



Development of a Capillary Electrophoresis Chip with Integrated Electrochemical Sensors

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Abstract: Capillary electrophoresis (CE) chips with amperometric integration offers improved portability, high detection throughput, small sample and reagent volumes, low driving voltages and sample injection and separation. This article reviews recent CE chip developments and applications in the integration of amperometric sensors. We describe the development of three different configurations (in-channel, off-channel and end-channel). CE chips with integrated EC detectors have great promise in applications including diagnostics, environmental monitoring and biological assays.

Keywords: electrochemical electrode, capillary electrophoresis chip, end-channel, off-channel

Introduction

Since the emergence of lab-on-a-chip (LOC) technology in the 1990s, considerable attention has focused on the development of miniature and autonomic analytical devices. Capillary electrophoresis (CE) chips emerged as one of the earliest LOC products, capitalizing on the high separation frequency efficiency of charge-varied analytes to drive instrument miniaturization. CE chips integrate several functions on a single substrate, including sample injection, mixing, derivatization, transportation, separation and detection, thus achieving the LOC concept. Miniaturized CE instruments provide improved portability, high throughput detection, small sample and reagent volume requirements, low driving voltages and sample injection and separation. CE chips are widely used in the detection of proteomics [1], amino acids [2], neurotransmitters [3-5] and inorganic ions [6].

CE chips have been designed to execute various detection methods, such as photometry, mass spectrometry and electrochemistry. Electrochemical (EC) detectors are more suitable for use in CE chips through the use of microfabrication techniques. Amperometry and conductometry are the most widely used methods for CE detection. Conductometric methods can detect

charged organic and inorganic ions by measuring the conductivity difference between the background electrolytes and the analytes [7]. Amperometric methods can quantify the concentration of electroactive analytes by applying a redox potential at the working electrode (WE) [8].

CE chips with EC detectors have great promise for the development of portable analysis instruments. For example, MicruX Technologies has developed a commercial end-channel amperometric sensors-integrated CE platform. Although the integration of electrodes with a CE chip is beneficial for instrument miniaturization and automated detection, the separation field and the electrophoretic current of the CE determines the signal-to-noise ratio of the EC measurement and the durability of the EC electrodes. Therefore, the layout and position of EC electrodes relative to the CE microchannel outlet are key issues for the development of EC detector-integrated CE chips. This review considers the CE principle and focuses on the recent development of amperometric detector-integrated CE chips and their corresponding applications.



CE Separation Principle

Electrophoresis

CE separation is driven by two well-known mechanisms: the electrophoretic flow and the electroosmotic flow (EOF). In electrophoresis, charged particles migrate toward the oppositely polarized electrode in an electric field. The mobility (μ_E) of charged particles in an electric field depends on the magnitude of their charge-to-size ratio and is described as

$$\mu_E = \frac{q_i}{6\pi\eta r} \quad (1)$$

where q_i is the charge of the particle, r (Stokes radius) is the radius of the hydrated particle, and η is the solution viscosity. Tiselius was the first to mention the electrophoretic technique for the separation of differently charged species. The Joule heat effect and viscous action in an electrophoretic system are inherent limitations for analyte separation, and may cause broad separating peaks and low resolution [9]. In the 1960s, Hjertén used a fused-silica capillary, presenting a high ratio of surface area to volume, to decrease the effect of Joule heat on separation efficiency [10].

EOF Phenomenon

Jorgenson and Lukacs presented the first CE technique in 1981, significantly improving the separation efficiency through the control of EOF. The fused-silica capillary is taken as an example to explain the EOF influence. The silanol group (Si-OH) of the capillary wall can be dissociated as a negatively charged group (Si-O⁻) in pH >3 buffers and cations in the solution are adsorbed to the Si-O⁻ group to form an electrical double layer (EDL) on the surface of the capillary's inner wall.

As the electric field is applied to both ends of the capillary, the hydrated cations in the EDL migrate and simultaneously drag the water molecules around the cations toward the cathode by viscous force, driving a bulk flow to the cathode. When this so-called EOF

counterbalances the friction force, the flow profile of analytes can present a plate flow which maximizes the peak height and separation efficiency of the analytes. Figure 1 shows the scheme by which the analytes are separated in a CE channel. EOF mobility (μ_{EOF}) can be written as Eq. (2), where ζ is the zeta potential of the wall surface, ϵ_0 is the permittivity of the vacuum and ϵ is the relative permittivity of the solution.

