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Capillary zone electrophoresis: Opportunities and challenges in miniaturization for environmental monitoring

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ABSTRACT

After a decade of research, development, and instrument commercialization, capillary electrophoresis (CE) has firmly established itself as a recognized analytical technique. CE is a separation method that segregates charged species based on their charge and size. In the field of environmental science, CE instruments have emerged as an ideal choice due to their simplicity, efficiency, affordability, and compact design. Furthermore, CE's equipment requirements are straightforward, making it well-suited for easy miniaturization. This review provides a comprehensive overview of the latest advancements in the CE technology, with a focus on its miniaturization. It delves into portable CE and microchip-based CE, exploring their structural characteristics, advantages, and limitations. Additionally, it investigates a modular approach that consolidates all essential components onto a single board, offering a holistic perspective on the innovative possibilities within the realm of miniature capillary electrophoresis.

1. Introduction

Recent advancements in qualitative and quantitative analysis have marked significant progress in various aspects, particularly in refining methods for the extraction, separation, and quantification of environmental pollutants. Extraction methods play a crucial role in separating analytes from the sample matrix. Techniques such as solid-phase extraction (SPE), liquid-liquid extraction (LLE), and solid-phase microextraction (SPME) are commonly utilized to isolate analytes of interest [1]. Various separation techniques, including chromatography, magnetic separation, electrophoresis, and other physical methods, are employed for the identification of analytes. Enhanced resolution and sensitivity are achieved through methods such as High-Performance Liquid Chromatography (HPLC), Gas Chromatography (GC), and Liquid Chromatography-Mass Spectrometry (LC-MS) [2]. Electrophoresis, a versatile tool for diverse analytical separations, is used for quantitative analysis by comparing the intensity of bands or peaks in the resulting pattern. This feature proves valuable in determining the relative abundance of specific molecules within a sample, providing high resolution for the clear separation of closely related molecules. The rapid expansion of research into electrophoresis instrumentation has showcased its efficacy in various analytical separations [3]. Electrophoresis can be classified into capillary zone electrophoresis, paper electrophoresis, and gel electrophoresis [4], emphasizing its adaptability across different applications and settings. This review specifically focuses on capillary zone electrophoresis.

Capillary Electrophoresis (CE) is an analytical separation technique used to separate charged species based on their charge and size. The separation is achieved by observing the different rates at which these charged species migrate in an electric field within a capillary. Since its introduction by Jorgenson and Lukacs in 1981 [5], modern CE has undergone substantial advancements, becoming a sophisticated and adaptable separation method. Following a decade of development studies and commercialization of instruments, CE has firmly established itself among the well-recognized analytical techniques. Over the years, it has proved to be a valuable tool in analytical chemistry, biochemistry, pharmaceuticals, and other scientific fields [6,7]. Fig. 1 shows some significant milestones in the evolution of CE.

- Early Developments (1980s): Jorgenson and Lukacs pioneered capillary zone electrophoresis (CZE), a technique that separates analytes in a capillary filled with an electrolyte solution based on their charge-to-size ratio. In the initial stages, researchers concentrated on fundamental investigations and methodological

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advancements, experimenting with various separation modes and detection techniques [8].

- Instrument Commercialization (1990s): During the 1990s, the introduction of commercial CE instruments increased the accessibility of this technique to a broader community of researchers and laboratories. The wider adoption of CE was facilitated by enhancements in automation and the development of user-friendly interfaces [6,9].
- Expanding Modes of CE (1990s to 2000s): Various CE modes were developed, each catering to specific analyte types and separation needs. These include capillary gel electrophoresis (CGE), capillary isoelectric focusing (CIEF), micellar electrokinetic chromatography (MEKC), and more. The introduction of these modes expanded the versatility of CE and its capability to separate and analyze a wide range of analytes.
- Miniaturization of Electrophoresis (Lab-on-a-Chip) (2000s and 2020s): The miniaturization of CE into microchips (lab-on-a-chip) enabled faster separations and reduced sample and reagent consumption. Microchip electrophoresis found applications in point-of-care diagnostics and portable analytical devices [10–12].

As CE progressed, it became a reliable and established analytical technique, alongside other traditional approaches such as high-performance liquid chromatography (HPLC) and gas chromatography (GC). What sets CE apart from these conventional methods is its ability to separate vastly diverse compounds, including inorganic ions, organic molecules, and large biomolecules [13], all using the same instrument and, in many cases, the same column with only variations in the running buffer composition. Moreover, it offers short analysis time, high resolution, and minute consumption of samples and reagents [14]. Additionally, due to its plug flow characteristics and minimal diffusion, CE exhibits excellent resolving power compared to other liquid separation techniques [15]. Nevertheless, CE's direct analysis of complex samples is limited by matrix interference, leading to reduced sensitivity and repeatability. Consequently, the implementation of sample pretreatment techniques before CE analysis becomes crucial [16]. As pretreatment techniques continue to advance, CE, in conjunction with various detection methods, has found extensive application across diverse fields. CE has been commonly combined with UV detection, fluorescence detection, MS, and electrochemical detection, encompassing conductivity detection (CD) and amperometric detection (AD) [16] for analyzing substances in environmental analysis [17], industrial analysis [18,19], and medical analysis [18,20].

In environmental science, the portability of analytical instruments plays a crucial role in on-site real-time detection and miniaturized laboratory analysis of substances in the environment [21]. In this context, the CE instrument has emerged as an ideal option due to its simplicity, efficiency, affordability, and compact design. It employs a high voltage rather than high pressure for driving the analytes in a micro separation channel. As a result, it offers a more cost-effective and higher-throughput option. It proves to be a suitable choice for analyzing pollutants, encompassing both organic and inorganic compounds found in the environment [16,22,23]. CE has gained significant prominence in the domain of clinical medical diagnosis. It finds application in disease diagnosis by analyzing various biomolecules such as amino acids [24], small ions, organic acid-base compounds, peptides, proteins, and nucleic acids in biological body fluids due to its exceptional selectivity and capacity to handle matrix components effectively [16]. CE has found applications in various industries, including food, pharmaceuticals, and dairy [16,25]. As society evolves, ensuring food safety has become a crucial concern related to public health. Food can contain numerous main components, additives, and residues, and when their levels exceed safety standards, they pose risks to human health. CE has shown its potential in inspecting food quality security, assessing nutritional value, and monitoring food processing and storage. In the food industry, CE is primarily used to analyze principal components, additives, and residues to ensure the safety and quality of food products [26–28]. Among all applications, CE has found the most extensive use in pharmaceutical analysis [29]. In pharmaceutical analysis, two main categories exist: the analysis of chemical medicines and the analysis of biological medicines [16]. In clinical analysis, despite the extensive utilization of immunomagnetic separation to isolate target biomolecules [30,31], CE approaches offer distinct advantages in terms of assay speed and flexibility [32]. Due to its ability to rapidly detect adulteration in milk mixtures and cheese, CE has become a well-established method for investigating the authenticity of dairy products through protein analysis. CE is commonly used to perform protein profiling of key bovine milk proteins, including whey and casein proteins. As a result, CE has become a beneficial tool in the dairy industry for quality control and ensuring product integrity [33,34]. Fig. 2 summarizes the CE applications in brief.

An extra benefit of capillary electrophoresis (CE) lies in the simplicity of its required equipment, making it suitable for easy miniaturization. This feature enables CE and miniaturized CE to combine most of CE's benefits, including sample handling, customizable design, and

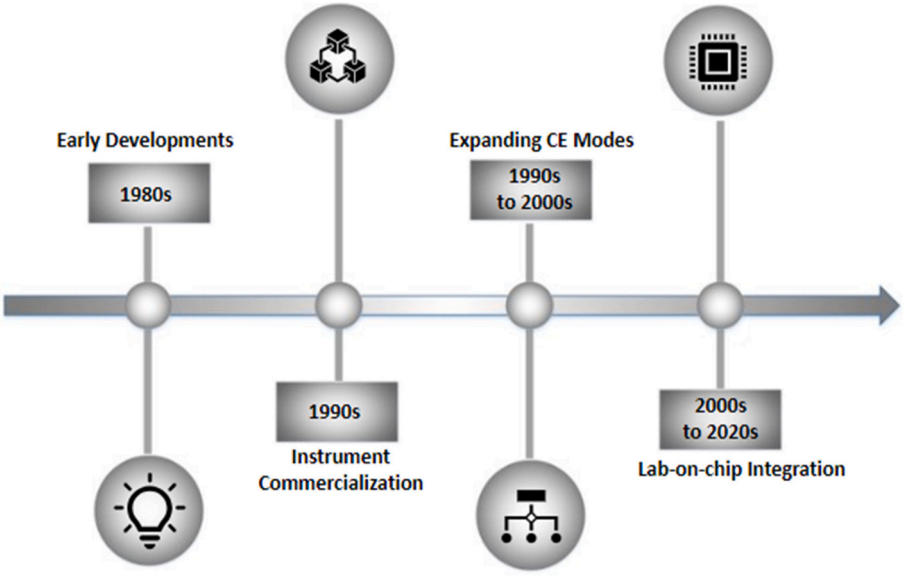

Fig. 1. Evolution of capillary electrophoresis.

