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Review

Recent advances of capillary electrophoresis-mass spectrometry instrumentation and methodology

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ABSTRACT

Capillary electrophoresis-mass spectrometry (CE-MS) is a powerful separation and analytical technique in the field of analytical chemistry. This review provides an update of instrumentation developments in the methodology of CE-MS systems. A selection of relevant articles covers the literatures published from Jan. 2013 to Feb. 2017. Special attentions were paid to the sample injection and ionization processes. Applications of these CE-MS systems were also introduced through representative examples. General conclusions and perspectives were given at the last.

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1. Introduction

In the field of analytical chemistry, especially in bioanalysis, the complex sample system requests an effective separation technique. Compared with gas and liquid chromatography, capillary electrophoresis (CE) is increasingly used in routine analysis due to its rapid separation speed, high resolving power, small sample volume consumption and flexibility in choosing separation modes. However, the limitations of CE are also obvious such as its low sensitivity caused by the nanoliter sample introduction. Coupling CE with mass spectrometry (MS) will significantly improve the limitation of detection. Furthermore, MS can provide the mass to charge ratio and structural information of an ion.

Several issues need to be overcome when combining CE with MS, specifically the interfacing techniques and the selection of a proper separation methodology. A series of review articles on similar topics were given by Kleparnik [1,2]. Commercially available interfaces, such as electrospray ionization (ESI) and inductively coupled plasma (ICP) interfaces, are widely used in CE-MS systems nowadays. The matrix assisted laser desorption ionization (MALDI) interface usually combines CE-MS with an off-line mode, and some other ambient ionization interfaces have also been reported in recent years. The use of microfluidic devices makes a breakthrough as an interface of CE-MS, and a number of CE separation modes have been successfully combined with various mass spectrometers, such as capillary zone electrophoresis (CZE), capillary gel electrophoresis (CGE), capillary isotachophoresis (CITP), capillary isoeletric focusing (CIEF), capillary electronchromatography (CEC), micellar electrokinetic chromatography (MEKC), nonaqueous capillary electrophoresis (NACE), etc. With unique features (such as mixture, reaction, and separation), the procedure of sample injection, treatment, separation, and ionization can be integrated on a chip. Another trend is the improvement of sampling and injection method, which is closely related with analysis objectives. An efficient, micro-volume, robotized sample injection method is suitable for single cell analysis, while a high throughput and repeatability sample injection method is necessary for the bio-omics analysis and rapid detection. Online sample treatment and enrichment, coating technologies are increasingly applied in CE-MS systems. Applications of CE-MS have been ranging from small inorganic ions to complex biomolecules. A considerable amount of reviews were published on bio-omics research [3–5] (such as proteomics [6] and metabolomics [7–10]), biomarker [11,12] and clinical [12–15] applications. Thus applications of CE-MS will not be emphasized in this paper.

This paper focuses on the recent instrumentation and methodology developments of CE-MS systems. More than 1000 hits were retrieved by the keyword “CE-MS” in Web of Science in

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years between 2013 and 2017; and papers were selected; which covers the topic of injection modes; ionization interfaces and CE separation modes. The latest analytical applications were briefly introduced and classified based on the usage of different mass spectrometers.

2. Development of capillary electrophoresis-mass spectrometry interfacing techniques

2.1. Sampling/injection interfaces

An efficient and reproducible sample injection interface is the precondition ensuring the performance of CE separation. Two main driving modes of CE injection are electrokinetic and hydrodynamic injection. In order to improve the quantitation accuracy, sensitivity and resolution of CE separation, a number of injection methods were applied in CE-MS systems and some new injection interfaces were also developed.

Electrokinetic sample injection is one of the most widely used injection modes in CE-MS. Both electrophoretic migration of charged sample ions and electroosmotic flow of the sample solution provide the injection driving force while the sample charge discrimination is inevitable. Device improvements are usually focusing on target analyte enrichment. Wang *et al.* proposed a preconcentration approach for CE-MS using the counterflow-assisted electrokinetic injection [16]. The interface assembled by a polydimethylsiloxane (PDMS) microfluidic device, which provided liquid-film electrical conduction as shown in Fig. 1a. A hydrodynamic counterflow was introduced into the separation capillary to retard the stacking boundary and achieve a long injection time. Using the dynamic coated technique, system sensitivity was improved by 750–1480 for peptide samples. D'Ulivo *et al.* expanded the applicability of pressure-assisted electrokinetic injection (PAEKI) to online pre-concentrated positively charged analytes [17]. L-Arginine, L-lysine, and imidazole were analyzed by CZE-Q-TOF and a limit of detection (LOD) of 18–28 pg/mL was obtained. Park *et al.* developed another sampling and injection interface, which couples ambient pulsed mid-IR laser into the CE-ESI–MS system (as shown in Fig. 1b) [18]. Samples were ablated by the IR laser and captured instantly in the sampling solvent, then injected into a separation capillary by electrokinetic injection. A mixture of peptide and protein standards was separated and analyzed by this system. The author suggested that the interface has potential applications in MS imaging as well as rapid sample analysis.

Hydrodynamic sample injection could be classified by the driving force, such as gravity flow, pressure and vacuum injection. With hydrodynamic sample injection, sample charge discrimination could be eliminated. Under automatic operations, sample injection volume can be accurately controlled with high repeatability. Wang *et al.* reported a hydrodynamic flow assisted double junction CE-MS interface to alleviate signal suppression resulting from nonvolatile positive ion additives [19]. A 20-fold signal enhancement for triazines was obtained. Kelly *et al.* introduced a pneumatic microvalve-based hydrodynamic sample injection system to achieve high-throughput and quantitative [20]. A three-layer PDMS microchip was used to achieve high injection repeatability (Fig. 1c), and a mixture of peptide standards was tested by the CE-nano-ESI-QqQ-MS. Similar effects have been achieved by Kuehnbaum and his coworkers, in which they proposed a multi-segment injection (MSI) technique based on the hydrodynamic injection [21,22]. Injection of discrete sample segments in a series can be achieved within a single capillary. Detected by TOF-MS, high throughput metabolic analysis was performed. To minimize the sample injection volume, Matysik *et al.* demonstrated the concept of capillary batch injection (CBI) [23]. Consisting of a microcontroller, a micropump and micro-syringes, the improved CBI cell (as illustrated in Fig. 1d) could remove an ultra-small sample volume (about 500 pL) into the separation capillaries with an efficiency of ~100% [24]. The cyclic nucleotide (cGMP) in human urine samples was detected by the CBI-CE-TOF-MS.

