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Review

Integrating amperometric detection with electrophoresis microchip devices for biochemical assays: Recent developments

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ABSTRACT

Recent advances in microfluidic systems, particularly in the Micro Total Analysis System (μTAS) or Lab On a Chip (LOC), drive the current analysis tools and equipment towards miniaturization, rapid at-line testing and mobility. The state-of-the-art microfluidic technology targets a wider range but smaller volumes of analytes, making the analytical procedure relatively easier and faster. This trend together with faster electronics and modern instrumentation systems will make real-time and in situ analysis a definite possibility. This review focuses on microchip capillary electrophoresis with amperometric detection (MCE-AD) for the detection of DNA and other electroactive analytes. The problems associated with the microchip design, in particular the choice of materials and the configuration of electrodes are discussed thoroughly and solutions are proposed. Significant developments in the related areas are also covered and reviewed critically.

Contents

1. Introduction

Microchip capillary electrophoresis (MCE) is increasingly becoming important tool for point-of-care, vitro diagnostics, and modern environmental and biomedical analyses. Recently, microchips meant for DNA study such as the integrated microfluidic devices, are gaining popularity among scientists and engineers, owing to their benefits in terms of improved speed, low-cost, high portability and stable performance. With the advent of microelectronic technology, DNA microchips with integrated analytical capability could affordably be fabricated so that most laboratory assays could be quickly and cheaply performed.

Currently, there are various methods and techniques in MCE for the sequencing and detection of DNA and electroactive analytes. In the literature, these types of DNA MCEs are referred to as the DNA biosensors. Depending on the detection mechanism and sensing characteristics, the working principle of MCE can generally be categorized as: (i) optical detection, and (ii) electrochemical detection (ECD). In general, optical detectors use Laser Induced Fluorescent (LIF) [1–5] and UV light [6–9]. ECD can be further classified as (i) the amperometric, (ii) the potentiometric [10–12], (iii) the voltamperometric [12–16], and (iv) the impedimetric [17,18]. Despite having good sensitivity and high specificity [2,19–21], the optical techniques suffer from several major drawbacks such as,

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limit of detection (LOD), larger size, heavier in weight and higher power supply requirements. More importantly most of the optical-based assays require bio-markers like ethidium bromide, to enable fluorescence and viewing. This poses safety and health issues since this type of bio-markers is toxic and poisonous. Therefore, the latest development on MCE is gravitating towards ECD, especially when electroactive analytes are targeted. Moreover, ECD is approaching the fluorescence sensitivity, easy to fabricate, and inexpensive. Among the ECD methods, the amperometric detection (AD) is widely accepted as the best method for microchip integration. The procedure requires intercalation in which the electroactive dye is added to analyte [22,23] in order to enable detection. Intercalation could not only enhance the electrical properties of analytes, but also impart electrical properties to inorganic compounds [24,25]. Thus with the aid of intercalation, MCE-AD could target a wide range of analytes. Moreover, intercalation enables detection of non-electroactive analytes [26,27]. These outstanding features make MCE-AD an attractive and effective tool for designing a truly μTAS.

Amperometric detection is achieved by measuring current while applying modest potential to the working electrode. This technique was reported for the first time by Woolley et al. [28], then found its way through many researches, and currently available as the most effective detection method, due to its superiority over other techniques. Amperometric detection is more suitable for electroactive analytes under modest potential. Being negatively charged, DNA is an electroactive analyte; when DNA comes in contact with the working electrode, it triggers redox reaction, causing the formation of electrical charges. Therefore, it is possible to design a detection circuit based on amperometric measurement, for all electroactive analytes including DNA.

Recent developments in μTAS necessitate the discussion of some of the key aspects influencing the microchip performance and miniaturization. Few researchers have provided excellent reviews on μTAS. For instance, Xu et al. [29] outlined the progress in integration of electrochemical elements in μTAS, while Kailasa and Kang [30] focused on developments and applications of ME for detection and separation of DNA fragments. Teles and Fonseca [31] reviewed various DNA immobilization techniques, as well as new micro and nanotechnological platforms for biosensing, and geno sensor transduction.

