

# Recent development in capillary ion chromatography technology

## Review Article

Bingcheng Yang<sup>1\*</sup>, Feifang Zhang<sup>1</sup>, Xinmiao Liang<sup>1,2</sup>

<sup>1</sup>School of Pharmacy, East China University of Science and Technology, Shanghai 200237, China

<sup>2</sup>Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China

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**Abstract:** This review summarizes the development of capillary ion chromatography (CIC) over approximately the last 5 years. It mainly focuses on the technologic aspects of several key components associated with CIC, including micropump, microscale electrodynamic eluent generator, microscale suppressor and the detector.

**Keywords:** Capillary ion chromatography • Micropump • electrodynamic eluent generator • Microscale suppressor • Charge detector

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## 1. Introduction

Since its introduction in 1975, ion chromatography (IC) has been a well-established analytical technique for the determination of ionic species. As a branch of IC, capillary IC (CIC) has attracted much attention in recent years due to some advantages such as low consumption of sample or eluent, high efficiency and good compatibility with detectors like ICP or MS [1,2]. For CIC, presently there is no clear definition and, for convenience, it refers to the separation column with the inner diameter ranging from 0.1 to 0.5 mm. Relative to the conventional columns (e.g. 4 mm i.d.), the decrease of column size requires other components to match this change. Thus CIC is not a simple decrease of conventional IC equipment and it needs novel design. Two specific reviews were presented in 2004 in which the basic theoretical aspects of CIC and the capillary columns were discussed [1,2]. Significant advances of CIC have been achieved during this period [3]. The purpose of this review is to give a short summary of CIC, which is based on the development of key components of CIC; this includes micropump, microscale electrodynamic eluent generator, microscale suppressor and the detector. As one of the key components of CIC, capillary ion exchange columns function to separate the analytes of interest. This topic

has been recently reviewed in detail [3] and will not be covered in this review.

## 2. Development of several key components of CIC

### 2.1. Micropumps

Pumps serve to drive the eluent to flow through the system at a given flow rate. The typical flow rate in CIC ranges from 0.5 to 12  $\mu\text{L min}^{-1}$ . For a piston mechanical pump, it is difficult to accurately provide such low flow rate due to a small amount of leakage from the check valve. Thus splitting the flow rate is always needed for a capillary scale chromatography system. Although there are some commercially available nanopumps, they are bulky and extremely costly. It is necessary to develop novel micropumps which are well suited with CIC. In spite of many kinds of novel micropumps reported, most of them are not compatible with CIC due to their low pressure output [4]. Three kinds of micropumps with high pressure output that have been or will be potentially used in CIC will be mentioned; they are the syringe pump, electroosmotic pump (EOP) and the thermal expansion pump (TEP).

\* E-mail: bcyang@ecust.edu.cn

Syringe pumps can accurately provide extremely low flow rates (e.g. nL/min-  $\mu$ L/min scale), which is very useful in the microscale analytical system. Other advantages include low price and small size. However, most commercial syringe pumps could not bear higher pressures and are solely used in low pressure systems. By replacing a glass syringe with a PEEK or stainless steel syringe and the associated sealing component, some high pressure syringe pumps are commercially available (<http://kloehn.openfos.com/web/syringe-pumps.htm>). Dasgupta *et al.* demonstrated some applications of such kind of pumps for CIC [6,7].