$$\mu_{EOF} = \frac{\zeta\epsilon_0\epsilon}{\eta} \quad (2)$$

Migration time (t_m) can be determined by measuring the retention time in the analyte's capillary. The μ_{EOF} can be calculated from the retention time of a neutral analyte. The total mobility (μ_m) of an analyte in a CE system can be thought of as:

$$\mu_m = \mu_E + \mu_{EOF} \quad (3)$$

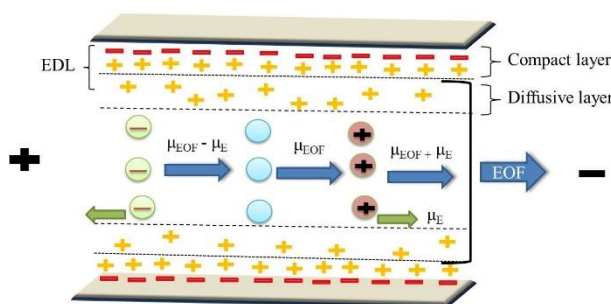


Figure 1. Analytes separated in the CE channel.

Separation Efficiency of CE

The theoretical plate number (N) is used to represent the separation efficiency of CE [11] as in Eq. (4), where t_m is the retention time and σ is the standard deviation. Moreover, N is represented as Eq. (6) in terms of the width at half the peak height ($W_{1/2}$) and the t_m .

$$N = \left[\frac{t_m}{\sigma} \right]^2 \quad (4)$$

$$\sigma = \frac{W_{1/2}}{2\sqrt{2 \ln 2}} \quad (5)$$

$$N = 5.54 \left[\frac{t_m}{W_{1/2}} \right]^2 \quad (6)$$

Development of EF Detector-integrated CE Chips

A typical CE system consists of a high-voltage power supply, a sample introduction system containing reservoirs, a capillary tube (2-100 μm inner diameter), a detector and a readout device. In principle, the reservoirs, the shape-different microchannels and the EC detectors can be integrated in a substrate to form a CE chip. The sample introduction system of CE chips can be carried out by electric injection and EOF control. Moreover, the CE

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chips can use a shorter microchannel due to the high separation efficiency of CE, allowing for lower driving voltages. CE chips with sample injection, separation and detection match the requirement of a μ -TAS platform [12].

According to the position of electrodes relative to the channel outlet, CE chips with integrated EC electrodes can be categorized as in-channel, off-channel and end-channel types, as shown in Fig. 2. The following describes the development of the three electrode configurations in recent years.

In-channel Detection

In-channel detection directly places EC electrodes in the CE separation channel under a high electric field as shown Fig. 2(a). The advantage of in-channel detection is to obtain a high theoretical plate number because the analytes passing through the WE can maintain the plate flow profile. However, the in-channel EC detection is vulnerable to interference from the CE separation field, causing large background current and a voltage drop at the WE. The voltage drop results from the electrophoretic current passing the solution resistance between WE and reference electrode (RE), which may alter the potential of WE with the change of electrophoretic current. The interference of the separation field may result in the amperometric detector having a high limit of detection (LOD). Most strategies to reduce separation field interference focus on reducing the size of the separation channel and buffering low conductivity. However, the voltage drop between WE and RE is difficult to reduce. To solve this problem, Chen et al. [13-14] proposed a dual channel design to place the WE and RE in different microchannels but with the same distance to the microchannel outlet, thus eliminating the voltage drop and reducing the background noise to 0.42 pA. Furthermore, the EOF mobility also significantly affects the CE separation efficiency. Qiu et al. developed a PDDA/TiO₂-modified polydimethylsiloxane (PDMS) channel to increase EOF stability and detection reproducibility [15]. Saylor et al. [19] used modified the PDMS channel walls with a surfactant to increase dopamine migration time.

Off-channel Detection

Figure 2(b) shows the electrode configuration of off-channel detection. A decoupling electrode, called a decoupler, is positioned in front of the WE as a ground electrode to shunt the high electrophoretic current to ground. Wu et al. were the first group to fulfill the off-channel EC detection in a PDMS-glass bonding CE microchip [20]. This method can reduce the background current from the EC detection and improve the WE

lifetime. To prevent hydrogen bubble formation on the cathodic decoupler, hydrogen absorption materials, such as Pt and Pd, are generally used as the decoupler substrate. Wu et al. electrically deposited Pt nanoparticles on the thin-film Au electrode to serve as the decoupler, which could isolate the electrophoretic current from the EC detection under a 100 V/cm separation field. The baseline offset of the detection current could be decreased to ~ 0.05 pA [20]. Presently, various materials, such as Pd [20-22], Pt [22], Au [24] and C [25], have been proposed for use as the decoupler. In particular, Pd metal has become a popular choice due to the high diffusion coefficient ($2-3 \times 10^{-7}$ cm²/s) of hydrogen on the Pd surface [26].

