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Review

Microchip capillary electrophoresis system with amperometric detection: A review of the theory, recent developments and future evolutions

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ABSTRACT

Microchip Capillary Electrophoresis (μCE) represents another step forward for the development of analytical "micro-scale" devices and the possibility of integration for "Lab-on-a-chip" systems. The high performance of detection of μCE devices combined with amperometric detection make them a useful application in the fields of biochemistry and analytical chemistry for the study of explosives, environmental pollutants, nerve agents, clinical and food analysis. This paper intends to provide an overview of the μCE devices with amperometric detection presenting the principles of separation in capillary electrophoresis systems, the parameters to describe the performances in a separation process, the primary electrochemical detection methods as well as the state-of-the-art of these devices.

KEYWORDS: microchip capillary electrophoresis, amperometric detection, electrochemistry, separation science

1. INTRODUCTION

Capillary electrophoresis (CE) is a technique for the separation and analysis of chemical compounds.

The power of this method of analysis has been evident since its first use. CE analysis could support or even overcome methods such as HPLC or slab gel electrophoresis. This is due to the highly efficient and fast separations, low-cost and long lasting capillary columns, small sample requirements and low reagent consumption. CE works with polar ionic, polar non-ionic, and non-polar non-ionic compounds, as well as high molecular weight biomolecules, and chiral compounds [1].

Over the last few years particular attention has been given to the development of the microchip capillary electrophoresis system (μCE) because of its fast and efficient separation capabilities. These systems also offer a series of advantages such as integration, high performance, portability, speed, cost and minimal sample/solvent consumption [2].

While microchip technology has improved over the last decade, the techniques of detection have lagged behind. Previously the preferred techniques such as laser induced fluorescence (LIF) and mass spectrometry (MS) have been investigated. Although these techniques allow high sensitivity of detection, they require off-chip control instrumentations that limit the mobility and portability of this system. Electrochemical detection (EC) seems to be the meeting point between the concept of portability (low volume requirement of the control instrumentation) and the need for increased sensitivity and resolution.

Electrochemistry is also highly compatible with integration processes and microfabrication technologies. In practice, there are three electrochemical detection modes that can be used

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for microchip capillary electrophoresis systems (μCE-EC): amperometric detection, potentiometric detection, conductivity detection. The amperometric detection is generally considered the most powerful method in terms of resolution, but it is limited to the electroactive compounds. For this reason, the other two methods are seen as complementary methods for the non-electro-active compounds [3]. A general limitation for the amperometric detection method lies in the fact that the detector electrodes are in direct contact with the solution and may therefore deteriorate due to corrosion or fouling.

2. Outline of the theory for a CE process

2.1. Principles of separation

Electrophoresis is the movement of electrically charged particles or molecules in a conductive liquid medium, usually aqueous, under the influence of an electric field [1]. Cations migrate toward the negatively charged electrode, the cathode, and anions migrate toward the positively charge electrode, the anode. (the velocity of migration is influenced by the charge-to-size ratio of the analyte: ions with higher charge migrate faster than those with lower charge, and small ions migrate faster than larger ions which are impeded by the viscosity of the buffer).

The *electroosmotic flow* (EOF) of the buffer usually moves toward the negative electrode and drags every analyte with it: cations, neutrals and even anions which are attracted from the positive electrode. The EOF is then an additive force to the ion motion. In fact cations move faster than the electroosmotic flow, neutral at the same time rate and anions move slower. The negative electrode is reached in the order by cations, neutrals, than anions [1].

The reasons for the EOF can be found on the ionisation of the capillary surface or adsorption of ions from the buffer onto the capillary (Fig.1.). In fused silica capillaries, the silanol (Si-OH) groups on the surface are ionised to negatively charged silanoate ($Si\text{-}O^-$) group at pH 3. Treatment with a KOH or NaOH solution is used for conditioning of the silica capillaries. The silanoate groups attract positive cations from the buffer forming an inner layer of cations close to the capillary wall.

Since an electrical balance is not reached a second layer of cations forms. The inner layer is strongly held by the $Si\text{-}O^-$ groups, so called the *fixed layer*. The outer layer, further away from the silanoate groups, is not so strongly linked to the silanoate groups and it is called the *mobile layer.* These two layers are also referred to as the *diffuse double layer* of cations.