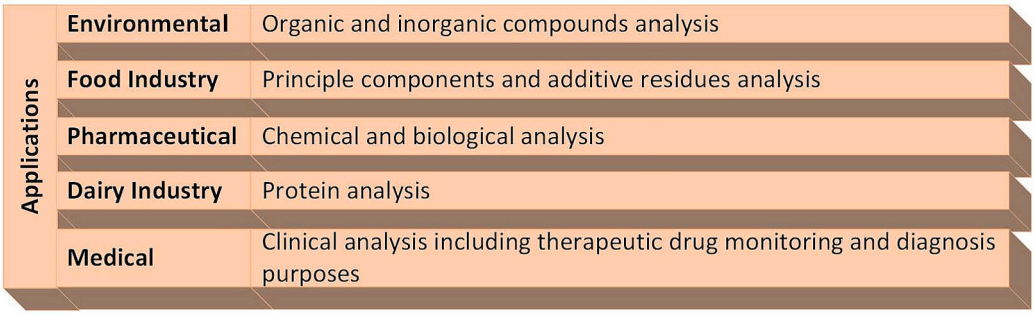

Fig. 2. Applications of capillary electrophoresis.

portability, while also providing analytical performance similar to that of standard bench-top instrumentation. Further merits of sensors based on CE possess the ability to utilise numerous established separation techniques, perform analyses with low power usage, and attain complete electronic control over the system. Currently, CE and miniaturized-CE devices are extensively adopted as versatile analytical platforms in diverse fields such as biomedical research, pharmaceuticals, environmental monitoring, and forensics [35]. Over the past two decades, a thoroughly examined area of research has played a pivotal role in the process of miniaturization. This encompassed reducing the size of both injection and detection systems, as well as the entire CE apparatus. Because the fundamental components are straightforward, constructing a CE system is feasible even for individuals without specialized expertise. Additionally, research endeavours have focused on creating open-source and modular CE instrumentation, encompassing controls and systems for data acquisition [36].

This review aims to offer an in-depth exploration of the evolution and miniaturization of capillary electrophoresis (CE) and its use in environmental monitoring. It provides an overview of the historical developments, current state-of-the-art advancements, and the core principles and instrumentation associated with CE. The miniaturization of CE can be broadly categorized into two main types: portable CE and microchip-based CE, depending on the technology and format employed for the electrophoresis process. Both approaches have distinct advantages and are applied in various contexts, tailored to the specific needs of analytical or research endeavours. The discussion within this review encompasses advancements in automated injection systems and simplified operation, which have been pivotal in achieving portable CE systems. Similarly, significant progress in microchip-based CE is thoroughly examined, including the evolution of microchip materials and technologies. Furthermore, this review provides a comprehensive analysis of both portable CE and chip-based CE, delving into their structural characteristics, advantages, and limitations. Additionally, it explores a modular approach that integrates all essential components onto a single board, offering a holistic view of the innovative possibilities within the realm of miniaturized capillary electrophoresis.

2. Theoretical functioning of capillary electrophoresis

The basic version of CE is referred to as capillary zone electrophoresis or free-solution capillary electrophoresis. When an electric field is introduced within a channel, an ionic compound moves through the channel at a speed determined by its electrophoretic mobility and the strength of the electric field [37–39]. Common electric field strengths vary from 50 to 250 V cm^{-1}, although instances as high as 53 kV cm^{-1} have been reported. As the introduced sample traverses the channel, distinct ionic constituents move at varying speeds due to their diverse mobilities. Consequently, they encounter a detector positioned close to the end of the channel at distinct time points. The measurement of migration time determines the ionic species. Widely used techniques include laser-induced fluorescence (LIF), UV detection, and more recently, electrochemical detection, encompassing methods such as potentiometry, conductometry, and amperometry [40].

2.1. Principle of capillary electrophoresis

The velocity of the analyte's migration when moving in response to an electric field with intensity "E" is determined by the analyte's electrophoretic velocity and the electroosmotic velocity of the buffer within the capillary. The solute's electrophoretic mobility is contingent on distinct attributes of the solute, including electric charge, molecular dimensions, and configuration, and the characteristics of the buffer, such as the ionic strength of the electrolyte, pH, viscosity, and additives, also play a role in this mobility. When an electric field is applied to a capillary filled with buffer solution, it triggers a fluid movement known as electroosmotic flow (EOF) within the capillary. This phenomenon is also termed electroosmosis or electroendosmosis. This flow occurs due to the surface charge on the capillary walls and their interaction with the buffer solution. The speed of the electroosmotic flow is contingent upon the electrophoretic mobility, which itself relies on the charge density of the capillary's inner wall and the characteristics of the buffer.

The subsequent equation provides the electrophoretic velocity V_{ep} of the solute:

$$V_{ep} = \mu epE = (q/6\pi\eta r)(V/L), \tag{1}$$

where

η = viscosity of the electrolyte solution,
V = applied voltage,
L = length of the capillary,
r = Stoke's radius of the solute,
μep = is the electrophoretic mobility of the solute, and.
q = effective charge of the solute.

The following equation gives the electroosmotic velocity (V_{eo}):

$$V_{eo} = \mu eoE = (\varepsilon\zeta/\eta)(V/L), \tag{2}$$

where

ε = buffer's dielectric constant,
ζ= zeta potential of the capillary surface,
η = viscosity of the electrolyte solution,
V = applied voltage,
μeo = electrophoretic mobility, and.
L = length of the capillary.

And the solute's velocity (V) is given by:

$$V = V_{ep} + V_{eo}. \tag{3}$$

The electroosmotic and electrophoretic mobility of the analyte can either align or oppose each other, depending on the solute's charge. In conventional capillary electrophoresis, anions migrate in the direction opposite to electroosmotic flow, but at velocities lower than the electroosmotic velocity. Conversely, cations move in the same direction as electroosmotic flow, yet their velocities surpass the electroosmotic

velocity. In scenarios where the electroosmotic rate substantially exceeds the electrophoretic rate of the solutes, both cations and anions can be separated within a single run.

2.2. Instrumental set-up and working of CE

A standard capillary electrophoresis setup consists of a high-voltage power source, a sample injection mechanism, a capillary, a detector, and an output device. Both the anode and cathode electrodes are linked to the power supply. The capillary is made of fused silica. Both ends of the capillary tube are submerged into a vial that holds an electrode and an electrolytic buffer solution (Fig. 3a). The electric field induced between electrodes causes the migration of the sample from the anode to the cathode. The inner surface of the silica capillary acquires a negative charge when the pH of the buffer solution is greater than three. This generates an EOF directed toward the negative electrode. For positively