Field amplified sample injection (FASI) is a traditional on-line preconcentration technique in CE field. When applying a high voltage, a large amount of sample ions in the lower ionic strength buffer will transfer into the higher ionic strength buffer filled in the separation capillary. Martinez-Villalba *et al.* used the FASI-CZE-IT-MS equipment to analyze the amprolium residues in egg samples and a LOD of 75 μg/kg was achieved with optimized parameters [25]. Cheng *et al.* developed a microchip electrophoresis-

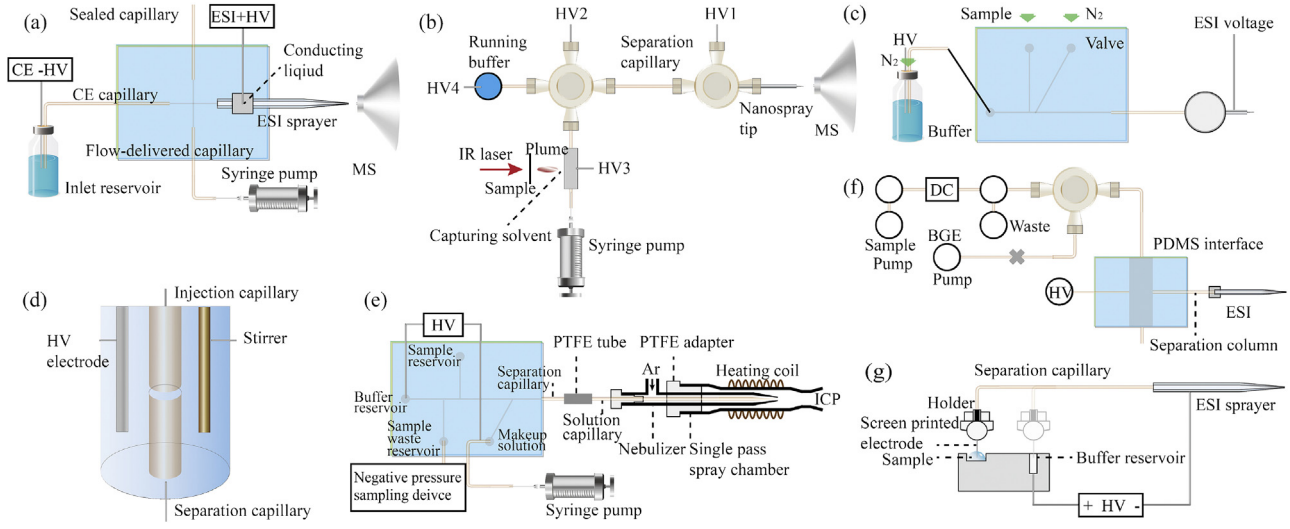


Fig. 1. Injection interface designs. (a) the counterflow-assisted electrokinetic injection device schematic diagram reported in ref [16]; (b) ambient laser ablation sampling device schematic diagram reported in ref [18]; (c) pneumatic microvalve-based hydrodynamic injection device schematic diagram reported in ref [20]; (d) capillary batch injection device schematic diagram reported in ref [24]; (e) field-amplified sample injection microchip electrophoresis device schematic diagram reported in ref [26]; (f) field-amplified sample-stacking device schematic diagram reported in ref [28]; (g) electrochemically assisted injection device schematic diagram reported in ref [32].

inductively coupled plasma-mass spectrometry (MCE-ICP-MS) system coupled with the FASI technique to analyze the bromine speciation in bread samples (as shown in Fig. 1e) [26]. A three-step experimental procedure was optimized to achieve sample enrichment (more than 12 times) and rapid separation (35 s). Similar techniques such as field-amplified stacking, field-amplified sweeping, and transient isotachophoresis (tITP) can enhance sample loading volume as well as detection sensitivity. He *et al.* reported field-amplified sample-stacking (FASS) method combined with CE-ESI–MS to on-line enrich and detect four beta(2)-agonists in human urine samples [27]. Hung *et al.* proposed a strategy based on FASS-CE-ESI–MS/MS to analyze haloacetic acids (HAAs) in tap water samples [28], as shown in Fig. 1f. Four HAAs were detected at ppb level with 300- to 1400-fold signal improvements. Ito *et al.* utilized the high-sensitivity CE-ESI-Q-TOF to characterize four kinds of pyridylaminated (PA) oligosaccharides [29]. A LOD of 25 amol/μL was obtained by using the head-column field amplified sample stacking (HC-FASS), which is a sheathless ionization interface and narrow mass range repeated high-speed switching technique. Wuethrich *et al.* reported an approach of field-enhanced sample injection-micelle-to-solvent stacking to improve sensitivity of CZE-ESI–MS, and eight penicillins and sulfonamides were detected with LODs from 0.11 to 0.55 ng/mL [30].

Electrochemically assisted injection (EAI) is a new sample injection concept for CE, which enables neutral analytes being charged by an electrochemical conversion during the injection process. Matysik's group developed a fully automated EAI injection device to enhance the performance of CE-MS, and applied to study the reduction of 4-nitrotoluene (4-NT) [31]. Three different carbon-based screen-printed electrodes (SPEs) were compared. In a later research, the fully automated EAI-CE-MS system was used to simulate the oxidative stress and DNA mutationsand (Fig. 1g) [32]. The oxidation products of targets were generated electrochemically, separated by CE, and detected by ESI-TOF-MS.

2.2. Ionization interfaces

Analytes were first transferred from liquid phase to gas phase and then ionized by an ionization interface. Some commercial interfaces are available in hybrid CE-MS instruments, such as ESI and ICP interfaces. On the other hand, new ionization interfaces are being developed for methodology improvement. Two main ionization interfaces were sheath-flow and sheathless devices. Sheath-flow interface can be divided into coaxial sheath flow and liquid junction. The performance of a CE-MS system depends largely on a robust and efficient ionization interface. Lindenburg *et al.* introduced the developments in interface designs for CE-MS and the applications in proteomics and metabolomics [4]. Jarvas *et al.* reviewed the computer modeling and simulation technologies for CE-ESI–MS interface designs [33].

