes. This has resulted in the development of new methods for the determination, as well as in the use of various kinds of working electrodes.

Selective detection in FIA systems can be achieved by choosing properly the working electrode material and the applied potential. Working electrodes utilized for monitoring in FIA systems have been fabricated with several materials. There are two general types of working electrodes: unmodified and modified electrode. Carbon electrodes rather than metal electrodes were commonly used in FIA systems due to their minimal fouling, lower over-potential and background noise, and wider potential range for organic compounds. The carbon-based electrodes used in FIA systems and other related techniques were composed of glassy carbon (GC) electrode [13-20], screen-printed carbon (SPE) electrode [21, 22], and carbon fiber [23-26].

However, metal electrodes are still used in FIA systems. The determination of gas diffusion-flow injection of total inorganic carbon (TIC) in water using tungsten oxide electrode has been reported [27]. The method is not only rapid and sensible, but also simple and feasible with satisfactory accuracy and precision. It could thus be used for the monitoring of TIC in water. Pre-reactions were also applied to FIA systems because of their simplicity and the decrease in electrode fouling. An amperometric flow-injection assay was used for the determination of tannin [28] in tea at a platinum electrode with a pre-mix of tannic acid and ferricyanides in order to avoid the electro-oxidation of tannin. A working potential of -0.1 V (vs. Ag/AgCl) and a flow rate of 2.28 mL/min were the optimal conditions. The results showed two linear ranges of 10-50 μg/mL and 100-500 μg/mL for tannic acid.

Glassy carbon (GC) electrodes have also been popularly used in FIA. Orthophosphate in fresh and marine water samples was analyzed in the form of dissolved reactive phosphorous (DRP) using GC electrode by flow-injection amperometry with and without on-line column pre-concentration [29]. The reduction of the products obtained by reaction of DRP and acidic molybdate could be detected at 220 mV vs. Ag/AgCl. The electrolyte and eluent in the pre-concentration were in a 0.1 M potassium chloride solution. Using FI amperometry without pre-concentration, the results showed a detection limit of 3.4 μg/L and a sample throughput of 70 determinations per hour. The relative standard deviations (R.S.D.s) for orthophosphate concentrations of 50 and 500 μg/L were 5.2% and 5.9%, respectively. For the FI amperometry with an ion exchange pre-concentration, a detection limit of 0.18 μg P /L for a 2 min of pre-concentration time was attained. Other interferences such as organic phosphate, sulfide, silicate, and sodium chloride were examined. Finally, both designed FIA systems were applied to the determination of orthophosphate in water samples. Carbofuran and fenobucarb, which are pesticides in water samples and phytopharmaceutical, were also detected by a GC electrode [30]. The anodic oxidation of phenolic-based compounds occurred after alkaline hydrolysis. Under optimal conditions, linear concentrations of carbofuran and fenobucarb were obtained between 1 x 10^{-7} and 1 x 10^{-5} mol/L with a detection limit of 2 ng/mL. This method was applied to the determination of spiked waters and commercial formulations. The proposed method could analyze 90 samples per hour and provided the benefits of simplicity, accuracy, precision, and automation. Sample pretreatment with dialysis was used for the determination of ascorbic acid using a GC electrode and a flow injection analysis with an amperometric detection [31]. The sample solution was injected into a donor stream and passed the dialysis unit through an acceptor stream. The electrochemically oxidized ascorbic acid was then recorded. A linear calibration range of 50-800 mg/L for ascorbic acid and an R.S.D. of 1.5% for 50 mg/L ascorbic acid were achieved. This method was applied to the determination of ascorbic acid in vitamin C and fruit juice samples. The important advantage of this method was the absence of interference of colored and colloidal substances in the sample.

Moreover, Yeh et al. [32] presented the detection of dopamine (DA) in the presence of sodium 4-aminobenzenesulfonate (ABSA) by voltammetry and FIA with an amperometric detection at a glassy carbon electrode. A detection limit of 10^{-8} M for dopamine was achieved. The proposed method provided high sensitivity, low detection limit, and excellent analytical features.

Recently, boron-doped diamond thin film (BDD) electrodes have gained popularity in a variety of electrochemical applications, including flow-based systems. Thus, the use of diamond as an electrode material in electrochemistry has been extensively reviewed [33]. Several analytes have been detected at BDD electrodes such as captopril [34], tiopronin [35], malachite green [12], iodide ion [36], tetracyclines [37], lincomycin [38], sodium thiosulphate [39], chlorinated phenols [40], cysteine [41], myoglobin and hemoglobin [42], bromide and iodide ions [36], oxalic acid [43], sulfonamides [44, 45]. Fig.1 displayed HPLC-EC chromatogram of a 10 µg/mL mixture of seven standard sulfonamides separated on a monolithic column using a BDD electrode.

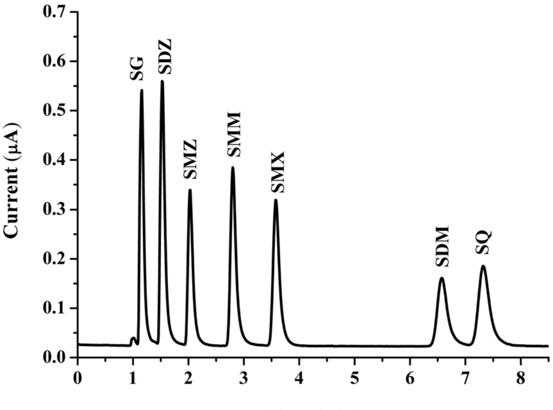

Fig. 1. HPLC-EC chromatogram of 10 µg mL^{-1} of seven standard SAs mixture separated on monolithic column (100 mm x 4.6 mm i.d.) using mobile phase of phosphate buffer (0.1 M, pH 3), acetonitrile and ethanol in the ratio of 80:15:5 (v/v/v). The detection potential was 1.2 V vs Ag/AgCl at BDD electrode. The injection volume was 20 µL and flow rate is 1.5 mL/min. [From Ref. 45, H. Sangjarusvichai, et al. *Talanta,* **2009**, *in press*, with permission from the Elsevier B.V. © 2009].

Chemically modified electrodes can be used as detectors in FIA, HPLC, and CE. Modified electrodes containing a surface-bound redox mediator were employed to reduce the over-potential for redox processes of various compounds. At lower detection potentials, fewer compounds undergo a redox reaction, which leads to enhanced selectivity. A Prussian blue-modified electrode was used as an amperometric sensor in FIA systems for the detection of ultratrace amounts of arsenite [46]. A detection limit of 25 nM was observed at an operational potential. The sensitivity obtained for the detection of arsenite is lower than the one obtained with the EPA method. Moreover, this modified electrode did not show any interference from common ions. More applications of Prussian blue-modified electrodes to detect other classes of analytes have been reported. For example, they were used for the detection of a variety of species of biological interest such as cosmetics (persulfate [47]), sucrose [48]. Similarly, a glassy carbon electrode was modified with a Prussian blue and polypyrrole film for the amperometric detection of hydrogen peroxide resulting from a cholesterol enzymatic reaction [49]. Concentrations of cholesterol in the range of 10^{-5} - 10^{-4} mol/L were determined with a detection limit of 6 x 10^{-7} mol/L. This modified electrode displayed a high sensitivity and selectivity. Additionally, a bioelectrode was utilized for the determination of glycolic acid [50] by FIA with amperometric detection. The bioelectrode was prepared on a carbon paste electrode by mixing 20% (w/w) of sunflower leaves tissue, a source of glycolate oxidase and peroxidase, and 5% (w/w) of ferrocene at 0 V vs. Ag/AgCl. Amperometric results gave a linear response between 1 x 10^{-6} and 2 x 10^{-3} mol/L, a detection limit (S/N = 3) of 1 x 10^{-6} mol/L for glycolic acid, and a quantification limit (S/N = 10) of 3.3 x 10^{-6} mol/L. The proposed method was successfully applied to the detection of glycolic acid in human urine samples by FIA amperometry and HPLC. Stability, low cost, and ease of preparation were the advantages of this method.

Electroconducting polymers modified on the electrode surface served as a good probe for electroanalysis. A new polyvinyl chloride (PVC)/tetrathiafulvalene-tetracyanoquinodimethane (TTF-TCNQ) composite graphite electrode was prepared and the electroanalytical performance was tested [51]. The voltammetric and flow-injection responses of the electrode to ascorbic acid (AA) were measured and compared with those of a PVC-graphite electrode. This modified electrode provided good electrode kinetics with a low background current and a relatively reproducible signal. Electrocatalytic oxidation and flow-injection determination of AA using a graphite electrode modified with a polyaniline film containing electrodeposited palladium and poly-1-naphthylamine-modified glassy carbon electrode were also reported [52]. This modified electrode showed a good electrocatalytic oxidation of AA and a good sensitivity for FIA amperometry. The presented method was applied to the analysis of AA in pharmaceutical products and beverages. The obtained results showed a good correlation with those obtained with a reference method. Next, polyvinylpyrrolidone (PVP)-capped CdS semiconductor nanocrystals (quantum dots, QDs) were prepared and used to modify a GC electrode for hemoglobin detection [53]. The results indicated that the prepared electrode exhibited good current responses. In addition, the use of a PVP/CdS QD modified electrode in flow injection analysis further offered a high stability and reproducibility. For the determination of iodide using a conductive polymer, a vanadium oxide-polypropylene carbonate coated glassy carbon electrode was introduced [54]. FIA-amperometry exhibited a good linear relationship with the concentration of iodide in the range of 5 x 10^{-7} mol/ L and 1 x 10^{-3} mol/ L, and the detection limit was 1 x 10^{-7} mol/L. This described method has been successfully used to determine iodide in dry edible seaweed. Other electroconducting polymer modified electrodes coupled with FIA for electrochemical applications have been proposed, including a poly-toluidine blue polymerized on a GC electrode for the detection of NADH [55], a poly (N,N-dimethylaniline) film-coated GC electrode for the simultaneous detection of uric acid and ascorbic acid [56], and an enzyme monoamine oxidase (MAO) immobilized on a polypyrrole film on a platinum electrode for antidepressant drugs detection [57].

Furthermore, polymeric films and polymer nanotubule nets were prepared on platinum electrodes [58]. A poly (1,3-DAB) film was the most suitable due to its permeability and permselectivity, as well as practical and long-standing stability for nitrite. The modified electrode was applied to the detection of nitrite in drinking water using FIA. The results showed a concentration linear range between 10 and 100 μM, a detection limit of 2 μM, and a reproducibility (R.S.D.) of 0.4%. Similarly, electrochemically doped polypyrrole nanowire (PPy-NW) electrodes as nitrate-selective sensors were developed for nitrate ion detection using flow-through analysis, cyclic voltammetry, and amperometry [59]. The flow-through micro-fluidic platform was appraised. The sensor response for nitrate was linear in the range between 10 μM and 1 mM with a sensitivity of 1.17 – 1.65 nA/μM. This electrode was also applied for chloride, sulfate, phosphate, and perchlorate ions without any ion interference. Additionally, poly (3,4-ethylenedioxythiophene) film (PEDOT) was plated on a screen-printed electrode (SPE) for the electrocatalytic detection of cysteine using cyclic voltammetry and flow-injection amperometry [22]. The flow-injection amperometry results showed a linearity from 0.05 μM to 200 μM for cysteine and a detection limit (S/N = 3) of 0.03 μM under optimal conditions. This method provided high sensitivity and excellent analytical features.

Felix et al. [60] reported the use of FIA with an amperometric detection using carbon film resistor electrodes for the analysis of acetaminophen in pharmaceutical formulations. A wide linear range from 8.0 x 10^{-7} to 5.0 x 10^{-4} mol/L in phosphate buffer and a low detection limit of 1.36 x 10^{-7} mol/L were observed. The repeatability was 3.1% and 1.3% for acetaminophen solutions of 5.0 x 10^{-6} M and 5.0 x 10^{-5} M, respectively. This method was useful for a qualitative analysis in other similar applications. Thus, Luisa et al. [61] presented a multicommutated flow system with amperometric detection for the determination of piroxicam in pharmaceutical formulations using a Nafion film modified glassy carbon electrode. The Nafion film prevented electrode fouling and improved the repeatability of measurements. A multicommutated flow system was developed to determine piroxicam and various hydrophilic and lipophilic excipients in different pharmaceutical formulations. A linear range up to 5 x 10^{-4} mol/L and a detection limit of 1 x 10^{-5} mol/L were obtained. This method displayed no statistically significant difference with a reference method for a confidence level of 95%.

To study the catalytic properties of hydrogen peroxide as a biocatalytic product in the presence of oxidase, PdO, OsO_2, IrO_2, and PtO_2 were mixed with carbonaceous materials [62]. Glucose oxidase was immobilized in the Nafion film on the screen-printed carbon electrode and the electrode was used for the detection of glucose by FIA. The best electrochemical property was found with IrO_2 because of the low potential. Subsequently, the analysis of ambroxol in pharmaceutical formulations by FIA with amperometric detection on carbon film resistor electrodes was also described [63]. The results provided a linear dynamic range from 5.0 x 10^{-7} to 3.5 x 10^{-4} mol/L in a 0.1 mol/L sulfuric acid electrolyte, a high sensitivity of 0.11 A L/mol cm^2, a detection limit of 7.6 x 10^{-8} mol/L, and a repeatability in term of R.S.D. of 3.0% and 1.5% for ambroxol solutions of 6.0 x 10^{-6} and 6.0 x 10^{-5} mol/L, respectively. The results were satisfactory compared with UV spectrophotometric and acid-base titration methods.