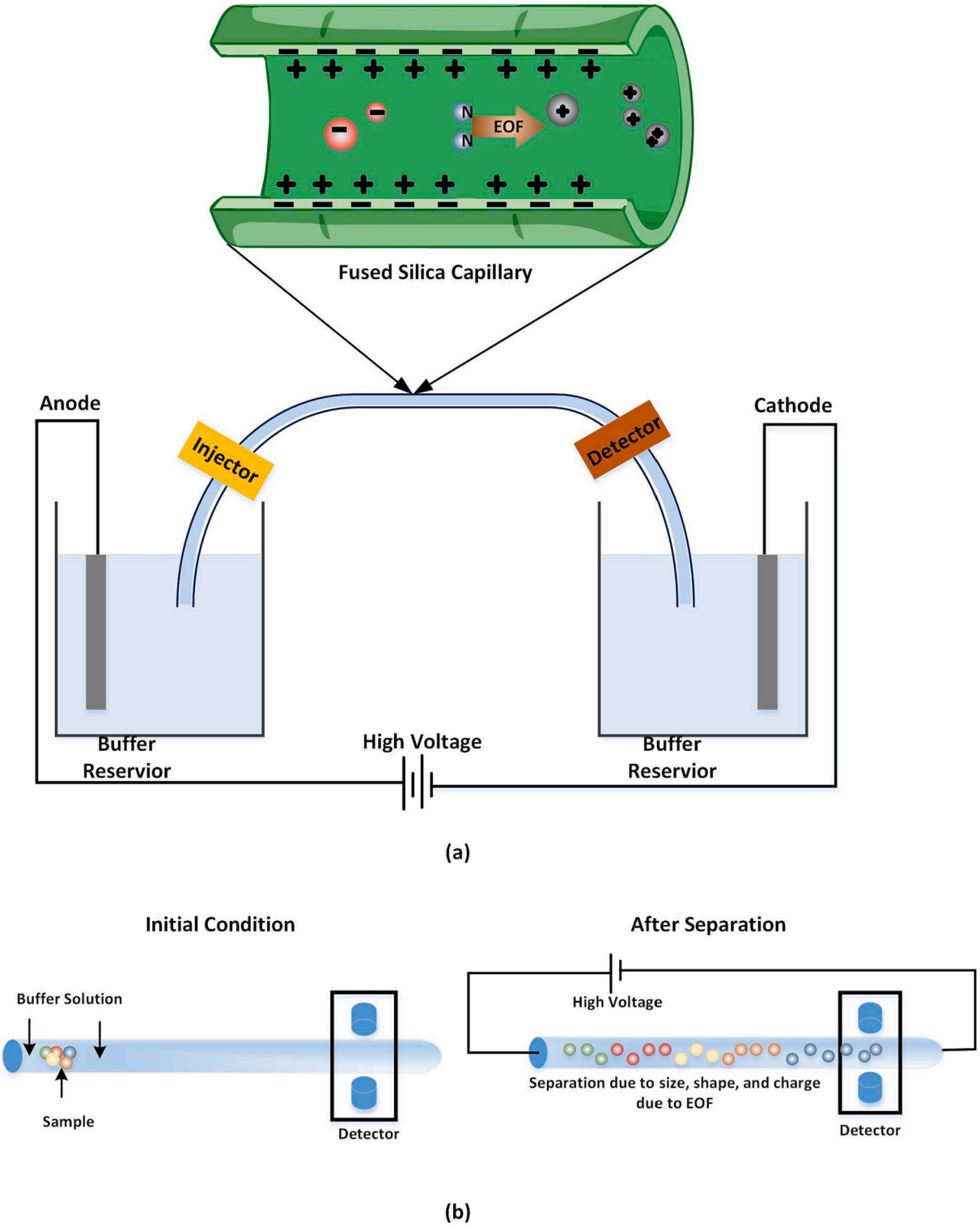

Fig. 3. Pictorial representation of (a) Capillary electrophoresis, (b)Working of capillary electrophoresis.

charged ions (cations) in a bare fused silica capillary, their migration direction aligns with the EOF direction, causing them to move toward the cathode and reach the detector first. Neutral analytes have a "zero" electrophoretic velocity, so their migration velocity is solely determined by the EOF velocity, leading them to reach the detector second. As for negatively charged ions (anions), their electrophoretic movement direction opposes the EOF direction. However, if the EOF velocity is higher than that of the anions, they will still migrate toward the cathode and reach the detector third, following the neutral analyte (Fig. 3b). The combination of electrophoretic and electroosmotic movements in CE allows for the efficient separation of charged species based on their migration rates in the electric field within the capillary [16].

2.3. Various types of CE operations

There are six types of capillary electro-separation techniques available, each with its unique characteristics and applications:

1. Capillary Zone Electrophoresis (CZE): In CZE, analytes are separated based on their charge-to-size ratio as they migrate through a continuous buffer-filled capillary under the influence of an electric field [41,42].
2. Capillary Gel Electrophoresis (CGE): CGE utilizes a gel-filled capillary, where the separation is influenced by both electrophoretic and sieving effects of the gel matrix, allowing for enhanced separation of larger molecules [41,43].
3. Micellar Electrokinetic Capillary Chromatography (MEKC): MEKC incorporates micelles (aggregates of surfactant molecules) in the background electrolyte to improve the separation of neutral compounds [41,44,45].
4. Capillary Electrochromatography (CEC): CEC combines the principles of both chromatography and electrophoresis, utilizing a stationary phase in the capillary to enhance separation [41,46,47].
5. Capillary Isoelectric Focusing (CIEF): CIEF separates analytes based on their isoelectric points, utilizing a pH gradient along the capillary [41,48,49].
6. Capillary Isotachophoresis (CITP): CITP separates analytes based on their mobility differences between leading and trailing electrolytes, creating discrete zones of analytes [41,50,51].

These techniques can be classified into two systems based on the arrangement of the electrolytes:

1. Continuous System: In a continuous system, a background electrolyte is present throughout the capillary, acting as a buffer to facilitate separation [52]. Continuous systems can be further classified into
   (a) Kinetic: In this constant electrolyte composition system, the buffer remains unchanged throughout the process [52].
   (b) Steady-state: In this varying electrolyte composition system, the buffer composition changes during the process [52].
2. Discontinuous System: In a discontinuous system, the sample is divided into distinct zones, each separated by different electrolytes [52]. This allows for specific and targeted separations.

3. Environmental analysis

The ongoing demand to ensure the quality of water used for municipal, industrial, and environmental purposes has led to a continuous quest for enhancing analytical methods and tools. This is particularly crucial for analyzing inorganic macro- and micro-components and organic compounds found in trace amounts. Given the widespread demand for these analyses, the advancement of analytical techniques that allow for the simultaneous detection of multiple components is highly advantageous [53]. In the field of environmental science, the ability to carry analytical instruments to the site of interest is crucial for real-time, on-site analysis and scaled-down laboratory testing of environmental substances. Capillary electrophoresis (CE) instruments have emerged as a favourable option in this regard. They are straightforward, efficient, cost-effective, and compact analytical tools capable of analyzing both organic and inorganic compounds present in the environment [16].

3.1. Organic analytes

Organic compounds are indeed a diverse group of chemicals that contain carbon atoms bonded to hydrogen, oxygen, nitrogen, and other elements. Due to their widespread use, organic compounds have become pervasive in the environment. They can enter the environment through various pathways, such as emissions from industrial processes, runoff from agriculture, and disposal of consumer products. As a result, they can be found in soil, water bodies, and even in the air. Some organic compounds are known to be toxic, carcinogenic, or disruptive to ecosystems even at low concentrations [54,55]. For instance, the extensive use of Aniline and its derivatives in industrial processes has resulted in the release of chemical by-products into aquatic environments. These substances are notable for their high toxicity and suspected carcinogenic properties. To address this issue, a simple and efficient method has been developed [56] for detecting these compounds in environmental water samples by CZE with field-enhanced sample injection. It demonstrates a detection limit falling within the range of 0.29–0.43 ng/mL. Additionally, a method was created [57] to detect organic amines in both drinking water and wastewater using capillary electrophoresis. To facilitate indirect photometric detection, a combination of benzimidazole and tartaric acid was employed as the leading electrolyte. The samples were introduced into the system through hydrodynamic injection. This method's performance was assessed using samples from both drinking water and wastewater sources. The precision of the outcomes was gauged using the standard addition approach. The method's detection capability ranged from 0.25 to 5 mg/L, and the analysis was completed within a brief timeframe of 4 to 5 min. Certain organic additives, such as synthetic dyes, are considered potentially hazardous and have been linked to neurological, mutagenic, genotoxic, and carcinogenic diseases. Azo dyes, in particular, fall into this category. To address this concern, a magnetic solid phase extraction method combined with capillary electrophoresis has been proposed [58] for the simultaneous detection of three azo dyes (sunset yellow, allura red, and tartrazine) in wastewater samples. This developed method has been successfully applied as a routine procedure for the identification and quantification of azo dyes in actual wastewater samples collected from various locations. The proposed technique offers several advantages, including simplicity, sensitivity, high efficiency, cost-effectiveness, and a short analysis time. As a result, it presents a viable alternative for analyzing azo dyes in water samples and other complex matrices. Despite an enrichment factor of 500/300, this method still provides satisfactory results in terms of sensitivity and accuracy. In another study, H. Oliver et al. [59] demonstrated the capabilities of CE-MS (Capillary Electrophoresis-Mass Spectrometry) for analyzing organic and inorganic micropollutants in drinking water. This was achieved without the need for sample pretreatment, and they accomplished it by coupling CE to an Orbitrap mass spectrometer via a nanoflow sheath liquid interface (Fig. 4). The concentrations of the target analytes in the water samples spanned from 0.1 to 6.2 μg/L. They emphasized the potential for more extensive utilization of CE-MS in environmental and water analysis, especially when combined with further advancements in nanoESI (nano Electrospray Ionization) interfaces aimed at improving automation, user-friendliness, and durability.