As one of the most widely used CE-MS interface, the advances of (nano-)ESI were published in many articles. However, the compatibility of CE electrolytes with ESI solvent restrains the applications of ESI interfaces. Flow rate compatibility is another problem of ESI interface. Bonvin *et al.* reviewed the fundamental concepts and technical developments of CE-ESI–MS interfaces [34]. Some improvements in engineering also facilitate the use of CE-MS interface. Krenkova *et al.* reported a construction of self-aligning subatmospheric hybrid liquid junction electrospray interface for CE, which helps to eliminate the manual adjustment and improve the ion transport [35].

Sheath-flow interfaces have been popular since the early years of CE-MS applications. The eletrokinetically pumped nano-ESI devices reported by Dovichi's group was a typical automated sheath-flow interface. (see Section 3.1) Lindenburg *et al.* investigated the performance of the flow-through microvial (MV) assisted CE-MS interface for cationic metabolomics (Fig. 2a) [36]. A mixed sample comprising 45 cationic metabolites was tested. A three-time sensitivity improvement and five-time LOD reduction were obtained. Linhardt *et al.* demonstrated an electrokinetic pump-based sheath-flow ESI interface [37,38]. Reverse polarity CE separation was used to analysis of heparin oligosaccharides. Choi *et al.* reported a tapered-tip CE-nanoESI interface for MS [39]. A 260-zmol lower limit of detection for angiotensin II was obtained, and 217 different protein groups were detected using 1 ng mouse cortex digest protein.

With higher sensitivity, sheathless interfaces regain popularity in CE-MS. The porous tip sheathless interfaces were commercially available now. (see Section 3.1 Jeong *et al.* described a high

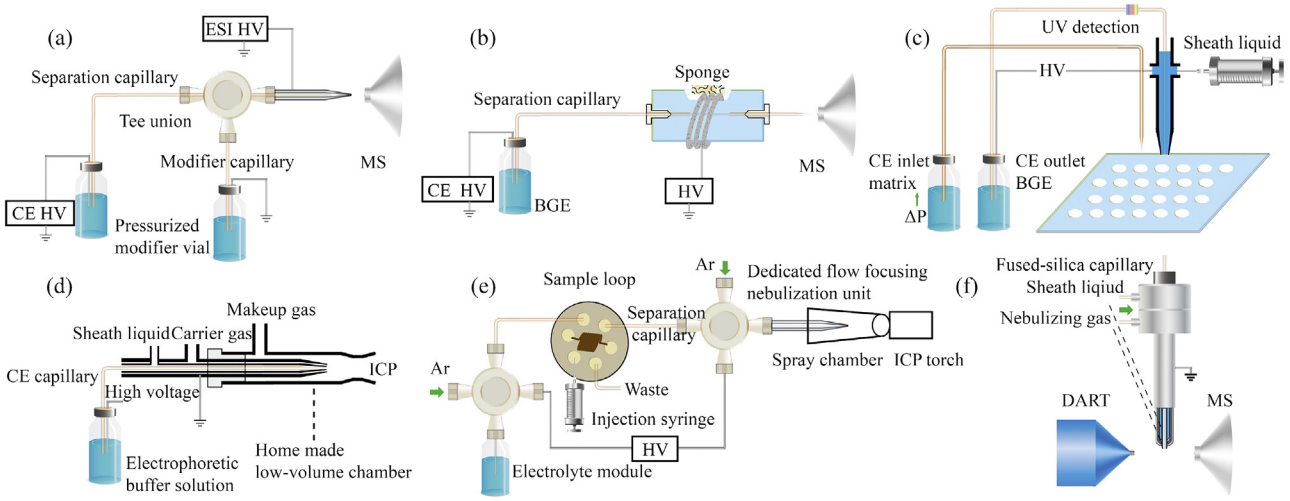


Fig. 2. Ionization interface designs. (a) the flow-through microvial assisted interface schematic diagram reported in ref [36]; (b) the sheathless ESI interface schematic diagram reported in ref [40]; (c) MALDI interface schematic diagram reported in ref [47]; (d) ICP interface schematic diagram reported in ref [53]; (e) flow focusing nebulization ICP interface schematic diagram reported in ref [55]; (f) DART interface schematic diagram reported in ref [72].

durability sheathless electrospray ionization interface based on an ionophore membrane-packed electro-conduction channel (Fig. 2b) [40]. Coupled with QqQ-MS, the interface was applied for the rapid determination of underivatized amino acids, phenylalanine and tyrosine extracted from a dried blood spot (DBS). Her's group developed a series of sheathless ESI interfaces for CE-MS [16,41,42]. Huang *et al.* constructed a two column sheathless CE-MS interface using a PDMS microdevice [41]. In a subsequent paper, Wang *et al.* developed a sheathless CE-MS interface using a robust PDMS membrane emitter and liquid-film electric conduction [42]. The utility of interfaces was demonstrated by the analysis of peptide mixtures. Tycova *et al.* explored an "interface-free" approach, where the CE-MS analysis was performed in narrow bore electrospray capillary [43,44]. The separation capillary and electrospray tip formed one entity and shared the same high voltage. Cytochrome C digest was analyzed by the system. Kammeijer *et al.* used dopant enriched nitrogen gas combined with sheathless ESI for glycopeptide analysis, and 25-fold higher sensitivities were obtained [45].

