Portable capillary-based (non-chip) capillary electrophoresis

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Miniaturized, portable instrumentation has been gaining popularity in all areas of analytical chemistry. Capillary electrophoresis (CE), due to its main strengths of high separation efficiency, relatively short analysis time and low consumption of chemicals, is a particularly suitable technique for use in portable analytical instrumentation. In line with the general trend in miniaturization in chemistry utilizing microfluidic chips, the main thrust of portable CE (P—CE) systems development is towards chip-based miniaturized CE. Despite this, capillary-based (non-chip) P—CE systems have certain unmatched advantages, especially in the relative simplicity of the regular cylindrical geometry of the CE capillary, maximal volume-to-surface ratio, no need to design and to fabricate a chip, the low costs of capillary compared to chip, and better performance with some detection techniques. This review presents an overview of the state of the art of P—CE and literature relevant to future developments. We pay particular attention to the development and the potential of miniaturization of functional parts for P—CE. These include components related to sample introduction, separation and detection, which are the key elements in P—CE design. The future of P—CE may be in relatively simple, rugged designs (e.g., using a short piece of capillary fixed to a chip-sized platform on which injection and detection parts can be mounted). Electrochemical detection is well suited for miniaturization, so is probably the most suitable detection technique for P—CE, but optical detection is gaining interest, especially due to miniaturized light sources (e.g., light-emitting diodes).

Keywords: Capillary electrophoresis (CE); Chemiluminescence detection (CLD); Electrochemical detection (ECD); Injection; Laser diode (LD); Light-emitting diode (LED); Miniaturization; Optical detection (OD); Portable instrumentation; Power supply.

1. Introduction

1.1 Trends in miniaturization

Miniaturization has become a important factor in all spheres of modern society, reflected strongly in science and technology, including electronics [1], medicine [2], chemistry [3,4] and other areas [5,6]. Miniaturization in chemistry was given a new dimension in the 1990s with the concepts of lab-on-a-chip and micro-total analysis systems ([μTAS) [7-11]. Micro fluidics is now a thriving multidisciplinary area from which all areas of science, including analytical chemistry, strongly profit.

Progress in electronics, engineering, material science and other areas has supported development of scientific instrumentation. Increased availability of small, inexpensive, portable computers for data acquisition and evaluation has also aided that development. In parallel with the advances in microfluidics-based miniaturization (lab-on-a-chip and μTAS),analytical instrumentation utilizing miniaturized classi-cal technologies also has a strong potential for creating portable instrumentation.

1.2. Portable instrumentation

In general terms, a portable object is defined as "easily movable, convenient for carrying, and capable of being transferred or adapted in altered circumstances" [4]. More specifically, in scientific instrumentation, a portable device can be used outside the laboratory, in the absence of mains power, usually to some degree miniaturized and relatively easy to move and deploy [4]. The dimensions, weight and power consumption of a por-table device are key parameters; however, there are several other requirements for a field analytical instrument to be considered portable, including mechanical rigidity, minimal sample preparation, minimal consumables (including gases and solvents), ease of operation, fast analysis times and satisfactory analytical performance (i.e. sufficient accuracy, sensitivity and selectivity) [12].

Field-portable instrumentation allows chemists to conduct analysis where the sample is taken, thus avoiding sample decomposition during transportation, and reducing the time and the cost of analysis. In environmental [13] or point-of-care (POC) clinical analyses, it is often necessary to obtain required sample information in a short period of time and at the sample location [14,15].

The most widely-used portable instruments in chemi-cal analysis include mobile pH meters, conductometers and ion-selective electrodes. Numerous types of more complex field-portable instruments (e.g., optical and mass spectrometers [16-18], X-ray fluorescence devices [12,19], and chromatography-based instruments [20,21]) have also been developed, and, in some cases, commercialized. Portable analyzers have used separation or flow-analysis methods (e.g., flow-injection analysis [22,23], and gas chromatography (GC) [24-26] and liquid chromatography (LC) [27-30]).

1.3. Portable capillary electrophoresis

Capillary electrophoresis (CE) is well suited to portability because only a separation capillary, a high voltage (HV) power supply and small volumes of solutions are needed to perform the separation [31]. We know of one portable CE (P—CE) instrument that is currently commercially available (CE Resources, Singapore) [32]. However, several laboratory-built instruments have been pre-sented in the literature [31,33-35]. Commercial P—CE instruments may not be more widely available because of the perception that CE is inferior in robustness to high-performance liquid chromatography (HPLC) [36]. This may have resulted in CE having a smaller market segment than HPLC, as well as there being perceived challenges in design and construction of a P—CE. We therefore pay special attention in this review to factors in the design of a P—CE that may increase its suitability.

1.4. Conventional capillary-based CE versus CE-on-a-chip

CE can be considered a mature technique that has been used for a wide range of applications [37,38]. Achieving further miniaturization and portability presents a significant challenge in CE, where the separation takes place in a narrow capillary and the volumes and the consumption of the sample and the electrolyte are already at the μL-μL range. Understandably, utilizing the potential of microfluidics and lab-on-a-chip led to an early realization of CE-on-a-chip [39]. The small size, low consumption of sample, chemicals and

power and a wide variety of applications of the microfluidic chips present a tremendous potential for the development of portable analytical instrumentation [40].

Chip-based separation technologies have been commercialized by numerous companies (e.g., Agilent, Caliper, Cepheid, Fluidigm, Gyros and Micronics) [40]. Chip-based CE (chip-CE) can be utilized in proteomic analysis [41], DNA separation, including sequencing [42-44], fragment sizing and genotyping [45], analysis of low-molecular-weight compounds (e.g., explosive residues and warfare agents) [46], food analysis [47], and analysis of pharmaceuticals, drugs and various analytes in body fluids [48]. Despite the trend towards increasing utilization of microfluidic chips in analytical chemistry, confirmed by the steadily growing number of scientific publications focusing on microfluidic chips (Fig. 1), chip-CE has to overcome significant challenges in comparison with classical capillary-based CE, especially in regard to its relative complexity and a number of technical hurdles, ruggedness, reliability and ease of operation [49].