3.2. Inorganic analytes

When it comes to determining inorganic ions, the use of conductivity detection, especially C^4D, is highly suitable. This detection method re-

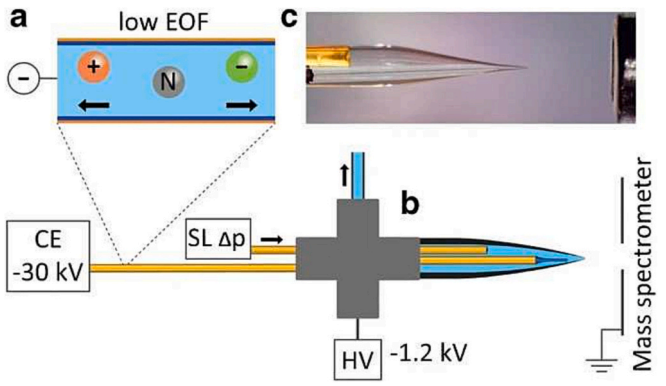

Fig. 4. Setup of the nanoflow sheath liquid CE-MS interface for the analysis of strongly acidic compounds in drinking water. (A) 10% (*v*/v) acetic acid exhibits a low pH (~ 2.2) which causes a low electroosmotic flow enabling negative CE polarity. The separation capillary and a capillary to deliver sheath liquid are guided through a PEEK cross (B) into the borosilicate glass emitter (C). The third arm drains excess liquid and opens the emitter to ambient pressure while the fourth arm is used to ground the CE current and apply the electrospray voltage [59].

sponds to all ions, making it versatile [60]. A simple and cost-effective in-house-made CE-C^4D [61] for analysis of various inorganic ionic species in different water matrices was built. This system was used to determine major inorganic ions and trivalent arsenic levels in various water matrices in Vietnam. The results from in-house-made CE-C^4D-instruments were cross-checked with those obtained using the standard methods (AAS, AES, UV and IC), with correlation coefficients $r^2 \geq 0.9$ and deviations from the referenced results less than 15. In recent years, research efforts have also been directed toward the analysis of water by simultaneously separating specific anions and cations using CE. It allows the simultaneous determination within the same capillary in a single run. Often, this can be accomplished in a shorter time frame compared to traditional ion chromatography methods. For example, a method based on the capillary filling method (CFM) [62] took 80 s for the detection of ions at concentrations in the parts per million (ppm) range. This method was developed for the simultaneous detection of three anions (chloride, sulfate, nitrate) and five cations (ammonium, potassium, sodium, magnesium, calcium). It was then applied for the analysis of inorganic anions and cations in commercial mineral waters, tap water, urine, and exhaled breath condensate. A few previous efforts have utilized a unique injection technique. For example, the samples were hydro-dynamically injected from both ends to enable the simultaneous detection of inorganic ions in drinking water [63]. To achieve a satisfactory ion separation, it was essential to optimize the position of the C^4D detector along the capillary due to the counter-current migration of the analytes. Utilizing a 60 cm-long fused silica capillary coated with PVA, separation of 11 cations and anions was accomplished in under 3 min, with detection limits falling within the range of 0.07 to 2 $mg{\cdot}L^{-1}$. Mai and Hauser [64] explored the use of CE-C^4D with hydrodynamic pumping, offering multiple possibilities for optimizing simultaneous separations of anions and cations using a sequential injection analysis (SIA) manifold. They used dual single-end injections and dual C^4D cells to obtain separate electropherograms for cations and anions as shown in Fig. 5. Furthermore, Fukio R. et al. [65] demonstrated that by carefully optimizing the SIA-CE setup, including parameters such as capillary length, pressure levels, and separation time, it was feasible to achieve the separation of inorganic cations and anions in wastewater in a single run.

4. Miniaturization of capillary electrophoresis

Developments in fields like electronics, engineering, and material science have played a crucial role in promoting the evolution of scientific instruments. The wider accessibility of compact, cost-effective, and portable computers designed for data collection and analysis has further supported this progress. Concurrently, in alignment with the strides made in miniaturization through microfluidics (examples include lab-on-a-chip and micro total analysis systems - μTAS), the potential remains significant for developing portable analytical instruments by applying downscaled conventional technologies. Frequently cited benefits of these compact systems include enhanced portability, facilitating on-site monitoring, decreased expenses associated with equipment, disposability options for some applications, reduced sample volume needs, expedited analysis times, and simplified generation of substantial electric fields [40]. An effectively engineered portable device must possess a compact and durable design, capable of running on battery power for extended periods without requiring frequent recharging. Additionally, it should be lightweight and have compact dimensions to facilitate effortless transport by a single individual.

CE is particularly suitable for portability due to its minimal requirements, which include only a separation capillary, a high voltage (HV) power supply, and small solution volumes, to conduct the separation [66]. CE has extensive applications across diverse sectors like water quality evaluation, drug research and quality assurance, proteomics and DNA examination, counter-terrorism (identifying explosive substances), and corrosion tracking. Nevertheless, it is often limited to laboratory use due to its demand for high electric fields, sensitive detection mechanisms, and fluidic control systems. For addressing these issues, CE-based sensors have caught much attention toward miniaturized or portable sensors recently. The drive for miniaturizing CE arises from two primary motives: to enhance the portability of CE analysis; and to facilitate the creation of point-of-care and lab-on-a-chip devices. The

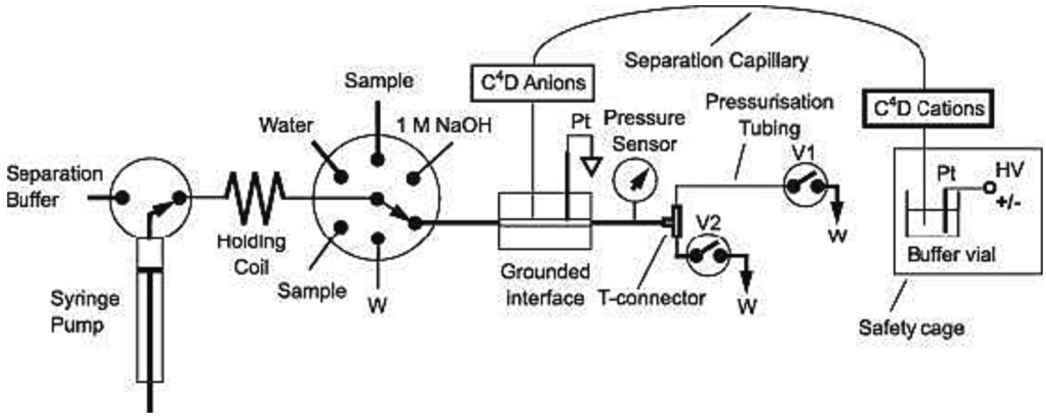

Fig. 5. Schematic drawing of the SIA-CE-C4D-system with dual contactless conductivity detectors for concurrent separation of cations and anions. C4D: contactless conductivity detector; HV: high-voltage power supply; W: waste; and V1, V2: stop valves Reproduced with permission from Elsevier [64].

objectives of both endeavours are centred around expanding the convenience and usefulness of CE analysis [40]. There are two primary approaches to developing these portable CE systems: one involves the utilization of shortened capillaries, while the other employs chip-based micromanufacturing techniques. The shortened capillary strategy involves using a shortened capillary column for the separation. The distance required for separation is reduced, by reducing the capillary length, resulting in faster analysis times. This approach is mainly beneficial for applications where speed is crucial, such as point-of-care testing. On the other hand, Chip-based micro manufacturing solutions involve integrating capillary electrophoresis components onto a microchip. These systems based on chips provide the benefit of being portable and can be seamlessly incorporated into smaller devices [40].