This article focuses on MCE-AD, which is the most widely employed ECD method for DNA and electroactive assays. A comprehensive survey on the recent developments of the key factors of MCE-AD, such as microchip design, electrodes configuration, and microchip and electrode materials, will be presented.

2. Microchip design

Configurations and design of amperometric microchips play a major role in MCE characteristics. Among the various factors affecting the MCE characteristics, the important issues are, the performance, and the cost of fabrication. Each of these issues needs to be studied separately in order to understand the problems and technical limitations associated with the microchip design. Another influential factor is properties of the targeted analyte, since analytes have different electrical properties. For instance, the nucleic acids are negatively charged at low pH due to the phosphate group ions. On the other hand the amino acid at 7.4 pH is either negatively charged (e.g. aspartic acid and glutamic acid), or positively charged (e.g. arginine and lysine). Hence, the analyte's net charge is crucial to the alignment of electrodes in microchips. Another influential factor is the alignment of working electrodes as different alignments give different configurations, and every configuration has its own features and performance characteristics. Since detecting analytes is the basic function of the working electrode, placement of this electrode/s in the separation channel is quite sensitive and meaningful. Alignment of electrodes is also important to isolate them from being subjected to the high separation voltage during amperometric detection. In general, isolation is achieved by three basic approaches: (a) in-channel detection, (b) end-channel detection and (c) off-channel detection (a decoupler is employed here), as shown schematically in Fig. 1.

This review focuses on in-channel and off-channel configurations, because they are the most preferred choices in amperometric MCEs. These two configurations are introduced to get rid of some of the issues of end-channel detection, specifically, the decreased detector response due to diffusion, and band broadening, which will be elaborated in the ensuing section.

2.1. End-channel detection

This is the most popular configuration used in ECD. Here, the detection electrode is located inside the separation channel outlet (buffer waste/detection reservoir), about 5–50 μm away from the end of the separation channel. This type of alignment was introduced by Shiddiky and Shim [32] who placed a modified gold detection electrode at the end of the separation channel. The sensitivity was improved through field-amplified sample stacking (FASS) preconcentration method, and the electrical field strength for separation was optimized through adequate experiments. They found that the field strength ranging from 125 to 200 V/cm was sufficient to achieve separation, and further increase could cause Joule heating, incomplete separation and band broadening.

Another design under this group used two end-channel electrodes made of thermoplastic olefin polymer of amorphous structure (Topas) instead of the usual polydimethylsiloxane (PDMS) material. The two end-channel electrodes could reduce the high background current, which is one of the main drawbacks of end-channel detection, thereby resulting in improved signal-to-noise-ratio. Castano-Alvarez et al. [22] detected single stranded 30-mer sequence (ssDNA) through methylene blue (MB) intercalator interactions, in order to enhance the electrical properties of DNA. A cyclic voltammetry was used to study the redox process of the MB, which produced the best analytical signal. This study was extended to investigate the interaction between MB and double-stranded DNA (dsDNA), and the hybridization between a ssDNA and the complementary DNA (cDNA) [33]. They discovered that the intercalation reaction between MB and dsDNA increased the signal but slowed down the migration time.

Dawoud et al. [34] proposed positioning of the working electrode relative to the end of the separation channel, by using hybrid PDMS and glass MCE. They established that the optimum position of the 35 μm size working electrode was approximately 15 μm away from the exit of the 90 μm wide channel.

A combination of photochemical micropatterning with selective electroless gold plating technique was used to fabricate end-channel MCE with better electrode dimensions on the substrate and low fabrication cost [35]. Wang et al. [36] reduced band broadening by positioning the working electrode against the separation channel exit. In another attempt [37], a dual microchannel with end channel configuration in each channel, which was designed based on two electro osmotic flows (EOFs), could handle separation process for two analytes concurrently. A similar design was proposed by Shiddiky et al. [38] with three microchannels having a working electrode aligned at the end of the separation channel while the other two channels were used as pre-concentration channels.