The plane of shear between these two layers and the electrical imbalance created at that plane is the zeta potential, ζ. The electroosmotic flow is proportional to the thickness of the double layer. The zeta potential is equal to:

$$\zeta = 4\pi\delta e/\varepsilon \qquad (1)$$

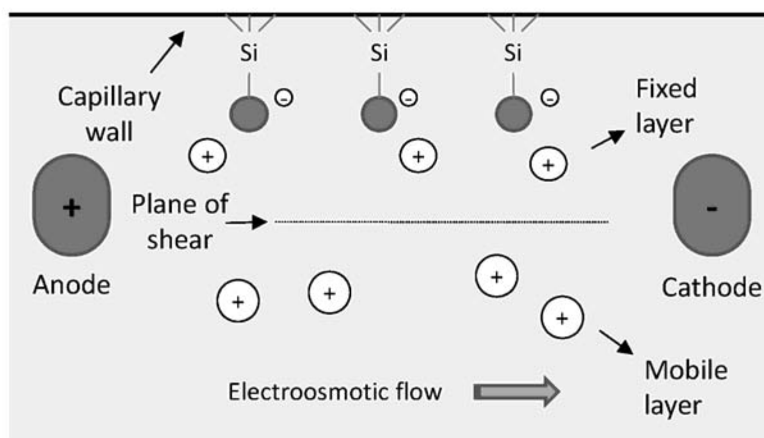

Fig. 1. Representation of the electroosmotic flow creation process.

where δ is the thickness of the diffuse double layer in *m*, *e* is the charge per unit surface area in C/m^2 and ε is the dielectric constant in *F/m* of the buffer. The diffuse double layer has a thickness that is inversely proportional to the concentration of the buffer. When an electric field is applied, the mobile layer of cations is attracted to the cathode. These solvated cations drag the buffer solution, thus causing the electroosmotic flow.

Capillary electrophoresis is often performed with the detector side of the capillary having a negative charge. It therefore attracts the positively charged cations in the double layer. In this way, the electroosmotic flow is toward the cathode, and the order of elution is cations, neutrals, and then anions. In some applications it could be necessary to reverse the order of elution such that it is anions, neutrals, than cations. This is the case where the analyte is an anion: an example is the analysis of DNA which is performed with the anode at the detector side and the EOF reversed. Reversing the EOF can be done by introducing a quaternary amine in the buffer.

The velocity of electroosmotic flow, υEOF, is given by

$$\upsilon_{EOF} = \varepsilon\zeta E/4\pi\eta \quad (2)$$

where ε is the dielectric of the buffer, ζ is the zeta potential, E is the applied electric field in *V/cm*, and η is the dynamic viscosity of the buffer in Pas. The electroosmotic mobility, μ_{EOF}, of the buffer is given by

$$\mu_{EOF} = \varepsilon\zeta/4\pi\eta \quad (3)$$

An electrically charged solute will migrate through the buffer with an electrophoretic velocity, υ_{EP}, in cm/s, given by

$$\upsilon_{EP} = \mu_{EP}E \quad (4)$$

where μ_{EP} is the electrophoretic mobility and E the applied electric field. Electrophoretic mobility is expressed as

$$\mu_{EP} = \frac{q}{6\pi\eta r} \quad (5)$$

where q is the charge of the ionised solute, η the buffer viscosity, and r the solute radius.

The velocity of a solute is influenced both by its electroosmotic mobility and the electroosmotic flow. The observed electrophoretic velocity, υOBS, is given by

$$\upsilon_{OBS} = \upsilon_{EP} + \upsilon_{EOF} \quad (6)$$

where υ_{EOF} is the velocity of the electroosmotic flow, also in *cm/s*. In the same way the observed electrophoretic mobility of a solute, μ_{OBS}, could be expressed by

$$\mu_{OBS} = \mu_{EP} + \mu_{EOF} \quad (7)$$

2.2. Parameters in a separation process

The parameters of an electrophoretic separation are *time, efficiency, selectivity,* and *resolution*. Influences on these separation parameters are represented by voltage, electrophoretic mobilities, electroosmotic flow, and capillary length [1].