An off-channel arrangement requires an adequate distance between the decoupler and the WE to prevent the electrophoretic background current from interfering with the EC measurement. An overly long distance may result in the analyte's separating peak from broadening, thus reducing separation efficiency. As shown in Table 1, the distance between the decoupler and the WE is kept at approximately 200 – 700 μ m. Furthermore, several methods are proposed for decoupler fabrication, including physical vapor deposition, (PVD) [21], chemical reduction [24], print [25] and electrodeposition [20-22]. PVD-made Pd film provides more effective decoupling but at higher cost due to the complex and time-consuming chemical reduction. In contrast, electrodeposition is cost-efficient and simple and produces a thicker Pt film, thus improving decoupling efficiency [20]. Table 2 compares the design, operating parameters and LOD of different off-channel EC-CE chips. The WE of the off-channel design can tolerate larger separation fields than the in-channel design.

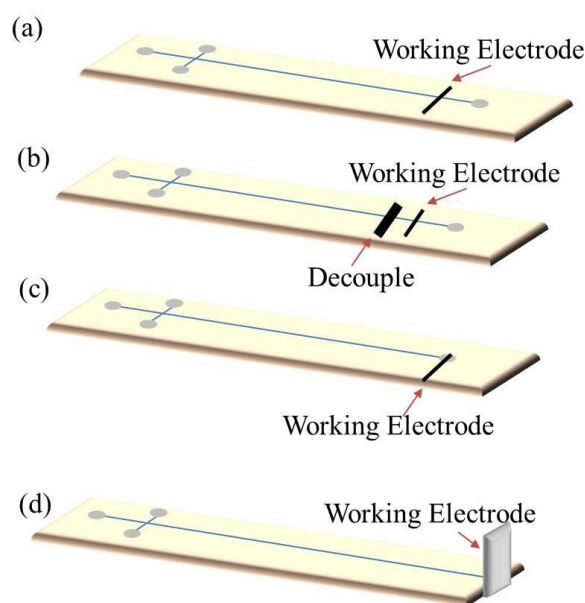


Figure 2. Layout modes of EC electrodes with integrated CE chip: (a) in-channel, (b) off-channel, (c) end-channel on-chip and (d) end-channel off-chip.

Table 1 Applications of CE chips with integrated in-channel amperometric detectors.

Channel (deep ×wide)	Buffer (pH)	Electrode	Separation field (V/cm)	Analyte (LOD, μM)	Ref.
20 μm×50 μm	100 mM acetic acid (4.0)	AuNP(200 nm)-deposited Au (50 μm wide)	250	<i>p</i> -AP (0.0146), <i>o</i> -AP (0.0106), <i>m</i> -AP (0.0153)	[13]
20 μm×50 μm	100 mM acetic acid (4.0)	AuNP(100 nm)-deposited Au (100 nm wide)	250	<i>p</i> -AP (0.002), <i>o</i> -AP (0.0014), <i>m</i> -AP (0.001)	[14]
18 μm×50 μm	5.0 mM STB (9.2)	Carbon fiber (ϕ = 8 μm)	324	Arg (9.5), Phe (11.8), Ser (12.6), Thr (11.2)	[15]
15 μm×80 μm	25 mM MES (6.5)	Au (10 μm wide)	200	DA (100), CAT (150)	[16]
14 μm×50 μm	10mM boric acid with 2mM TTAB (11)	Pt	417	NO ₂ ⁻ (2.6)	[17]
14 μm×40 μm	10 mM boric acid, 7.5 mM NaCl and 2 mM TTAC buffer (10.3)	Pt wire (ϕ = 15 μm)	417	NO (-)	[18]
15 μm×40 μm	15 mM phosphate, 15 mM SDS, and 2.5 mM boric acid (7.4)	Carbon fiber (ϕ = 33 μm)	278	L-DOPA (-)	[19]

STB: Disodium tetraborate decahydrate solution, MES: 2-(Nmorpholino) ethanesulfonic acid, TTAB: tetradecyltrimethylammonium bromide, TTAC: tetradecyltrimethylammonium chloride, DA: dopamine, CAT: catechin, Arg: arginine, Phe: phenylalanine, Ser: serine, Thr: threonine *p*-AP: *p*-aminophenol, *m*-AP: *m*-aminophenol, *o*-AP: *o*-aminophenol, PA: paracetamol

Table 2 List of applications for CE chips with integrated off-channel detectors.