Pai et al. [39] fabricated an ECD microchip with end-channel three dimensional electrode, as illustrated in Fig. 2. The basic idea behind this design was to increase the contact surface of the working electrode in order to increase the sensitivity of the detection.

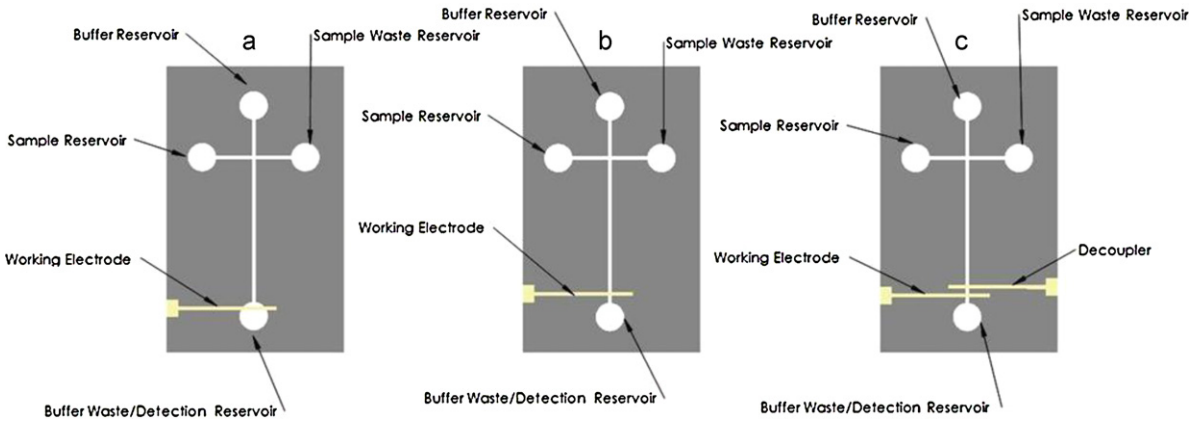

Fig. 1. Schematics of electrode alignments for amperometric MCE detection: (a) end-channel electrode alignment, (b) in-channel electrode alignment, and (c) off-channel electrode alignment.

A golden 3D electrode made by microfabricated silicon molds was placed at the exit of the separation channel; this could improve the collection efficiency of the MCE.

Various electroactive analytes and species other than DNA were successfully separated and detected. For instance, dopamine (DA) and catechol (CA) were used as testing analytes for end-channel amperometric MCE [35]. Also DA and epinephrine (EP) analytes were detected by a new microdevice with integrated amperometric detector [36,40]. Similarly P-aminophenol and hydroquinone were separated and detected by using end-channel detection with dual channel MCE made of hybrid PDMS/glass [37]. Morphine and codeine were also detected in an end-channel microchip [41].

A novel end-channel microchip fabrication technique, referred to as the filmy channel was reported by Wang et al. [42]. Filmy channels were capable in dissipating more Joule heat than that by conventional MCEs. They fabricated an amperometric microchip with a separation channel 20 μm deep and 2.3 mm wide, which was effective in dissipating the Joule heat at separation voltages up to 588 V/cm. Furthermore, the relatively wider separation channels could load more samples, thereby increasing the sensitivity.

A hybrid contact and contactless end-column microchip conductivity detector was designed and tested by Wang et al. [43]. The receiving electrode was insulated and dipped in bulk solution in the detection reservoir. The proposed design enhanced the LOD and signal-to-noise ratio compared to the conventional in-channel contactless conductivity detection due to the detector circuit insulation from the high voltage.