2.2.1. Time

The migration time of a solute, t_m, is the time that it takes to pass from the inlet to the detector:

$$t_m = \frac{l}{v_{OBS}} \quad (8)$$

where v_{OBS} is the observed velocity, expressed as

$$v_{OBS} = \mu_{OBS}E \quad (9)$$

Since E=V/L, in the equation E can be replaced giving

$$t_m = \frac{lL}{\mu_{OBS}V} \quad (10)$$

Substituting Equ. 7 into Equ. 10 gives

$$t_m = \frac{lL}{(\mu_{EP} + \mu_{EOF})V} \quad (11)$$

2.2.2. Efficiency

Efficiency, N, expressed as the number of theoretical plates, is calculated by measuring the migration time and the peak width, w, measured at the base of the peak:

$$N = 16\left(\frac{t_m}{w}\right)^2 \quad (12)$$

If the peak width is measured at half the peak height, $w_{1/2}$, Equ. 12 becomes

$$N = 5.54\left(\frac{t_m}{w_{1/2}}\right)^2 \quad (13)$$

2.2.3. Selectivity

Selectivity describes the distance between adjacent solutes when they pass through the detector that corresponds to the distance between the apices of adjacent peaks in an electropherogram. The expression for calculating the selectivity in a capillary electrophoresis separation is:

$$\alpha = \frac{t_2 - t_{nm}}{t_1 - t_{nm}} \quad (14)$$

where t_2 and t_1 are migration times of adjacent peaks. t_2 is the migration time of the later eluting solute, and t_{nm} is the migration time of a neutral marker.

2.2.4. Resolution

The resolution intends to provide a general idea of the performance of the separation comparing the distance between peaks in the electropherogram with their widths. Resolution, R, is calculated from an electropherogram as

$$R = \frac{\delta_t}{w_{AVE}} \quad (15)$$

$$R = \frac{2(t_2 - t_1)}{w_1 + w_2} \quad (16)$$

where w_1 and w_2 are peak widths of adjacent peaks. Resolution between two adjacent peaks can also be determined as

$$R = \frac{1}{4}\sqrt{N}\left(\frac{\delta v}{v_{AVE}}\right) \quad (17)$$

where δv is the velocity difference between two solutes and v_{AVE} is their average velocity.

2.3. Overview of the electrochemical detection methods

Three methods are usually used in CE systems: amperometric detection, potentiometric detection, conductivity detection.

2.3.1. Amperometric detection

The amperometric detection is a technique which aims to measure the current involved in an oxidation or reduction process. A potential drop across an electrolyte is used to drive the redox reactions: potential is applied between two electrodes called working and reference. For better performances most detectors use a three electrode system where a third electrode, auxiliary electrode, is employed to ensure a more stable potential between the working and reference electrode. The current, being proportional to the number of electrons transferred, indicates the concentration of the solute. Typical amplitude of current in electropherograms is nA or pA.

When the detector is operative in oxidative mode, a negative potential is applied by the auxiliary electrode. This causes a positive potential difference at the working electrode compared to the reference electrode. Therefore, negatively charged electrons are transferred to the working electrode.

In the reductive mode, a positive potential is applied by the auxiliary electrode.

Typical detection potentials are in the range of 0.4-1.2V.

Various strategies have been developed for coupling amperometric detection to CE-microchips: in-channel, end-channel, and off-channel. For *in-channel* detection, the working electrode in inserted within the separation channel, avoiding the problem of alignment. It is often not used as coupling of the high voltage of the CE process affects it. In *off-channel* mode, a decoupler is introduced to reduce the coupling effect of the high voltage with the detector. In the *end-channel* mode, the working electrode is placed close to the outlet of the microchannel in the outlet reservoir. For this last case usually the electrodes are directly evaporated onto the bottom layer of the chip to avoid such alignment problems with the outlet of the channel. Lastly it is going to be investigated, a replaceable electrode system approach as a possible solution to get over electrodes failure. A strategy for the alignment is obviously required to maintain high resolution.

2.3.2. Potentiometric detection

From an instrumental point of view potentiometric detection is in principle the most straight-forward method as no excitation signal is required. However, this method is the least widely available of the three electrochemical means described [3]. The detection principle is based on a potential that

arises between two solutions with different ionic activities: a semipermeable ion-selective membrane of an ion-selective electrode (ISE) is crossed by the analyte so creating a potential difference between the internal and external solution of the electrode. The potential is measured against the fixed potential of a reference electrode and monitored by a sensitive pH or millivolt meter. The response of the signal does not reduce by decreasing the electrode area. The potential of the electrode is logarithmically correlated to the concentration of an analyte [4]:

$$E = E^0 + \frac{RT}{F} ln\left(\sum K_i^{pot} c_i^{\frac{1}{zi}} \right) \quad (18)$$