MALDI interfaces have better tolerance for separation background electrolyte (BGE) and frequently coupled with CE in an offline mode. In this way, mass spectra acquisition is not limited by the instrument scan rate. Zhong *et al.* reviewed the recent advances in CE coupling to ESI- and MALDI-MS [46]. Investigation trends are the automatic process control and separation/ionization compatible buffer. Biacchi *et al.* reported the instrumental development of the automated off-line CE-UV/MALDI-MS/MS with a homemade delivery matrix system (Fig. 2c) [47]. Five intact proteins and a tryptic digest mixture were tested to evaluate the method performance. Tomalova *et al.* developed an method, which couples CE separation to both MALDI and substrate-assisted laser desorption inductively coupled plasma (SALD ICP) mass spectrometry by using a liquid junction and subatmospheric deposition chamber [48]. CE fractions were extracted from a separation capillary and collected on a custom-built polyethylene terephthalate glycol (PETG) target plate coated with a 10-nm gold layer. A mixture of rabbit liver metallothionein isoforms was analyzed by the system. Springer *et al.* presented an approach for the determination of ciprofloxacin, norfloxacin and ofloxacin in milk samples by CE-MADLI-TOF-MS [49]. Chen *et al.* introduced a CE-MALDI-MS system with an interface consisting of a robot to drive the separation capillary and MALDI-MS target [50]. A compatible buffer was investigated and tested on protein and peptide samples.

CE interfaced with ICP-MS has been widely used in elemental analysis and commercial CE-ICP-MS interfaces were available. Timerbaev *et al.* reviewed the advances of speciation analysis by CE-MALDI-MS and CE-ICP-MS [51]. Device innovations are committed to improve nebulization and transport efficiency of the interface including nebulizer and spray chamber. Jiang's group reported an interface of CE-ICP-MS for the determination of ten arsenic compounds under optimized conditions [52]. In a following research, an improved interface with a novel direct-injection high-efficiency nebulizer (DIHEN) chamber was developed by Liu and coworkers (Fig. 2d) [53]. Six arsenic species and five selenium species were separated and determined within 9 min. Another method for the identification and accurate size characterization of nanoparticles (NPs) in complex media based on CE-ICP-MS was developed by the same group [54]. Kovachev *et al.* assembled a system for CE-ICP sample introduction with a dedicated flow focusing based nebulizer (Fig. 2e) [55]. The system was coupled to an inductively coupled plasma-optical emission spectrometer (ICP-OES) and a ICP-MS for Cr(III) and Cr(VI) speciation. The interfaces of CE-ESI–MS and CE-ICP-MS were

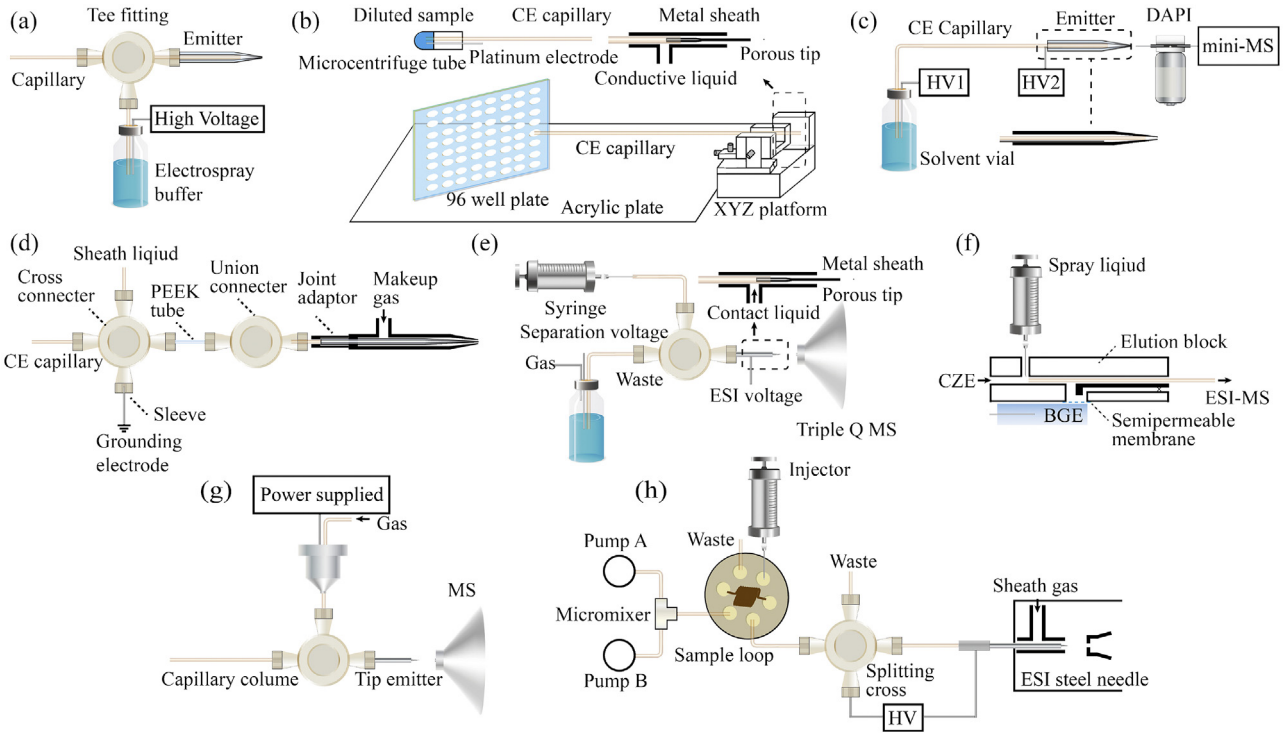


Fig. 3. Instrumental improvement to match CE modes. (a) electrokinetically pumped sheath flow interface schematic diagram reported in ref [82]; (b) UFCE-MS system schematic diagram reported in ref [89]; (c) miniature CE-MS system schematic diagram reported in ref [91]; (d) CGE-ICP-MS system schematic diagram reported in ref [106]; (e) CITP/CZE-QqQ-MS system schematic diagram reported in ref [107]; (f) CITP/CZE-MS/MS system schematic diagram reported in ref [112]; (g) CEC-MS system schematic diagram reported in ref [132]; (h) pressurized CEC-MS system schematic diagram reported in ref [133].

compared for the speciation analysis of free aluminum and aluminum fluoride complexes by Nakamoto *et al.* [56].