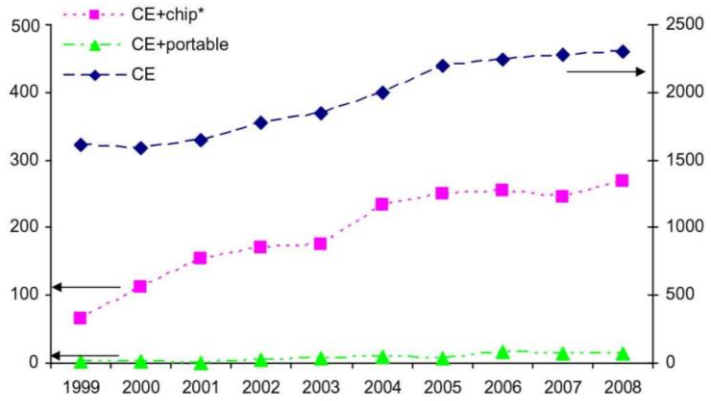

Figure 1. Comparison of the number of publications published for capillary electrophoresis (CE), chip-based CE and portable CE in the past 10 years (Web of Knowledge: Search terms = capillary electrophoresis, chip* AND capillary electrophoresis, portable AND capillary electrophoresis).

Despite the continuing improvements in chip technology, classical CE using fused-silica capillary has numerous unmatched advantages, so that CE capillary remains a very effective and attractive separation format:

• more symmetrical geometry of a cylindrical CE capillary, resulting in maximal volume-to-surface ratio;

• often a better detection performance in on-capillary design;

• direct availability; and,

• low costs (no time and costs otherwise associated with chip design and fabrication).

The polyimide-coated fused-silica capillary introduced by Dandeneau in 1979 [50] became an example of enabling technology that allowed a successful break-through of major analytical techniques including capil-lary gas chromatography and later CE [37]. After decades of development, fused-silica capillaries used in CE are recognized for ruggedness, affordability and well-characterized silica surfaces [51,52]. We therefore anticipate that the capillary-based CE will not only remain a well-used format of CE, but will increasingly be used in miniaturized CE systems, in parallel with growth in chip-CE systems.

1.5. Scope of this review

Unlike chip-CE, which has been reviewed numerous times in recent years [40,41,53–55], no review has focused specifically on P–CE instruments using a capillary as the CE-separation format. This appraisal of current status and future development options in P–CE is structured into three sections. The first part presents a critical review of current commercial bench-top and P–CE instruments. In Section 2, we present selected examples of research-based CE systems, including analysis and discussion of their functional parts. Section 3 focuses on miniaturized functional elements of CE that may, in future, play a role in miniaturization of P–CE instrumentation.

2. Overall design of P—CE instruments

2.1. Current commercial CE instruments

The design of bench-top instruments using a capillary as the separation column has been influenced by the general trend towards miniaturization in instrumentation and this is reflected in the decreasing size of commercially-available CE devices. Fig. 2 summarizes commercially-available CE instruments, including their size, weight and power consumption. This graph covers only commercially-available, general-purpose CE instruments. It excludes specialized application-targeted CE-based analyzers (e.g., multi-capillary DNA analyzers).

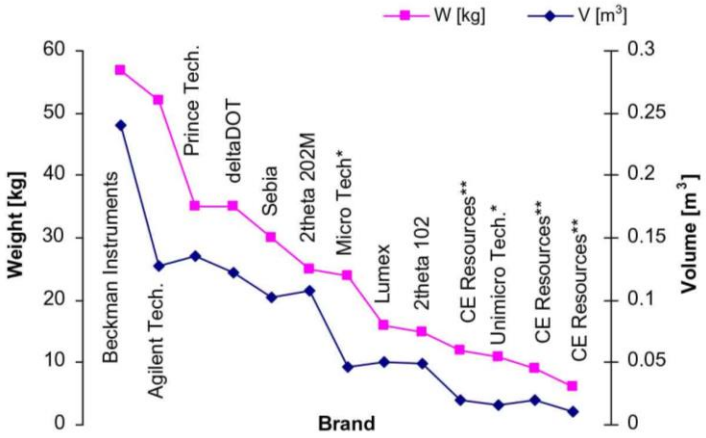

Figure 2. Comparison of volume and weight of commercially available capillary electrophoresis instruments (*capillary electrochromatography, ** portable CE).

2.2. P—CE design

A well designed field-portable instrument needs to be compact, robust, and efficiently battery-powered for sufficient run-time without re-charging. In addition, it needs to be of low weight and overall dimensions in order to be easily carried by one person (Fig. 2). For the purpose of this review, a portable instrument is defined as a battery-powered device operated independently of mains power with a maximum weight 10 kg. In comparison with the current sophisticated bench-top instruments, operation of a portable instrument has to be simplified to allow use by a non-expert or an operator with little experience. We already discussed some additional specific requirements in Sub-Section 1.2 while Section 3 analyzes the design of the individual functional parts of CE with a view to trends that will aid future miniaturization and portability of CE.

2.3. Current commercial portable instruments

Despite some classical bench-top CE instruments having become relatively small, so that they are potentially compatible with portability, there are only a few instruments specified as "fully portable CE". Further-more, the predominant focus in research on chip-based

separations may have detracted from the importance and further potential of portable capillary-based CE analyzers.

As noted previously, one commercial P—CE is available (Fig. 3). The system is enclosed in a compact attaché case and connected to a laptop [56-63]. Li et al. presented the first version in 2001 for environmental applications [63]. The instrument weighed 3kg or 6 kg, depending on configuration, and was the size of a notebook case.

Figure 3. Commercial portable capillary electrophoresis design with ultraviolet detector [32].

Miniaturization of the detector was a key step for the development of this instrument. Potential gradient detection (PGD) was used in this instrument and this electrochemical-detection method led to the relatively small overall size suiting the requirements of portability. Analysis of inorganic ions in mineral water separating K^+, Na^+, Ca^{2+} , $Mg^{2+,}$ Cl^- ,NO_3^-, SO_4^{2-} , CO_3^{2-} was an application example.

A second version of the system extended the detection options and the PGD provided [58,61,63] with the possibility of connection to other different types of detector {e.g., spectrophotometric UV-Vis [57,60], contactless conductivity [56,59], or a custom-built photometric detector using light emitting diodes (LEDs) [62]} . Even though the option of the several external detectors brought versatility in detection modes, a significant increase in weight to 10 kg was reported. Later, a third version weighing 12 kg became avail-able on the market. It is obvious that the gradual increase in versatility of the P-CE device design, combining a suitcase-based CE unit with external detectors, although aimed at convenient operation, necessitated compromises in the size and the weight of the P-CE instrument. The benefit of the broad range of available detectors allowed new applications to be developed for this P-CE, e.g.: determination of low-molecular-weight organic acids in the presence of chlorinated herbicides [59]; determination of toxic pyrrolizidine alkaloids in traditional Chinese medicine [60]; and, analysis of post-blast residues for identification of inorganic improvised explosive devices [62]. Even though the weight of the newest upgraded model of the P-CE was double that of the first model, it remains a commercial portable P-CE. Fig. 4 shows an example of analysis of anions extracted from post-blast residues performed on it.