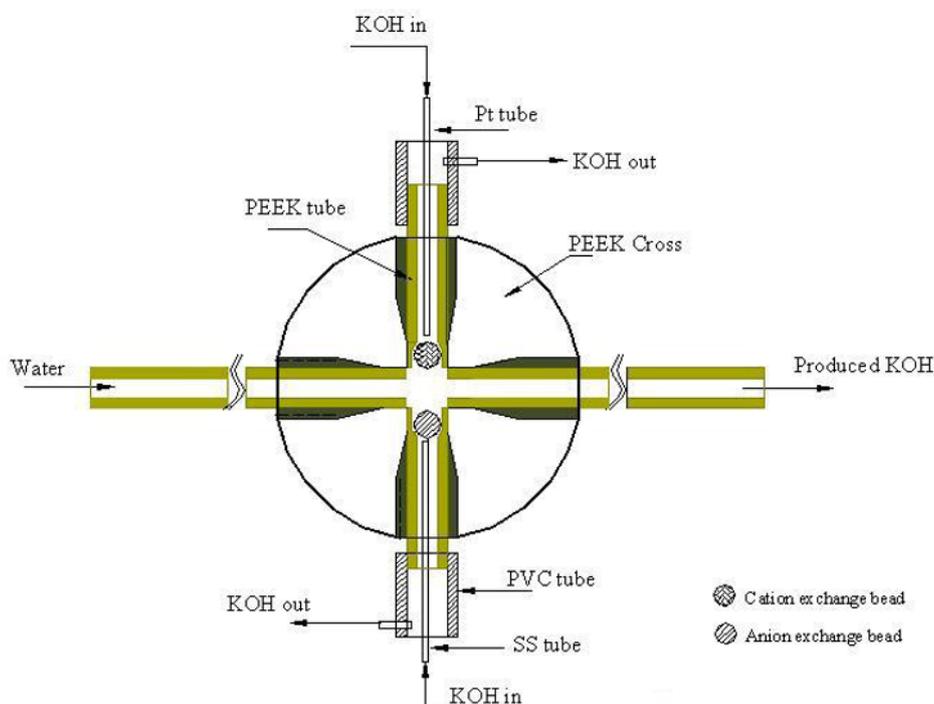
Electroosmotic pumps (EOP) are based on the electroosmotic flow to drive liquid through the conduit [8]. The advantages of EOP include no moving parts, substantial pressure output, pulseless flow, and simple fabrication. Because the flow from an EOP is driven by the electric field, precise flow control (flow direction or magnitude) can be easily achieved by changing the direction or the magnitude of the electric field. These advantages allow an EOP to be practical for a CIC system. The drawback of EOP is poor long-term stability due to the interference of the electrolytic product (gas or hydroxide). To eliminate the effect of electrolytic products, a special electrode [8] or an electric-field decoupler [10,11] have been utilized. By using Ag/Ag<sub>2</sub>O electrode replacing common Pt wire, Shin *et al.* demonstrated a miniaturized gas-free EOP with extremely low operation voltage (0.5 V) [9]. The electric field decoupler eliminates the interference of electro-dialytic products by directly isolating the electrode from the pumping fluid. Commercial Nafion cation exchange membrane tube has been widely used as a decoupler for EOP due to its excellent current transmission efficiency. Its disadvantage is poor pressure tolerance and could not be used in high pressure chromatographic systems. By using a cation exchange resin (CER) bead to replace Nafion tube, Yang *et al.* have fabricated a novel high-pressure electric-field decoupler for EOP [12]. The decoupler demonstrated rather high pressure-bearing ability (up to 3200 psi) and proved to eliminate interferences from electrolytic gas and electro-dialytic ions (typically, hydroxide), which seems to be a practical high-pressure interface between EOP and capillary-based chromatographic systems. Pure water driven by the above mentioned high pressure decoupler-based EOP could be changed on-line into the KOH eluent needed for CIC via a microscale KOH electro-dialytic generator [12]. It is believed that the combination of EOP and a micro EDG ( $\mu$ EDG) would be a good micropump option for CIC. In addition, as the conduit of electroosmotic flow produced, a packed capillary column or monolithic column determines the final pressure output and the

flow rate produced. Relative to the packed column, monolithic columns show many merits including easy preparation and frit-free features [11,13,14]. The frit-free feature is really important for EOP long-term stability considering that the frits are often thought of as the source of gas formation in the running process due to the variance of the surface property between the packed bed and the frit [15]. The preparation of a monolithic column is always a tedious process, at least 40 h [11] or 88 h [13] is needed for silica or polymer monolith preparation, respectively. To address the lengthy preparation process encountered, Wang *et al.* presented a fast way to prepare silica xerogel-based monolithic columns applied for EOP and the whole process was less than 4 h [16]. The fabricated EOP demonstrated good performance in terms of flow rate and pressure output produced. In their subsequent work, a novel cascade EOP has been reported recently [17]. Cascade EOP is an effective way to increase pressure output of EOP without the need to increase the applied voltage [18,19]. In their new design [17], cascade EOP was fabricated by alternatively connecting cation monolithic column (CMC) and anion monolithic column (AMC) in serial. Since forward voltage was applied through the CMC while reverse voltage was applied through the AMC, the produced electroosmotic flow had the same direction to the cathode. Obviously, this design allows for easy change of the electric polarity between each stage of cascade EOP and the minimal amount of connection units needed.

Thermal expansion pumps (TEP) are based on the principle of liquid thermal expansion. TEP is capable of generating high pressure output and also generating a stable flow ranging from nL min<sup>-1</sup> to  $\mu$ L min<sup>-1</sup>. By using a digital program temperature control system, Zhang *et al.* presented a TEP with pressure output up to 1000 bar. It was successfully used for capillary liquid chromatography (CLC) and both isocratic and gradients of binary solvent delivery by TEP were performed [20]. Without any doubt, TEP can be potentially applied for CIC. In fact, if TEP is combined with a  $\mu$ -EDG, the above complicated configuration used for gradient operation could be greatly simplified and only a sole chamber is needed to drive pure water to flow through  $\mu$ -EDG and then changed into the eluent needed.