Where E is electrode potential, E^0 is a constant, R is the gas constant, T is the temperature, F is the Faraday constant, K_i^{pot} is the selectivity coefficient for species I, and $c_i^{1/zi}$ is the concentration of species I with a charge of z. Some developments on the ISE performed in 1971 by Cattrall and Freiser allowed fabrication of microelectrodes necessary for microchip analysis. The development consisted of covering a metal wire with a polymer film that acts as the ion-selective membrane. There are several disadvantages in this detection method because the membrane should be semi permeable to more than one ionic species but not highly permeable to the background buffer ions. It is a method which has been limited for the most part to use in conventional CE.

2.3.3. Conductivity detection

The basis of conductivity detection is the change in the electrical conductivity of a solution when an ionic solute is introduced into it. A conductivity detector has two electrodes in the cell, and a high-frequency alternating potential is applied to the electrodes. The effluent from the capillary flows between the electrodes, and when an ionic solute comes into the cell, it decreases the electrical resistance of the solution, thus increasing the electrical conductance. Conductivity detection is considered a universal detection method because the analyte is detected without chromophore, fluorophore or electroactive compounds. The detector consists of two electrodes which can be in direct contact with the buffer solution or externally and capacitively coupled to the buffer (contactless). While alternating current (AC) is applied across the electrodes, the conductivity signal is measured. The signal amplitude is low when there are no analytes at the detector. The signal amplitude is then altered as the analyte passes over the electrodes. The concentration of analyte can be correlated with the change in conductivity through the equation below:

$$L = \frac{A}{l} \sum \left(\lambda_i c_i \right) \quad (19)$$

Where L is the conductivity of the solution, A is the electrode area, l is the distance between the two electrodes, c_i is the concentration of the ion I and λ_i is its molar conductivity [4]. The choice of the buffer solution is fundamental because if the buffer and the analyte had similar conductivities, identifying the peak of the analyte would be difficult. For contact conductivity detection there are two different configurations available: on-column configuration in which the electrodes are integrated in the separation channel, and end-column configuration in which the electrodes are placed in the outlet reservoir. This is different for contactless conductivity detection in which on-column configuration has been used. The resulting decrease in background current allows for lower limits of detection.

Over the past number of years, contactless conductivity has had more success in microchip CE devices. The reason behind this success can be found in a lower level of noise due to the distance between the electrodes and the buffer solution, and the absence of bubble creation.

3. State-of-the-art of CE-microchips with amperometric detection

3.1. Microchip designs

3.1.1. Materials

Various different materials and ideas have been used to develop chips for CE. The most important feature of a material for CE microchips must be the effective heat dissipation to allow for the use of high separation voltage. For this reason, the first microchips were usually fabricated using silicon and glass. However, polymeric materials

have also been used because of their properties such as, low cost, high flexibility, and simple fabrication procedures, thus facilitating mass production of devices. Several polymers such as polydimethylsiloxane (PDMS) [5], poly(methylmethacrylate) (PMMA) [6], poly carbonate (PC) [7], polyester [8], and poly(ethylene terephthalate (PET) [9] have been reported for this purpose. Recently, cyclic olefin polymers and copolymers such as Topas and Zeonor [10] have also received attention due to their high chemical resistance, good machinability, and optical transparency. In some cases, the polymeric material is matched with a glass substrate containing the electrodes [11].

3.1.2. Typical geometries

Usually the microchip geometry consists of four reservoirs and micro-channels: sample, inlet, and sample waste reservoir, connected with an outlet reservoir by a double T channel (Fig. 2(a)). The high-voltage electrodes are inserted in the buffer reservoir and in the outlet reservoir. Two other electrodes are inserted between the sample reservoir and the sample waste reservoir to perform the injection of the sample in the separation channel. Under the effect of a potential that acts for some seconds, the injection is carried out (electrokinetic injection). The detection of the analyte takes place in the outlet reservoir where a three electrode system is usually used. The dimensions of the channels are of the order of microns, variable between 10 μm and 100 μm.

The separation channel is often presented with different geometries with the aim of maximum elongation of the central path. With a longer separation channel it is possible to increase the migration time t_m (Equ.8), so enhancing the efficiency (Equ.12), and subsequently the selectivity (Equ.14) and the resolution (Equ.17). Typical geometry of the separation channel is serpentine [12] [13] (Fig. 2(b)).