Electroconducting polymers can not only be used for the modification of various kinds of electrodes, but also for metal or metal complexes that can be utilized for these purposes. The amperometric detection of insulin at a chemically modified carbon ceramic electrode containing nickel powder and potassium octacyanomolybdate (IV) was investigated by cyclic voltammetry and flow amperometry [64]. Flow injection amperometric determination of insulin yielded a calibration curve with the following characteristics: a linear dynamic range of 100-500 pM and a detection limit of 40 pM (based on S/N = 3). The inherent stability over a wide pH range, high sensitivity, low detection limit, low cost, and ease of preparation are the main advantages of this insulin sensor. Copper is one of the most widely used metals for the modification of electrode surfaces. Some examples are a copper plated screen printed carbon electrode for the analysis of ascorbyl glucoside [65], copper-modified gold electrode for monosaccharide detection [66] and simultaneous detection of glucose and starch, and carbon paste electrode modified with copper (II) phosphate immobilized in a polyester resin for the determination of ascorbic acid in pharmaceutical preparations [67].

In 2007, a palladium-platinum-palladium film was sequentially deposited on a graphite electrode from 0.5% m/v $PdCl_2$ + 28% m/v NH_4OH and 2% m/v H_2PtCl_6 + 10% v/v H_2SO_4 solutions for the determination of phosphite in fertilizer using flow-injection amperometry [68]. The optimal catalytic activity for phosphite oxidation was found at 0.15 V. This method could analyze 50 samples per hour with a sampling volume of 70 μL. A detection limit of 5 x 10^{-4} mol/L and an amperometric sensibility of 1.5 mA L/mol were obtained. The results showed good recoveries (96-109%) of spiked samples. The R.S.D. (n =12) of a 0.01 mol/L Na_2HPO_3 sample was 2%. In the same year, Salimi et al. [69] discussed the advantages of a carbon composite electrode (CCE) modified with nickel powder for the detection of insulin by flow injection with amperometric detection and hydrodynamic voltammetry. Under optimal conditions, the flow injection amperometric detection at the modified electrode exhibited a linear dynamic range of 15-1000 pM, a sensitivity of 8659.23 pA/pM cm^2, and a detection limit of 2 pM. The use of this electrode as an insulin sensor was found advantageous because of the simple preparation method, low detection limit, high sensitivity, outstanding catalytic activity, short response time, long-term stability, and extraordinary antifouling property. In 2008, de Abreu Franchini et al. [70] also presented a rapid determination of hydrogen peroxide in honey using the electrochemical deposition of platinum on a modified gold electrode by FIA with a differential amperometric detection and a tubular immobilized enzyme reactor. Hydrogen peroxide in 14 samples of Brazilian commercial honey was measured at +0.60 V vs. Ag/AgCl. A tubular reactor containing immobilized peroxidase on Amberlite IRA-743 resin was used for the enzymatic consumption of H_2O_2. The reproducibility of the peak current showed a R.S.D. of less than 1% for H_2O_2 in a concentration range of 10^{-5} mol/L. The results obtained with both methods were in good agreement with those obtained with the spectrophotometric method.

Due to its high reproducibility, the activated barrel plating nickel electrode (Ni-BPE) was used to determine sugar by FIA-amperometry and HPLC [71]. A good separation of four sugars in honey (glucose, fructose, sucrose and maltose) was obtained by HPLC and a favorable sensitivity at a detection potential of +0.55 V (vs. Ag/AgCl) was observed. Because it is a rapid method, the differential amperometric method using a platinum modified gold electrode coupled with FIA was also applied to the detection of glucose in honey utilizing glucose oxidase and peroxidase immobilized in a tubular reactor [72]. The results exhibited a linear dynamic range from 5 x 10^{-5} to 2 x 10^{-4} mol/L and a detection limit of 1.7 x 10^{-5} mol/L. The reproducibility as measured by R.S.D. was lower than 4%.

A ruthenium complex is another choice to modify an electrode because of its excellent electrocatalytic property. A graphite electrode modified with ruthenium (III) hexacyanoruthenate (II) film was developed as a detector in flow system for the determination of water-soluble vitamin B-1, B-2, and B-6 [73] and sulfur-containing amino acids [74]. The electrocatalytic oxidation of amino acids at the modified electrode resulted in a decrease in the oxidation potentials of amino acids and an increase in the currents of their oxidation peaks. Oxidized hydrazine was examined with excellent selectivity at bisruthenium (II) chloride hydrate modified glassy carbon electrodes using cyclic voltammetry and FIA with amperometric detection [75]. The FIA results presented a detection limit of 8.5 μM for hydrazine with the ruthenium complex modified electrode and a linear range from 10^{-5} to 10^{-2} M. A Ce(III)-EDTA complex modified electrode was used to study the electro-oxidation of nitrite [76]. The electrochemical properties of the Ce(III)-EDTA complex for the oxidation of nitrite ions were investigated using cyclic voltammetry and hydrodynamic voltammetry. A μM detection limit was obtained. Tungsten oxide films deposited on GC electrode surfaces were also utilized for the detection of iodate [77]. The modified electrode was successfully employed as an amperometric sensor for iodate in a flow injection apparatus.

Recently, an electrode modified with a bismuth film (BiFE) has been reported as a promising alternative to mercury and other solid electrodes for the electrochemical detection of various analytes. For example, BiFE was used in both batch voltammetry and flow injection amperometric detection of some nitrophenols [78]. Under flow conditions, a simple in-line electrochemical bismuth film renewal procedure was tested and displayed a very good inter- and intra-electrode reproducibility of the current signals at low μg/L analyte concentrations. Additionally, BiFE was also commonly used in electrochemical analysis for the determination of various substances in pharmaceuticals products. Tetracycline was analyzed by flow injection with amperometric detection using the bismuth film modified glassy carbon electrode [79]. Moreover, BiFE was also utilized for the determination of diclofenac sodium in pharmaceutical formulations by a multisyringe flow injection system with tubular amperometric and tubular voltammetric detections [80]. BiFE was automatically refreshed during the injection of each of the 30 samples. This method provided a continuous regeneration of BiFE, prevented the passivation of detector, and improved the sensitivity of detection. To our knowledge, the BDD electrode is a promising electrode material. Therefore, modified diamond surfaces are extensively used, particularly in FIA systems. The iridium oxide-modified BDD electrode was also used by Salimi et al. in 2004 [81] for the amperometric detection of ultratrace amounts of arsenic (III). A stable electrochemically reversible signal was noted at the modified surface in both acidic and basic medium. An electro-catalytic activity for the oxidation of arsenic (III) was found over a wide pH range (2 -8). An excellent analytical performance for the amperometric measurement was also observed. In the same year, this group also developed a method for the detection of lead in blood using a bismuth film-modified BDD electrode [82]. Additionally, Salimi et al. [83] have also reported in 2006 the use of an iridium oxide-modified BDD surface for the amperometric detection of ultratrace amounts of Hg (I). An allyltriethylammonium bromide (ATAB)-modified BDD electrode was also used to detect oxalate and compared to an unmodified BDD electrode by cyclic voltammetry and flow-injection analysis with amperometry [84]. The ATAB-BDD electrode could detect an anodic current 2 times larger than an unmodified BDD electrode and the stability was also improved.

The ion implantation method can also be used for the modification of the surface. Ivandini and coworkers [85, 86] have described the use of Pt-implanted BDD electrodes for the electrochemical detection of hydrogen peroxide. The electro-oxidation of hydrogen peroxide was investigated by cyclic voltammetry and FIA. The Pt-BDD electrode displayed high catalytic activity and excellent electrochemical stability, with a very low background current in comparison to the one obtained with a Pt metal electrode. A very low limit of detection (nanomolar level) was obtained with an R.S.D. of 2.91%. These results indicated that the implantation of metal provides a promising technique for the control of the electrochemical properties of the BDD electrode. Thus, research involves the use of ion implantation, especially nickel-implanted BDD electrodes (Ni-DIA) that were prepared in order to examine their usefulness. These interesting characteristics of the Ni-DIA electrode as a working electrode were utilized in flow injection [87] and HPLC systems [37] for the electroanalysis of tetracycline.

Recently, microchip has been utilized as an electrochemical tool with amperometric detections due to attractive properties such as cheapness, rapidity, selectivity of detection, and automation feasibility. Glucose was also measured by electroosmotic flow and amperometric detection with glucose oxidase immobilized in poly(dimethylsiloxane) electrophoretic microchip [88]. The length of the enzyme microreactor was varied from 0.5 to 3.0 cm. A linear range from 0-8 mM to 0-30 μM and a detection limit between 42 and 6.5 μM were observed. A polycation-modified poly(dimethylsiloxane) (PDMS) capillary electrophoresis microchip was also utilized for the rapid determination of ascorbic acid and uric acid [89]. The microchip was prepared by coating the PDMS microchannel surface with solutions of polycations, poly(allylamine) hydrochloride, poly(diallyldimethylammonium chloride) or chitosan. A reversed electroosmotic flow and a rapid and efficient separation were obtained. This method was rapid, cheap, and led to the successful analysis of human urine in the clinical field. Additionally, dopamine in the presence of ascorbic acid (AA) was also determined selectively by using a microchip-based FIA-amperomety at a mercaptopropionic acid modified gold microelectrode [90]. The selectivity of the detector was developed by using a gold working microelectrode modified with polycarbonate (PC) and a self-assembled monolayer of 3-mercaptopropionic acid (MPA). Under optimal conditions, a detection limit of 74 nmol/L for DA and a throughput rate of 180 samples per hour were obtained.

Currently, nanotechnology has become more important in various fields, and in particular in analytical chemistry. Copper-based nanoparticles supported on the gold surface were used as enzymeless glucose sensors. The combination of a modified electrode and a flow injection amperometry resulted in high sensitivity, excellent stability, and good reproducibility for the determination of glucose with a detection limit as low as 1.0×10^{-8} mol/L [66]. In addition, the disposable copper nanoparticles plated on the screen-printed carbon electrode provided a new sensor for the determination of native amino acid. Interestingly, all underivatized amino acids could be sensitively determined at 0.0 V vs. Ag/AgCl. Using flow injection with this proposed material exhibited stable detection responses with detection limits in the range of 24 nM-2.7 μM [91]. Also, copper-palladium alloy nanoparticles were plated on screen-printed carbon electrodes and were reported as sensors in flow analysis for the electrocatalytic determination of hydrazine [92]. The resulting flow injection analysis of hydrazine using SPE/Cu-Pd displayed a wide linear detection range at lower applied potential (+0.2 V vs. Ag/AgCl). A detection limit of 270 nM was obtained.

Gold nanoparticles were also used to modify electrode surfaces for FIA-amperometry to determine arsenite [93]. The sensitivity obtained was significantly improved by the electrochemical deposition of gold nanoparticles on a dual GC electrode. A nano PbO_2 modified electrode has also been reported for the determination of chemical oxygen demand (COD) [94]. This method was applied to determine COD in environmental applications. The advantages were no sample pretreatment, short analysis time, simplicity, and easy automation. Anatase TiO_2 nanoparticles composed a TiO_2 film that was coated on a Ti/TiO_2 photoelectrode that can be used for the determination of COD by FIA [95]. The total phenol content in olive oil mill wastewater (OMW) was evaluated using a tyrosinase-gold nanoparticles modified graphite-Teflon rigid electrode by continuous stirring and FIA. Additionally, flow injection using nanosized cobalt hexacyanoferrate (CoHCF) has been developed for the electroanalysis of hemoglobin [96]. The method was shown to be beneficial in terms of sensitiveness, rapidity, ease to control, and small sample-consumption. In addition, MnO_2 nanoparticles and dihexadecyl hydrogen phosphate (DHP) composite film were applied as sensitive sensors for the detection of hydrogen peroxide (H_2O_2) by amperometry [90]. Finally, this sensor can be applied to analyze H_2O_2 in toothpaste and hair dye.

Electrochemical immunosensors are attractive because of their lower consumption time, low detection limit (in picograms), and good reproducibility. Lui et al. [97] reported picograms detection of hormone 17 beta-estradiol using gold nanoparticles in a vertical bar protein G-(LC-SPDP)-scaffold as an electrochemical immunosensor. The results provided a linear response up to 1200 pg/mL, a sensitivity of 0.61 μA/pg mL, and a detection limit of 6 pg/mL.

Carbon nanotubes (CNT) are particularly attractive nanomaterials due to their unique structure-dependent electronic and mechanical properties. CNT can be divided into single-wall carbon nanotubes (SWCNT) and multi-wall carbon nanotubes (MWCNT). The remarkable properties of CNT raised the possibility of developing superior electrochemical sensing devices. Recently, vanadium-Schiff base complexes have been introduced on MWCNT modified GC electrode for the detection of iodate, periodate, bromate, and nitrate [98]. The modified electrode showed inherent stability over a wide pH range, fast response time, high sensitivity, low detection limit, and remarkable positive potential reduction of oxoanions that decrease the effect of interferences in analysis. The modified electrode can also be used as an amperometric detector for the monitoring of oxoanions in chromatography or flow injection systems. Similarly, catalase-modified MWCNT on a glassy carbon rotating disk electrode also led to a good analysis of nitrite, iodate, and periodate by FIA with an amperometric detection [99]. The catalase-MWCNT showed excellent electrochemical properties and stability. It was also catalytically active for the reduction of nitrite, iodate, and periodate. The results demonstrated good reproducibility, high sensitivity, high stability, wide linear range, low detection limit, long lifetime, short analysis time, simplicity, and ease of preparation. Thus, CNT has received much attention as a sensor in flow system such as carbon nanotubes modified with copper microparticles for amino acid detection [100], carbon nanotubes modified GC electrode for the electrochemical measurements of enzymatically generated thiocholine [101], trace insulin [102], and carbohydrates [103].