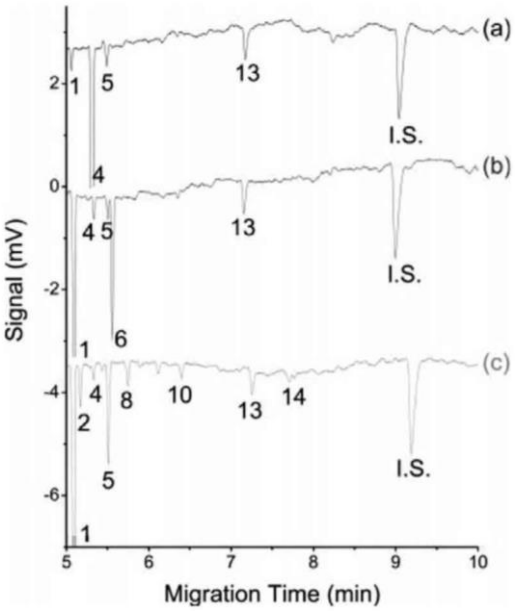

Figure 4. Analysis of anions extracted from post-blast residues resulting from improvised (a) ammonium nitrate/fuel oil (ANFO), (b) potassium perchlorate/sugar, and (c) sodium chlorate/sulfur/ aluminum explosive devices. Conditions: the post-blast residue aqueous samples were injected without dilution. Reprinted with permission from [62]. Copyright 2007 American Chemical Society.

2.4. Research-based portable instruments

Mainly in the initial development stages of CE in the early 1990s, a significant proportion of researchoriented, in-house-designed CE instrumentation, often constructed as light-weight Perspex boxes, could be claimed to be portable, in principle. For the purpose of this overview, we focus on those designs of research CE instruments that had a specific focus on portability.

One of the smallest ever P—CE instruments was pre-sented in 1999 by Gerhardt (see Fig. 5). It was an automated P—CE system connected to a laptop PC and using end-capillary electrochemical detection (ECD) [64]. In this system, reliable, relatively easy alignment of the capillary end and the detection electrode was achieved using an end-capillary detection cell and flexible data acquisition. This system allowed for both amperometric detection (AmpD) and voltammetric detection modes. Despite its small size, the instrument was equipped with an addressable vial tray, and a vial lifting and pressure-rinsing system for completely automatic operation. The P—CE was used in square-wave voltammetry detection mode for analysis of neurotransmitters, and the results were comparable to those achieved with AmpD with a bench-top CE.

However, the first custom-built P—CE instrument was presented a year earlier in 1998 by Kappes et al. [34]. This P—CE was encased in an acrylic glass box (340 x 175 x 175 mm), weighed 7.5 kg and could be easily carried by one person. It employed end-capillary potentiometric detection (PotD) implemented using a miniature coated-wire ion-selective electrode placed in a special holder to provide precise alignment with the capillary end. The system was tested with a model mixture of inorganic ions and was demonstrated in Rhine river-water analysis. The dynamic range of the method was over more than two orders of magnitude and limits of detection (LODs) for nitrate and calcium (S/N = 3) were 8 x 10^{-6} mol/L and 9 x 10^{-6} mol/L, respectively.

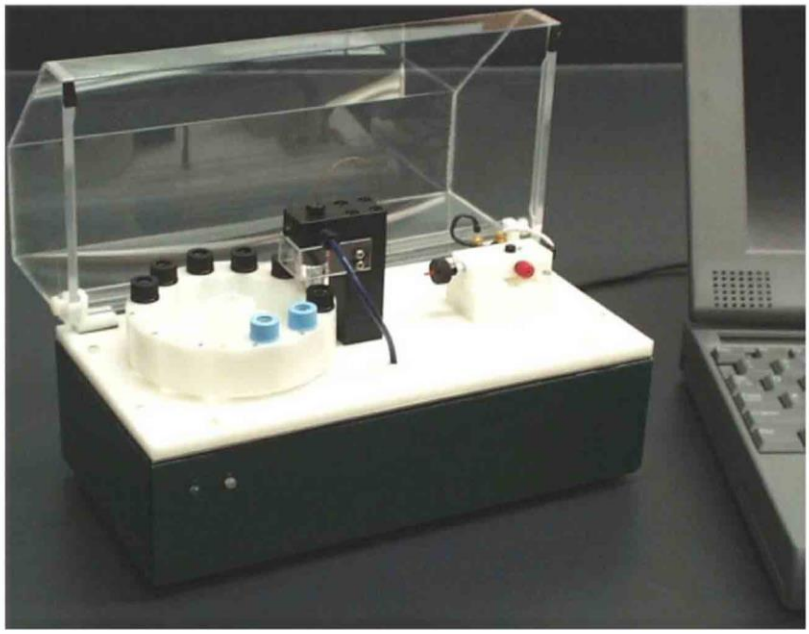

Figure 5. In-house constructed automated capillary electrophoresis system with electrochemical detection (CE-ECD) [64].

While the concept of the compact CE design remained in the following work [35], AmpD was added to extend the applicability of the P-CE instrument. A further improvement of the detection system resulted in simpli-fied AmpD for this P-CE instrument [65].

In 2001, Kappes et al. published a study in which a P-CE design combined even more simplified AmpD, PotD and CD [33]. AmpD was applied to the analysis of carbohydrates and amino acids in grapefruit juice (using a copper electrode) and of heavy metals in a road-dust leachate (with a mercury-impregnated gold electrode). PotD was demonstrated for the determination of artificial sweeteners and preservatives, including cyclamate, sac-charin and benzoic acid in soft drinks. Capacitively-coupled contactless conductivity detection (C4D) was implemented as the most versatile detection technique applicable, especially for small inorganic ions. A model separation of Br^-, Cl^-, NO_3^- and SO_4^- was performed with samples of river water and white wine. The versatility of its detection made this P-CE system suitable for many applications, including environmental and food analysis. The low power requirements, the small size (340 x 175 x 175 mm) and the low weight (7.5 kg) provided relatively comfortable field usage. Recently, a new fully portable CE instrument, an improved version of the P-CE with C^4D [33], was reported by Kuban et al. [31]. This instrument was battery powered and could operate for more than one day at a voltage up to ±15 kV. LODs in the range ~0.2-1 mM were achieved for inorganic ions, including heavy-metal ions ($Mn^{2+}Cd^{2+}$, Co^{2+} and Zn^{2+}) and arsenate. On-site testing of the instrument proved that nitrite and ammonium could be determined at concentrations as low as 10 ppb, in excess of other common inorganic ions. LODs in the range 0.1-0.4 μM were determined for 10 cations and anions.