Current research is interested in dual channel architecture systems, with the aim of multiple-sample analysis. Attempts to use a dual-channel architecture were performed by Sukas *et al.* [14] using a fluorescence detection in a Parylene-C microchip. The channel was divided by a thin wall to obtain two identical side-by-side channels.

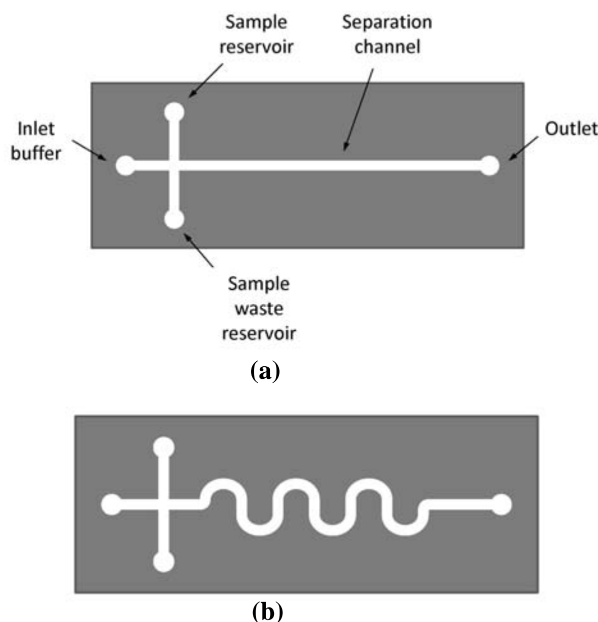

Fig. 2. (a) Definition of the geometry in a typical CE microchip device, (b) CE microchip device with a serpentine geometry of the separation channel.

A four channel PDMS-glass hybrid microdevice is employed for quantitative double-strand DNA analysis using laser-induced fluorescence (LIF) [15]. Castaño *et al.* [16] described for the first time a dual-channel glass microchip with amperometric detection for simultaneous measurement at the same or different detection potentials. Only one injection channel crosses the two separation channels. The system was composed of a glass bottom substrate and an upper PDMS layer with the microchannels.

3.1.3. Channel coating

Since the most common flow source in microfluidic devices is EOF, which results from the surface charge of the internal microfluidic walls; the chemical functionality of the capillary surface plays an important role in CE separation.

Hydrophobic PDMS surfaces have a strong interaction with the hydrophobic domains of the analytes often causing loss of separation efficiency. For this reason, the magnitude and stability of the EOF on polymeric microchips needs to be controlled with surface modification methods. García *et al.* [17] reported the use of anionic surfactants, such as sodium dodecylsulfate,

phosphatidic acid, and deoxycholate, as modifiers of the background electrolyte used in PDMS microchips. They observed an increase in the EOF and an improvement in the electrochemical response for several biomolecules. Jang *et al.* [18] reported how to perform a rapid microchip-based electrochemical enzyme immunoassay. The interior walls were modified with a silane monolayer with three repeated PEG groups and surface exposed biotin molecules to immobilize biomolecules via avidina-biotina linkage. Bi *et al.* [19] developed a simple protocol for surface modification and protein immobilization in PMMA microchannels for analysis of chiral interactions.

Qiu *et al.* [20] employed titanium dioxide nanoparticles (TiO_2 *N Ps*) to construct a functional film on PDMS microfluidic channel surface formed by sequentially immobilising poly (diallyldimethylammonium chloride) and TiO_2 *N Ps* on PDMS surface by layer-by-layer assembly technique. The modified PDMS microchip exhibited a decreased and stable EOF, favourable for the separation of biomolecules with similar migration times. The analytes used to evaluate the performance of the microchip were arginine, phenylalanine, serine and threonine.

3.1.4. Future objectives

A modular system is the new challenge in the development of μCE-EC devices (Fig. 3). In fact following this concept we will have interchangeable sensor modules, an interchangeable separation channel or an interchangeable injection system. By changing the sensor it is possible to overcome the limit of passivation of the sensor after a certain time. A different variety of electrodes could be used (with different materials or dimensions suitable for the analyte in question). An interchangeable separation channel would allow for the best fit of the channel geometry. It would also allow adaption of the electroosmotic flow (EOF) by affording choice of channels with different coating materials.