2.2. Off-channel

The only distinction between in-channel and off-channel configuration is that the latter utilizes additional decoupler in front of the working electrodes in order to isolate the separation voltage from the detection electrodes (Fig. 1). Unlike the in-channel and end-channel configurations, the potentiostat is not used in off-channel configuration. In contrary a decoupler electrode is used to keep the working electrodes isolated.

During ECD measurement, the hydrogen gas bubbles are generally formed on the surface of the decopler due to the electrochemical reaction. Therefore, the off-channel decouplers are usually fabricated from either palladium (Pd) or platinum (Pt), owing to their higher capacity to adsorb hydrogen gas bubbles compared to gold or silver electrodes. However, Pd and Pt are harder to fabricate due to their relatively higher melting points.

In a study on separation and detection of DNA adducts by off-channel amperometric MCE, Dawoud et al. [44] established

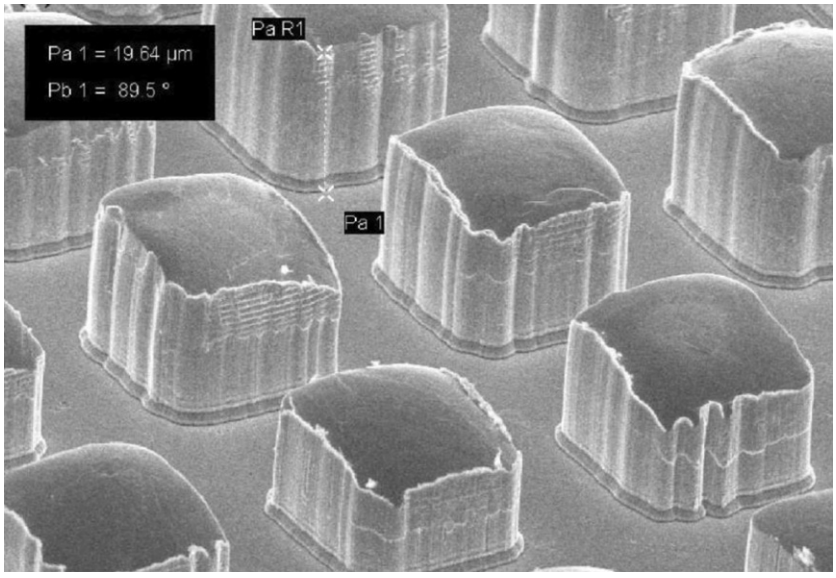

Fig. 2. Scanning electron microscopy image: a close-up of the final three-dimensional microelectrode [39].

that the optimum distance between the working electrode and the decoupler was approximately 600 μm, which was arrived at based on the separation field strength and background current. Electroplating was used to fabricate the Pd decoupler inside the separation channel. Unlike the thermal deposition and sputtering techniques, electroplating could deposit multilayer of metals on the same surface. The integrated PDMS/glass microchip with Au microelectrodes and Pd decoupler was able to detect approximately 100 nM of 8-hydroxy-deoxyguanosine DNA adduct with low noise of approximately 5 pA.

A low voltage (~5 V) electrophoresis chip with a relatively tiny area (1 cm) and dynamic electric field was proposed for DNA separation and ECD, by Wake and Brooke [45] who achieved dramatic reduction in the separation voltage by employing the principle of enhancing the electric field strength by decreasing the electrode gap.

One of the major problems with MCE is that the working electrode usually gets polluted after a repeated use, due to the presence of analytes and chemicals in the separation channel. In order to solve this problem, an off-channel MCE with renewable working electrode was developed by Lin et al. [46]; with the renewable working electrode, the detection was highly reproducible in addition to more stable potential, and longer life of the microchips. In another design a sensitive and reproducible current measurement microchip has utilized a renewable copper electrode [47].

Mecker and Martin [48] utilized off-channel microchip for integrating microdialysis (MD) sampling technique, microchip electrophoresis (ME) and ECD. They used PDMS based-valves to produce a reproducible and fixed alignment of the MD/ME and ME/EC interfaces. A Pd decoupler and a carbon ink electrode were employed, and the analytes used were CA and DA.