For the development of novel methods, numerous flow-injection systems were studied using electrochemical assays in order to improve the sensitivity of detection. A FIA with electrochemical detection was used to determine lidocaine with a detection limit of 11.7 ng. This method was useful to determine the purity of lidocaine in drugs listed in the Japanese Pharmacopoeia. Using FIA-ECD was more attractive because it required only one hundredth of the amount of lidocaine and one twentieth of the measuring time. It also produced less waste compared to the classical method [104]. An inhouse designed computerized flow injection (FI) system with electrochemical detection was reported for a low-level aluminum speciation analysis. Al-labile and Al-total were determined by measuring the sample by amperometry at +0.6 V before and after UV irradiation [105]. The electrochemical behavior of 1-naphthol allowed the development of an FIA system with an amperometric detector in which 1-naphthol can be determined. Thus, the concentration of carbaryl can be measured. A detection limit of 1.0×10^{-8} mol/ L was obtained. Another FIA manifold was constructed but this one used a colorimetric detector. The % R.S.D.s of 12 consecutive injections of one sample were 0.8% and 1.6% for the amperometric and colorimetric systems, respectively [106]. For the determination of apomorphine, few analytical methods are currently available. The simplicity and rapidity of the FIA-EC method described, as well as its reproducibility and sensitivity make it suitable for the quality control of pharmaceutical preparations of apomorphine [107]. In addition, the optimized FIA system also allowed the determination of hydroquinone with a minimum detectable net concentration of 10 μg/L [108]. A new method, a reverse pervaporation-flow injection (rPFI) method coupled with an on-line derivatization, was developed for the determination of traces of phenol in aqueous samples using amperometric measurements at a glassy carbon electrode at +0.62 V [109]. For a rapid and sensitive analysis, an online-preconcentration and flow-injection amperometry was proposed for the determination of phosphate in fresh and marine waters. The assay was based on the reduction of the product formed by reaction of phosphorus with molybdate in acidic media. For the FI manifold with preconcentration, a detection limit of 0.18 μg P/L was achieved [110]. Other analytes using FIA amperometric detection have been presented including carbaryl [106], apomorphine [107], 3,6-dihydroxyphenanthrene [111], dihydrocodeine [112], melatonin [113], and glucose and (L)-lactate [114].

Chlorpromazine hydrochloride in pure form and pharmaceutical formulations was analyzed by a simple and sensitive flow-injection spectroelectroanalytical method [115]. Electro-oxidation in sulfuric acid medium (0.1 mol/L) generated a stable cation radical that was detected at a wavelength of 524 nm. The proposed method was manipulated and corresponded to the reference method.

In 2007, Masawat et al. [21] studied the electrochemical analysis of tetracycline residues in food using a gold screen-printed electrode by cyclic voltammetry (CV) and flow injection analysis with amperometric detection. FIA with amperometry using a wall-jet flow through cell was utilized with a potential at 1.2 V and a flow rate of 2.0 mL/min. The concentration range for tetracycline, chlortetracycline, and oxytetracycline was 1 to 500, 5 to 50, and 1 to 500 μmol/L, respectively, and the detection limits were 0.96, 0.58, and 0.35 μmol/L, respectively.

Several applications have been developed for the biamperometric detection in FIA. FIA/biamperometry was first reported in 1993 for the catalytic determination of Cu (II) in blood plasma and reducing sugars and sucrose in syrups [116, 117]. Recently, biamperometric detection in FIA was described for the on-line determination of vitamin B-1. The detection was based on dead-stop end-point biamperometry by using two platinum foil electrodes with an applied potential difference of 150 mV. The method is simple, highly efficient (180 samples/h), highly selective, and is suitable for the determination of vitamin B-1 in pharmaceutical preparations [118]. In addition, a novel flow-injection irreversible biamperometric method was described for the direct determination of iodide. The method was based on the electrochemical oxidation of iodide at the gold electrode and the reduction of permanganate at the platinum electrode to form an irreversible biamperometric detection system. The proposed method was applied to the analysis of iodide in table salt with satisfactory results [119]. Furthermore, a flow-injection biamperometric method for the detection of iron (III) in soil was reported [120]. The reduction of iron (III) at one platinum electrode was involved in the oxidation of hydrogen peroxide at the other platinum electrode forming a reversible system when an iron (III) solution and a hydrogen peroxide solution flowed through the two chambers. The biamperometric system could analyze iron (III) with no external potential difference. A linear range between 1×10^{-6} and 1×10^{-4} mol/L and a detection limit of 6×10^{-6} mol/L were achieved. The reproducibility with a relative standard derivation (R.S.D.) was 1.4%. This method was applied to the analysis of iron in soil.

The sequential and batch injection analysis (SIA, BIA) techniques were also employed with amperometric detection. The sequential injection analysis using electrochemical detections was reviewed by Perez-Olmos, R. et al. in 2005 [9]. This article presented an overview of the principles of operation and applications of this emergent methodology with electrochemical detection. Moreover, SIA with amperometric detection dual electrogenerated chemiluminescence/amperometric detection were reported for vitellogenin [121] and pesticide metabolite [122]. In 2008, Chinvongamorn et al. [123] also reported the use of a gas diffusion sequential injection system with amperometric detection for the determination of sulfite at a BDD electrode. To prevent interference, a gas diffusion unit (GDU) was used. The experimental set up was shown in Fig.2. Sulfur dioxide was produced by adding an acid solution in the sample and diffused through the PTFE hydrophobic membrane into a carrier solution of 0.1 M phosphate buffer (pH 8.0)/ 0.1% sodium dodecyl sulfate in the channel of GDU to obtain sulfite. The sulfite was detected by amperometry using a BBD electrode at 0.95 V (vs. Ag/AgCl). The results showed a concentration range of 0.2-20 mg SO_3^{2-}/L and a detection limit (S/N = 3) of 0.05 mg for SO_3^{2-}/L. This method was applied to the detection of sulfite in wine and compared to an iodimetric titration method. Both results were in agreement. BIA was the newest of the injection techniques in the field of analytical measurements. In this technique, the sample is directly injected onto the surface of the working electrode.

Many publications describe the applications of this method. One example is the BIA-amperometric determination of salbutamol in pharmaceutical products. This method is simple, rapid, and reproducible for the determination of salbutamol with a detection limit of 2.5×10^{-7} mol/L [124]. The last report of BIA-amperometry concerned the determination of isoniazid in tablets. This paper proposed a new, fast, and precise method to analyze isoniazid based on the electrochemical oxidation of the analyte at a glassy carbon electrode in alkaline media. A fast sequential analysis in an unusually wide linear dynamic range, with high sensitivity and low limits

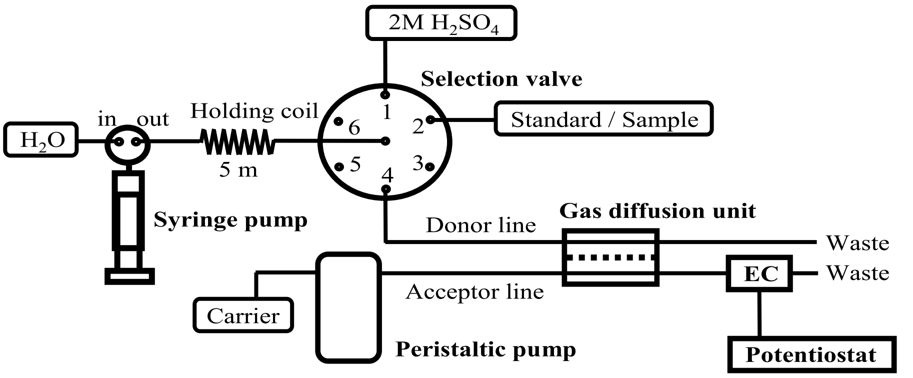

Fig.2. SIA manifold for the determination of sulfite: EC, electrochemical flow cell. [From Ref.123, C. Chinvongamorn et al. *Sensors,* **2008**, 8, 1846-1857, with permission from the Molecular Diversity Preservation INT © 2008]

of detection was achieved [125]. A rapid and dependable amperometric detection of the polyphenolic compound in wines was performed using a lactase biosensor by batch injection analysis (BIA) and flow injection analysis (FIA) [126]. A biosensor was prepared by immobilizing lactase onto a glassy carbon electrode with glutaraldehyde. The results of BIA-amperometry at -200 mV displayed a detection limit of 7.2×10^{-4} and 2.6×10^{-3} mg/L for caffeic acid and gallic acid, respectively. These results were in good agreement with the Folin-Ciocalteu method. The lactase biosensor was successfully used for the determination of polyphenol index in wines. Hsu et al. [127] studied the voltametric and BIA-amperometric detection of vitamin C using a polyviologen-modified glassy carbon electrode (PVGCE). The PVGCE was able to aggregate vitamin C at the electrode in a basic solution that was detected by hydrodynamic amperometry at +0.1 V (vs. Ag/AgCl). The results showed a linear concentration range from 5.00×10^{-7} to 1.22×10^{-4} M and were in accordance with the results obtained with iodimetric titration method.

A thermal adjustment in amperometric detection at an electrochemical sensor was reported. Short heat pulses directly applied to a gold electrode with a gold layer, a pseudo reference, and a counter electrode were coated with a low temperature cofired ceramic (LTCC) substrate [128]. Hexacyanoferrate (II) and picric acid were analyzed and thermal modulation led to a peak shaped amperometric signal. It was found that thermal modulation inhibited the analysis of picric acid. The linear calibration was in the range of 0.2 to mmol/L and the minimal background was obtained when a potential of 0.7 V was applied to the gold electrode. These conditions could be applied to flow injection analysis, high performance liquid chromatography, capillary electrophoresis, and environmental control.

As it has been previously mentioned, the FIA system is a powerful tool for analytical chemistry because of its rapidity, precision, and accuracy. Combined with a high selective immunoassay, this methodology has been widely applied. Recently, FIA has been combined with immunosensors based on a screen-printed carbon electrode for the amperometric detection of carcinoembryonic antigen [129], p-nitrophenol [130], or based on glassy carbon electrode for the detection of insecticide biomarker, 3, 5, 6-trichloro-2-pyridinol [122].

2.2.2. Flow Analysis with Pulsed Amperometric Detections

Amperometric detection has been widely used in flow analysis systems because it offers high sensitivity and simplicity. However, the main disadvantage of amperometric detection is the deposition of the by-product or solution impurity on the electrode surface. Pulsed amperometric detection (PAD) is an alternative technique for the quantitative detection of numerous organic compounds such as sugar and carbohydrate that adsorb on noble metal electrodes and cannot be detected satisfactorily by conventional amperometry. PAD is generally based on a triple potential waveform that incorporates amperometric measurement together with potentiostatic cleaning and reactivation of the electrode surface after each measuring cycle. Thus, PAD can be used to reduce fouling of the electrode surface that causes loss of electrode activity. Recently, PAD has been applied to a flow injection system (FI-PAD) for the determination of antibiotics such as tetracycline [131], doxycycline, and chlortetracycline [132]. A gold disk electrode was used in FI-PAD system for the determination of tetracycline in a pharmaceutical formulation with a very low detection limit (1 μM) [131]. Thiraporn et al. [132] used FI-PAD at a gold disk electrode to analyze doxycycline and chlortetracycline. The linear dynamic range of doxycycline hydrochloride and chlortetracycline hydrochloride was 1 μM - 0.1 mM. A FIA system was also developed for the analysis of formalin with a rapid, sensitive, and reproducible PAD method [133]. Oxidation of formalin occurs at negative potentials on a gold electrode where the electrode is not covered with oxide and shows a high activity for this reaction. The limit of detection of this method (0.01 mM) is low enough for the regulations of the Occupational Safety and Health Administration (OSHA). Moreover, FI-PAD was developed for the determination of L-cysteine [134] in commercial dietary supplementary food samples using a polycrystalline gold rod as the working electrode (0.07 cm^2).

Recently, Ortuno et al. [135] have developed a flow-injection pulse amperometric method for the determination of imipramine based on ion transfer across a plasticized poly(vinyl chloride) (PVC) membrane. The influence of the applied potential, the flow-injection variables, and the pH on the detection signal was investigated. This methodology was employed to determine imipramine in pharmaceuticals and human serum. The same researchers [136] also applied the concept of ion transfer across a plasticized poly(vinyl chloride) (PVC) membrane for the determination of tacrine. Dos Santos [137] reported the use of flow injection analysis with multiple pulse amperometric detection for the simultaneous detection of paracetamol and ascorbic acid. The compounds are detected by applying four steps as a function of time. The linear response range was optimized between 5 and 24 mg/L for ascorbic acid and 50 mg/L and 240 mg/L for paracetamol.

Even though FI-PAD has been used for a sensitive, rapid, and reproducible detection of numerous organic compounds, it cannot be used to separate various compounds in a sample solution. Hence, PAD was coupled with a chromatographic system that related to flow injection analysis and was used to separate components in mixtures. Moreover, it is not limited by the volatility or stability of the analyzed compound. Innocenzo et al. [138] developed a liquid chromatography with a pulsed amperometric detection for the determination of several low molecular weight aliphatic aldehydes without the use of any derivatization procedure. High performance liquid chromatography coupled with pulsed amperometric detection (HPLC-PAD) has been recently used to determine several sugars in a beverage, an artificial sweetener, and serum [139]. The determination of ethyl glucuronide and methyl glucuronide, a biomarker of ethanol consumption, in urine using reversed-phase HPLC-PAD has been developed [140]. Ethyl glucuronide and methyl glucuronide are readily separated using a mobile phase consisting of 1% acetic acid/acetonitrile (98/2, v/v). In this system, derivatization is not necessary, and the cost is much lower than LC–MS. Furthermore, this method is promising for the determination of alcohol consumption, and it can be used to distinguish between alcohol ingested prior to death and alcohol formed post-mortem during decomposition.

HPLC with integrated pulsed amperometric detection (IPAD) was used for the detection of antibiotics such as tetracycline and tobramycin. IPAD differs from PAD with respect to the signal current that is integrated through a rapid cyclic scan during the detection potential step within a pulsed potential time waveform. IPAD can easily diminish baseline offset and drift occurring in PAD due to small variations in the mobile phase and changes in the total surface area of the noble-metal electrode as well as analyte-induced effects. A multi-IPAD waveform at a gold working electrode was investigated for the determination of three tetracyclines in the acidic mobile phase. It was composed of a multicycle detection step, a positive cleaning step, and an activating potential step [141]. Hanko et al. [142] have also proposed HPLC-multicycle IPAD for the determination of tobramycin and impurities, including kanamycin B and neamine.