3.2. Electrode designs

Detection cell design is very important in μCE-EC devices in order to ensure electrical isolation from the high separation voltage. Amperometry is by far the most common method used on-chip to date. The advantages of this method are ease of operation, minimal background-current contribution and tuneable selectivity through correct choice of the detection potential.

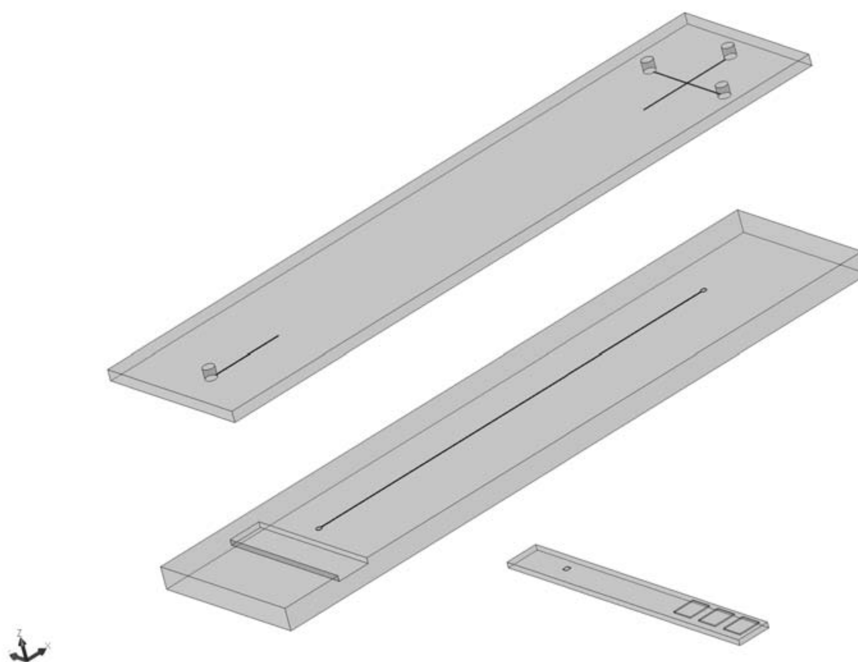

Fig. 3. Concept of a modular microchip capillary electrophoresis system.

3.2.1. Further developments of traditional detection modes

In amperometric detection the power of detection can be improved by using more than one working electrode. Martin *et al.* [21] reported on a dual-electrode end-channel amperometric detection in the series for improving the peak identification in complex electropherograms. The first electrode of the series can be used to develop an electroactive species that is more easily detected at the second electrode of the series. Electroactive species that undergo reversible redox reactions will be detected at both electrodes, whereas electroactive species that do not have reversible redox couples can only be detected at one of the electrodes. For example, catecholamine neurotransmitters (dopamine and norepinephrine) have reversible redox couples: oxidation to the related quinine and reduction to the original species.

Recently also Pulsed Amperometric Detection (PAD) has been applied to CE-EC microchips [22]. It is useful to avoid the problem of the inactivation of the noble metal electrode associated with the fixed-potential detection. PAD consists of a process of anodic detection with anodic cleaning and cathodic reactivation of a noble metal electrode. This results in a cleaned and active electrode surface. To achieve this three-step potential waveform are usually applied: a high positive potential in order to clean the electrode surface, a negative potential step to reactivate the surface and a third moderate potential for detecting the analyte.

Indirect Amperometric Detection is another approach which transforms the negative effects of the separation high-voltage field into a new detection approach. The potential difference induced by the separation electric field between the working and reference electrode can be used as detection potential. This new approach was introduces by Xu *et al.* [23]. They dissolved oxygen in the buffer solution as an electroactive indicator. The potential difference induced by the separation electric field between the working and the reference depends on the local resistance of the solution. Therefore the electrodes and high-field potential has to be arranged in order to obtain the potential for oxygen reduction between the working and the reference electrode. A baseline current starts to be visible on the electropherogram. When a sample plug of different conductivity passes through the working electrode, the altered solution resistance will induce variation of the potential difference. This is due to the altered solution resistance producing a visible peak in the electropherogram.