2.3. In-channel

This technique is referred to as the in-channel method because the detection occurs inside the separation channel where the working electrode/s is placed. In-channel detection was introduced to MCE's design by Martin et al. [49] who observed that in-channel configuration could decrease the plate height by a factor of 4.6, and lower the peak skew by a factor of 1.3. Furthermore, the plate height and peak skew were essentially equal for both in- and end-channels, compared to LIF with comparable performance.

Coating the microchannels of the in-channel PDMS/PDMS microchip by proteins could enhance the stability and the reproducibility of the overall detection system [50,51]. Moreover, adsorption was reduced, leading to enhanced separation efficiency as well as EOF stability. Aminophenol isomers were used by Liang et al. [52], to test the performance of in-channel MCE-AD. The surfaces of PDMS microchannel were modified by chitosan and DNA using the layer-by-layer (LBL) assembly technique, creating a perfect resistance to adsorption of analytes, which is one of the drawbacks of PDMS microchannels.

Anin-channel MCE-AD for DNA separation and detection was fabricated from PDMS microchannel placed on a glass substrate [53]; the separation voltage used was 100 V DC applied across the two only reservoirs of the microchannel as shown in Fig. 2. The size of the microchip was relatively small (3 cm × 2.5 cm), with separation channel of only 2 cm long. In this design, two decoupler electrodes were deposited in front of the three-electrode AD system, as shown schematically in Fig. 3. Golden electrodes deposited on an adhesion titanium layer were chosen in this microchip. The system was tested on ssDNA and dsDNA and concluded that the time taken to completely separate these analytes was much longer compared to other designs discussed previously. On an average, this system took approximately 60 min compared to in-channel MCE for which it was less than 160 s [44].

A relatively new in-channel technique detection driven by external electric field was reported by Ordeig et al. [54]. Twenty golden microband electrodes fabricated by lithographic and lift-off techniques were placed inside microchip within the only separation channel. The proposed system was based on the fact the potential difference between the two microband electrodes relied on the strength of the external electric field as well as the distance separating the electrodes. Thus by adjusting the potential difference, different electroactive species could be detected when two appropriate electrodes from the array were selected. The use of external electric field could exclude the decouplers and potentiostat thereby simplifying the design.

The coulometric efficiency (Ceff) of a hybrid PDMS/glass amperometric microchip could be enhanced by increasing the surface of the Au electrode [55]; the LOD for DA has decreased by factor of 2 and 3 for CA with 60 s separation time. The PDMS channel surface was intensified with coating by titanium dioxide nano-particles (TiO_2 NPs). This has resulted in the decreased and stable electro osmotic flow (EOF) thereby enhancing the separation time to 100 s in a channel 3.7 cm long [56]. A twisted PDMS channel fabricated using Prussian blue (PB) modified indium tin oxide (ITO) electrode with in-channel AD was able to detect bisphenol A (BPA) with LOD as low as 59 nM for analyte [57].

A flow injection microfluidic microchip with in-channel ECD was fabricated by Karuwan et al. [58], by using the standard photolithographic fabrication technique as shown in Fig. 4. In the proposed design (Fig. 5) a syringe was used for flow injection, instead of electrical injection. Inlets P1 and P2 were, respectively, used for buffer and analyte injection. Salbutamol was detected with good stability in flowing system and excellent reproducibility for AD. Micropipette tips were cut for connection between reservoirs (Fig. 5c) and the micro-tubing (Fig. 5d).

Recently Godino et al. [59] used a magnetic field in MCE with AD; the integration of magnetic field with AD made detection more sensitive and efficient. They coupled the magnetic capture with the in-channel ECD by placing a magnetic bead under the working electrode. The main benefit of the magnetic field was to magnetize the analyte particles to the working electrode surface until they were detected precisely, and after detection, the particles could be released. Moreover, as the electrodes could be replaced when spoiled, the LOD and sensitivity could be enhanced.