Seiman et al. [66] presented another fully portable CE instrument in 2009. This P-CE instrument (dimensions 330 x 180 x 130 mm, weight 4 kg) was powered by 10 rechargeable batteries with operating time of 4 h. The system was equipped with a cross-sampler based on microchip-electrophoresis principles. However, since the injection could be influenced by instability of manual sample flushing through the injector, the authors recommended use of internal standards. This problem may be solved with a pump; nevertheless, it could reduce the portability of the instrument. Detection was realized by a C^4D cell with 8-mm long electrodes and 0.8-mm electrode gap. The design was successfully applied for analysis of phosphonic acids extracted from sand and loamy soil.

3. Design of functional parts with potential for portable P—CEs

There are numerous publications on the specific aspects of a CE system that should be considered for automation, portability and miniaturization of the individual parts of the P—CE instrument. Design, size and efficiency of operation of the individual functional parts (e.g., detectors, injectors, and capillaries with connected fluidic components allowing automation) will influence the further progress and applicability of P—CE. Also, the possibility of integrating sample pretreatment with the separation has to be taken into account. The following sub-sections contain analysis and discussion on selection of the miniaturized functional parts potentially suitable for P—CE instruments.

3.1. Injection systems

For sample introduction in CE, the main challenge is the extremely low volume of injected sample — of the order of several nL [67]. Either classically-driven injection technique of pressure or voltage [hydrodynamic (HD) and electrokinetic (EK)] are found used in CE instruments (bench-top and P—CE) [68]. For opti-mal mechanical rigidity, the P—CE design needs to be protected from unexpected manipulation. Traditional injection modes (HD and EK) do not offer sufficient robustness combined with the automation required in a P—CE design. The HD injection technique, relying on pressure difference caused by different levels of electrophoretic reservoirs, can require either a long injection time or a large level difference to achieve a sample plug sufficiently long. Injection by applying overpressure or vacuum systems results in undesirable increases in size and weight of the P—CE due to the requirement for additional pumps. EK injection is known to pose a risk of electromigration discrimination for charged analyte ions. For these reasons, different types of injection have been investigated and described in the literature. Kuldvee and Kaljurand [69] gave a comprehensive review of sample introduction, which also includes injection methods combined with sample pre-treatment (e.g., interfaces employing membranes and sorbents) and injection techniques for microchip-CE.

3.2. Injection valves

Due to the small i.d. of commonly used capillaries, the injector for CE, compared with HPLC, should have a sample volume of the order of nL (e.g., for a 75-μm i.d. capillary, a 1-mm sample-plug length corresponds to ~4.4nL). Sample injection using a rotary-valve injector was introduced as early as in 1987 by Tsuda et al. [70]. However, the injected volume was relatively large (~350 nL).

The nano-injector presented by Hanai and Tsuruta allowed an injection volume of 2 nL [71]; however, connections with relatively large-volume sleeves resulted in loss of separation efficiency.

Due to the [IL-injection volume of conventional HPLC-type injectors, they are not directly applicable to CE, so split-injection devices have been adopted. A splitter followed by an auto-rotary injector was demonstrated by Tsuda et al. [72]. The main advantage of this injector was the possibility of injection under a continuously applied voltage. Since it is technically difficult to make a very narrow sample chamber using conventional machining, Iizuka et al. [68] embedded a fused-silica capillary tubing with i.d. 50-100 μm in a resin-housed rotor. In this way, they achieved a volume-defined injection of the order of nL. Although commercially-available HPLC valves have too large a volume for application in CE, Ponton et al. [73] described utilization of a six-port HPLC valve for CE. These authors used partial-loop injection by manually switching to the inject position for a set amount of time and then returning to the load position. While utilization of an nL injection valve removes the necessity to dip the capillary into the sample to make it into a "LC-like" apparatus, the availability of suitable, inexpensive nL injection valves may be a prohibiting factor.

3.3. Flow injection (FI)

FI-CE has proved a powerful tool for rapid, automated sample injection capable of including pretreatment. A number of developments and advantages in FI-CE could find use in sample injection in P—CE systems. The advantages in combination with CE are primarily reproducibility, high throughput and the possibility of incorporating an on-line sample pretreatment. Ruzicka et al. [74] first introduced FI in 1975 and FI for sample introduction was combined with CE in 1997 by Kuban et al. [75] and Fang et al. [76]. Coupling FI and CE has been reviewed briefly by several groups [77-79]. One of the main factors limiting successful combination of FI and CE is the problematic decoupling of the HV applied for CE separation from the FI system. A cross type of injector employing HV switching similar to typical injection used in CE-on-a-chip was described by Evans in 1997 [67]. This type of on-line injection, where no manipulation with open sample reservoirs is necessary and injection is done only by voltage switching, offers sufficient rigidity for P—CE instruments. The peak height and peak area relative standard deviations (RSDs) were acceptable for reliable quantitative analysis. The cross-injection method for CE was also used by Hooker and Jorgenson [80], Tsukagoshi et al. [81], Rainelli and Hauser [82] and Kulp et al. [83]. Wang et al. presented an inexpensive, efficient FI-CE interface, where the FI-CE flow-through cell comprises a thick-wall silicone tube and a conical pipette tip [84]. Recently, the FI-CE design was miniaturized with the separation capillary acting as a part of an H-channel structure with the ends of the capillary inserted into the tubing. The whole system was fixed on a planar plastic microscope slide [85,86]. This simple, small system presented a useful step forward for the miniaturization of P—CE.

FI-CE is an elegant option for automated sample injection, introducing sample volumes far exceeding those that could be injected in CE. FI-CE removes the need for a nano-injector, so it presents an attractive, inexpensive option. Moreover, the possibility of intro-ducing the next sample while the previous separation is still running increases sample throughput.

3.4. Sequential injection (SI)

Generally, SI-CE [87,88] offers an alternative to FI-CE with a potential for more flexibility in sample handling by the SI switching valve, while the interface can be identical to the FI-CE interface. The first work on SI analysis was published in 1990 [89] and SI-CE coupling has been investigated since 1997 [90-93]. It has become apparent that the combination of microSl (μSI), allowing handling of liquid volumes down to the nL range with CE (liSI-CE), holds promise of further simplifying the system by integrating the SI-CE interface into the SI valve. The p.SI system, driven by a single syringe pump, can pressurize the system to carry out HD injection [94,95]. This completely automated injection method, which can also provide potential for integrated sample pretreatment, should be even more advantageous for future systems than the FI-CE previously described [91].