Numerous HPLC-PAD systems were developed using non-metallic electrodes such as carbon, boron-doped diamond (BDD) and modified electrodes in order to enhance selectivity and sensitivity. A cylindrical carbon fiber microelectrode was used in HPLC-PAD for the determination of furosemide with a 0.55 µM detection limit [143]. HPLC-PAD has been developed for the analysis of tetracyclines with a BDD electrode in a ppb level [37]. A glassy carbon electrode modified with gold nanoparticles was used in HPLC-PAD for the detection of histamine in the presence of other biogenic amines and indole [144]. Moreover, the BDD thin film electrode was used for flow injection analysis with pulsed amperometric detection of beta-agonists in pharmaceutical products, such as salbutamol, terbutaline and clenbuterol [145]. The linear range of sabutamol, terbutaline, and clenbuterol were 0.5-100 µM, 1.0-100 µM and 0.5-50 µM, respectively. Fig.3 showed the performance of the use of PAD to prevent the electrode fouling.

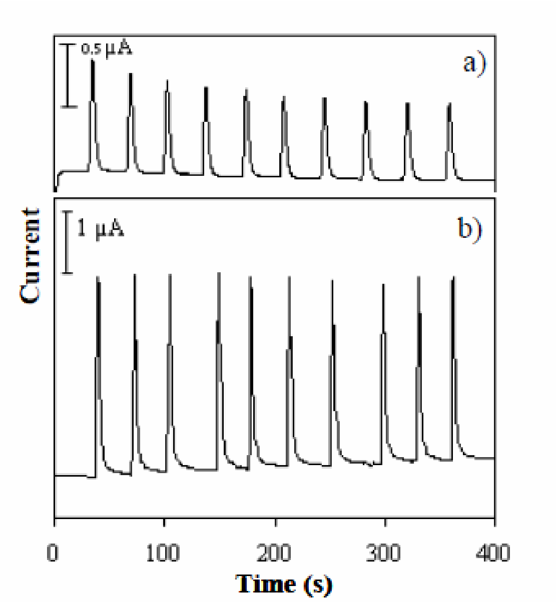

Fig.3. Examples of fouling (a) and anti-fouling (b) of BDD electrode for FI detection, Results were obtained from replicate injections of standard salbutamol 1x10^{-5} M (a) amperometric FI with detection potential fixed at 0.6 V. (b) pulsed amperometric FI [From Ref.145, C. Karuwan et al. *Sensors,* **2006**, 12, 1837-1850, with permission from the Molecular Diversity Preservation INT © 2006].

Another interesting system is a microchip capillary electrophoresis with pulsed amperometric detection. Microchip devices have been increasingly used for analysis in recent years due to the reductions in sample and reagent volumes, materials and instrumentation cost, and analysis times. The glass chip was the original microchip but it is relatively difficult and expensive to micromachine, requiring expensive cleanroom time and corrosive etching (HF). As a consequence, there is a significant interest in the development and use of polymer as substrates for microchip CE. Pulsed amperometric detection with poly (dimethylsiloxane) PDMS fabricated microchips has been applied to determine several compounds such as carbohydrates [146], amino acid [147], antibiotics [147], phenolic pollutants [148], nonsteroidal anti-inflammatory drugs [149], and renal function markers [150]. Even though PDMS has many advantages, the velocity of the electro-osmotic flow (EOF) is extremely susceptible to drift. Thus, maintaining EOF at a particular magnitude over time can be challenging. In order to control the magnitude and stability of the EOF on PDMS microchips, several approaches have been reported including the coating with inorganic anions and polyelectrolytes and the addition of surfactants to the background electrolyte. The addition of sodium dodecyl sulfate into the mobile phase and detection reservoir stabilized flow rates and enhanced the detection signal of glucose [150] and sucrose [151]. A modified electrode can also be used in this technique. The micromolded carbon ink electrodes modified with cobalt phthalocyanine can be used as a PAD in microchip CE for the determination of cysteine in the presence of rabbit erythrocytes with a low detection limit [152].

2.2.3. Flow Analysis with Voltammetric Detections

In voltammetry, a potential scan is applied to a working electrode, and the resulting current obtained when the redox active species are reduced or oxidized on the electrode surface is measured. Voltammetry is advantageous because it is sensitive, versatile, simple, and robust. Compared to potentiometry, voltammetry is less influenced by electrical disturbances and will thus have a favorable signal to noise ratio. In addition, voltammetry offers a number of different analytical techniques, including linear, cyclic, stripping, and pulse voltammetry. Depending on the technique, different types of information can be obtained. Typically, redox active species are being measured at a fixed potential. However, the study of the transient responses when Helmholtz layers are formed using pulse voltammetry, for example, also provide information about the diffusion coefficients of the charged species. Different types of metals as the working electrode or different stripping techniques also provide more information. Several possibilities are available obtained in order to gain information by voltammetry.

In 2004, Pezzatini et al. [153] reported the development of flow cell for the on-site determination of chlorite in drinking water using differential pulse voltammetry coupled with a flowing system. The calibration curve was linear up to 1.5 mg/L. The reproducibility of the procedure with different concentration of standard solutions was 0.07-1.2 mg/L. In addition, the above procedure was applied to determine chlorite in actual water samples. This proposed method is simple, inexpensive, and compares in terms of results to an anionic chromatographic procedure.

In 2006, Gutes et al. [154] have reported the development of a voltammetric electronic tongue for a flow injection system in order to characterize wastewaters from the paper mill industry. Flow injection analysis coupled with voltammetry offers an automated surface polishing of the electronic tongue that is a key parameter in drift correction and a requirement for the cleaning of the measuring cell. The studies focused on two different applications. The first one was the classification of samples according to their origin, using PCA as a multivariate data analysis tool. The second one was the use of the obtained data in correlation with three important control parameters: COD, conductivity, and pH. Reported results have shown the possible use of the proposed system for the monitoring of these three parameters in paper mill wastewaters.

In the same year, Silva et al. [155] have described the construction of a modified glassy carbon tubular electrode as a detector for a multi-commutated flow system for the voltammetric detection of acetaminophen. Coupled to a flow system, it also prevented electrode fouling thus leading to a longer operation time. In addition, a multi-commutated system offered a high versatile manifold that was easy to adapt for each determination without any special reconfiguration. The method was applied to serum and pharmaceutical samples.

Pulse voltammetry is another technique that is interesting for electrochemical measurement. Possari et al. [134] have used differential pulse voltammetry for the operational optimization and pulsed electrochemical detection in combination with a flow-injection analysis for the detection of cysteine. The linearity range obtained was between 1.0×10^{-6} and 6.0×10^{-6} mol/L with a good reproducibility. The developed method was successfully utilized to determine cysteine in commercial supplementary food samples.

Square-wave voltammetry is one of the procedures often coupled with a flow-based system. For a long time, only few papers described FIA systems with square wave voltammetry detection because it was difficult to automate the flow injection analysis using a square wave or differential pulse voltammetry. Due to the concentration gradient in the sample zone, the potential scan is applied to a working electrode immersed in a solution of varying concentration. Among various types of flow-based systems, a sequential injection can be used to overcome the problems mentioned. Dos Santos et al. [156] have developed a sequential injection analysis method to automate the detection of atrazine by square wave voltammetry employing the concept of monosegmented flow analysis to perform in-line sample conditioning and standard addition. Using this proposed method, the sensitivity could be improved. The linear dynamic range observed was for atrazine concentrations between 1.16×10^{-7} and 2.32×10^{-6} mol/L. The sample throughput was 37 per hour, when the standard addition protocol was followed. This frequency could be increased to 42 per hour when the protocol to obtain the in-line calibration curve was used for quantification. The method was applied to the determination of atrazine in spiked river water samples. The accuracy was evaluated by comparison with the batch standard addition approach. No statistically significant differences between the two methods were observed. The same research group [157] also applied this methodology to the determination of picloram in natural waters in 2007.

Stripping voltammetry has recently become an attractive technique for trace element detection applications and some organic compounds. This technique has always been considered as one of the most sensitive technique available for trace metals detection. The sensitivity of voltammetric methods is due to the use of a pre-concentration or accumulation step, in which the analyte is accumulated at the electrode by either an anodic or cathodic stripping or an absorptive process. The analytical signal is then generated by the subsequent voltammetric stripping step, where the voltage is swept or stepped in order to remove the adsorbed analyte from the electrode. The current is usually recorded during this process as a function of voltage (for a voltage sweep) or time (for a voltage step), and the current wave produced (proportional to the charge passed) is measured.

Anodic striping voltammetry (ASV) is a voltammetric technique particularly valuable for trace metal analysis. Combining ASV with on-line systems is advantageous in terms of speed, accuracy, precision, and scope for automation and cost effectiveness. Therefore, many studies with various procedures have been continuously published. Flow injection (FI) and sequential injection (SI) systems with anodic stripping voltammetric detection have been proposed for the simultaneous determination of some metals by Suteerapataranon et al. [158]. Under the optimal conditions, detection limits of 1 µg/L for Cd(II), 18 µg/L for Cu(II), 2 µg/L) for Pb(II) and 17 µg/L for Zn(II) with precisions of 2-5% (n = 11) were obtained for the FI system. For SI voltammetry, the detection limits for Cd(II), Cu(II), Pb(II) and Zn(II), were 6, 3, 10, and 470 µg/L, respectively. Subsequently, a procedure for the determination of mobile thallium in soil was developed by Lukaszewski et al. [159]. After extraction, the free thallium (I) in extracts was determined by differential-pulse anodic stripping voltammetry in a flow-injection system. The proposed procedure was applied to the determination of mobile thallium in a sample of ground from a waste dump, which was a potential source of thallium pollution.

The determination of tin (II, IV) chloride species was performed on an unmodified glassy-carbon electrode and on a modified electrode by electrooxidation of pyrogallol and morin using flow-injection /anodic stripping voltammetry [160]. Tin (II) was preconcentrated from flow solutions without applying a polarization voltage. The interference effect of lead (II) was reduced by choosing an appropriate accumulation medium. For the determination of trace amounts of Sn(II) in the presence of Sn(IV) and Pb(II) and for the determination of the total inorganic tin in model solutions. In 2006, Kefala et al. [161] proposed a polymer-coated bismuth film electrode for the determination of trace metals by sequential-injection/anodic stripping voltammetry. The polymeric Nafion film was initially coated on a glassy carbon electrode forming part of the flow-through electrochemical cell. The subsequent steps of the bismuth layer generation, analyte preconcentration, voltammetric measurement, and electrode cleaning were conducted on-line. In addition, Economou et al. [162] have reported an on-line stripping voltammetry of trace metals at a flow-through bismuth-film electrode by means of a hybrid flow-injection/sequential-injection system. The presented analytical flow methodology was applied to the determination of Cd(II) and Pb(II) by anodic stripping voltammetry (ASV) and to the determination of Ni(II) and Co(II) by adsorptive stripping voltammetry (AdSV).

Chuanuwatanakul et al. [163] reported the use of sequential injection–square-wave anodic stripping voltammetry (SIA-SWASV) for the simultaneous determination of Pb(II), Cd(II), and Zn(II). The schematic diagram of the SIA-SWAVS was demonstrated in Fig.4. Using the optimal conditions, the linear ranges were 0 – 70 µg/L for Pb(II) and Cd(II) and 75 – 200 µg/L for Zn(II). The limits of detection (S/N = 3) were obtained at concentrations as low as 0.89 µg/L for Pb(II) and 0.69 µg/L for Cd(II) for a 180 s deposition time. The proposed method was applied to the determination of Pb(II), Cd(II), and Zn(II) in water samples and led to satisfactory results. The on-line coupling of sequential injection lab-on-valve to differential pulse anodic stripping voltammetry for the determination of Pb in water samples was proposed by Wang et al. [164]. Deposition and stripping processes occurred between the renewable mercury film carbon paste electrode and the sample solution. Thus, the automation of lab-on-valve and the properties of integrated system not only offer fast analysis but also reduce the sample/reagent consumption. The described methodology was successfully used for the determination of Pb in environmental water samples.

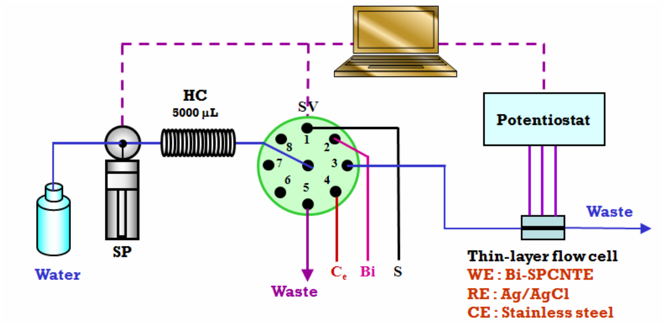

Fig.4. Schematic diagram of the SIA-SWASV system for the determination of Pb(II), Cd(II) and Zn(II). SP, Syringe pump; SV, selection valve; HC, holding coil; Ce, electrode cleaning solution (0.5 M HCl); Bi, Bi(III) plating solution; S, sample solution; WE, working electrode; RE, reference electrode; CE, counter electrode [From Ref.163, S. Chuanuwatanakul, et al. *Anal. Sci.,* **2008**, 589, 589-594, with permission from the Japan Society for Analytical Chemistry © 2008]

A less commonly used method of flow injection analysis is batch injection analysis (BIA). Even though it is claimed that the possibility of on-line sample processing is lacking, Trojanowicz et al. [5] have described a BIA stripping voltammetry for trace metals with an on-line sample pretreatment by changing the plastic trip of the automatic micropipette used for sample injection. The presented method employed a bed of commercial chelating resin Chelex-100 for preconcentration. A ten-fold preconcentration could be obtained on the packed sorbent bed.