3. Fabrication materials

Fabrication materials can have a significant effecton the performance of microchips (MCs). Electrodes and microchannels can be made of several materials, which can influence the efficiency of the MC. Therefore, choosing the fabrication material is an important factor for better results.

3.1. Microchip materials

A major problem in most MCEs is the heat generation when a high electric field is applied to the electrodes; this can alter the original dimensions of the microchannels especially those made from polymers. Hence, dissipation of heat is crucial in the overall design of the MCE. Fused silica, quartz, and soda lime glass substrates were the most widely used at the early stages of development [28,60,61], but recent microchips use glass as the base substrate while the top substrate is made of polymers such as polydimethylsiloxane (PDMS) [36,37,39,46,48,50,52,53,55,58,62–65], polymethylmethacrylate (PMMA) [59,66–71], polyethylene terephthalate (PET) [72–76], polycarbonate (PC) [35,36,59,77,78], thermoplastic olefin polymer of amorphous structure (Topas) [22,33,40], and silicon [59,79].

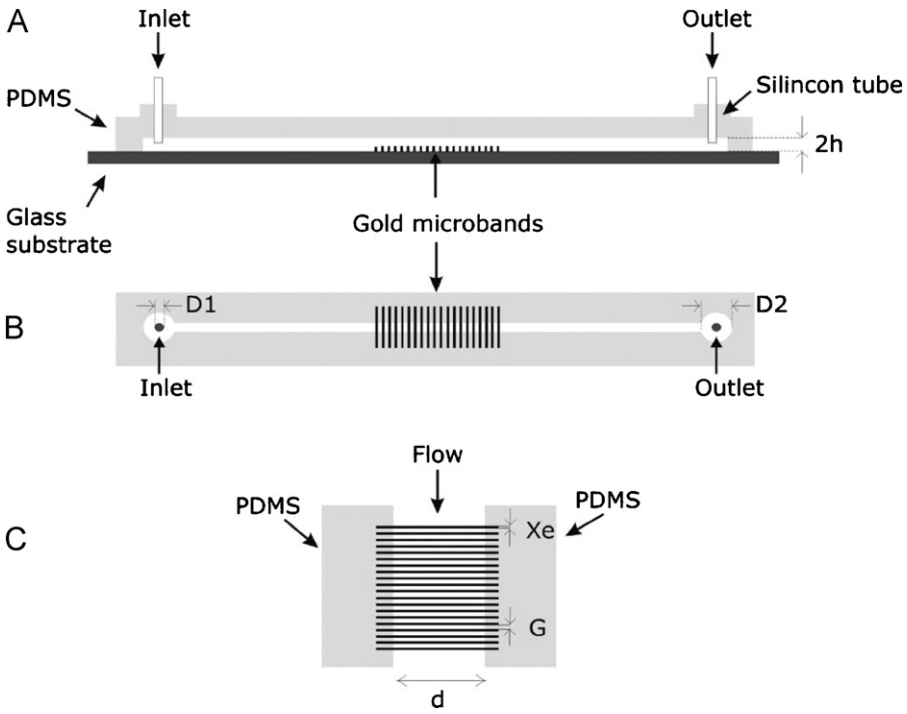

Fig. 3. (a) Lateral and (b) top views of the microfluidic devices used in this work. (c) View of microband electrodes (Xe = 20 μm, *G* = 50 or 250 μm, *d* = 95 μm) in the microchannel (2 h = 77 μm, *d* = 95 μm) [54].

Recently, PDMS and PMMA have attracted the researchers due to the excellent features such as low cost, ease of fabrication, and transparency. A study of PMMA processing and applications was reported by Chen et al. [80]. By means of a variety of fabrication techniques they observed that, PMMA was easy to fabricate, and could be re-used when subjected to high temperature. Improved performances of polymers over silicon, and PDMS over PMMA, were observed by Tambe and Bhushan [79] who compared them in terms of absorbing asperity impacts created during sliding under high velocity. PMMA was found to be friction independent under low velocities, while high velocities created heat. On the other hand, PDMS exhibited stability and low friction under high velocities, due to its ability to absorb impacts.