Sample pretreatment methods were also developed to improve the sensitivity and specificity of a CE-MS system. Qu *et al.* reported the development and optimization of CE-ICP-MS system for speciation and characterization of metallic nanoparticles in a dietary supplement [57]. In the next paper, they introduced a method for the quantification of common arsenic species in rice and rice cereal using CE-ICP-MS [58]. An enzyme-assisted water-phase microwave extraction procedure was used to increase the injection volume and enhance the signal response. Chen *et al.* utilized the ultrasonic-assisted extraction for the detection of trace Cr (VI), Cr(III), and chromium (III) picolinate (CrPic) in foods and the microwave-assisted extraction for the analysis of Pb^{2+}, trimethyl lead chloride (TML), and triethyl lead chloride (TEL) using CE-ICP-MS [59,60]. Yang *et al.* described a method for the quantification of labeled lysozyme based on the CE-ICP-MS [61]. Furthermore, several applications using CE-ICP-MS were published in the investigation for metal complexation behavior [62–64], metallomics for drug development [65–68], food safety [69,70], *etc.*

To improve the compatibility of CE separation modes, some ambient ionization techniques were applied in CE-MS. Cheng *et al.* used the atmospheric pressure chemical ionization (APCI) interface to connect the online pre-concentration CEC and MS [71]. This interface has high compatibility with non-volatile BGEs, and is more suitable for ionizing less polar compounds. Chang *et al.* developed a coaxial tip interface to realize the online coupling of CE with ambient direct analysis in real time mass spectrometry (DART-MS) as shown in Fig. 2f [72]. The setup can tolerate higher concentrations of detergents and salts. CZE and MEKC modes were achieved to the separation a mixture of 4-aminoantipyrine, zolmitriptan and quinine. The detection of endogenous caffeine in Chinese white tea was demonstrated using the system. Zhang *et al.* developed a CE-MS interface with dielectric barrier discharge ionization (DBDI), the mixture of metronidazole and acetaminophen solutions were separated as a proof-of-concept experiment [73].

3. Instrumental improvement to match capillary electrophoresis modes

The wide applications of capillary electrophoresis could be attributed to its various separation modes. Most CE modes are interchangeable by changing the composition of the background electrolyte and experimental procedures. However, the CE buffers in different modes may not be compatible with MS, due to the suppression of analyte ionization. Therefore, it is necessary to develop novel instrumentations to couple different separation methods with the different mass spectrometers.

3.1. Capillary zone electrophoresis (CZE)

CZE is the most commonly used separation mode in CE due to its simple operation, although only charged species can be separated in this mode. A single buffer solution is used in CZE, and the separation mechanism is based on the different electrophoretic mobilities of analytes which depend on their charge/mass ratios. Both porous tip interfaces and microfluidic devices based liquid junction interfaces are frequently used to couple CZE with MS. Pejchinovski *et al.* reviewed the clinical proteomics studies using CZE-MS [74].

Dovichi's group reported plenty of work on online CZE-MS analytical techniques [75–77], especially in the applications of proteomics research [78–86]. A series of electrokinetically pumped sheath flow nanoelectrospray interfaces to CZE-MS were developed by Dovichi's group, as depicted in Fig. 3a [80,82,85,87,88]. A review on CZE-ESI coupled with Orbitrap Velos and linear Q-trap mass spectrometers was given by Sun *et al.* [80]. Moini *et al.* introduced an ultrafast capillary electrophoresis (UFCE) mass spectrometry method [89]. An in-house portable CE apparatus with porous tip interface was built (Fig. 3b), and a peptide mixture and protein digests were analyzed within 1 min. In the following paper, Moini *et al.* utilized a low-flow rate ESI to reduce the suppression effect of cyclodextrins salts. Cathinone derivatives and their optical isomers were separated and detected [90]. Xu *et al.* developed a mini CE-MS system to improve the performance of portable IT-MS and the design was showed in Fig. 3c [91]. The isobaric peptides were separated by CZE, and charge competition effects in nano-ESI interface was relieved. Another portable battery operated CE/ESI source was introduced by Moini *et al.* [92]. Detected by LTQ Velos, amino acids and their optical isomers were separated in ~1 min. Bergstrom *et al.* used CZE-MS to separate small native/deamidated peptide pairs and identify the potential sites for deamidation [93]. Kohl *et al.* introduced a heart-cut 2D-CE separation system using ESI–MS detection. 2D analysis of BSA tryptic digest sample was performed by the system using a nonvolatile background electrolyte in the first dimension [94].

More methods based on microfluidic devices and capillary modification technology were reported in CE-MS systems to

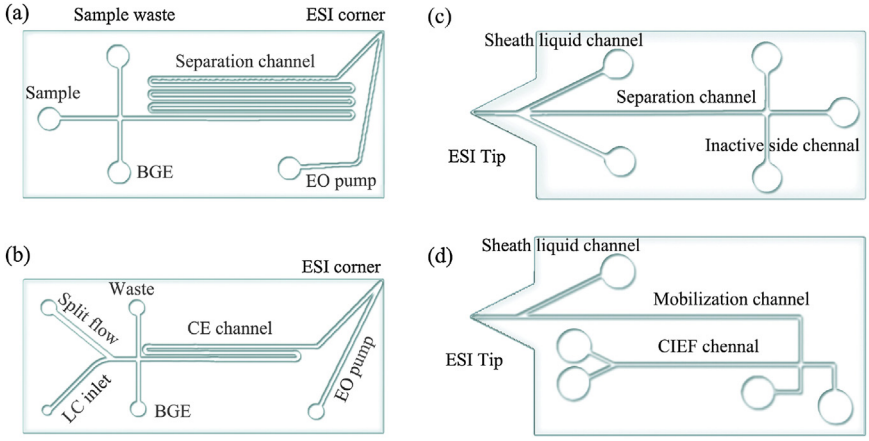


Fig. 4. Microfluidic chip to couple CE-MS. (a) microfluidic device design reported in ref [98]; (b) microfluidic chip design reported in ref [102]; (c) (d) isoelectric focusing microchip designs reported in ref [128].

achieve special features. Nordman *et al*. reported the fabrication of shape-anchored porous polymer monoliths (PPMs) for on-chip SPE prior to online microchip electrophoresis (ME) separation and on-chip ESI–MS [95]. 15- to 23-fold enrichment factors were obtained in a 25-s loading time. More applications using microchip electrophoresis ESI–MS were reported by the same research group [96,97]. Mellors *et al*. built a hybrid multidimensional separation system, which integrates capillary liquid chromatography in a microfluidic device (Fig. 4a) [98]. A mixture of peptides yielding an approximately peak capacity of 1400 was analyzed in 50 min. Black *et al*. demonstrated the utility of the same microchip CE-ESI device for hydrogen exchange (HX) MS [99]. A bovine hemoglobin pepsin digestion was performed in 1 min with a peak capacity of 62. Redman *et al*. developed the online CE-ESI–MS device for the separation of intact monoclonal antibody charge variants [100,101]. Batz *et al*. described a chemical vapor deposition (CVD) method for the surface modified of microfluidic devices by aminopropyl silane reagents [102]. The microfluidic chip design was showed in Fig. 4b, and peptides sample yielding a peak capacity of 64 was separated in less than 90 s. Mikuma *et al*. used the chemically modified capillary containing sulfonated groups to identified 8 amphetamine-type stimulants (ATS) enantiomers by chiral CE-MS/MS [103]. Li *et al*. reported a microchip electrophoresis-mass spectrometric platform for single cell analysis [104,105].