Decoupler/WE	Gap (μm)	Separation field (V/cm)	Analyte (LOD, μM)	Ref
PtNP-deposited Au (200 μm)/Au (100 μm)	200	75	DA (0.125)	[20]
Pd (500 μm)/C (27 μm)	400	250	DA (6.7), NE (1.1)	[21]
Pd (50 μm)/Au (50 μm)	350	200	4-OHE ₂ -1-N3Ade (0.4), 4-OHE ₂ -NACcys (0.4)	[22]
Pt (ϕ = 500 μm)/Cu (ϕ = 200 μm)	200	150	DA (2.8), CAT (12.7)	[23]
AuNP-deposited Pt (1 mm × 3 mm)/ AuNP-deposited Au (3 mm × 3 mm)	700	140	DA (1)	[24]
Carbon ink (550 μm)	200	200	DA (0.05), CA (0.12)	[25]

NE: noradrenaline, 4-OHE₂-1-N3Ade: 4-hydroxyestrone depurinating adducts at the N3 position of adenine, 4-OHE₂-2-NACcys: 4-hydroxyestradiol-2-N-acetylcysteine, Gap: interelectrode gap between decoupler and WE

End-channel Detection

The electrode configuration of end-channel EC detection is shown in Fig. 2(c-d). The EC electrodes are placed in the waste reservoir and close to the outlet of the separation channel. The end-channel electrode designs can be categorized as on-chip or off-chip, meaning that the EC electrodes are respectively positioned on and off the CE chip. The width of the waste reservoir is much larger than the cross-sectional area of the CE microchannel, which can drastically reduce the interference of the separating field from the

amperometric measurement. However, the flow speed may be significantly reduced due to fluidic resistance in the waste reservoir, causing a broad separating peak and a low resolution. Therefore, the position of WE must be aligned with an optimal distance from the outlet of the separation channel.

In end-channel on-chip detection, the distance between the WE and the separation channel outlet can be controlled using microfabrication techniques. Castaño-Alvarez et al. used photolithographic techniques to create

a 20 μm distance between the EC electrode and the CE separation channel outlet. The end-channel on-chip detection obtained a DA LOD of 450 nM [27]. Vázquez et al. deposited a Pd thin-film electrode (40 μm width) on a glass substrate for amperometric detection and the Pd electrode was aligned at 5–20 μm from the end of the separation channel using an optical microscope. The LOD of NO_2^- (electroactive) species was 20 μM [28]. Moreover, Vázquez's study found that amperometric detection can obtain a better NO_2^- sensitivity than that produced by contactless conductivity detection. Although the on-chip WE has an advantage in terms of ease of alignment, it is difficult to replace a contaminated or damaged WE, thus increasing the cost of measurement and manufacturing.

In contrast, the end-channel off-chip detector *can* be separately fabricated, and then assembled with a CE chip. This design facilitates the individual replacement of the WE or CE chip due to channel pollution or damage, thus reducing fabrication complexity and measurement cost. However, the alignment between the off-chip WE and the CE channel end is a bottleneck which determines the sensitivity and reproducibility of detection. Presently, micro-disk electrodes [29–31] or planar-type electrodes [32–33] are used for the off-chip detection, as listed in

Table 3. If the gap between the WE and channel end is well controlled, end-channel detection can obtain a low LOD. Furthermore, the relative position between the WE and the channel outlet generally needs to be fixed using a micro positioning stage with the help of an optical microscope, which creates difficulty for robust, real-time and on-site operation.

Figure 3 illustrates our previous patent [33], a self-aligned thin-film WE chip and a mechanical alignment device, proposed to automatically facilitate the alignment and control the gap between the sensitive area of WE and the microchannel outlet. The self-aligned WE can be fabricated using microfabrication techniques, making it suitable for mass production and allowing for WE replacement. The thickness of the insulator covering the WE surface can be used to control the gap without the help of an optical microscope [33]. Moreover, repeated DA measurements in this end-channel off-chip detection scheme resulted in a relatively small standard deviation of about 7%, meaning the device has good reproducibility. Table 3 compares the sensing properties and the gap between the WE and the separation channel outlet for different analyte detection configurations. The results show that the optimum gap is in the range of 10– 40 μm .

Table 3. Comparison of CE chips with integrated end-channel detectors.