Tokachichu and Bhushan [81] observed that PDMS had better adhesion in ambient than PMMA because of the high electrostatic charge on the surface, and was relatively more hydrophobic. However, when the surface of PDMS and PMMA were coated, both became similar in terms of adhesion. The effect of temperature on the adhesion between PMMA and fused silica was tested by Kim et al. [70] who reported that the PMMA changed from glassy state to viscous flow state when temperature was increased from 300 to 443 K. Increasing the heat would enlarge the contact area of microchannels. Since PDMS was observed to be superior over PMMA, the former is mainly used in microchip fabrication, although the non-specific protein adsorption on PDMS is an issue. Two viable solutions keep PDMS stable and unchanged are: (i) physical mod-

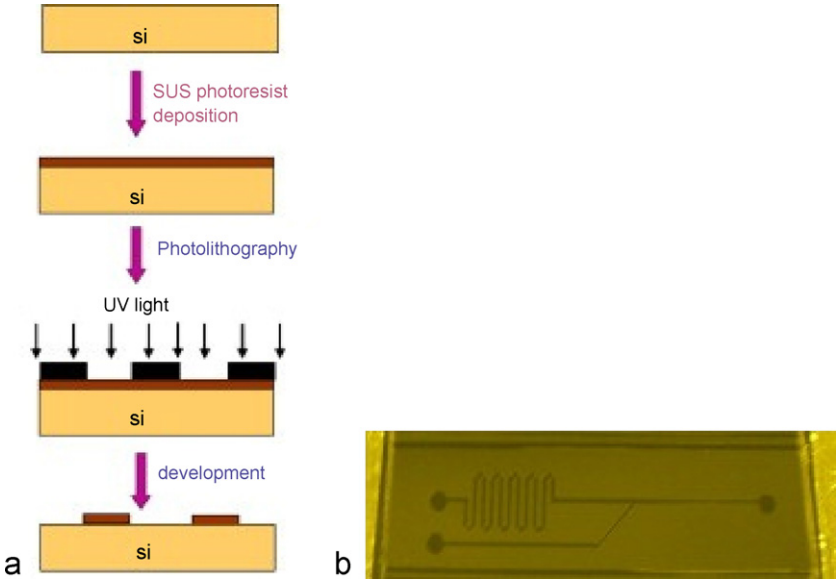

Fig. 4. (a) Fabrication process and (b) photograph of SU-8 mold [58].

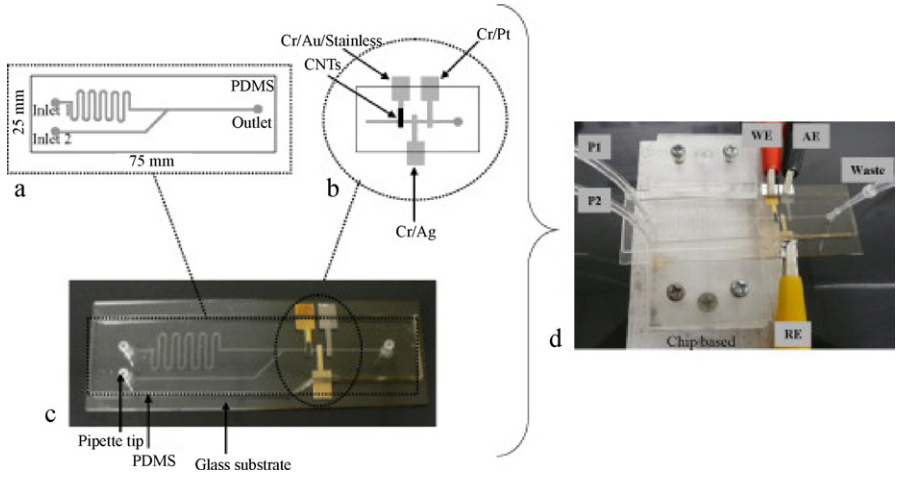

Fig. 5. Microchip and in-channel amperometric detector [58] (WE: working electrode; AE: auxiliary electrode; RE: reference electrode).

ification of the surface and (ii) chemical modification by adding self assembled monolayer (SAM) as an intermediate anchor layer between PDMS surface and a subsequent material [62,82].