3.2. Capillary gel electrophoresis (CGE)

CGE is a separation mode combining the effective resolution of gel electrophoresis with the simple CZE devices. In CGE, the capillary is filled with gel as a molecular sieve. The separation mechanism is based on the different mobilities of the components via the gel due to their molecular size. Small size components migrate faster and will be detected earlier than the larger one. The solution system compatibility is the decisive factor when coupled to MS.

Fujii *et al*. developed a CGE-ICP-MS system to detect the double-stranded (ds) DNA [106]. An interface was designed to seamless connect the CGE and ICP-MS with a high performance concentric nebulizer (HPCN) (Fig. 3d). Fragments of dsDNA were separated and analyzed by measuring $^{31}P^{+}$, and the LOD and absolute detection limit of P were 3.7 μg/kg and 0.6 pg, respectively.

3.3. Capillary isotachophoresis (CITP)

The CITP mode is based on the use of a discontinuous buffer system without EOF. Analytes are injected between the terminating electrolyte with a lower electrophoretic than the sample and the leading electrolyte with a higher electrophoretic mobility than the sample. When applying electric field, the analytes are distributed in adjacent zones and move within the capillary at the same velocity between the buffers of different mobility. A two-dimensional separation combining CITP and CZE was the typical pattern in the CE-MS system.

Tang *et al*. demonstrated a sheathless CITP/CZE-QqQ-MS interface to achieve large sample loading capacity and stable nano-ESI operation [107–109]. A schematic plot of the setup was showed in Fig. 3e. Leu-enkephalin and angiotensin II, spiked in a BSA tryptic digest matrix were analyzed under the optimized parameters. A picomolar LOQ with measurement reproducibility of the CV less than 22% was obtained. Kler *et al*. presented a modular two-dimensional electrophoretic separation (ITP/CE) coupled to MS by using a glass microfluidic chip [110]. Four different human angiotensin peptides were pre-concentrated, separated, detected and identified by the system. After that, a nonaqueous ITP (NAITP) method using dimethylsulfoxide (DMSO) as solvent was applied in the similar system to analyze 20 proteinogenic amino acids [111]. Piestansky *et al*. developed an approach based on two-dimensional column coupled CE (ITP/CZE) hyphenated with tandem mass spectrometry (QqQ) as shown in Fig. 3f [112–114]. The optimized method was applied for the direct identification and ultratrace (pg/mL) determination of varenicline, pheniramine (PHM), phenylephrine (PHE), paracetamol (PCM) and their potential metabolic products in untreated/diluted human urine.

Different modes of ITP were applied to CE-MS system as methodology improvements. Marak *et al*. investigated the impact of buffer salts/matrix effects on the signal in direct injection MS with an electrospray interface (DI-ESI–MS) following pITP fractionation [115]. Mala *et al*. demonstrated a model of extended ITP and its applicability on the thiabendazole (Tbz) analysis in orange juice by full-format ITP-ESI–MS [116]. A LOD of 10^{-10} mol/L (20 ng/L) was obtained. Gahoual *et al*. reported the complete characterization of the primary structure of a multimeric glycoprotein by CE-MS [117]. Transient isotachophoresis (tITP) was introduced as a preconcentration technique in this work.

Capillary electrokinetic fractionation (CEkF) is investigated as an approach for semi-preparative and analytical method based on pK_a-dependant pH-driven electrophoretic mobility. CITP is principally the closest technique to CEkF. He *et al*. proposed a method to fractionate constituents based on their pK_a values by coupling CEkF to FT-ICR-MS [118]. Strong acids and phenols from two wine samples were tested by this technique.

3.4. Capillary isoeletric focusing (CIEF)

The separation of CIEF is based on the pI differences of solutes. CIEF enables the separation of amino acids, peptides, proteins and other substances of amphoteric character. A large sample loading volume can be achieved in the CIEF mode. When an electric field is applied, the pH gradient is established within the capillary filled with the ampholytes solution, and sample components will migrate until the solution environment pH value equals to their pI. On the other hand, the ampholytes may lead to many problems when coupling with a MS, such as degraded sample ionization and polluted instruments. The focused sample zone may be broadened when transferring to MS.

An overview of capillary isoelectric focusing-mass spectrometry coupling strategies was given by Huhner [119]. Then Huhner *et al*. combined CIEF with CZE-ESI–MS by a multiple heart-cut approach [120]. Model proteins were analyzed on intact level. Dovichi's group did a series of investigation in online CIEF-MS methodology for protein and peptides analysis [121–123]. Zhu *et al*. reported the application of CIEF coupled with Orbitrap Velos MS for quantitative analysis of a complex proteome [121]. A set of amino acids were used as the ampholytes, and this approach identified 835 protein groups and produced 2329 unique peptides IDs. Li *et al*. presented a strategy of IEF-HPLC–MS-ELISA for hemoglobin (Hb) detection [124]. The proposed GSS-HbA(1c) was separated and purified by micro-preparative CIEF and the target fractions were pooled and identified by ESI–MS. Przybylski *et al*. demonstrated a non-denaturing detection mode by on-line hyphenation of CIEF with ESI–MS [125]. 40% glycerol-water medium was used as anti-convective agent in CE capillary. The highly basic cytokine human interferon-gamma (IFN-γ) was characterized as a non-covalent homodimer and its pI under the experimental conditions was determined with a value of 9.95. Horka *et al*. introduced a method, in which CIEF in tapered fused-silica capillary was coupled with MALDI-TOF-MS for unambiguous identification of probiotic bacteria in real sample [126,127]. CIEF analysis of both cultivated bacteria and bacteria in milk was