Method	Gap (μm)	Electrode	Separation field (V/cm)	Analyte (LOD, μM)	Ref.
on-chip	20	Ti/Pt (100 μm wide)	214	DA (0.45), EP (0.45)	[27]
on-chip	5–20	Pd (40 μm wide)	319	NO_2^- (20)	[28]
on-chip	–	Au ($\varnothing = 25 \mu\text{m}$)	320	Cholesterol (0.001)	[29]
off-chip	20	Nano carbon fiber ($\varnothing = 100\text{--}300 \text{ nm}$)	131	DA (0.57), IP (0.57)	[30]
off-chip	10	Cu disk ($\varnothing = 127 \mu\text{m}$)	432	Arg (7), Pro (6), His (5), Val (6), Ser (5)	[31]
off-chip	40	Cu film (0.5 \times 2.0 mm)/ Au film (0.5 \times 2.0 mm)	450	Arg (7.1), Val (9.3), His (10.2), Cys (9.4)/ DA (0.14)	[32]
off-chip	30	Au (20 μm wide)	280	DA (0.25), CAT (0.157)	[33]
off-chip	20	Carbon paste ($\varnothing = 150 \mu\text{m}$)	208	DA (1.2), CAT (4)	[34]
off-chip	20	CoHCF modified MWCNTs/graphite ($\varnothing = 1 \text{ mm}$)	232	HZ (0.91), ISZ (1.3)	[35]
off-chip	10	U-form Pt (0.3 mm \times 0.2 mm)	400	CEA (0.00025), AFP (0.00013)	[36]
off-chip	20	mv-RuO-RuCN-GC ($\varnothing = 3 \text{ mm}$)	333	Ethanolamine (23), tryptamine (27), tryptophane (34)	[37]

EP: epinephrine, IP: isoprenaline, Val: valine, His: histidine, Cys: cysteine, Pro: proline, mv-RuO-RuCN : mixed-valent ruthenium oxide/hexacyanoruthenate polymeric film, CoHCF: cobalt hexacyanoferrate, MWCNTs: multi-walled carbon nanotubes, HZ: hydrazine, ISZ: isoniazid



Moreover, the resolution declined significantly as the gap increased to 60 μm [34]. Compared with the on-chip scheme, the end-channel off-chip design presents good lifetime [32] and reproducibility [31]. Furthermore, the end-channel EC detectors can tolerate a larger separation field than the in-channel detectors, and have an LOD comparable with off-channel detectors.

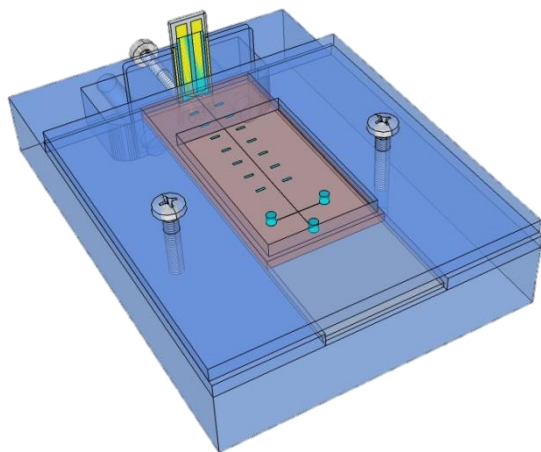


Figure 3 Schematic view illustrating a disposable CE-EC detecting device and the fixing device. (a) CE chip, (b) sample waste reservoir, (c) buffer reservoir, (d) sample reservoir, (e) buffer waste reservoir, (f) EC electrode and (g) fixing device.

Conclusion

CE chips integrated with EC electrodes allow for the production of portable miniaturized analysis instruments. The versatile CE chips can be produced by microfabrication techniques and have a wide range of applications for the compositional analysis of biological, food and environmental samples. The in-channel EC detection exhibits a higher separation theoretical plate number, but suffers for a larger background current to obtain a higher LOD. The off-channel EC detection needs a decoupler to shunt the high separation field to the ground, which can effectively reduce interferences by the electrophoretic current. Therefore, this electrode configuration can obtain a better LOD result than the in-channel arrangement. Similarly, the end-channel WE design can significantly reduce separation field interference by adequately adjusting the relative position of the WE versus the separation channel outlet. Furthermore, end-channel off-chip EC detectors can simplify the fabrication of CE chips with EC electrodes. This model allows for the simple replacement of damaged EC detectors and reduce chip manufacturing costs. However, the alignment of the WE position is an important issue for end-channel detection. Currently, CE-EC chip designs include multi-channels equipped with multi-detectors, and the use of novel nanomaterials for

WE modification will enhance detection sensitivity. CE chips with integrated EC detectors give great promise for applications including faster and more convenient clinical diagnosis, environmental monitoring and DNA testing.

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