Adsorptive stripping voltammetry is based on the physical adsorption of a complex of the analyte metal on a ligand possessing adsorptive properties on the working electrode. Brett et al. [165] determined the concentration of chromium(VI) by batch injection analysis and adsorptive stripping voltammetry. The method used a square wave adsorptive stripping voltammetry (AdSV) in conjunction with an electrochemical batch injection analysis technique at mercury thin-film electrodes. The determination of chromium was performed in the presence of cupferron as ligand. It is a highly sensitive method with a detection limit of 32 nM. Gun et al. [166] proposed the use of a mercury coated gold wire-electrode as a sensor in continuous flow analysis for the determination of iron in seawater. The principle is based on the adsorption of iron as a complex of dihydroxynaphthalene in the presence of oxidants and the detection of iron by catalytic adsorptive cathodic stripping voltammetry. The results obtained showed a higher sensitivity than the ones obtained with a bromate/mercury drop system.

Electroanalytical methods based on square-wave adsorptive-stripping voltammetry (SWAdSV) and flow-injection analysis with square-wave adsorptive-stripping voltammetric detection (FIA-SWAdSV) were developed for the determination of fluoxetine (FXT) by Nouws et al. [167]. The methods were based on the reduction of FXT at a mercury drop electrode and on the accumulation of the product at the electrode surface. With an automated system, this method enables the analysis of up to 120 samples per hour.

As mentioned above, stripping voltammetric methods were used for the determination of metal ions and some organic compounds. The application of these techniques obviously requires fast accumulation and detection of the analyte. To support these requirements, ultramicroelectrodes (UMEs) can be used for electrochemical measurements. UMEs have been used, for instance, as sensors in various techniques such as flow injection analysis. After 2005, Norouzi et al. [168] have started proposing a novel indirect method for the determination of metoclopramide (MET) using flow-injection systems by fast stripping continuous cyclic voltammetry (FSCCV). The potential waveform, consisting of the potential steps for cleaning, accumulation, and potential ramp of analyte, was applied to a gold disk microelectrode in a continuous way. The developed technique is very simple, precise, accurate, and rapid compared to other previously reported methods. The detection limit of the method for metoclopramide was minimized to pg/mL. Subsequently, the same authors continued to publish on the use of fast stripping continuous cyclic voltammetry for the detection of ultra trace amounts of timolol maleate [169], loratadine [170], nalidixic acid [171], and ketotifen [172]. Another problem arises from the changes in the characteristics of the electrode surface during the potential scan. The electrode signal has a large background current when the surface of the solid electrode is oxidized and reduced during voltammetric measurements. This leads to high levels of noise due to the structural changes of the electrode surface. Such currents can interfere with the desired electrode processes, and may adversely affect the detection limits of the methods used. However, application of a potential sweeping technique, such as cyclic voltammetry or square wave voltammetry associated with a potential waveform for electrode conditioning can be very helpful. Fast Fourier transform continuous cyclic voltammetry (FFTCV) is a promising procedure that enhances the S/N ratio by using a fast Fourier transform of the analyte and the signal integration. Norouzi et al. first reported on the use of a Fast Fourier transform continuous cyclic voltammetry (FFTCV) coupled with a flow system for electroanalytical purposes. They developed this method for pico-level monitoring of amikacin sulfate [173]. For a very sensitive determination, the currents were integrated over a whole potential scan range including oxidation and reduction at the gold electrode. The detection limit for amikacin sulfate was 2.0×10^{-11} M and the relative standard deviation for 10 determinations of 1.0 ng/mL of amikacin was 3.2%.

The benefits of a Fast Fourier transform continuous cyclic voltammetry (FFTCV) with a flow system are: a) a very low detection limit (picomolar level), b) the fact that is not necessary to remove oxygen from the test solution, and c) the fact that is a rapid and appropriate method for monitoring. Norouzi's group applied this method to the detection of penicillin G [174], gentamycin [175], gluthion [176], paromomycin [177], citalopram [178], tramadol [179], chloropromazine [180], ranitidine [181], tetracycline [182], penicillin V [183], lidocaine [184], thiamine [185], flunixin [186], piroxicam [187], morphine [188], propylthiouracil [189], nortriptyline [190], naltrexone hydrochloride [191], lorazepam [192], sotatol [193], clindamycin [194], bisacodyl [195], and tamoxifen [196]. In addition, this group designed an adsorptive fast Fourier transform coulometric technique with a flow system as a novel method for the determination of nanomolar concentrations of sodium valproate in pharmaceutical preparations [197]. The detection was performed by adsorptive fast Fourier transform coulometry (AFFTC), in which the potential waveform consisted of potential steps for cleaning, accumulation, and a potential ramp that was continuously applied at a gold disk microelectrode. Moreover, a special computer program based on a numerical method was introduced to calculate the analyte signal and noise reduction. The detection limit of the method for sodium valproate was 9.0×10^{-9} M. The relative standard deviation of the method at a concentration of 1.3×10^{-7} M was 2.0% for 10 runs.

To improve the sensitivity, Daneshgar et al. [198] have reported the use of other types of electrodes such as a carbon paste electrode modified by nanostructures to determine L-dopa in human serum and urine samples. The signal-to-noise ratio was significantly increased when a discrete fast Fourier transform (FFT) method was used.

2.2.4. Flow Analysis with Potentiometric Detections

Potentiometric detection is based on the measurement of electrical potentials without drawing appreciable current. The electrical potentials are related to the analytical quantity of interest, generally the concentration of some component in the analyte solution. The potentiometric detection in flow injection analysis is at a great advantage over stationary measurements because the manipulation of the solution is simpler and because minor errors due to displacement of the electrode between measurements are avoided. Moreover, the fact that the electrolyte is continuously flowing leads to the cleaning of the electrode surface.

Potentiometric detections using ion-selective electrodes coupled with flow systems have found wide applications because these methods are usually fast, highly selective, highly sensitive, portable, and do not require extensive training to be performed. There are several types of ion-selective electrodes such as crystalline membrane electrodes (e.g., LaF_3, Ag_2S, etc.) and noncrystalline membrane electrodes (e.g., glass electrode, cross-linked polymer electrode, etc.). The fluoride ion-selective electrode (FISE) with a LaF_3 membrane was used in a flow injection system for the analysis of Fe (III) ion with a detection limit 9×10^{-5} M [199]. A highly sensitive and stable potentiometric biosensor for the determination of creatinine using FIA with an ammonium ion selective electrode has also been developed [200]. This method is based on the detection of ammonia generated from the enzymatic hydrolysis of creatinine by creatinine deiminase. Creatinine deiminase is chemically immobilized on the surface of the ion-sensitive membrane that is located on the outer layer of the electrode. Hassan et al. also reported the determination of creatinine in human serum using tubular and coated wire creatinine tungstophosphate membrane sensors [201]. Additionally, a membrane-based potentiometric biosensor with immobilized creatinine deaminase has been developed for the analysis of creatinine with portable devices [202]. The miniaturized portable devices for creatinine analysis are easy to handle and allow a rapid analysis with a low consumption of chemicals.

Table 1 Analytical applications of flow-based with electrochemical detection

Technique	Instrument	Analyte	Sample (s)	Limit of detection	Ref.
DC Amperometry	FIA	Tetracyclines	Pharmaceutical samples	0.96, 0.58, 0.35 µM for tetracycline, chlortetracycline, oxytetracycline	21
Amperometry	FIA	Tannin	Beverage samples	-	28
Amperometry	FIA	Orthophosphate	Fresh and marine water samples	0.18 µg/L	29
Amperometry	FIA	Carbofuran and Fenobucarb	Water	2 ng/mL	30
Amperometry	FIA	Dopamine	-	10-8 M	32
Amperometry	FIA/HPLC	Phenol and chlorinated phenols	-	-	40
Cyclic voltammetry	FIA	Sulfonamides	Egg samples		44
Amperometry	FIA	Arsenite	-	25 nM	46
Amperometry	FIA	Hydrogen peroxide	-	6 x 10^{-7} mol/L	49
Amperometry	FIA/HPLC	glycolic acid	Human urine samples	1 x 10^{-6} mol/L	50
Amperometry	FIA	iodide	dry edible seaweed	1 x 10^{-7} mol/L	54
Cyclic voltammetry	FIA	NADH	-	3.3 µmol/L	55
Amperometry	FIA	Nitrite	Drinking water samples	2 µM	58
Amperometry	FIA	Acetaminophen	Pharmaceutical samples	1.36 x 10^{-7} mol/L	60
Amperometry	FIA	Piroxicam	Pharmaceutical samples	1 x 10^{-5} mol/L	61
Amperometry	FIA	Ambroxol	Pharmaceutical samples	7.6 × 10-8 M	63
Amperometry	FIA	Ambroxol	Pharmaceutical samples	7.6 x 10^{-8} mol/L	63
Amperometry	FIA	Insulin	-	40 pM	64
Amperometry	FIA	Phosphite	Fertilizer	5 x 10^{-4} mol/L	68
Differential Amperometry	FIA	Hydrogen peroxide	Honey	2.9 × 10-7 M	70
Amperometry	HPLC	Sugars	Honey	-	71
Amperometry	FIA	Glucose	Honey	1.7 x 10^{-5} mol/L	72
Amperometry	FIA	Hydrazide	-	8.5 µM	75
Amperometry	MSFIA	Diclofenac sodium	Pharmaceutical samples	4.3 µmol/L	80
Amperometry	FIA	Arsenic (III)	Groundwater	70 nM	81
Amperometry	FIA	Oxalate	-	-	84
Amperometry	Microchip FIA	Dopamine	-	74 nmol/L	90
Amperometry	FIA	Arsenite	-	0.25 ppb	93
	FIA	COD	-	15 mg/L	95
	FIA	hemoglobin	-	1.4 X 10-8 M	96
Amperometry	FIA	Hormone 17 beta-estradiol	-	6 pg/mL	97
Amperometry	FIA	Carbaryl	-	1.0 x 10^{-8} mol/ L	106
Biamperometry	FIA	Vitamin B1	Pharmaceutical samples	8.0 X 10-7 mol/L	118
Biamperometry	FIA	Iron (III)	Soil	60 mol/L	120
Amperometry	SIA	Vitellogenin	-	-	121
Amperometry	SIA	Sulfite	Wines	0.05 mg/L	123
Amperometry	FIA	Phenolic compounds	-	-	124
Amperometry	BIA	Salbutamol	Pharmaceutical samples	2.5 x 10^{-7} mol/L	124
Amperometry	SIA	Isoniazid	Tablets	4.1 × 10$^{-9\,M}$	125

Table 1 Analytical applications of flow-based with electrochemical detection (Cont.)

Technique	Instrument	Analyte	Sample (s)	Limit of detection	Ref.
Amperometry	BIA/FIA	Polyphenolic compound	Wines	7.2×10^{-4}, 2.6×10^{-3} mg/L for caffeic acid, gallic acid	126
Impedance	FIA	Carcinoembryonic antigen	Human serum	0.5 ng/mL	129
Pulse Amperometry	FIA	Imipramine	Pharmaceutical samples and human serum	-	135
Pulse amperometry	FIA	Paracetamol and Ascorbic acid	-	-	137
Pulse amperometry	FIA	Beta-agonists	Pharmaceutical samples	-	146
Pulse voltammetry	FIA	Chlorite	Drinking water	-	153
Amperometry	SIA	Picloram	Water	0.036 mg/L	158
Differential Pulse Anodic Stripping Voltammetry	FIA	mobile thallium	Soil samples	-	159
Square-wave anodic stripping voltammetry	SIA	Cadmium, Lead and Zinc	-	2 µg/L for cadmium and lead, 6 µg/L for zinc	162
Squre-wave adsorptive-stripping voltammetry	FIA	Fluoxetine	Pharmaceutical samples	-	167
Fast stripping continuous cyclic voltammetry	FIA	Metoclopramide	Pharmaceutical samples	1.0×10^{-11} M (3 pg/mL)	168
Amperometry	FIA	L-dopa	Human serum and urine samples	-	198
Potentiometry	FIA	Carbaryl	Complex biological samples	10 µg/mL	221

Poly(vinyl chloride) (PVC) membrane ion-selective electrodes with different ionic exchange and mediator solvents have been constructed for highly selective analyses in various fields. Selective PVC membrane electrodes coupled with a flow system for the determination of hyoscyamine ion based on hyoscyamine tetraphenylborate or hyoscyamine phosphotungstate were also proposed [203]. This sensor with a flow system is fast and selective. Nernstian slops over a concentration range from 1.0×10^{-5} to 1.0×10^{-2} M were obtained [204]. A flow injection analysis system comprising a cysteine selective electrode was also developed for the determination of cysteine in pharmaceuticals [205].

Ion-selective electrodes fabricated from nylon membrane immobilized with lysine oxidase can be used to detect lysine in mixture samples containing small amounts of ammonium with an acceptable accuracy [206]. A new pH sensitive electrode for FIA acid-base titrations was developed on the basis of a graphite/quinhydrone composite electrode [207, 208]. Hydrochloric acid and acetic acid were titrated by injection of samples into a sodium hydroxide carrier solution. FIA acid-base titrations reduce the volume of reagents and sample and the analysis time because the handling of the solution is automated and does not require manual operations such as pipetting, dispensing, mixing, and separation.

A membrane electrode containing bis(4-chlorothiophenolato)mercury(II) [Hg(CTP)(2)] was found to be very useful for iodide detection [209]. The performance of the system was evaluated with regard to the parameters of the membrane electrode and the flow system. The presented assay was applied to the determination of iodide in a pharmaceutical preparation and the results were compared with those obtained with a standard potentiometric method based on a silver electrode.

Recently, El Nashar et al. [210] described a flow system for orciprenaline with potentiometric and spectrophotometric detectors. An ion-selective electrode made of orciprenaline ion-associated with phosphotungstic acid was incorporated in a PVC matrix membrane and a sequential spectrophotometric detection of the same sample using the reaction of orciprenaline with phosphomolybdic acid in alkaline medium was performed.