optimized, and pIs of the examined bacteria were determined. In another article, eight strains of bacteria from plant-tissue-containing samples were identified by the same method. Nordman *et al*. developed an interface of microchip CIEF with online MS detection *via* a fully integrated on-chip sheath flow ESI emitter [128]. The two-dimensional separation chip for two-step CIEF-tITP was used for peptide analysis, and schematic views can be found in Fig. 4c and d. Zhang *et al*. reported a design of immobilized pH gradient (IPG) based on monolithic column CIEF-MALDI-MS platform for the complex neuropeptides analysis [129]. The separation time of peptide mixtures was less than 10 min, while the MS signal was enhanced.

3.5. Capillary electrochromatography (CEC)

The advantages of HPLC (high selectivity) and CE (high efficiency) are combined in CEC mode. Charged solutes are separated by the partition between stationary phase and mobile phase as well as by the differences in electrophoretic mobility. The incompatibility of CZE-MS with many separation buffers can also be overcome by using CEC.

Cheng *et al*. introduced a method about online pre-concentration CEC coupled with atmospheric pressure chemical ionization mass spectrometry (APCI-MS) [71]. Poly(stearyl methacrylate-divinylbenzene) (poly(SMA-DVB)) monolith was used as the separation column and 16 PAHs were analyzed. An LOD of 10 ng/g for PAH residues in seafood samples was obtained. Tiala *et al*. reported an on-line open-tubular CEC-MS method [130]. The model steroids were separated within coated fused silica capillaries under the optimized CEC conditions. Bragg *et al*. presented an approach for high throughput enantiomeric separations and detection of chiral analytes [131]. A short 7 cm CEC column packed with cellulose was used for CEC coupled to a single-quadrupole MS.

D'Orazio *et al*. developed a nano-liquid-junction interface for coupling both CEC or nano-liquid chromatography (nano-LC) with MS (Fig. 3g) [132]. The sample of organophosphorus pesticides (OPPs) and some acidic drugs were separated by CEC-MS, and the LOD ranged between 0.03 and 6.80 μg/mL.Wu *et al*. introduced a pressurized CEC (pCEC) method coupled to Q-TOF-MS (Fig. 3h) [133]. Three interfaces were compared and a sheathless interface was selected. The method was applied to lung cancer metabolomics under the optimized conditions. Simpson *et al*. developed an interface for the hyphenation of CEC with a hybrid IT-TOF-MS [134]. IR laser desorption and UV photoionization occurred within a quadrupole ion trap in order to simplify instrument. Trace analysis of naphthalene was achieved with an LOD of 500 nmol/L.

3.6. Micellar electrokinetic chromatography (MEKC)

In MEKC, surfactants were added in the buffer solution to form micelles moving at a different velocity from the EOF. The neutral analytes can be separated by their distributions between the aqueous and the micellar phases. Ammonium salt of perfluorooctanoic acid, as MS friendly surfactant, is frequently used as BGE in MECK coupled to MS.

D'Orazio *et al*. evaluated a methodology based on dispersive liquid–liquid microextraction (DLLME)-MEKC-MS/MS. The aqueous solution of perfluorooctanoic acid (PFOA) and ammonium PFO (APFO) were used as BGE to separate and determine 12 estrogenic compounds [135]. Furthermore, the method was applied for the analysis of four endoestrogens and their major metabolites from milk and yogurt samples [136]. LODs in the low mg/L range were attained. Twelve new designer drugs of synthetic cathinones were identified by Svidrnoch *et al*. using the MEKC-MS/MS [137]. Akamatsu *et al*. described a method for the simultaneous determination of 12synthetic cannabinoids by MEKC-MS/MS, and LODs were 6.5–76.5 μg/g [138]. Moreno-Gonzalez *et al*. included a MEKC-ESI–MS method for the analysis of amino acids (AAs) in human urine [139]. LODs ranging from 9 to 26 ng/mL. Wang *et al*. used polysodium *N*-undecenoyl-*L*,*L*-leucylvalinate (poly-*L*,*L*-SULV) as a chiral pseudophase in MEKC-MS/MS baseline separation of warfarin (WAR) metabolites [140]. The LOD and quantitation limit were at levels of 2 and 5 ng/mL, respectively. Franze *et al*. used MEKC-ICP-MS for separation, size characterization, and speciation of gold and silver nanoparticles [141]. LODs were in the sub-microgram per liter range.

3.7. Nonaqueous capillary electrophoresis (NACE)

NACE is the CE mode using the nonaqueous solvents as electrolytic solutions. The nonaqueous electrolyte can charge the analytes or interact with them, so that a selectivity separation can be achieved in NACE. Many natural products and drug-like small molecules can be separated and identified by the NACE-MS method.

Rodriguez *et al*. determined sunitinib, *N*-desethyl sunitinib and pregabalin in human urine using the NACE-TOF-MS, and LODs were 0.07 mg/L, 0.15 mg/L, 0.03 g/mL, respectively [142,143]. Zhang *et al*. developed a NACE-ESI-IT-MS method for separation, identification, and quantification of the Amaryllidaceae alkaloids [144]. The LOD was lower than 240 ng/mL, and the fragmentation pathways of main fragment ions were studied by tandem mass spectrometry. Matrine and oxymatrine were determined by the same group [145], with LODs of 37.5 ng/mL and 50.0 ng/mL, respectively. Chen *et al*. identified tetrandrine (TET), fangchinoline (FAN), and sinomenine (SIN) using NACE-IT-MS with nano-ESI interface [146]. The LODs of TET, FAN, and SIN were 0.05, 0.08, and 0.15 μg/mL, respectively. Bonvin *et al*. compared the aqueous CZE and the NACE coupled to negative ESI–MS, the separation performance and sensitivity of several pharmaceutical acidic compounds were evaluated [147]. Tho Chau Minh Vinh *et al*. applied the NACE-MS to analyze the alkaloids in Nelumbo nucifera leaves [148]. Montealegre *et al*. investigated the glycerophospholipid fraction in olive fruit and olive oil samples by NACE method with electrospray-mass spectrometric detection [149]. Roscher *et al*. used NACE in metabolism studies of harmane, and 26 products were detected in NACE-MS analysis [150]. Malik *et al*. reported an approach for the determination and speciation of organotin compounds with NACE hyphenated to TOF-MS [151].