## 2.2. Microscale electro-dialytic eluent generator ( $\mu$ -EDG)

Electro-dialytic eluent generators (EDG) are based on the electrolytic principle and can online produce high-purity eluent used for IC [21]. The concept of driving water through an EDG and varying the current to achieve gradient elution is well established in IC. An EDG eliminates the need of constant manual



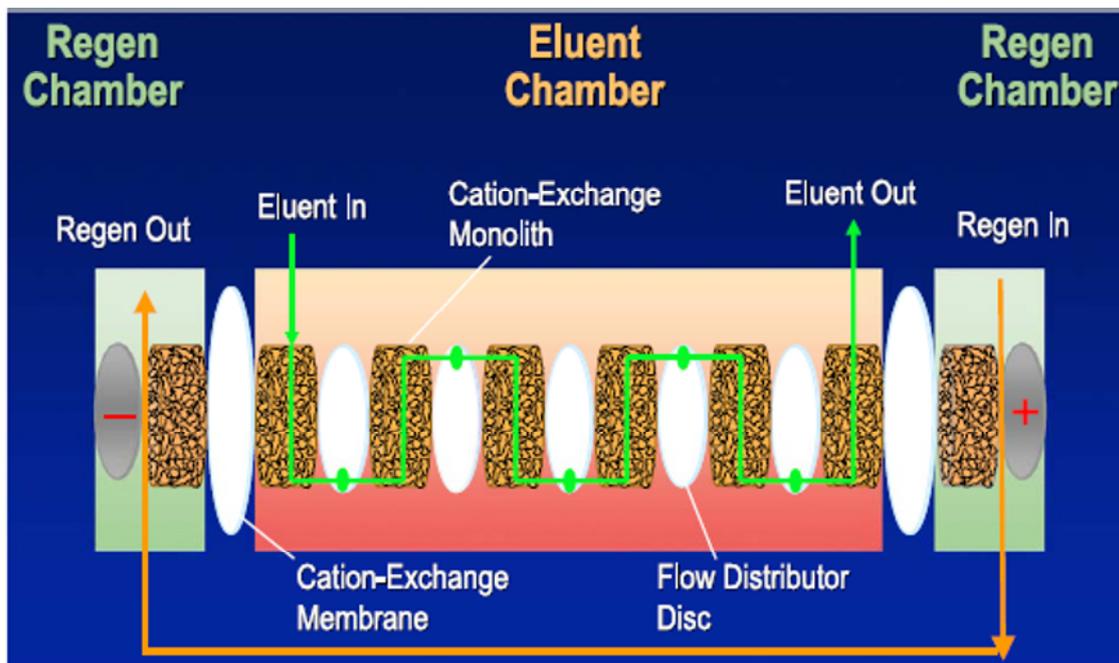
**Figure 1.** The scheme of two-membrane electrodiolytic eluent generator.

eluent preparation and associated problems such as contamination-prone and operator errors that could also be avoided. Dasgupta *et al.* firstly introduced a micro-scale NaOH EDG for CIC and successfully demonstrated its benefits for the analysis of anions [22]. A drawback of such design is its poor ability of bearing backpressure (< 800 psi) due to the poor mechanical strength of the membrane sheet used. A miniaturized version of a conventional EDG is commercially available (<http://www.dionex.com/>), in which membrane sheets are stacked together to withstand high pressure. By using ion exchange resin (IER) beads in place of the membrane sheet, Yang *et al.* fabricated a KOH high pressure  $\mu$ -EDG with dual-membrane configuration, as schematically illustrated in Fig. 1 [7]. A cation exchange resin (CER) bead and an anion exchange resin (AER) bead is used to isolate the eluent chamber and the regenerant channel respectively, and two electrodes are placed respectively in an anodic and cathodic chamber. In contrast, the majority of extant EDGs belong to single-membrane configurations (including commercial versions), in which one electrode is in direct contact with the eluent and the electrolysis gas is accompanied with the produced eluent. Dual-membrane design ensures the production of gas-free eluent, obviating the need of a gas removal device encountered in single-membrane configuration. IER bead has some advantages over ion exchange membrane sheet in view of its significant thickness and smaller size. Their spherical shape