4.1. Non-chip portable CE

A non-chip portable CE system (pCE) is a compact CE setup in which the fluidic channel is not incorporated within a substrate. Instead, a capillary tube is used. pCE systems offer distinct benefits, particularly due to the straightforward cylindrical structure of the CE capillary, the optimal volume-to-surface ratio it provides, the absence of chip design and fabrication requirements, the cost-effectiveness of capillaries compared to chips, and the enhanced performance achievable with certain detection methods [66]. Furthermore, additional procedures for cleaning and preparation have been developed, and the material constituting the channel walls remains uniform. Fused silica capillaries are recognized for their durability and extensively documented characteristics. However, securing consistent, accurate, and reliable sample injections poses a notable challenge for pCE systems [40]. Overall, the development of a pCE system centred on the characteristics highlighted in Fig. 6.

In 1998, Kappes T. and Peter C. Hauser [67] introduced a significant early example of a portable pCE system. This system is encased within a PVC housing measuring 340 × 3175 × 3175 mm, with a total weight of 7.5 kg. The key factor contributing to weight reduction was the inclusion of two 12 V DC lead-acid batteries. Depending on the particular sample under analysis, the instrument utilized a capillary with a length of either 72 cm or 90 cm. The implementation of narrow capillaries with a 25μm inner diameter constrained the flow of electrophoretic current, resulting in a 5-h charge duration for the lead-acid batteries. The detection method employed was potentiometric. This pioneering instrument served as a cornerstone for extensive research in the field of portable pCE systems. One challenge faced by portable CE systems is detection. Optical detection methods can only be applied using nonstandard light sources like light-emitting diodes (LEDs) or laser diodes due to the substantial power demands of conventional UV or visible sources. These nonstandard sources are not well-suited for non-light-absorbing inorganic or organic ions. In contrast, electrochemical detection methods are more suitable for portable CE systems. Their entirely electronic setup can be readily miniaturized and adapted into a compact, low-power format [68]. Among the various forms of electrochemical detection methods, capacitively coupled contactless conductivity detection (C^4D) holds significant appeal. This method is mainly attractive due to its universal applicability to all ionic species, including the non-active in UV/vis range [69,70]. Kappes, Thomas, et al. [71] introduced contactless conductivity detection in pCE, followed by an upgraded detector version by Kuban, Pavel, et al. [72]. Over the following decade, portable CE instruments have witnessed a range of improvements and design innovations.

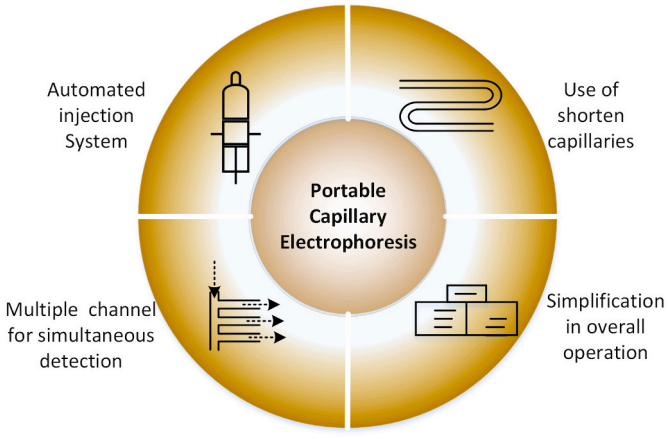

Fig. 6. The characteristics that influenced the development of the pCE system.

The existing drawbacks observed in the researched field-portable CE systems were centred around their injection mechanisms. These mechanisms required typically exhibited fragility, necessitating cautious manual handling. There was a clear need for a durable and automated injection system to make these instruments feasible for regular application in field analysis. In response to this challenge, Mai, Thanh Duc et al. [68] developed a novel portable capillary electrophoresis device. This innovative instrument incorporated an automated injection system that employed sturdy valve-based mechanisms. This enhancement in the injection mechanism was anticipated to enhance the dependability and user-friendliness of the portable CE instrument, making it more suitable for routine field analysis. The instrument possessed a compact configuration, with all components neatly arranged within a briefcase measuring 45 × 35 × 15 cm (width × depth × height) and weighing approximately 8 kg. It was capable of continuous operation for up to 9 h when powered by batteries. Simultaneously separating anionic and cationic species in capillary electrophoresis (CE) is advantageous for significantly improving analytical efficiency. However, using a common buffer isn't always optimal. A portable triple-channel CE system was developed in 2016 [73] to address this problem. This innovation allows for the concurrent separation of three distinct analytes through parallel channels. By employing separate background electrolytes, individual optimization becomes feasible. The instrument was characterized by its compact design, housing all components within a briefcase that measures 45 cm in width, 35 cm in depth, and 15 cm in height, with a weight of approximately 15 kg. When utilizing a single electrophoresis channel, it could operate continuously for 8 h in battery-powered mode. While simultaneous use of three channels, the operational duration was around 2.5 h. Furthermore, M. Zang et al. [74] presented an affordable portable CE (pCE) apparatus, featuring an automated sampling interface, intended for monitoring of metal ions. The limits of detection for Co(II), Cu (II), and Zn(II) were measured at 0.46 *mu*M, 1.14 *mu*M, and 0.58 *mu*M, respectively. The viability of on-site metal testing was demonstrated through field measurements of Zn(II) in western Tasmania. The device underwent a continuous operation test in the laboratory for up to 3 months. The apparatus was constructed using miniature peristaltic pumps and valves, with hydrodynamic injection executed at precise intervals in the pump cycle. The portable instrument, with dimensions of 21 cm × 10 cm × 7 cm, was powered through the USB port of a laptop computer and assembled using off-the-shelf components that amounted to approximately USD 1200 in cost. While the study served as a proof-of-concept, aspects like temperature and humidity effects were not investigated. Temperature variations could influence migration time and derivatization processes. Consequently, efficient temperature control for the system is imperative, ensuring both accurate and energy-conscious operation.

The majority of proposed designs for portable CE instruments still necessitate the expertise of a trained analytical chemist to operate and maintain the device. Simplification of their operation is crucial to ensure ease of use for non-experts. Conversely, for an instrument to be effectively portable and applicable in the field or at point-of-care settings, it must possess robustness. Taking this into consideration, a recent development by Kaljurand, Mihkel, et al. [76] introduced a compact and

affordable sampling device for portable capillary electrophoresis. This device aims to monitor common inorganic ions in drinking water samples. The sampling apparatus utilizes peristaltic and vacuum pumps, a check valve, and a pinch valve. The pCE devices are summarised briefly in Table 1.

4.2. Microchip-based CE

Microchip-based CE (M-CE) involves fabricating tiny devices that integrate all the necessary components for electrophoresis onto a single chip or substrate. These devices often include microchannels, sample injection ports, electrodes, and detection regions. Over the past three decades, microchip capillary electrophoresis has experienced significant advancements since its inception. This approach to CE on microchips provides several advantages, including rapid analysis times, minimal utilization of samples and electrolytes, and reduced waste production. Additionally, the integration of multiple analytical steps within a single device streamlines the analysis process and reduces the risk of sample contamination. Nonetheless, it comes with certain drawbacks, such as the substantial expenses associated with microchips and equipment, specific operational prerequisites, limited automation, and a lack of resilience [77]. However, it has demonstrated its efficacy in examining a wide array of substances across a spectrum of sample complexities, spanning from straightforward samples like water to intricate biological fluids [78]. The predominant range of applications primarily revolves around the isolation of various inorganic cations such as NH_4^+, K^+, Ca^{2+}, Na^+, Mg^{2+}, Li^+, inorganic anions including Cl^-, NO_3^-, $SO4^{2-}$ (alongside Br^-, NO_2^-, F^-), and small-sized organic acids like oxalate, formate, malate, citrate, succinate, pyruvate, acetate, and lactate. These target substances are quantified within water samples as well as diverse varieties of alcoholic beverages and soft drinks [79]. Furthermore, the analysis encompasses both organic and inorganic compounds, including the determination of heavy metals.