3.5. Capillary

The capillary as a functional part of the P—CE design can be shortened very easily down to minimum lengths depending on the instrumental design, and there are many publications involving ultra-short capillaries for CE. The main reason for using a short capillary lies in the lower analysis time. This sub-section focuses on designs where the capillary total length is 10 cm or less [96,97]. In this context of P—CE development, we here pay attention to mounting such short capillaries on plat-forms that form devices often similar to microfluidic chips. This increases robustness and portability.

A miniaturized CE system with AmpD was presented by Chu et al. for several applications (e.g., determination of sugars in Coke [98], acetaminophen and p-amino-phenol [99], uric acid in human saliva and urine [100] and bioactive amines [101]). This system was a chip-

based design, where an 8.5 cm long capillary was placed on a Plexiglass plate (25 mm x 100 mm x 2 mm). An Ag/AgC1 reference electrode and a Pt-wire auxiliary electrode were used for the AmpD. This device provided very compact, small, simple system with potential for incorporation into miniaturized and portable instru-ments. Fig. 6 shows the design. Wuersig et al. presented rapid separations in a short capillary (8-cm length) combined with C^4D and SI analysis for sample loading [92].

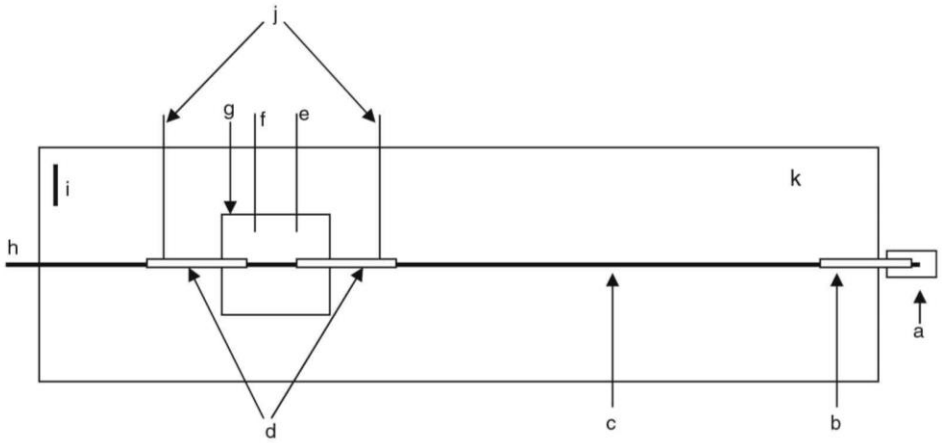

Figure 6. Schematic diagram of an integrated CE-AmpD system, (a) CE vial, (b) HV stainless steel tubular electrode, (c) fused silica capillary, (d) tubular electrodes for grounding, (e) Ag/AgCl reference electrode, (f) Pt auxiliary electrode, (g) detection cell, (h) Cu working electrode, (i) copper bar, (j) Cu wires, (k) Plexiglas plate. Adapted from [101].

This system, due to the relatively small size of the SI-CE interface, short capillary and small detector [102], is very well adapted for development into a field-portable analyzer. C^4D in combination with a 5-cm-long capillary was used in the work of Rainelli et al. [82]. In this work, a custom-built CE system was tested with concurrent determination of amino acids and carbohydrates in 160 s and major ions in a water sample within 1 min. Even shorter length capillaries (1 cm and 3 cm) in combination with chemiluminescence detection (CLD) were used by Tsukagoshi et al. [81]. Several other CE designs with short capillaries have been described with varying potential for portability [86,103-106]. Fig. 7 shows an example of fast separa-tion of DNA fragments in ultra-short capillary (5 cm).

Decrease of capillary length is a simple, effective approach to miniaturization. Although the separation power decreases with reduced length, capillaries moun-ted on a glass slide to create devices similar to the microfluidic chip have outstanding advantages, espe-cially in terms of manufacture and the possibility of capillary replacement. This approach has great potential for application in P—CE.

3.6. Detection

It is challenging to develop a detection system suitable for P—CE that can be battery powered and sufficiently sensitive and universal for the range of analytes with different properties that can be separated in CE [31]. The detection cell is the most widely miniaturized component of the CE system. This sub-section reviews literature with particular potential for P—CE, covering different types of detector developed to modify commercial instruments or to fit into custom-built designs. For ease of miniaturization at a relatively low price, ECD is the most widely used method in portable designs, followed by optical detection (OD) with solid-state light sources (LEDs and diode lasers).

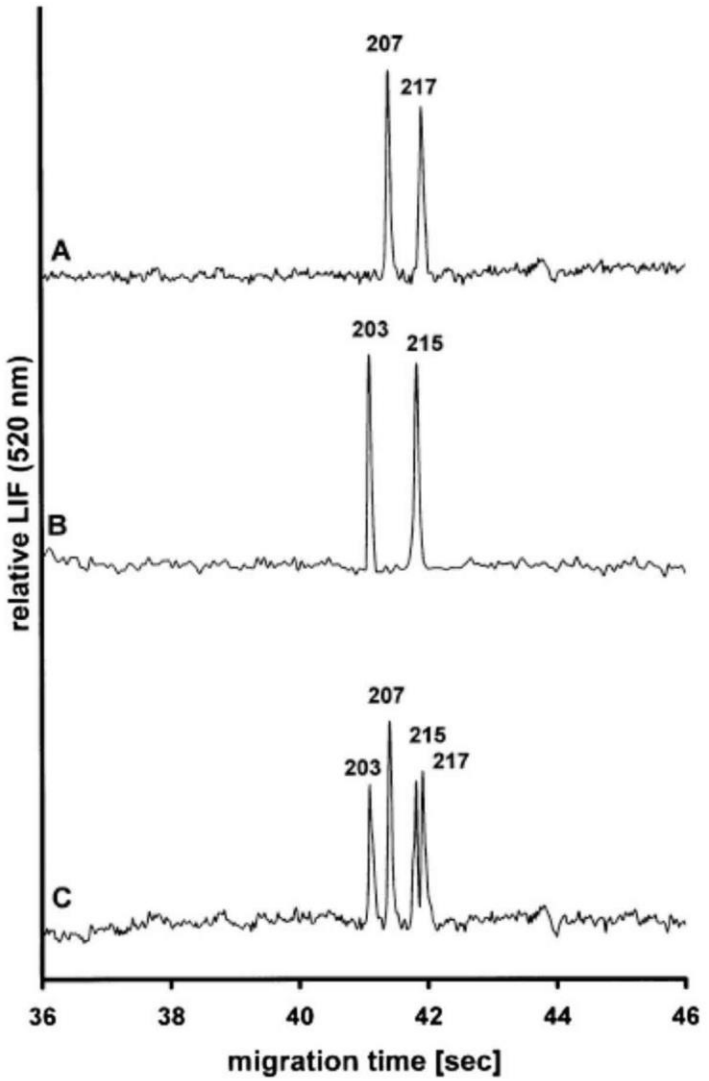

Figure 7. Ulatrafast separations in a short-capillary capillary electrophoresis (CE) of DNA fragments with known sequence (A) 207, 217 bp, (B) 203, 215 bp (C) mixture of samples A and B. Instrumentation: laboratory-made CE system with laser-induced fluorescence detection at 520 nm. Electrophoresis conditions: 4% w/v solution of agarose BRE in 0.1 M Tris-TAPS buffer (pH 8.3) with 7 M urea, injection for 3 s at 600 V/cm; electrophoresis at 600 V/cm; capillary 2.5 (5) cm, 50 µm i.d.; for more details, see [104]. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.