Flow systems with potentiometric stripping detections were also used due to their rapidity, sensitivity, accuracy, and precision in analysis. Moreover, potentiometric stripping detection has the great advantage of being unaffected by charging currents and highly resistive solutions. Therefore, various flow injection systems with a potentiometric stripping detection have been reported for the determination of heavy metals such as arsenic (III), zinc(II), cadmium(II) and lead(II) [211-213].

Sequential injection analysis (SIA) with potentiometric detection has been applied to the development of an automated system that detects several analytes such as chloride [214], nickel [215], and penicillin G [216]. SIA is more automated than simple flow-injection systems and is able to accommodate different analytical procedures in a single setup. Furthermore, SIA typically consumes lower amounts of reagent and produces a lower amount of waste. SIA with a potentiometric detection system is mostly used with an ion-selective electrode as the working electrode. For example, a tubular chloride selective electrode based on octaethyl porphyrinate indium (III) can be used to determine chloride in pharmaceutical formulations with a SIA system [214]. A tubular penicillin selective electrode based on tetraphenylporphyrinate manganese (III) was used for the determination of penicillin by SIA. Also, cyclodextrin-based potentiometric sensors can be used with SIA for the determination of midazolam and diazepam [217].

A potentiometric flow system is not only a method for the determination of different analytes but also for automated sample pretreatments. A simple flow system for a potentiometric detection of alkaline phosphatase (ALP) activity has been developed and adapted for the determination of selected inhibitors of this enzyme [218]. In this system, monofluorophosphate (MFP) was used as a specific ALP substrate. The use of this substrate enabled the application of a fluoride ion selective electrode. Moreover, the system also allowed the inhibitive detection of beryllium and vanadate ions. A flow system with a potentiometric detection has also been developed for the direct determination of arsenic (V) in water samples after on-line preconcentration in a minicolumn packed with adsorbent material. Iron oxyhydroxide was selectively embedded in silica gel as the adsorbent material and arsenic (V) was used as the selective component in a tubular potentiometric electrode [219]. A solid-phase extraction disk (SPE) for an automated preconcentration and determination of surfactants using a potentiometric FIA system has also been reported [220]. An octadecylsilica extraction disk was used as the solid-phase for the automated preconcentration and for the cleaning of the sample before it was detected by the potentiometric FIA technique. Hantash et al. applied an in-line imprinted polymer column with a potentiometric flow-injection chemical sensor to determine the concentration of the carbamate pesticide carbaryl in complex biological matrices (rat plasma) [221]. A new and simple device for the direct detection of chromium (III) in a batch with a flow analysis without previous oxidation/reduction and without any preconcentration of the samples was proposed in 2009 [222]. A FI-potentiometric analyzer was utilized for the evaluation of the total oxidation in palm olefin [223]. The proposed assay is fast and the results obtained were in agreement with those obtained with the official method.

2.2.5. Flow Analysis with Miscellaneous Detection

There are few papers that describe the use of the conductometric technique for the analysis of column effluents in flow-based systems including liquid chromatography. For example, the method is based on ammonia preconcentration in a wet cylindrical diffusion and subsequent on-line effluent analysis with a conductometric detection [224]. This method can be used for the determination of traces of ammonia in air samples. The detection limit is as low as 100 ppt for a flow injection analysis and 20 ppt for a continuous analysis of ammonia in a denuder effluent. Kuban et al. [225] have reported a flow injection-capillary electrophoresis system with high-voltage conductivity without any contact and an automated dual opposite end injection for the separation and detection of anions and cations in a variety of samples. A conductometric detector was coupled to a capillary isotachophoresis (ITP) for the separation and determination of promethazine hydrochloride (PRO) in commercial pharmaceutical preparations. Kuban et al. [226] developed an open tubular anion exchange chromatography as a new stationary phase for ionic separation. The method was utilized to separate anions using strong base eluent and suppressed contactless conductometric detection. Additionally, Kuban et al. [227] have also reviewed the recent achievements for efficient conductivity detections without any contact. Other studies have focused on the application of this detection method to other analytical methods such as ion chromatography, high-performance liquid chromatography, and flow-injection analysis.

Coulometric detection is related to the quantity of electricity generated by the analytes. Monosegmented flow analysis (MSFA) has been used as a flow-batch system to produce a simple, robust, and mechanic titrator with production of a coulometric reagent [228]. A flow-batch system was obtained, in which the liquid monosegment that is constrained by the interfaces of the gaseous carrier stream played the role of a sample of known volume. The system has been used for the determination of ascorbic acid and Fe(II). Oliveira et al. [229] developed a universal and simple coulometric flow cell for the generation of chemicals such as reagents, titrants, and standard solutions. This flow cell can be combined with a flow system for the production of micro-amounts of chemicals. One of the applications of this method has been the production of triiodide ions as carriers in a flow injection analysis system in order to determine the concentration of dipyrone in pharmaceuticals. Triiodide ions have also been used as titrants in a flow-batch analysis system for the analysis of ascorbic acid in natural orange juice samples. A flow-batch coulometric titration system has also been applied to the determination of the bromine index and bromine number of petrochemicals [230]. Enzymatic reactions coupled with flow-injection coulometric or amperometric detections were proposed as alternatives for the detection of pesticide contaminations of the environment [231]. The detection limits for the measurement of chloride anions with these detectors was 100 nM (coulometric) and 1 nM (amperometric).

A coulometric analysis method was combined with ion-exclusion chromatography to determine antimony (V) in a solution containing a large excess of antimony (III) [232]. Thus, the detection limit of antimony (V) in a solution of antimony (III) oxide was 0.004% of antimony (III). The amperometric method led to a detection limit of 0.002% of antimony (III).

A flow-injection coulometric detection based on ion transfer and its application to the determination of chlorpromazine was reported [233]. The detector used consisted of a flow-through cell that incorporated a plasticized poly (vinyl chloride) (PVC) membrane that contained tetrabutylammonium tetraphenylborate as the electrolyte. The linear range was between 1 x 10^{-6} and 1 x 10^{-4} M with a detection limit of 2 x 10^{-7} M. Finally, the use of rectangular thin-layer cells for the detection of electrochemically oxidizable/reducible substances in flow injection coulometry was studied [234]. The experimental results obtained were in accordance with the theoretical values obtained from a reliably developed method.

In addition, the example of analytical applications from flow-based system with electrochemical detection for the determination of wide range of analytes was summarized in Table 1.

3. Conclusions

The present article highlights the use of flow-based systems coupled with electrochemical detection methods for the determination of various compounds in diverse applications. The available flow-based electrochemical detection techniques in various flow technologies for the detection of biological, pharmaceutical, and environmental samples have been reviewed. The cited references emphasize the benefits of electrochemical sensors with flow-based systems. These benefits include a high sensitivity and selectivity, a low cost of equipment, a smaller amount of reagents used, an easy automation, and a multianalyte analysis. Electrochemical sensors are one of the most important developments in this research area. Indeed, as reported in this review, various types of analytes can be detected. The number of applications is steadily increasing due to the high performance of electrochemical detection methods with flow-based systems.

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References

[1] A. M. Bond., *Anal. Chim. Acta* **400**, 333 (1999).
[2] A. Manz, N. Graber, H. M. Widmer, *Sensors. Actuat B-Chem.,* **68**, 978 (1990).
[3] J. Ruzicka, E.H. Hansen, *Anal. Chim. Acta* **78**, 145 (1975); *Flow Injection Analysis*. (John Wiley & Sons, New York, ed. 2, 1988).
[4] J. Ruzicka, G. D. Marshall, *Anal. Chim. Acta* **237**, 329 (1990).
[5] M. Trojanowicz, P. Kozminski, H. Dias, C. M. A. Brett, *Talanta* **68**, 394 (2005).
[6] C. Pons, R. Forteza, V. Cerda, A. O. S. S. Rangel, *TrAC- Trend. Anal. Chem.* **25**, 583 (2006).
[7] J. M. Estela, V. Cerda, *Talanta* **66**, 307 (2005).
[8] H. Itabashi, H. Kawamoto, T. Kawashima, *Anal. Sci.* **17**, 229 (2001).
[9] R. Perez-Olmos, J. C. Soto, N. Zarate, A. N. Araujo, M. Montenegro, *Anal. Chim. Acta* **554**, 1 (2005).
[10] O. Chailapakul, P. Ngamukot, A. Yoosamran, W. Siangproh, N. Wangfuengkanagul, *Sensors* **6**, 1383 (2006).
[11] P. M. S. Monk, *Fundamentals of Electroanalytical Chemistry*. D. J. Ando, Ed., Analytical Techniques in the Sciences (AnTS) (John Wiley & Sons, Chichester, New York, Weinheim, Brisbane, Toronto, Singapore, 2001).
[12] P. Ngamukot, T. Charoenraks, O. Chailapakul, S. Motomizu, S. Chuanuwatanakul, *Anal. Sci.* **22**, 111 (2006).
[13] M. L. Agui, E. Calavia, P. Yanezsedeno, J. M. Pingarron, *Anal. Chim. Acta* **305**, 324 (1995).
[14] I. G. Casella, R. Marchese, *Anal. Chim. Acta* **311**, 199 (1995).
[15] I. G. Casella, *Anal. Chim. Acta* **311**, 37 (1995).
[16] M. H. Blanco, M. C. Quintana, P. Hernandez, J. Vicente, L. Hernandez, *Anal. Lett.* **28**, 2683 (1995).
[17] Q. J. Chi, S. J. Dong, *Anal. Chim. Acta* **278**, 17 (1993).
[18] M. DelCarlo, M. Mascini, *Anal. Chim. Acta* **336**, 167 (1996).
[19] C. D. Garcia, P. I. Ortiz, *Anal. Sci.* **15**, 461 (1999).
[20] T. Perezruiz, C. M. Lozano, V. Tomas, *J. Pharm. Biomed. Anal.* **12**, 1109 (1994).
[21] P. Masawat, J. M. Slater, *Sensors Actuat B-Chem.* **124**, 127 (2007).
[22] W. Y. Su, S. H. Cheng, *Electrochem. Commun.,* **10**, 899 (2008).
[23] P. Jaraba, L. Agui, P. Yanez-Sedeno, J. M. Pingarron, *Electrochim. Acta* **43**, 3555 (1998).
[24] C. D. Paras, R. T. Kennedy, *Electroanalysis* **9**, 203 (1997).
[25] M. F. Suaudchagny, P. Brun, M. Buda, F. Gonon, *J. Neurosci. Meth.* **45**, 183 (1992).
[26] W. H. Zhou, L. Xu, M. J. Wu, L. J. Xu, E. Wang, *Anal. Chim. Acta* **299**, 189 (1994).
[27] L. Monser, N. Adhoum, S. Sadok, *Talanta* **62**, 389 (2004).
[28] Y. T. Hung, P. C. Chen, R. L. C. Chen, T. J. Cheng, *Sensors Actuat B-Chem.* **130**, 135 (2008).
[29] Y. Udnan, I. D. McKelvie, M. R. Grace, J. Jakmunee, K. Grudpan, *Talanta* **66**, 461 (2005).
[30] M. G. F. Sales, M. C. V. F. Vaz, C. Delerue-Matos, S. A. A. Almeida, M. F. Barroso, H. A. O. Ferreira, *Int. J. Environ. Anal. Chem.* **88**, 37 (2008).
[31] P. Bunpeng, S. Lapanantnoppakhun, J. Jakmunee, *Chiang Mai J. Sci.* **35**, 345 (2008).
[32] W. L. Yeh, Y. R. Kuo, S. H. Cheng, *Electrochem. Commun.* **10**, 66 (2008).
[33] O. Chailapakul, W. Siangproh, D. A. Tryk, *Sensor Letters* **4**, 99 (2006).
[34] W. Siangproh, P. Ngamukot, O. Chailapakul, *Sensors Actuat B-Chem.* **91**, 60 (2003).
[35] W. Siangproh, N. Wangfuengkanagul, O. Chailapakul, *Anal. Chim. Acta* **499**, 183 (2003).
[36] J. Wu, X. Li, C. Lei, X. Wu, G. Shen, R. Yu, *J. Anal. Chem.* **60**, 1062 (2005).
[37] S. Treetepvijit , A. Preechaworapun, N. Praphairaksit, S. Chuanuwatanakul, Y. Einaga, O. Chailapakul, *Talanta* **68**, 1329 (2006).

[38] K. Boonsong, S. Chuanuwatanakul, N. Wangfuengkanagul, O. Chailapakul, *Sensors Actuat B-Chem.*, **108**, 627 (2005).

[39] V. Suryanarayanan, Y. Zhang, S. Yoshihara, T. Shirakashi, *Sensors Actuat B-Chem.***102**, 169 (2004).

[40] G. W. Muna, N. Tasheva, G. M. Swain, *Environ. Sci. Tech.* **38**, 3674 (2004).

[41] O. Nekrassova, N. S. Lawrence, R. G. Compton, *Electroanalysis* **16**, 1285 (2004).

[42] J. D. Zhang, M. Oyama, *Microchem. J.* **78**, 217 (2004).

[43] T. A. Ivandini, T. N. Rao, A. Fujishima, Y. Einaga, *Anal. Chem.* **78**, 3467 (2006).

[44] A. Preechaworapun, S. Chuanuwatanakul, Y. Einaga, K. Grudpan, S. Motomizu, O. Chailapakul., *Talanta* **68**, 1726 (2006).

[45] H. Sangjarusvichai, W. Dungchai, W. Siangproh, O. Chailapakul, *Talanta* **In Press, Corrected Proof**.

[46] J. M. Zen, P. Y. Chen, A. S. Kumar, *Anal. Chem.* **75**, 6017 (2003).

[47] M. F. De Oliveira, A. A. Saczk, J. A. G. Neto, P. S. Roldan, N. R. Stradiotto, *Sensors* **3**, 371 (2003).

[48] B. Haghighi, S. Varma, F. M. Alizadeh, Y. Yigzaw, L. Gorton, *Talanta* **64**, 3 (2004).

[49] J. P. Li, H. N. Gu, *J. Chinese Chem. Soc.* **53**, 575 (2006).