M-CE involves conducting analyses on thin solid plates known as microchips. These microchips typically have an area of several square centimeters. They are made of materials such as glass, quartz, or various types of plastics like polymethylmethacrylate (PMMA), PEEK, polycarbonate (PC), and PDMS (polydimethylsiloxane) [80,81]. In the initial phase of M-CE device development, the commonly used chip materials were glass and quartz substrates due to their exceptional EOF, optical transparency, and compatibility with silicon chemistry similar to fused silica capillaries. However, the fabrication process for these glass chips, involving photolithography and wet-etching techniques, is characterized by its high cost, time-intensive nature, and dependence on labour-intensive procedures. Moreover, the fabrication process of glass chips demands access to advanced clean room facilities and specialized equipment. Recently microchips constructed from polymers have experienced a surge in popularity, primarily as they offer a range of inherent benefits. These advantages include lower costs, relatively simple fabrication infrastructure and techniques, and simplified microchannel design processes [82]. The microchannel systems are made on the surface of the plate with diameters of several tens of micrometres. These channels are created using techniques like soft lithography or laser ablation. It includes inlets and outlets for sample and buffer solution [83,84] as shown in Fig. 7. The channels are then sealed from the top using a thin cover lid, creating a microfluidic network [79]. The production of polyester toner microchips has been described through a direct printing technique executed on a laser printer [85]. An M-CE device build-up in low-temperature co-fired ceramics (LTCC) multilayer technology has also been presented for the analysis of major inorganic ions in water samples in less than 80 s [86]. In a separate study, Masár, Marián, et al. [87] investigated the potential use of PMMA-based microchip for M-CE.

M-CE involves performing a series of analytical operations within this microfluidic network. The main operations include sample injection, electrophoretic separation, and detection. The first step involves introducing the sample to be analyzed into the separation channel. Microfluidic channels cannot be physically manipulated in the same way as conventional CE. Consequently, new injection protocols needed to be developed for M-CE. Gated injection and cross injection are two common types of injection used in M-CE [88]. In gated injection, a flow boundary is established between two solutions—the mobile phase and the sample solution—at the intersection of multiple channels. There is no significant mixing of solutions at this intersection due to the short interaction time, which minimizes diffusion, while the flow regime remains laminar. At a specific time point, the voltage is turned off in the mobile phase channel, allowing the sample solution to be injected into the separation channel. After a designated period of time, the voltage to the mobile phase reservoir is restored, defining the injection plug. However, gated injection tends to bias sample injection toward cations over anions due to their higher mobility under normal flow conditions. Cross injection, although more complex, avoids introducing bias during injection. In the cross-injection technique, the sample solution is directed across the separation channel utilizing two side channels. Subsequently, after a predetermined time interval, the voltage is altered to guide the flow down the separation channel. The size of the injected sample plug is determined by the volume at the point where the channels intersect. In order to prevent any inadvertent leakage into the separation channel throughout the analysis, minor “push back” voltages are implemented to the side channels during the separation process. An additional advantage associated with cross-injection is its capability to precisely determine the volume of the injection plug using double-T injectors. In these injectors, the two side channels are deliberately positioned at a fixed distance from being directly opposite each other. This design leads to a scenario during injection where the larger volume intersection becomes occupied by the sample, thereby resulting in an amplified injected volume. Following sample injection, an electric field is applied across the microchip’s channels to induce electrophoretic separation of ions contained within the sample. Separations in M-CE occur in a similar manner to conventional CE separations. Capillary zone electrophoresis, MEKC, CEC, CGE, and CIEF have all been used to achieve the expected separation [88].

As the separated ions migrate through the channels, they can be

Table 1
The summary of pCE devices.

Detection method	Analyte	LOD	Instrument Size(cm)	Capillary Size Length, Dia. cm,μM	Ref
Optical	Heavy Metals Co (II),Cu(II), and Zn(II)	0.46, 1.14, and 0.58μM	21X10X7	25 to 40, 10–50 ID	[74]
Potentiometric	Inorganic ions (K^+, Na^+, and Mg^{2+})	0.49, 0.41, and 0.35	34 × 317.5 × 317.5	72 to 90, 25 ID	[75]
C^4D	Inorganic ions (Nitrite)	Below 1	45X35X15	36 to 50, 50 ID	[68]
C^4D	Inorganic ions (Cl^-, Na^+, K^+, and Ca^{2+})	2, 2,2 and 1 mg/L		30, 75 ID	[76]
C^4D	Inorganic cations (NH_4^+,K^+, and Mn^{2+})	3, 3, and 1.5	45X35X15	44 to 60, 25 ID	[73]
	Inorganic Anions (Cl^-, NO_3^-, and SO_4^{2-})	0.995, 6, and 3.5			

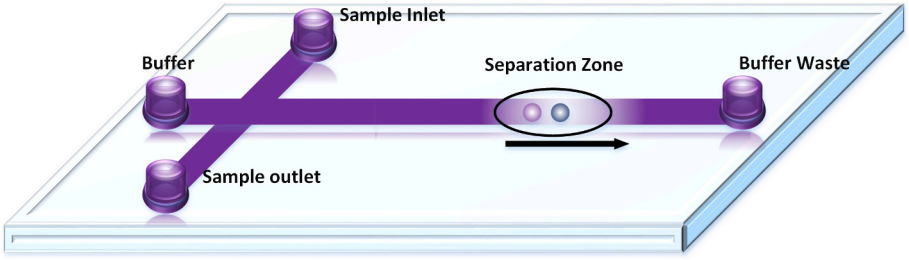

Fig. 7. Microchannel system.

detected using various methods. Common detection techniques include fluorescence, absorbance, or electrochemical detection. Fluorescence detection is the predominant optical detection technique employed in microchip analysis, attributed to its exceptional sensitivity and selectivity. Laser-induced fluorescence (LIF) is easily adapted to the dimensions of the microchips. The coherence and divergence of a laser beam enable precise focusing on extremely small detection volumes, resulting in high irradiation levels and subsequently, low detection limits. A microchip-based capillary electrophoresis system connected to a confocal laser-induced fluorescence (LIF) detector was successfully developed [89]. This integrated setup was designed for the measurement of heavy metals in environmental samples. An innovative fluorescent dye named RBPhOH, derived from rhodamine B through synthesis, was used within a glass microchip platform to achieve the specific and highly sensitive detection of copper. However, a notable drawback of LIF detection is the necessity for pre- or post-column derivatization with a fluorophore. Furthermore, the larger size and non-portable nature of most lasers in comparison to microchips limit their application, making them unsuitable for point-of-care testing scenarios. Infrared analysis proves effective for examining solid samples. However, it is unfit for fluidic systems as the samples are in solution. In such cases, the solvent's absorption can considerably saturate the IR signal [82]. The cost of traditional optical equipment, the frequent requirement for analysis derivatization, and the constrained portability of LIF have initiated considerable interest in electrochemical (EC) detection. This approach is viewed as a compelling alternative detection method when coupled with M-CE [35]. The enthusiasm for M-CE-EC detection has grown significantly due to the exceptional attributes that EC detection brings to M-CE like remarkable sensitivity, inherent miniaturization and portability, cost-effectiveness, low power demands, and seamless compatibility with microfabrication technologies [82,90]. Conductometry and amperometry represent the main electrochemical (EC) detection modes with CE and M-CE. Conductometry is categorized into two distinct types: contact conductivity and contactless conductivity. Conductometry is classified into two main types: contact conductivity and contactless conductivity. In contact conductivity detection, the detection electrodes are placed directly in touch with the electrolyte solution, utilizing configurations both at the end-column and on-column. Capacitively coupled contactless conductivity detection (C^4D) involves placing two flat detection electrodes outside the separation channel. This configuration offers distinct advantages over the contact mode, notably including a significant reduction in background noise and the prevention of bubble formation [82]. Different arrangements have been investigated for integrating C^4D with microchips. These investigations have resulted in different design approaches, which can be categorized based on how the electrodes are positioned. In an external type setup, the electrodes for C^4D are placed on a distinct support plate. This plate is affixed to the microchip, and the conductivity signal is detected using the microchip's cover lid. In the deposited type configuration, the planar electrodes are directly deposited onto the microchip's cover lid using vapour deposition techniques. In embedded-type design, miniature electrodes are employed and are incorporated directly into the microchip's material during its manufacturing process. These small-scale electrodes are situated alongside the separation channel, with one electrode on the left side and the other on the right. A thin insulating layer isolates them from the solution in the channel [91]. Additionally, a dual top–bottom C^4D configuration has also been detailed. This setup involves placing a pair of planar electrodes (one transmitting and one receiving) on the microchip from both the top and the bottom. This arrangement leads to approximately twice the sensitivity, as outlined by Mahabadi, Rodriguez et al. [92]. Tanyanyiwa, Jatisai, and Peter C. [75] evaluated the high-voltage approach for C^4D detection within the context of microfabricated planar electrophoresis devices. Their study demonstrated that raising the excitation voltage for C^4D on a microfabricated electrophoresis device resulted in a significantly enhanced signal intensity in inorganic ions detection. This improvement allowed for successful detection through a substantial cover and yielded heightened sensitivity when electrodes were positioned within troughs to achieve closer proximity to the separation channel. Whereas, Gertsch, Jana C., et al. [93] found that the increase in the field strength resulted in reduced analytical time. Furthermore, Liu, Benyan, et al. [94] reported the development of an M-CE system incorporating C^4D for rapid and simultaneous heavy metals detection. This method integrated a straightforward electrophoresis microchip design with an integrated detection circuitry based on a lock-in amplifier, effectively enabling the detection of various heavy metals. The system stands out for its simplicity, speed, high integration level, sensitivity, and cost-effectiveness. The outcomes highlight the effectiveness of microchip CE-C^4D as a compelling strategy for constructing a portable analytical tool that can promptly conduct on-site analyses of heavy metals. On the other hand, a microfluidic electrophoretic nutrient sensor focused on C^4D has been reported with the ability to effectively separate and quantify inorganic anions within small volumes (microlitre) of soil solution samples [95].