4. Analytical applications with different mass spectrometric analyzers

Mass analyzers provide a sensitive detection solution for the analytes separated by CE, especially in unknown components identification. The characteristics of different MS analyzers (such as resolution, scan speed, quantitation, cost and so on) should be taken into consideration under different situations. Rodriguez Robledo and Smyth reviewed the performance of CE-MS platforms from this perspective [5]. In recent years, almost all kinds of MS analyzers have been applied to CE detection, such as quadrupole and triple quadrupole mass spectrometer (Q/QqQ), ion trap mass spectrometer (IT), time-of-flight mass spectrometer (TOF), Fourier transform ion cyclotron resonance mass spectrometer (FT-ICR) and Orbitrap mass spectrometer.

Less expensive but with relatively low-resolution, the quadrupole mass analyzer is one of the earliest mass analyzers coupled with CE. Bonvin *et al*. developed a sheath liquid interface with a make-up liquid, and intact proteins were analyzed by the CE-Q-MS

[152]. More applications using quadrupole analyzer were reported in the analysis of nucleosides [153,154], food [155], and drugs [27].

QqQ analyzers can be considered as a linear combination of three quadrupoles and show an improved resolution and more accurate quantification. Furthermore, collision induced dissociation (CID) process can be achieve in QqQ, so that ion structural information can be inferred from the ion fragments. Some papers about CE-QqQ-MS were published by Wang [107,108], Piestansky [112,113], Marakova [156,157] and their coworkers. More applications in the analysis of glycan [158], toxins [159] and food [160,161] using triple quadrupole analyzer were reported.

IT analyzers with varied geometrical structures can store and analyze sample ions. MS^n and several gas phase ion reactions can be performed in an IT, and molecule structural information can be obtained by bioinformatics technique, especially in biological molecules such as proteins and peptides. Portable IT-MS coupled with CE is suitable for the on-site detection [91]. Ortiz-Villanueva *et al*. prepared and evaluated of open tubular C18-silica monolithic micro-cartridges for pre-concentration of five neuropeptides analyzing by CE-IT-MS [162]. Dong *et al*. reported a pH-mediated stacking CE coupled with ESI–MS/MS method to determine the phosphorylation sites of three synthetic phosphopeptides containing structural isomers [163]. More applications using IT analyzer were reported in the analysis of peptides [164], natural products [165,166], soil [167,168], therapeutic albumin [169], and organic dyes [170].

The TOF analyzer is the most popular mass analyzer in CE-MS system. With high resolution and scan rate, TOF analyzer is especially suitable for the omics analysis such as proteinomics and metabolomics. Causon *et al*. demonstrated a concept in using two types of sheath-flow reactions for CE coupled with Q-TOF-MS detection [171]. Medina-Casanellas *et al*. prepared an immunoaffinity (IA) sorbent with antibody fragments for the analysis of opioid peptides by on-line immunoaffinity solid-phase extraction CE-TOF-MS [172]. A variety of CE-TOF-MS applications were reported in the analysis of peptides and proteins [172–183], nucleic acids [184], glycans [185,186], proteomics [187], metabolomics [188–202], drugs [49,203–206], toxicologic [207–209], natural products [210,211], single cell [212], organics [151,213–216] and so on.

High resolution mass spectrometric (HRMS) analyzers provide accurate mass information in element level. Fourier transform mass spectrometers, such as FT-ICR analyzer, have a high-resolution but expensive cost, and it rarely used for CE-MS at present. He *et al*. identified wines by CEkF-FT-ICR-MS, and addressed the existence of different species responding to flavor or color [118]. Michalke *et al*. investigated the relevant Mn-carrier species which are responsible for transport across neural barriers (NB) by FR-ICR-MS [217]. Yassine *et al*. analyzed acidic constituents of atmospheric organic aerosol an approach combining of CE-MS and FT-ICR-MS [218]. The Orbitrap mass analyzer is another fast developing HRMS and commonly used in proteomics research. Dovichi's group did a lot of work coupling CE with the Orbitrap MS [78,80,82,84,121,219,220].

5. Conclusion

Capillary electrophoresis is a conventional separation method with high separation efficiency, short separation time and low sample consumption. Among many analyzers, mass spectrometer is one of the most rapid development analytical techniques with high resolution, sensitivity and the capacity of obtaining unknown molecule structure information. The combination of CE and MS shows a broader outlook in applications of analytical chemistry. A large amount of literatures published in past years give a powerful evidence for it. Nevertheless, many problems remain to be solved for the system. This review introduced the latest advances of the instrumentation and methodology in CE-MS.

An ionization process between CE and MS is necessary, which limits the applications of some CE separation modes. Only a few specific combinations are frequently used at present, such as CZE-ESI–MS, CIEF-MALDI-MS, CZE/CITP-ICP-MS. The interfacing techniques play an important role in promoting the combination of CE-MS. Several ESI based interfaces were developed, such as the electrokinetically pumped sheath flow nanoelectrospray interfaces and the porous tips based interfaces. Furthermore, increased microfluidic devices were designed to couple CE-MS for special functions, such as 2D separation. A targeted design of injection interface can reduce components charge discrimination and achieve sample preconcentration.

There are two main trends in the development of instruments, high performance or portability. CE-MS shows a great potential in both two aspects. As a complementary technology for HPLC–MS, commercial sheathless CE-ESI–MS instrument was introduced in 2015, and more applications were reported. With higher sensitivity and analysis speed, an ultra-trace (single cell analysis) and high-throughput analysis (omics analysis) could be carryied out using CE-MS. It is possible to study the structure of biological molecules combining native MS method and novel CE buffer system, especially in obtaining time-dependent information, such as interaction of enzyme and substrate. On the other hand, portable CE-MS system facilitate the rapid detection. With improved quantitative detection performance, complex sample analysis could be achieved in a short time.

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