3.2. Electrode materials

A recent review by Eckermann et al. [83] focused on electrode metals for thiol-based SAMs. However, this article presents electrode materials for general electroactive analytes. Electrode material has a significant impact on the performance of the MCE, and many researchers have focused on this area, in order to achieve more stable and sensitive microchips with higher resolution. Working electrodes, at which the reactions occur, generate the interested signal or data by which ECD of the analytes takes place. Redox reactions of analytes at the detection electrodes produce very small current of the order of few picos to micros of amperes, based on the testing analyte. This small current imposes designers to be very selective when choosing the electrode material.

Various materials have been proposed for electrodes of MCE, including gold [22,32–37,39,40,53–55,62,64,73], platinum [28,42,72,84], palladium [44,49,85], copper [46,47,86], indium tin oxide (ITO) [57,87–89], diamond [90–92], and several forms of carbon such as carbon ink [41,48], carbon fiber [50–52,56,65,85], carbon paste [93–96], glassy carbon [41,97], pyrolyzed carbon [15,98,99] and carbon nanotubes (CNT) [58,92,100–102].

Many researchers were interested in ITO electrodes. The PB-modified ITO electrodewas a preferred material because of its high sensitivity and ease of fabrication. Although ITO electrodes work as redox mediator to enhance electrode sensitivity [57], the main disadvantage is low separation voltage (60 V/cm), as higher voltage deteriorates the electrode rapidly due to heat. Therefore, ITO electrodes are recommended when lower separation voltages are preferable. Carbon-derived electrodes have increasingly become popular due to their outstanding features as recognized by many researchers [16,41,92,95,101]. It has been established by Qureshi et al. [92] that CNT and other polymorphs of carbon are highly recommended due to electrocatalytic ability, enhanced active surface area and the anti-fouling capability of the surface. Pumera et al. [101] observed that carbon polymorphs was better compared to gold or platinum in terms of electrocatalytic effect towards oxidation and a significant shift of the half-wave potentials to lower values. Carbon polymorphs exhibited very good stability and reproducibility in amperometric detection of amino acids and other electroactive analytes [16,95]. Carbon ink was preferred over glassy carbon as working electrode for the analysis of illicit drugs [41].

A detailed study of electrodes and materials optimization with detection alignments and configurations was reported by Fischer et al. [99] who tested Pyrolyzed Photoresistant Film (PPF), carbon ink, carbon fiber and palladium, under end-channel, in-channel and off-channel configurations. They showed that PPF electrode was the best in terms of sensitivity, LOD and ease of fabrication, as well as high SNR. The carbon ink showed lower noise when placed at the end of the separation channel. The optimum distance of the working electrode to the exit of the separation channel was 5–20 μm.

4. Conclusion

Amperometric MCE has gained wide popularity as the ECD method, due to the inherent miniaturization, portability, low cost, and ease of fabrication. Recent advances in the core areas of MCE-AD, such as fabrication techniques, and electrode and microchip materials, paved the way for integrating microfluidic devices, thereby realizing a ready-to-use and truly portable LOC microsystem. Although these developments are promising, more exploration is needed to address various issues such as, application broadening, disposability, affordability and power supply requirement. Future works are expected to reduce the required high voltage by placing multiple working electrodes in separation channels, as well as to increase the scope of MCE by using derivatization schemes and intercalation. ECD is certainly the best choice to produce DNA biosensors and disposable microchips for electroactive analyte's separation and detection, for many environmental, biomedical, and in vitro diagnostic applications.

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