Apart from conductometric detection, amperometric detection (AD) can also be employed in conjunction with chip-based systems due to its improved selectivity and sensitivity. Lucas, Simone Bernardino, et al. [100] introduced the utilization of microelectrode-based amperometric detection (ME–AD) for quantifying nitrite in environmental water samples. The approach was developed using a commercially available and portable instrument that incorporates a potentiostat, a high-voltage power supply, and a microfluidic platform for assembling microelectrode (ME) devices with integrated electrodes. The practicality of this approach was demonstrated by successfully determining nitrite levels in water samples obtained from two distinct ecosystems, namely a small aquarium and a fish breeding dam. However, AD generally suffers from interferences caused by the CE separation voltage [82]. The M-CE devices are summarised briefly in Table 2.

Besides laboratory-made M-CE instruments, (M-CE) instruments, commercially available equipment can offer notable advantages. For example, eDAQ, a company based in Deninstone East, Australia, provides a microchip electrophoresis kit that includes an external (C^4D) detection cell, a high-voltage power supply with four channels mounted on a separate support, the chip platform and microchips with integrated electrodes from Micronit, a company based in Enschede, Netherlands.

Table 2
The summary of M-CE devices.

Detection method	Analyte	Microchip	LOD	Analysis time	Ref
C^4D	Inorganic ions K^+, Na^+, and Mg^{2+} Heavy Metals Mn^{2+}, Zn^{2+}, and Cr^{3+}	Glass	0.49, 0.41, and 0.35 μM	3 s	[75]
C^4D	Inorganic ions (K^+, Na^+, Ca^{2+} and Mg^{2+}	Ceramic	8, 13, 6 and 6 μM	<80s	[96]
C^4D	Inorganic ions (ClO_4^-)	PDMS	5.6 ± 1.7 ppb	within 60s	[93]
C^4D	Heavy Metals (Mn^{2+}, Pb^{2+}, Cd^{2+}, Co^{2+}, and Cu^{2+})	PMMA	0.7 to 5.4 μM	within 100 s	[94]
C^4D	Inorganic ions (nitrite, nitrate, chloride and sulfate)	Glass	2.0 and 4.9 μmol L^{-1}	within 60s	[97]
C^4D	Nitrate detection in Soil	PDMS	~ 7.25 μM	within 300 s	[95]
C^4D	phthenic acids in produced water	Glass	between 4.7 and 7.7 μmol L^{-1}	within 140 s	[98]
Amperometric detection	Heavy Metals ($Pb2^+$, $Cd2^+$, and $Cu2^+$)	PDMS	1.3, 3.3 and 7.4 μM	within 80s	[99]
Amperometric detection	Nitrate	Glass	1.3μmol L^{-1}	within 60s	[100]

Furthermore, the microfluidic-chipshop company offers an exceptionally compact electrophoresis system that enables label-free detection of small molecules using a (C^4D) detection scheme combined with a microchip featuring detection electrodes. This remarkably durable instrument, roughly the size of a cigar box, houses a bipolar high-voltage supply capable of separating both anions and cations, as well as a high-frequency detection circuit. It is conveniently operated through user-friendly software and draws power through its USB port. This integration of M-CE and C^4D remains widely employed in the field of environmental analysis. On the other hand, solutions from micruxfluidic Technologies company offer an automated, portable, and miniaturized microfluidic electrophoresis system that integrates a high-voltage power supply and biopotentiostat for detection. It supports high voltages up to ±3 kV and DC potentials up to ±2 V. The system is fully controlled by software and can be connected via Bluetooth or cable. It is compatible with microfluidic chip holders and microchip electrophoresis techniques. The microfluidic chip holder can be interfaced with external cables. The specifications of these instruments are detailed in Table 3.

4.3. Modular CE

Recently, a modular approach was introduced to facilitate more robust and suitable low-cost CE instruments. In this approach, readily available components, including a micro syringe pump, high-voltage power supply, pressure controllers, conductivity detector, and data acquisition device, were integrated into the breadboard [104]. The pressure regulators and high-voltage units were managed using an Arduino microcontroller board. Additionally, a Python script based on the open-source Instrumentino package was utilized to control and synchronize these individual modules. The incorporation of off-the-shelf modules and the configuration on a breadboard offered substantial flexibility, ease of modification, and cost-effectiveness for the CE instrument. The device exhibited the ability to operate in standard modes, including isotachophoresis and zone electrophoresis, while also accommodating specialized modes like gradient elution moving boundary. Furthermore, achieving full automation of the instrument was feasible [105].

Applying a similar methodology, Furter, Jasmine S. et al. [106] introduced a CE instrument built entirely from commercially accessible components, making it easy to reproduce. In this configuration, the authors employed electronic circuitry based on a ready-made Arduino microcontroller board. Liénard, Théo, et al. [107] developed an innovative instrumental design inspired by the concept of Lego toys. This approach facilitated the modular assembly of the complete CE instrument, including the modular LIF detector. Elena and Rudaz [108] presented a different method for DIY CE. They have recently introduced a novel instrument. Each separate part of this instrument is enclosed within a box that is shipped to the laboratory. At this point, the research personnel constructs the CE system, reminiscent of the process of assembling IKEA furniture. This strategy results in decreased CE costs overall, as researchers take charge of assembling the modular parts. As a result, this kind of CE system becomes more economically viable for a wider analytical community.

The key advantage of modular CE lies in its ability to enable users to create their analytical devices with a high degree of standardization, thus removing the necessity for them to have access to mechanical and electronic workshop facilities. The overall benefits of the three systems mentioned above are concisely presented in Table 4.

5. Discussion

CE is a powerful analytical technique used to separate and analyze molecules based on their size by applying an electric field within a capillary tube. The capillary tube, which is often made of fused silica, is very narrow (typically around 25–100 μm in diameter) and acts as the separation column. The schematic diagram (Fig. 8) explains the sequential stages involved in the operation of CE. The sample containing different molecules is introduced into one end of the capillary. An electric field is applied across the capillary, creating a potential difference between the two ends. This causes charged molecules in the sample to migrate toward the oppositely charged electrode. The migration

Table 3
Specification of commercialized instruments.

Brand	Instrument	Platform	Dimensions (mm)	Interfacing	Detection	Ref
eDAQ	ER455 Microchip Electrophoresis	Separate for Detection HV supply	200x65x250 200x65x 250	I2C Bus	C^4D	[101]
microfluidic Chipshop	ChipGenie edition E2	Same for Detection, HV supply & Microchip holder	Size of cigar box	USB port	C^4D	[102]
micrux Technologies	HVstat Electrophoresis System	Same for Detection & HV supply	165x150x85	Serial RS232/ USB Adapter/ wireless (Bluetooth)	DC amperometric	[103]

Table 4
Overall advantages of the three systems.

Methods	Advantages
pCE	The simple cylindrical design of the CE capillary offers optimal volume-to-surface ratio, Cost-effectiveness due to the absence of chip fabrication methods
M-CE	Rapid analysis times, The use of samples and electrolytes is minimized, leading to reduced waste generation, Incorporating various analytical steps into a single device simplifies the analysis process and lowers the chances of sample contamination
Modular CE	Users can make their own analytical devices with a significant level of standardization, Mechanical and electronic workshop facilities are not required.