3.2.2. Materials

Because the metallic surface can be easily oxidised or passivated, analytes such as peptides, aminoacids, carbohydrates, sugars and protein materials are detected with Cu, Ni, Pt and Au working electrodes. Several types of carbon electrodes have also been used such as carbon fibre, cabon paste, carbon ink, glassy carbon and photoresist carbon films. Carbon electrodes are commonly used in conventional CE-EC for their minimal fouling, lower over-potential and background noise and larger potential range for organic analytes than metal electrodes [24]. Carbon electrodes can be applied for use concerning neurotransmitter, enzyme, aminoacid, and carbohydrate detection [4]. Several metal electrodes have been used with microchip CE-EC (see Table 1).

Wang *et al.* have accomplished the detection of nitroaromatic explosives, phenols, purines and purine-containing compounds using a diamond electrode. The electrode was obtained via chemical vapour-deposition of boron-doped diamond with promising results compared to the thick-film carbon detector [25].

Table 1. Metal electrodes and related analytes.

Electrode	Analyte
Au	Catechols, neurotransmitters, aminoacids, carbohydrates, antibiotics, nitroaromatics, uric acid, ascorbic acid, DNA restriction fragments, creatine, creatinine
Pt	catechols, neurotransmitters, carbohydrates, ascorbic acid, uric acid
Cu	aminoacids, carbohydrates, peptides, catechols, neurotransmitters
Pd	neurotransmitters

3.2.3. Decoupler

The decoupler is often used in order to avoid the band-broadening effect that occurs when using end-channel detection. For microchip devices the decouplers have been integrated onto it to date. Lacher *et al.* [26] described the use of a Pd decoupler which resulted in good isolation from the separation field and in a discrete absorption of the hydrogen avoiding the formation of bubbles. They tried also to identify the optimum distance between the working electrode and the decoupler. Obviously when the working was too close to the decoupler, the noise was greater in the electropherogram. When the decoupler was too far, the resolution started to decrease. The optimum for their electrodes was 250 μm of spacing. Other experiments using a Pd decoupler were performed by Lai *et al.* [27] in a dual-electrode CE microchip using an off-channel approach. Mecker *et al.* [28] described the fabrication and evolution of micromolded dual carbon electrodes and their integration with a fabricated palladium decoupler. The mould was in PDMS and a mixture of carbon ink and solvent thinner were added to the mould in order to obtain the electrodes on the related Pd connections over a glass substrate. A temperature cure was necessary before the electrodes were ready to use. With this procedure the electrode fabrication is amenable to mass production.

3.2.4. Geometry

Different solutions concerning the geometry of the electrodes have been seen in the CE-EC devices. Typically the electrodes for on-channel, off-channel and end-channel are integrated into the chip. Only for the end-channel detection is there the possibility of using a screen-printed working electrode in an off-chip configuration. The advantage of this approach is the ease in which either the chip or electrode can be interchanged. Typically this solution is implemented on an end-channel detection method. The outlet of the separation channel ends in a reservoir where the working electrode is dipped and centered using a support. Recently Johirul *et al.* [29] have used a modified carbon screen-printed electrode for the analysis of neurotransmitters. The bare electrode was covered with a cellulose-ssDNA layer to amplify the electrocatalytic activity through interaction between the analyte and ssDNA. The analytes under study were dopamine, norepinephrine, 3,4-dihydroxy-L-phenylalanine, 3,4-dihydroxyphenylacetic acid and ascorbic acid. The sensitivity of the modified electrode was about 12 times higher than those of the bare ones.

CONCLUSION

CE microchips are of considerable promise for various applications such as explosives, environmental pollutants, nerve agents, clinical and food analysis. Drugs can be easily detected and quantified using microchip CE system as reported by Guihen *et al.* [30] in which a method for rapid separation and quantification of atorvastatin in a Lipitor tablet was investigated. Electrochemical detection has been proven as suitable in terms of detection performance, enabling low volume instrumentation and portability. Currently available in the market are hand-held devices that can perform amperometric detection. The development of modified electrode as well as the use of a dual-electrode detection system has demonstrated high performances. Dual-channel systems performing multiple analysis offer the possibility of reducing the analysis time and improving reliability simultaneously. Better usability is expected to be reached with the adjustment of a modular device as mentioned before.

CE has demonstrated that higher performance can be achieved with a microfluidic device. On-column amperometric detection shows good results since it is reduced to the minimum band-broadening effects. Future developments considering an interchangeable sensor would help to overcome the problem of fouling of the sensors as well as giving the chance of selecting them among different kinds of electrodes.

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