3.6.1. Electrochemical.

Miniaturized AmpD has been presented in number of papers [96,98-101,107-110]. The preferred arrangement is based on placing the detection and the separation (capillary) part on the microscope plate, which limits size and increases compactness. Several miniaturized nL-volume electrochemical end-capillary flow cells have been described and offered the advantage of the capillary-electrode alignment being relatively easy to realize, often in a sealed, liquid-tight cell [111-113]. Fig. 8 shows AmpD with a thin-layer, radial-flow cell and an integrated ring-shaped microarray electrode developed by Liu and co-workers [107]. This system reached LODs in the range 15-100 nM for dopamine, epinephrine, norepinephrine and catechol.

PotD as another electrochemical mode of detection that can be miniaturized as easily as AmpD, but it has not been as widely used in CE as AmpD. An example can be found in the work of Kappes et al. [34], in which potentiometry was first applied to a P—CE system. It seems that a lot of the reported problems relating to broadened peaks and unstable baseline may have origi-nated from the geometry of the capillary end, as found in later work by Macka et al. [114]. In this latter work, a well-controlled electrode arrangement and geometry

using a detection electrode coaxially positioned at a distance about the same as the capillary diameter (25 μm) achieved high efficiencies.

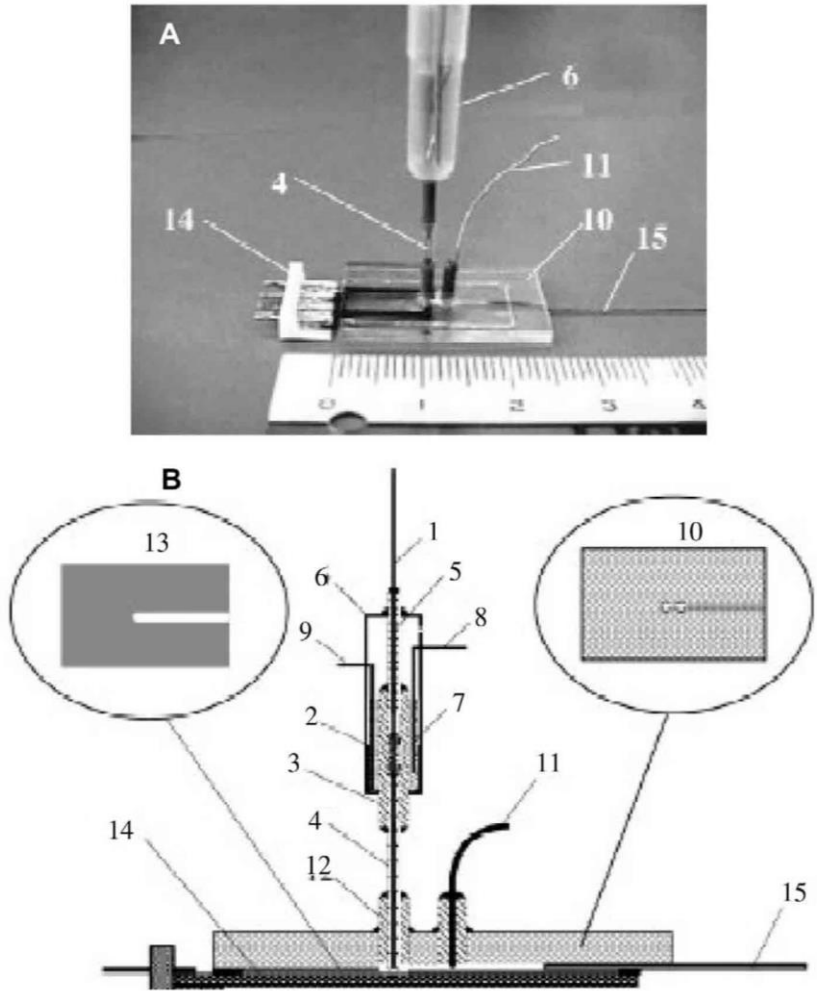

Figure 8. Photograph (A) and diagram (B) of an amperometric detector. The components are numbered as follows: fused-silica capillary (1); Nafion tubing joint (2); hard plastic tubes (3 and 12); stainless-steel tubes (4, 5 and 9); cylindrical plastics container (6); electrolyte solution (7); platinum wire (8); acrylic plate (10); Ag-wire reference electrode (11); PTFE gasket (13); IDRA microelectrode chip (14); and, outlet capillary (15) [107]. Reprinted with permission. Copyright Elsevier 2000.

To make PotD a robust method suitable for P—CE, the pulsed form of PotD demonstrated in 2000 by Zakaria et al. could present great potential for future develop-ments in CE and P—CE [115]. This system used the usual PotD electrode design but also had sophisticated elec-tronics to impose a defined ms potential pulse before the start of each cycle of data acquisition period in PotD mode. It greatly improved baseline stability and detec-tion sensitivity.

C^4D as a third option for ECD was introduced in coupling with CE by Zemann [116] and da Silva [117] in 1998. Its main strengths are contactless operation, high sensitivity, ease of miniaturization and quasi-universal detection [118]. Its main weakness is the need to have a significant difference between the conductivity (mobility) of the de-tected ion and the background electrolyte (co-ion mobility). However, most inorganic [119] as well as organic [120] cations and anions can be determined with typical LODs at the level of μM.

In terms of miniaturization, one of the smallest capil-lary C^4D cells allowing integration into the commercial Agilent cassette was the detector constructed by Macka et al. [121].

In this small design, the miniature electrodes and supporting plastic elements on a piece of CE capillary were encased in epoxy resin (as shown in Fig. 9). An advantage of the small size

of this cell was the possibility to move the detection cell along the effective length of the capillary, thus gaining the ability to choose the optimal position when injecting from both sides of the capillary in simultaneous cation-anion analysis [115].