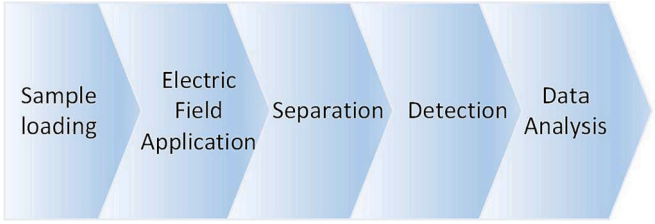

Fig. 8. Steps involved in CE operation.

speed is determined by the charge and size of the molecules. As the molecules migrate through the capillary, they experience varying resistance levels due to their size and charge. Smaller and more highly charged molecules move faster through the capillary, while larger and less charged molecules move slower. As the molecules separate, they pass a detection point. Different detection methods can be used, such as optical, fluorescence, or electrochemical. By analyzing the time at which each molecule reaches the detection point, their concentration and separation can be determined. The collected data, often in the form of chromatograms, can be analyzed to determine the composition of the sample and the quantity of each separated molecule. Fig. 8 illustrates the procedures associated with the operation of consumer electronics. CE offers several advantages, including high separation efficiency, rapid analysis times, small sample requirements, and compatibility with various detection methods along with simplicity, affordability, flexibility of design and robustness based on the ultimately simple geometry. It is commonly used in biochemistry, molecular biology, pharmaceutical research, environmental analysis, and more. In environmental monitoring, it can detect the level of heavy metals, and organic and inorganic ions.

Throughout its evolution, capillary electrophoresis has undergone transformative changes, making it a versatile and powerful analytical technique with diverse applications across scientific disciplines. Particularly, the process of miniaturization in CE has played a pivotal role in this transformation. Miniaturization of CE refers to the practice of reducing the dimensions of the analytical system, including the capillary tube and associated components, to create more compact and efficient CE platforms. The reduced size leads to lower consumption of reagents and samples, faster analysis times, and improved separation efficiency. The concept of miniaturization can be classified into two main categories: non-chip-based portable CE and microchip-based CE. Non-chip-based portable CE involves the utilization of shortened capillaries, along with miniaturized pumps and valves. On the other hand, microchip-based CE integrates the separation channel directly within the microchip itself. Microchip-based CE is often favoured for its miniaturization and automation capabilities, while non-chip-based portable CE offers versatility and compatibility with existing equipment. The distinction between the two approaches is briefly outlined in the Table 5.

Commercialization has indeed made significant progress in the field

Table 5
Differences between pCE and M-CE.

Features	pCE	M-CE
Fluidic channel	Capillary tube	Inbuilt
Channel length	In centimeters range	In millimeters range
Cost involved in	Pumps,Valves,injection system	Micro chip fabrication
Voltage requirement	Above 15 kV	Below 15 kV
Weight of system	Above 2 kg	Below 2 kg

of microchip electrophoresis (M-CE). However, it's worth noting that there is a lack of fully-commercial portable CE instruments currently accessible in the market. Nevertheless, numerous in-house-designed P-CE instruments have been documented, underscoring the importance of research into portable CE systems. While designing a pCE system, it is essential to take into account the following aspects:

1. System Size and Weight:The system should be compact and lightweight, ideally fitting within the palm of a hand and weighing less than a few kilograms. The size and weight of components like power supplies, detectors, and pumps should be considered.
2. Power Supply Lifetime: The necessary power supply lifetime should be determined based on the specific application, whether it involves field measurements or in-situ monitoring. In the case of field measurements, it's acceptable to accommodate daily battery changes or charging. Conversely, for in-situ monitoring, longer lifetimes on the order of weeks become essential.
3. Automation:To achieve user-friendly operation and minimize manual intervention, the system should be autonomous at various stages:

   (a) Sample Injection: The use of an autosampler enables the automation of sample injection.
   (b) Pumping: Programmable syringe pumps or microfluidic pumps to control the flow of samples and buffers can be used to manage the flow of samples and buffers.
   (c) Cleaning: Cleaning: Automated cleaning procedures to maintain system integrity can be incorporated.
   (d) Operation: This involves developing software controls and algorithms for the automatic execution of CE separations, encompassing voltage and temperature control.
   (e) Analysis: Implementation of automated data analysis and reporting features to provide users with results without manual data processing can be included.

4. Buffer and Sample Preparation: Consider integrating a buffering system with minimal/no sample preparation.

When designing a M-CE system, it's important to consider the following areas:

1. Channel Dimensions: The appropriate dimensions of the microfluidic channels, including width, depth, and length, should be determined to achieve the desired separation performance and sample throughput.
2. Microfluidic chip material: Suitable materials for constructing the microfluidic device should be selected by considering factors such as chemical compatibility, transparency (for optical detection), and ease of fabrication.
3. Channel path shape: The channel path geometry should be designed to optimize separation efficiency and minimize band broadening.
4. Sample Loading: It's essential to employ a precise and controlled sample injection method customized to these systems. This can involve techniques like gated injection or cross-injection.
5. Detector method and placement: Choosing the appropriate detection method (e.g., optical, electrochemical, or conductivity) for specific analytes and determining the optimal location within the

microfluidic channel for the detector are crucial to ensure high sensitivity and selectivity.
6. Electric field generation is another important factor to take into account.

In general, the ease of the flow process and the presence of suitable, scaled-down detectors are driving the increased favour for developing portable and miniaturized capillary electrophoresis devices. Particularly, detectors such as C^4D, amperometric, and LIF can be readily resized and operated using battery power. Remarkably, a significant number of research investigations have been carried out utilizing C^4D. This detection method could be the favouredd choice for both pCE and M-CE due to its minimal power consumption, potential for downsizing, remarkable adaptability, and straightforward assembly and use. Moreover, C^4D facilitates the utilization of narrow capillaries, which typically leads to improved separation efficiencies.

The overall reduction in size of CE results in a range of benefits, including:

- Miniaturization significantly reduces the volume of samples and reagents required for analysis, which is especially valuable when dealing with limited or expensive samples.
- The small dimensions of microchip devices allow for shorter migration distances, resulting in faster separations and analyses.
- The reduced dimensions can lead to improved separation efficiency due to minimized dispersion effects and enhanced heat dissipation.
- Multiple channels or separation lanes can be integrated on a single microchip, enabling high-throughput analysis of multiple samples simultaneously.

However, this approach presents several challenges:

- Integrating various components (injection, separation, detection) onto a single microchip while maintaining functionality can be complex.
- Precise sample loading and injection are challenging due to the small dimensions of microchannels.
- Achieving high sensitivity in detection methods integrated with microchips can be difficult.

A concise overview of the advantages and challenges related to the miniaturization process of CE are highlighted in Table 6.

Currently, researchers are exploring the potential of utilizing a modular approach in the field of CE. This method of modular construction offers a significant advantage in simplifying the creation of CE devices and cutting down on their overall costs. In the years ahead, this approach could be especially attractive to individuals who wish to understand the core principles of CE but lack the necessary skills to construct a complete instrument. It could also benefit laboratories with limited budgets. However, it's important to note that modular CE systems transfer some of the construction responsibility to the user, resulting in instruments that are less convenient (as they involve manual steps) and less flexible (due to a more limited choice of detectors) [106]. As these progressions continue to evolve, the significance of mobile phones and their software applications is predicted to play a role in the future development of real-time point-of-care CE. Furthermore, the open-source paradigm is expected to gain greater prominence, allowing a wide-ranging scientific community to actively participate in advancing this captivating separation technique.

6. Conclusion

The availability of high-quality miniaturized devices is essential for advancing the field of environmental analysis. Significant progress has been made in instrumental analysis, particularly in the domains of detection and separation. The evolution of compact and real-time capillary electrophoresis devices holds immense promise and is expected to continue in the years ahead. This trajectory aligns seamlessly with the ongoing trends in miniaturization and the continuous technological advancements in electronics, optics, and mobile technology. Ultimately, the development of software for mobile platforms, leveraging the existing capabilities of smartphones, and the integration of machine learning will also wield a substantial influence on shaping the future of point-of-care CE devices, particularly within the realm of environmental analysis.

Table 6
Advantages and challenges of CE miniaturization.

Advantage
Reduced sample and reagent consumption
Rapid analysis
Enhanced separation efficiency
High throughput
Challenges
Integration of all components
Precise sample loading
Detection sensitivity

CRediT authorship contribution statement

Swapna A. Jaywant: Conceptualization, Investigation, Methodology, Visualization, Writing – original draft. **Harshpreet Singh:** Conceptualization, Investigation, Methodology, Writing – original draft. **Khalid Mahmood Arif:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Visualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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