[50] S. Liawrungrath, P. Purachat, W. Oungpipat, C. Dongduen, *Talanta* **77**, 500 (2008).

[51] M. Cano, B. Palenzuela, R. Rodriguez-Amaro, *Electroanalysis* **18**, 1727 (2006).

[52] F. D'eramo, L. E. Sereno, A. H. Arevalo, *Electroanalysis* **19**, 96 (2007).

[53] P. Li, M.-C. Liu, C.-L.Zhang, Y.-X. Cheng, L. Zhang, L.-T. Jin, *Acta Chimica Sinica* **63**, 1075 (2005).

[54] L. Tian, L. Liu, L. Chen, N. Lu, H. D. Xu, *Talanta* **66**, 130 (2005).

[55] Y. L. Chen, J. H. Yuan, C. X. Tian, X. Z. Wang, *Anal. Sci.* **20**, 507 (2004).

[56] P. R. Roy, T. Okajima, T. Ohsaka, *J. Electroanal. Chem.* **561**, 75 (2004).

[57] M. H. Vela, D. S. de Jesus, C. Couto, A. N. Araujo, M. Montenegro, *Electroanalysis* **15**, 133 (2003).

[58] V. Biagiotti, F. Valentini, E. Tamburri, M. L. Terranova, D. Moscone, G. Palleschi., *Sensors Actuat B-Chem.* **122**, 236 (2007).

[59] S. Aravamudhan, S. Bhansali, *Sensors Actuat B-Chem.* **132**, 623 (2008).

[60] F. S. Felix, C. M. A. Brett, L. Angnes, *J. Pharm. Biomed. Anal.* **43**, 1622 (2007).

[61] M. Luísa S. Silva, M. Beatriz Q. Garcia, José L. F. C. Lima, E. Barrado, *Electroanalysis* **19**, 1362 (2007).

[62] P. Kotzian, P. Brazdilova, K. Kalcher, K. Handlir, K. Vytras, *Sensors Actuat B-Chem.* **124**, 297 (2007).

[63] F. S. Felix, C. M. A. Brett, L. Angnes, *Talanta* **76**, 128 (2008).

[64] A. Salimi, M. Roushani, B. Haghighi, S. Soltanian, *Biosens. Bioelectron.* **22**, 220 (2006).

[65] Y. Shih, J. M. Zen, *J. Chinese Chem. Soc.* **53**, 857 (2006).

[66] H. Mohammadi, A. Amine, M. El Rhazi, C. M. A. Brett, *Talanta* **62**, 951 (2004).

[67] M. F. S. Teixeira, L. A. Ramos, O. Fatibello, E. T. G. Cavalheiro, *Anal. Bioanal. Chem.,* **376**, 214 (2003).

[68] V. P. Franzini, C. S. Fugivara, A. V. Benedetti, C. A. Ribeiro, E. T. G. Cavalheiro, J. A. G. Neto, *Electroanalysis* **19**, 1794 (2007).

[69] A. Salimi, M. Roushani, S. Soltanian, R. Hallaj, *Anal. Chem.* **79**, 7431 (2007).

[70] R. A. de Abreu Franchini, M. A. C. Matos, R. Colombara, R. C. Matos, *Talanta* **75**, 301 (2008).

[71] J. W. Sue, C. J. Hung, W. C. Chen, J. M. Zen, *Electroanalysis* **20**, 1647 (2008).

[72] V. L. da Silva, M. R. F. Cerqueira, M. A. C. Matos, R. C. Matos, *Anal. Lett.* **42**, 154 (2009).

[73] L. G. Shaidarova, L. N. Davietshina, G. K. Budnikov, *J. Anal. Chem.* **61**, 502 (2006).

[74] L. G. Shaidarova, S. A. Ziganshina, L. N. Tikhonova, G. K. Budnikov, *J. Anal. Chem.* **58**, 1144 (2003).

[75] J. S. Pinter, K. L. Brown, P. A. DeYoung, G. F. Peaslee, *Talanta* **71**, 1219 (2007).

[76] A. Abbaspour, M. A. Mehrgardi, *Talanta* **67**, 579 (2005).

[77] J. R. C. da Rocha, T. L. Ferreira, R. M. Torresi, M. Bertotti, *Talanta* **69**, 148 (2006).

[78] E. A. Hutton, B. Ogorevc, M. R. Smyth, *Electroanalysis* **16**, 1616 (2004).

[79] S. Sattayasamitsathit, P. Thavarungkul, P. Kanatharana, *Electroanalysis* **19**, 502 (2007).

[80] J. A. Rodriguez, E. Barrado, Y. Castrillejo, J. R. Santos, J. L. F. C. Lima, *J. Pharm. Biomed. Anal.* **45**, 47 (2007).

[81] A. Salimi, R. Hallaj, *Electroanalysis* **16**, 1964 (2004).

[82] J. Kruusma, C. E. Banks, R. G. Compton, *Anal. Bioanal. Chem.* **379**, 700 (2004).

[83] A. Salimi, V. Alizadeh, R. Hallaj, *Talanta* **68**, 1610 (2006).

[84] T. Kondo, Y. Niwano, A. Tamura, T. A. Ivandini, Y. Einaga, D. A. Tryk, A. Fujishima, Takeshi Kawai, *Electroanalysis* **20**, 1556 (2008).

[85] T. A. Ivandini, R. Sato, Y. Makide, A. Fujishima, Y. Einaga, *Diam. Relat. Mater.* **14**, 2133 (2005).

[86] T. A. Ivandini, R. Sato, Y. Makide, A. Fujishima, Y. Einaga, *Chem. Lett.* **33**, 1330 (2004).

[87] S. Treetepvijit, S. Chuanuwatanakul, Y. Einaga, R. Sato, O. Chailapakul, *Anal. Sci.* **21**, 531 (2005).

[88] Q. Zhang, J. J. Xu, H. Y. Chen, *J. Chromatogr. A* **1135**, 122 (2006).

[89] Q. L. Zhang, J. J. Xu, H. Z. Lian, X. Y. Li, H. Y. Chen, *Anal. Bioanal. Chem.* **387**, 2699 (2007).

[90] S. J. Yao, J. H. Xu, Y. Wang, X. X. Chen, Y. X. Xu, S. S. Hu, *Anal. Chim. Acta* **557**, 78 (2006).

[91] J. M. Zen, C. T. Hsu, A. S. Kumar, H. J. Lyuu, K. Y. Lin, *Analyst* **129**, 841 (2004).

[92] C. C. Yang, A. S. Kumar, M. C. Kuo, S. H. Chien, J. M. Zen, *Anal. Chim. Acta* **554**, 66 (2005).

[93] E. Majid, S. Hrapovic, Y. L. Liu, K. B. Male, J. H. T. Luong, *Anal. Chem.* **78**, 762 (2006).

[94] S. Y. Ai, M. N. Gao, Y. Yang, J. Q. Li, L. T. Jin, *Electroanalysis* **16**, 404 (2004).

[95] J. Q. Li, L. Zheng, L. P. Li, G. Y. Shi, Y. Z. Xian, L. T. Jin, *Meas. Sci. Technol.* **18**, 945 (2007).

[96] M. C. Liu, P. Li, L. Zhang, Y-Z. Xian, H-C. Ding, C.-L. Zhang, F-F. Zhang, L. T. Jin, *Chinese J. Chem.* **23**, 983 (2005).

[97] X. Q. Liu, D. K. Y. Wong, *Talanta* **77**, 1437 (2009).

[98] A. Salimi, H. Mamkhezri, S. Mohebbi, *Electrochem. Commun.* **8**, 688 (2006).

[99] A. Salimi, A. Noorbakhsh, M. Ghadermarzi, *Sensors Actuat B-Chem.* **123**, 530 (2007).

[100] A. S. Arribas, E. Bermejo, M. Chicharro, A. Zapardiel, G. L. Luque, N. F. Ferreyra, G. A. Rivas., *Anal. Chim. Acta* **577**, 183 (2006).

[101] G. D. Liu, S. L. Riechers, M. C. Mellen, Y. H. Lin, *Electrochem.Commun.* **7**, 1163 (2005).

[102] J. Wang, M. Musameh, *Anal. Chim. Acta* **511**, 33 (2004).

[103] R. P. Deo, J. Wang, *Electrochem. Commun.* **6**, 284 (2004).

[104] M. Koitabashi, A. Kotani, F. Kusu, *Bunseki Kagaku* **52**, 1137 (2003).

[105] C. W. K. Chow, S. D. Thomas, D. E. Davey, D. E. Mulcahy, M. Drikas, *Anal. Chim. Acta* **499**, 173 (2003).

[106] D. C. Portela, I. M. F. Pereira, P. Paiga, C. Delerue-Matos, M. Vaz, *Anal. Bioanal. Chem.* **377**, 356 (2003).

[107] J. Garrido, C. Delerue-Matos, F. Borges, T. R. A. Macedo, A. M. Oliveira-Brett, *Anal. Lett.* **36**, 2199 (2003).

[108] M. E. Rueda, L. A. Sarabia, A. Herrero, M. C. Ortiz, *Anal. Chim. Acta* **479**, 173 (2003).

[109] S. Satienperakul, S. Y. Sheikheldin, T. J. Cardwell, R. W. Cattrall, M. D. Luque de Castro, I. D. McKelvie, S. D. Kolev, *Anal. Chim. Acta* **485**, 37 (2003).

[110] Y. Udnan, I. D. McKelvie, M. R. Grace, J. Jakmunee, K. Grudpan, *Talanta* **66**, 461 (2005).

[111] Y. R. Zhang, S. Asahina, M. Suzuki, S. Yoshihara, T. Shirakashi, *Surf. Coat. Tech.* **169**, 303 (2003).

[112] J. Garrido, C. Delerue-Matos, F. Borges, T. R. A. Macedo, A. M. Oliveira-Brett, *Anal. Lett.* **36**, 577 (2003).

[113] J. L. Corujo-Antuna, E. M. Abad-Villar, M. T. Fernandez-Abedul, A. Costa-Garcia, *J. Pharm. Biomed. Anal.* **31**, 421 (2003).

[114] T. Yao, T. Yano, Y. Nanjyo, H. Nishino, *Anal. Sci.* **19**, 61 (2003).

[115] D. Daniel, I. G. R. Gutz, *Anal. Chim. Acta* **571**, 218 (2006).

[116] J. Michalowski, M. Trojanowicz, *Anal. Chim. Acta* **281**, 299 (1993).

[117] J. Michalowski, A. Kojlo, M. Trojanowicz, B. Szostek, E. A. G. Zagatto, *Anal. Chim. Acta* **271**, 239 (1993).

[118] L. J. Li, H. Cheng, C. Zhao, X. G. Hu, *Chemical Research in Chinese Universities* **21**, 650 (2005).

[119] J. Jakmunee, K. Grudpan, *Anal. Chim. Acta* **438**, 299 (2001).

[120] J. Q. Chen, W. Gao, J. F. Song, *Sensors Actuat B-Chem.* **113**, 194 (2006).

[121] K. Hirakawa, M. Katayama, N. Soh, K. Nakano, T. Imato, *Anal. Sci.* **22**, 81 (2006).

[122] G. D. Liu, S. L. Riechers, C. Timchalk, Y. H. Lin, *Electrochem. Commun.* **7**, 1463 (2005).

[123] C. Chinvongamorn, K. Pinwattana, N. Praphairaksit, T. Imato, O. Chailapakul, *Sensors* **8**, 1846 (2008).

[124] M. S. M. Quintino, L. Angnes, *Talanta* **62**, 231 (2004).

[125] M. S. M. Quintino, L. Angnes, *J. Pharm. Biomed. Anal.* **42**, 400 (2006).

[126] M. Gamella, S. Campuzano, A. J. Reviejo, J. M. Pingarron, *J. Agr. Food Chem.* **54**, 7960 (2006).

[127] P. F. Hsu, W. L. Ciou, P. Y. Chen, *J. Appl. Electrochem.* **38**, 1285 (2008).

[128] F. Wachholz, K. Biala, M. Piekarz, G. U. Flechsig, *Electrochem. Commun.* **9**, 2346 (2007).

[129] J. Wu, J. Tang, Z. Dai, F. Yan, H. Ju, N. El Murr, *Biosens. Bioelectron.* **22**, 102 (2006).

[130] P. Fanjul-Bolado, M. B. Gonzalez-Garcia, A. Costa-Garcia, *Anal. Bioanal. Chem.* **385**, 1202 (2006).

[131] S. Palaharn, T. Charoenraks, N. Wangfuengkanagul, K. Grudpan, O. Chailapakul, *Anal. Chim. Acta* **499**, 191 (2003).

[132] T. Charoenraks, S. Palaharn, K. Grudpan, W. Siangproh, O. Chailapakul, *Talanta* **64**, 1247 (2004).

[133] S. Ngamchana, W. Surareungchai, *Anal. Chim. Acta* **510**, 195 (2004).

[134] R. Possari, R. F. Carvalhal, R. K. Mendes, L. T. Kubota, *Anal. Chim. Acta* **575**, 172 (2006).

[135] J. A. Ortuno, A. Gil, C. Sanchez-Pedreno, *Sensors Actuat B-Chem.* **122**, 369 (2007).

[136] J. A. Ortuno, C. Rueda, *Sensors* **7**, 1185 (2007).

[137] W. T. P. dos Santos, E. G. N. de Almeida, H. E. A. Ferreira, D. T. Gimenes, E. M. Richter, *Electroanalysis* **20**, 1878 (2008).

[138] I. G. Casella, M. Contursi, *J. Chromatogr. A* **1063**, 129 (2005).

[139] Y. Q. Cai, J. S. Liu, Y. L. Shi, L. N. Liang, S. F. Mou, *J. Chromatogr. A* **1085**, 98 (2005).

[140] R. Kaushik, W. R. LaCourse, B. Levine, *Anal. Chim. Acta* **556**, 267 (2006).