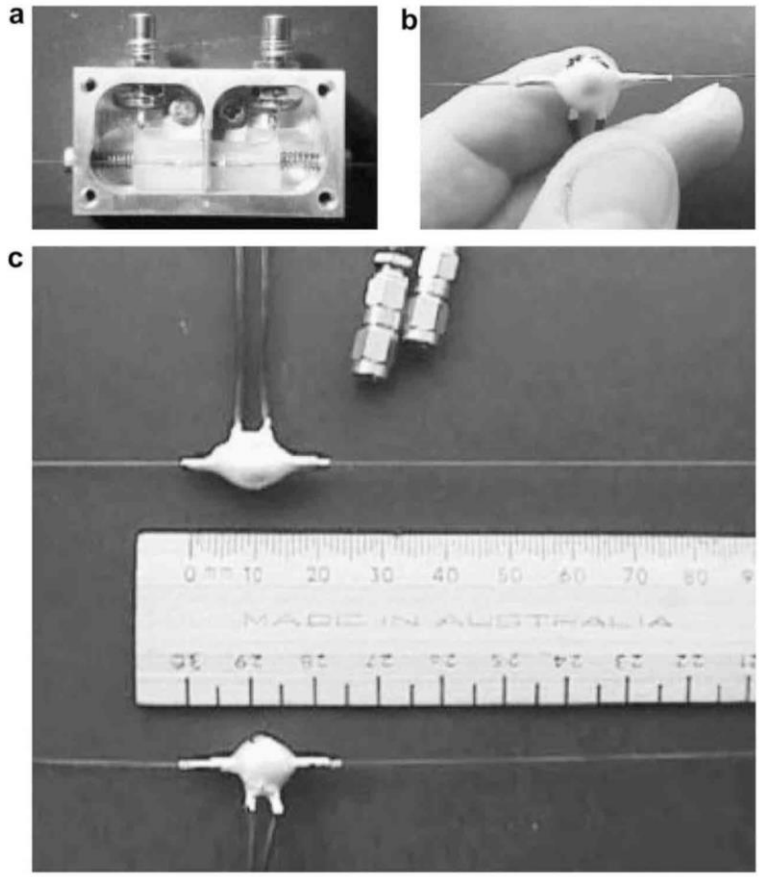

Figure 9. Photographs of: (a) the C4D cell used in previous work; (b) the new miniaturized mini-C4D cell No. 2; and (c) the mini-C4D cells No. 1 and No. 2. The photographs are adjusted to appear in scale, the dimensions of the cell body in (c) are 42 mm × 20 mm [121]. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.

Use of C^4D in battery-operated P—CE in Tasmanian wilderness was demonstrated by Kuban et al. [31]. Wang et al. [86] used C^4D in combination with a miniaturized CE design (20 x 70 x 1 mm) to create a compact CE system. This instrumentation was very compact and rigid, since the detector and the capillary were fixed on a glass slide.
Due to its versatility, ECD is very suitable for P—CE, especially because delicate focusing optics is not required.

3.6.2. Optical.

The main improvement in OD has been noticed due to the introduction of LEDs and laser diodes (ID) as light sources. In contrast to the commonly used lamps, they offer numerous advantages relevant to use in P—CE, including small size, low price, ease of operation, a wide range of wavelengths available from near infrared (NIR) through visible and down to low UV. An inherent ability to be pulsed up to GHz rates, low heat emission and low power consumption present useful advantages [12 2] .
Photometric detection (PD) can particularly benefit from use of LEDs as light sources. A miniaturized PD with LED light source (PD-LED) was reported in 2004 by Johns et al. [123] and subsequently used in numerous works, including Hutchinson et al. in 2007 [62], in coupling with a commercially-available fully-portable CE analyzer (CE Resources [32]). The

main advantage of the LED-PD detector for use in P—CE is its small size and low power consumption.
Although fluorescence detection (FD) is a very sensitive technique, it depends on spectral properties of the analytes and the variety of analytes for which FD is applicable is very limited. However, the advantages of the method in terms of sensitivity and LODs are so outstanding that FD should find use in P—CE. Lasers are currently the most important light sources for FD, especially LDs, and, due to their small size, compactness, low price and stable optical output, they are perfectly suitable for miniaturized portable devices [124]. The wavelength range available covers almost the whole spectrum from near IR [125] down to 405 nrn [126] and 375 nm [127]. As smaller dimensions of the device can be reached when employing LEDs and LDs as excitation light sources, the possibility of incorporation into the P—CE designs increases [128-130].
Other types of OD have been described. An example employing a liquid-core waveguide (LCW)-based fluori-metric detection (FD) cell was described by Kostal et al. [131] in 2006. This post-column detection was based on low-refractive-index fluoropolymer Teflon AF-coated sil-ica capillary that served as both separation channel and LCW.
A Teflon AF-coated fused silica capillary used for an LCW CE system was also presented by Wang et al. in 2001 [129].
A miniaturized fiber-optic-modified photothermal lens device was presented by Seidel et al. [132] in 1998, and reported LODs were one or two orders of magnitude better than a conventional absorption detector.
Other types of detection cells have been based on the optical properties of the analyte (e.g., an integrated
refractive-index, optical-ring-resonator detector was presented in the work of Zhu et al. in 2007 [133]).
Miniaturized surface plasmon resonance detection for CE was presented by Whelan et al. [134] in 2003.

3.6.3. Chemiluminescence

CLD can achieve concentration LODs even lower than those of FD. Moreover, in its classical arrangement, it does not require any light source, unlike other types of OD. However photo-initi-ated CLD (PICLD) has also been described [13 5].
Liu et al. [136] described a relatively simple method for constructing a chip-based CLD (20 x 15 x 1.7 mm) based on tris(2,2'-bipyridyl)ruthenium(II).
A post-column sheath flow CLD was presented by Peng et al. [137] in 2000. The main advantages of the arrangement described were given by the stainless-steel body of the detector, which decreased the electrical noise and the ambient light penetrating into the detection cell. At the same time, extremely close positioning of the photomultiplier tube to the capillary increased the solid angle for light collection.
In 2002, Tsukagoshi et al. [138] presented miniaturization of batch-type and flow-type CLD detectors, when Tsukagoshi et al. [81] described an even smaller chip-based CLD detector. As noted previously, the miniaturization of OD is mostly using LDs and LEDs. However, classical CLD benefits from the fact that no light source is required, but chemical reaction is essential, so difficulties with additional chemicals have to be overcome.
3.6.4. Mass spectrometry (MS) and miscellaneous tech-niques. CE can be easily coupled with a wide range of detection techniques. Swinney and Bornhop gave an overview including unconventional CE detectors [139]. MS probably has the best capability for complex and universal detection in portable analytical instrumenta-tion, especially due to its detailed composition analysis and suitability for a variety of sample types. Miniaturized and portable (hand-held) mass spec-trometers have already been described [140-142], but miniaturized

CE—MS or P—CE—MS has yet to arrive, as the miniaturized MS detectors require further development for easy use in portable systems. Coupling of CE with other detectors {e.g., NMR [143,144] and ICP-MS [145,146]} is not suited to miniaturization for the foreseeable future, despite the increasing use of CE-ICP-MS for inorganic speciation [147,148].