[141] Y. E. Cai, Y. Q. Cai, Y. L. Shi, S. Mou, Y. Q. Lu, *J. Chromatogr. A* **1118**, 35 (2006).

[142] V. P. Hanko, J. S. Rohrer, *J. Pharm. Biomed. Anal.* **40**, 1006 (2006).

[143] A. Guzman, L. Agui, M. Pedrero, P. Yanez-Sedeno, J. M. Pingarron, *J. Pharm. Biomed. Anal.* **33**, 923 (2003).

[144] V. Carralero, A. Gonzalez-Cortes, P. Yanez-Sedeno, J. M. Pingarron, *Electroanalysis* **17**, 289 (2005).

[145] C. Karuwan, T.Mantim, P. Chaisuwan, P. Wilairat, K. Grudpan, P. Jittangprasert, Y. Einaga, O. Chailapakul, L. Suntornsuk, O. Anurukvorakun, D. Nacapricha, *Sensors* **6**, 1837 (2006).

[146] C. D. Garcia, G. Engling, P. Herckes, J. L. Collett, C. S. Henry, *Environ. Sci. Technol.* **39**, 618 (2005).

[147] C. D. Garcia, C. S. Henry, *Anal. Chem.* **75**, 4778 (2003).

[148] Y. S. Ding, C. D. Garcia, *Analyst* **131**, 208 (2006).

[149] Carlos D. G. Yongsheng Ding, *Electroanalysis* **18**, 2202 (2006).

[150] C. D. Garcia, C. S. Henry, *Anal. Chim. Acta* **508**, 1 (2004).

[151] Charles S. H. Carlos D. Garc̊a, *Electroanalysis* **17**, 223 (2005).

[152] C. D. Kuhnline, M. G. Gangel, M. K. Hulvey, R. S. Martin, *Analyst* **131**, 202 (2006).

[153] G. Pezzatini, I. Midili, G. Toti, F. Loglio, M. Innocenti, *Anal. Bioanal. Chem.* **380**, 650 (2004).

[154] A. Gutés, F. Cespedes, M. del Valle, D. Louthander, C. Krantz-Rülcker, F. Winquist, *Sensors Actuat B-Chem.* **115**, 390 (2006).

[155] M. L. S. Silva, M. B. Q. Garcia, J. L. F. C. Lima, E. Barrado, *Anal. Chim. Acta* **573-574**, 383 (2006).

[156] L. B. O. dos Santos, M. S. P. Silva, J. C. Masini, *Anal. Chim. Acta* **528**, 21 (2005).

[157] L. B. O. dos Santos, J. C. Masini, *Talanta* **72,** 1023 (2007).

[158] S. Suteerapataranon, J. Jakmunee, Y. Vaneesorn, K. Grudpan, *Talanta* **58**, 1235 (2002).

[159] Z. Lukaszewski, B. Karbowska, W. Zembrzuski, *Electroanalysis* **15**, 480 (2003).

[160] L. K. Shpigun, V. K. Lunina, *J. Anal. Chem.* **58**, 1078 (2003).

[161] G. Kefala, A. Economou, *Anal. Chim. Acta* **576**, 283 (2006).

[162] A. Economou, A. Voulgaropoulos, *Talanta* **71**, 758 (2007).

[163] S. Chuanuwatanakul, Duangchai, W., Chailapakul, O., Motomizu, S, *Anal. Sci.* **24**, 589 (2008).

[164] Y. Wang, Z. Liu, X. Hu, J. Cao, F. Wang, Q. Xu, C. Yang, *Talanta* **77**, 1203 (2009).

[165] C. M. A. Brett, O. M. S. Filipe, C. S. Neves, *Anal. Lett.* **36**, 955 (2003).

[166] J. Gun, P. Salaun, C. M. G. van den Berg, *Anal. Chim. Acta* **571**, 86 (2006).

[167] H. P. A. Nouws, C. Delerue-Matos, A. A. Barros, J. A. Rodrigues, A. Santos-Silva, *Anal. Bioanal. Chem.* **382**, 1662 (2005).

[168] P. Norouzi, M. R. Ganjali, P. Matloobi, *Electrochem. Commun.* **7**, 333 (2005).

[169] P. Norouzi, M. R. Ganjali, A. Sepehri, M. Ghorbani, *Sensors Actuat B-Chem.* **110**, 239 (2005).

[170] P. Norouzi, M. R. Ganjali, *J. Anal.l Chem.* **63**, 566 (2008).

[171] P. Norouzi, M. R. Ganjali, B. Larijani, S. Karamdoust, *Croat. Chem. Acta* **81**, 423 (2008).

[172] P. Daneshgar, P. Norouzi, M. R. Ganjali, *Chem. Pharm. Bull.* **57**, 117 (2009).

[173] P. Norouzi, G. R. Nabi Bidhendi, M. R. Ganjali, A. Sepehri, M. Ghorbani, *Microchim. Acta* **152**, 123 (2005).

[174] P. Norouzi, M. R. Ganjali, T. Alizadeh, P. Daneshgar, *Electroanalysis* **18**, 947 (2006).

[175] P. Norouzi, M. R. Ganjali, L. Hajiaghababaei, *Anal. Lett.* **39**, 1941 (2006).

[176] G. N. Bidhendi, P. Norouzi, P. Daneshgar, M. R. Ganjali, *J. Hazard. Mater.* **143**, 264 (2007).

[177] M. R. Ganjali, P. Norouzi, P. Daneshgar, A. Sepehri, *Sensors Actuat B-Chem.* **123,** 1125 (2007).

[178] P. Norouzi, P. Daneshgar, M. R. Ganjali, A. Moosavi-Movahedi, *J. Brazil. Chem. Soc.* **18**, 231 (2007).

[179] P. Norouzi, R. Dinarvand, M. R. Ganjali, A. S. E. Meibodi, *Anal. Lett.* **40**, 2252 (2007).

[180] P. Norouzi, M. R. Ganjah, R. Farokhi, *J. Chinese Chem. Soc.* **54**, 1243 (2007).

[181] P. Norouzi, M. R. Ganjali, P. Daneshgar, *J. Pharmaco.Toxico. Meth.* **55,** 289 (2007).

[182] P. Norouzi, M. R. Ganjali, P. Daneshgar, *Turkish J. Chem.* **31**, 279 (2007).

[183] P. Norouzi, M. R. Ganjali, P. Daneshgar, T. Alizadeh, A. Mohammadi, *Anal. Biochem.* **360**, 175 (2007).

[184] P. Norouzi, M.R. Ganjali, P. Daneshgar, R. Dinarvand, A. A. Moosavi-Movahedi, A.A. Saboury, *Anal. Chim. Acta* **590**, 74 (2007).

[185] P. Norouzi, M. R. Ganjali, P. Daneshgar, A. Mohammadi, *Anal. Lett.* **40**, 547 (2007).

[186] P. Norouzi, M. R. Ganjali, R. Dinarvand, S. Labbafi, *Acta Chim. Slovenica* **54**, 840 (2007).

[187] P. Norouzi, M. R. Ganjali, S. Labbafi, A. Mohammadi, *Anal. Lett.* **40**, 747 (2007).

[188] P. Norouzi, M. R. Ganjali, A. A. Moosavi-movahedi, B. Larijani, *Talanta* **73,** 54 (2007).

[189] P. Norouzi, M. R. Ganjali, A. A. Sehat, S. Mirahmadi, B. Larijani, *Chemia Analityczna* **52**, 399 (2007).

[190] P. Norouzi, M. R. Ganjali, S. Shirvani-Arani, A. Mohammad, *J .Pharm. Sci.* **96**, 893 (2007).

[191] P. Norouzi, M. R. Ganjali, M. Zare, A. Mohammadi, *J .Pharm. Sci.* **96**, 2009 (2007).

[192] P. Norouzi, M. R. Ganjali, A. S. E. Meibodi, *Anal. Lett.* **41**, 1208 (2008).

[193] P. Norouzi, M. R. Ganjali, A. S. E. Meibodi, B. Larijani, *Russian J. Electrochem.* **44**, 1024 (2008).

[194] P. Norouzi, B. Larijani, M. Ezoddin, M. R. Ganjali, *Mater. Sci. Engin. C-Biomim. Supramol. Sys.* **28**, 87 (2008).

[195] P. Daneshgar, P. Norouzi, M. R. Ganjali, *Sensors Actuat B-Chem.* **136**, 66 (2009).

[196] P. Daneshgar, P. Norouzi, M. R. Ganjali, H. A. Zamani, *Talanta* **77**, 1075 (2009).

[197] P. Norouzi, S. Shirvani-Arani, P. Daneshgar, M. R. Ganjali, *Biosens. Bioelectron.* **22**, 1068 (2007).

[198] P. Daneshgar, P. Norouzi, M. R. Ganiali, A. Ordikhani-Seyedlar, H. Eshraghi, *Colloid Surf. B-Biointer.* **68**, 27 (2009).

[199] M. Bralic, S. Brinic, E. Generalic, L. Vrsalovic, *Talanta* **63**, 777 (2004).

[200] A. Radomska, E. Bodenszac, S. Glab, R. Koncki, *Talanta* **64**, 603 (2004).

[201] S. S. M. Hassan, E. M. Elnemma, A. H. K. Mohamed, *Electroanalysis* **17**, 2246 (2005).

[202] C. D. Rasmussen, J. E. T. Andersen, B. Zachau-Christiansen, *Anal.l Lett.* **40**, 39 (2007).

[203] S. S. Badawy, Y. M. Issa, A. A. Mutair, *J. Pharm. Biomed. Anal.* **39**, 117 (2005).

[204] M. G. F. Sales, J. F. C. Tomas, S. R. Lavandeira, *J. Pharm. Biomed. Anal.* **41**, 1280 (2006).
[205] M. G. F. Sales, A. Pille, P. C. B. Paiga, *Anal. Lett.* **36**, 2925 (2003).
[206] N. Garcia-Villar, J. Saurina, S. Hernandez-Cassou, *Anal. Chim. Acta* **477**, 315 (2003).
[207] H. Kahlert, J. R. Pörksen, I. Isildak, M. Andac, M.Yolcu, J. Behnert, F. Scholz, *Electroanalysis* **17**, 1085 (2005).
[208] H. Kahlert, J. R. Pörksen, J. Behnert, F. Scholz, *Anal. Bioanal. Chem.* **382**, 1981 (2005).
[209] S.S. Beheshti, M. K. Amini, *Int. J. Electrochem. Sci.* **2**, 778 (2007).
[210] R. M. El Nashar, *Anal. Lett.* **41**, 949 (2008).
[211] E. Munoz, S. Palmero, *Electroanalysis* **16**, 1528 (2004).
[212] E. Munoz, S. Palmero, *Electroanalysis* **16**, 1956 (2004).
[213] E. Munoz, S. Palmero, *Food Chem.* **94**, 478 (2006).
[214] A. M. Pimenta, A. N. Araujo, M. C. B. S. Montenegro, C. Pasquini, J. J. R. Rohwedder, I. M. Raimundo, *J. Pharm. Biomed. Anal.* **36**, 49 (2004).
[215] J. Edson da Silva, M. F. Pimentel, V. Lins da Silva, M.C. B. S. M. Montenegro, A. N. Araujo, *Anal. Chim. Acta* **506**, 197 (2004).
[216] E. M. G. Santos, A N. Araújo, C. M.C.M. Couto, M.C.B.S.M. Montenegro, A. Kejzlarová, P. Solich, *J. Pharm. Biomed. Anal.* **36**, 701 (2004).
[217] C. G. Amorima, A. N. Araujo, M. Montenegro, V. L. Silva, *J. Pharm. Biomed. Anal.* **48**, 1064 (2008).
[218] R. Koncki, K. Rudnicka, L. Tymecki, *Anal. Chim. Acta* **577**, 134 (2006).
[219] J. A. Rodriguez, E. Barrado, M. Vega, J. L. F. C. Lima, *Electroanalysis* **17**, 504 (2005).
[220] S. Martinez-Barrachina, M. del Valle, *Microchem. J.* **83**, 48 (2006).
[221] J. Hantash, A. Bartlett, P. Oldfield, G. Denes, R. O'Rielly, F. David, *Anal. Bioanal. Chem.* **387**, 351 (2007).
[222] R. A. Sanchez-Moreno, M. J. Gismera, M. T. Sevilla, J. R. Procopio, *Anal.Chim.Acta* **634**, 68 (2009).
[223] W. T. Wai, B. Saad, B. P. Lim, *Food Chem.* **113**, 285 (2009).
[224] M. Dobsik, P. Mikuska, Z. Vecera, *Chemicke Listy* **97**, 166 (2003).
[225] P. Kuban, P. Kuban, P. C. Hauser, V. Kuban, *Electrophoresis* **25**, 35 (2004).
[226] P. Kuban, P. K. Dasgupta, C. A. Pohl, *Anal. Chem.* **79**, 5462 (2007).
[227] P. Kuban, P. C. Hauser, *Anal. Chim. Acta* **607**, 15 (2008).
[228] E. V. de Aquino, J. J. R. Rohwedder, C. Pasquini, *Anal. Bioanal. Chem.* **386**, 1921 (2006).
[229] S. C. B. Oliveira *et al.*, *Microchem. J.* **82**, 220 (2006).
[230] C. Pasquini, E. V. de Aquino, M. D. Reboucas, F. B. Gonzaga, *Anal. Chim. Acta* **600**, 84 (2007).
[231] R. Mikelova, Z. Prokop, K. Stejskal, V. Adam, M. Beklova, L. Trnkova, B. Kulichova, A.Horna, R. Chaloupkova, J. Damborsky, R.Kizek, ,*Chromatographia* **67**, S47 (2008).
[232] A. Hioki, *Anal. Sci.* **24**, 1099 (2008).
[233] J. A. Ortuno, A. Gil, C. Sanchez-Pedreno, *Sensors* **8**, 3678 (2008).
[234] H. Hayashi, H. Shiraishi, M. Senda, *Bunseki Kagaku* **58**, 135 (2009).

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