3.7. Power and data acquisition

3.7.1. Power

In P—CE systems, power supplies are re-quired for HV generation, actuation and detection (e.g., LD, LED or electrochemical). The main requirements of the power source are that it should be lightweight, long-lasting and provide the voltage level(s) required. Many different types of battery power are available for portable micro-electronic systems. Cheap long-life but heavy systems can be used (e.g., 12 V car battery with DC converter if needed) [149]. Silver-zinc batteries have a high power-to-weight ratio. Due to cost, these are typically restricted to high-end applications (e.g., aerospace). Nickel-cadmium batteries are also relatively light, but can suffer from loss of charge and short lifetime due to early recharging cycles (known as memory effect).

Lithium-ion batteries are most popular now for low-voltage portable electronic applications (up to tens of Volts). Lithium-ion batteries are light, have high energy density and can hold a charge for longer periods than competing technologies. Typically, these batteries will have a useful life of about three years. That batteries have a finite life is due to either the build up of chemical or physical changes on the electrode surfaces during operation or the loss of active electrode material. Higher temperatures also increase the rate of unwanted chemical reactions, which results in reduced battery life. These power sources are now relatively cheap, provide high power and can be used for construction of light-weight, sensitive P—CE detection systems [150,151].

Care must be taken to minimize the effects of separation current on detection measurements. Nominally, the same power supplies can also give greatly varying results in chemical or bio-assay detection designs due to variability of the power-supply voltage level in electrophoresis. In some cases, this has resulted in variations in sensitivity and detection distribution broadening [152]. Typical currents in electrophoresis are in the range 1—100μA, while voltages can range from a few hundred Volts up to thousands of Volts, mainly depending on the capillary length used, with 10 kV often used in P—CE systems, compared with 30 kV in commercial instruments. This is primarily due to the much lower prices and smaller size of HV modules below 10 kV. Typical voltage accuracies of 0.1% of maximum voltage, resolutions in the μV range and stabilities of less than 50 mV peak to peak can be found from commercial suppliers [153-155]. When integrating these into a P—CE system, typically the power supply can be programmed to pro-vide the required voltage profile during detection. Erasable programmable read-only memory (EPROM) is re-writable hard wired control circuitry, which allows these devices to be programmed through conventional interfaces (e.g., serial, GPM, LAN, USB and DM while operating independently at a remote location. Small changes in programming (e.g., ensuring no power draw when detection is not taking place) can provide large increases in battery lifetime.

Recent developments that may provide a step change by reducing battery weight and increasing battery life-times relate to electrochemical double-layer capacitors (EDLCs), otherwise known as ultracapacitors, which do not have a dielectric separating plates but rather have two layers of the same substrate. The electrical properties of the surface provide effective electric separation, which, in turn, allows much larger surface areas and larger capacitances. While voltage levels are generally still low from such devices, this technology has shown promise for providing HV levels in small packages [156].

3.7.2. Data acquisition.

Primarily, it is the peak width of capillary-zone-electrophoresis peaks that define acquisition-rate requirements [157,158], with typical data-acquisition rates in the range 10-100 Hz, which is easy to achieve from current sampling electronics. Shorter capillary lengths can require faster acquisition rates, whereas slower rates may be satisfactory with longer capillaries.

Pulsed detection techniques may also need faster sampling. Acquisition rates in the MHz range have been reported [159]. Signal amplification is often required with some additional electronics to aid signal-to-noise ratio detection. Compared to battery technology, similar size reduction and portability has been achieved for this signal conditioning and sampling electronics. Advances in EPROM technology and wireless-signal communication also allow greater portability in new P—CE designs. The most common equipment for data acquisition in portable instruments is now a laptop equipped with commercial or custom-developed software. Due to progress in electronics, the integration of the acquisition system into the CE instrument or connection to a palm-size instrument will become increasingly easy.

4. Concluding remarks

Miniaturization influences all areas of science and technology, impacting positively on the size and the potential portability of existing bench-top CE instrumentation. In the field of analytical and separation sciences including LC and CE, a substantial source of progress in miniaturization will be from general progress in technology (i.e. reduced component sizes including those of separation columns, dimensions of detection cells and operating electronics). This will have positive influence on the development of P—CE instrumentation.

In the trends in P—CE, miniaturization efforts have focused on microfluidic chip-based CE and there is one commercial fully-portable CE instrument currently available on the market. However, numerous in-house-designed P—CE instruments have been reported, showing the importance of portable, capillary-based CE research. It is important to emphasize that capillary-based CE has outstanding advantages (namely, simplicity, affordability, flexibility of design and robustness based on the ultimately simple geometry and technology of polyimide-coated fused-silica capillary proved by decades of usage).

Separation in short capillaries is an elegant, very simple approach to miniaturization of CE and rapid analysis. This allows the advantage of short separation length, as in chip-CE, but with the advantages of simple capillary replacement, design and operation, which has clear potential for P—CE. Short capillaries can be moun-ted on platforms that allow integration with other functional parts, especially injection and detection.

We can conclude that miniaturization of CE injectors and detectors, as central parts of the CE design, are key to successful field P—CE development. HD and EK types of injection are the most common, but other sample-introduction techniques, in particular nano-valves, miniaturized FI-CE and SI-CE coupling hold promise for future developments in P—CE.

From the point of view of suitable detection for P—CE, ECD has the advantage of compatibility with miniaturization and portable instrumentation. However, miniaturized, low-cost light sources (e.g., high-power LEDs and LDs) are very efficient, inexpensive alternatives to traditional light sources (e.g., laser modules for LIF) so LEDs and LDs are also likely to find their way into P—CE. The drive for miniaturization comes from the needs in many application areas utilizing analysis techniques (e.g., sensor technologies and microfluidic chips), and modern technology-enabled traditional techniques (e.g., P—CE). These application-driven needs for miniaturization combine with the enabling developments in technology [e.g., fuel-cell technology, materials science, electronics (semi-conductor, power sources and other components) and miniature electromagnetic actuators]. Developments in these areas drive and enable future developments in miniaturization of

components and integrated systems. The enabling technologies are continually being developed and therefore available for further improvements in the miniaturization of P—CE devices.

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