makes them ideal candidates for fabricating high-pressure devices in a miniature simple format. In their subsequent work, they also presented an IER-bead based KOH  $\mu$ -EDG in single membrane configuration [23]. The device has been tested up to pressures of 3200 psi and has near-ideal Faradaic efficiency. One of the obvious merits of these above dual-membrane  $\mu$ -EDG is a multifunctional one that is capable of generating diverse eluents such as  $\text{Na}_2\text{CO}_3/\text{NaHCO}_3$ ,  $\text{CH}_3\text{SO}_3\text{H}$ , and  $\text{KNO}_3$  [24]. This merit has further been demonstrated to behave in an electrodiolytic reagent introduction device reported by Santosh *et al.* [25]. By using 4-(2-pyridylazo) resorcinol (PAR) as feed solution, which is a commonly used reagent for post-column derivatization of transition metals in IC, the device could electrodiolytically generate PAR by programmed current control. As only PAR is electrodiolytically introduced, volumetric dilution of the analytes of interest could be avoided. The electrodiolytic mode is also helpful to the mixing between the bulk flow and the introduced PAR, thus leading to better reproducibility. One drawback of this device is its poor Faradaic efficiency due to strong interaction between PAR molecule and the ion exchange membrane sheet used in the device.

### 2.3. Microscale suppressor

The basic purpose of a suppressor in IC are to reduce the background conductivity and noise of the eluent background while enhancing the conductivity of the

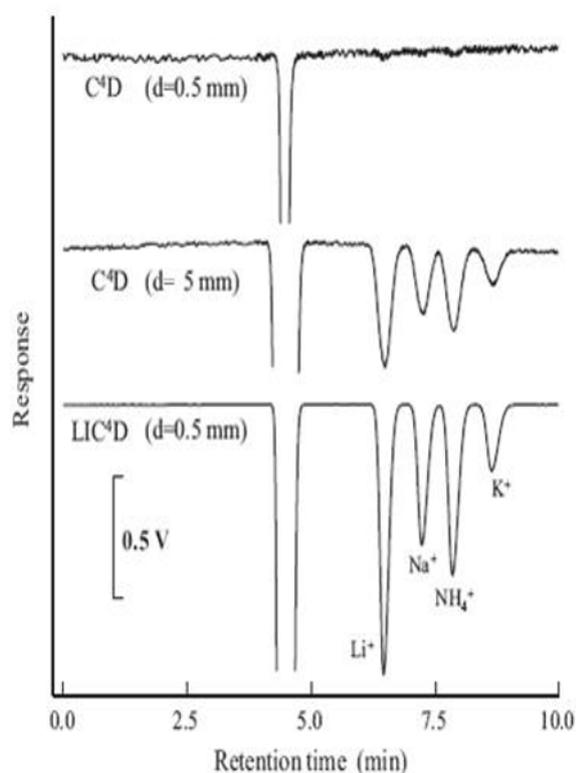


**Figure 2.** The scheme of Atlas® electrolytic suppressor.

analytes (*i.e.*, increasing the signal/noise ratio). IC with suppressed conductivity detection mode constitutes the current-state-of-the-art chromatography. Compared to conventional counterparts, the fabrication of a microscale suppressor is more difficult due to more stringent demands for effective suppression effect and minimal extra column broadening. Since Rokushika *et al.* presented a segment of Nafion fiber (200  $\mu\text{m}$  i.d.)-based suppressor for suppression of carbonate/bicarbonate eluent in 1983 [26], this kind of microscale suppressor is still found in many applications of CIC up to now [6,7,23,24]. As Nafion fibers with smaller diameters are not commercially available, custom-fabricated fiber is required in order to further reduce the dead volume. Kuban *et al.* fabricated a very small diameter fiber suppressor by casting Nafion solution onto a platinum wire inserted in a capillary as a mandrel [1]. Though this arrangement was effective to reduce dead volume, its fabrication procedures were rather complicated and at the same time its poor durability could be predicted due to possible swelling and even detachment of the Nafion film from the connection. Resembling commercial conventional design, Sedyohutomo *et al.* have described a pair of alternately regenerated and washed packed capillary suppressors that can be used with packed capillary columns [27]. Recently, a monolithic integrally attached membrane suppressor formed by casting a monomer mixture to make a controlled porosity monolithic membrane around a tungsten wire mandrel was presented [28]. Although the suppressed effect was

not so satisfactory, the use of ionic monolith material to replace common commercial Nafion tubes provide a new way to fabricate a microscale suppressor. More studies are still needed to further improve its performance.

A common drawback of the chemical suppressor is that chemical regenerant solution is required. In comparison, the electrolytic suppressor uses water splitting to generate regenerant ions (*e.g.*  $\text{H}^+$  for anion analysis or  $\text{OH}^-$  for cation analysis), leading to more convenient and much simpler operation. A miniaturized electrolytic suppressor for CIC (termed as Atlas electrolytic suppressor, AES) is commercially available, and its schematic diagram is provided in Fig. 2. The design utilizes an ion exchange membrane tube that is externally resin-packed [29]. This arrangement combines the features of the conventional electrolytic membrane-based suppressor and fiber-based suppressor. In addition, functionalized monolithic bed is also used in this design to reduce the system resistor. AES demonstrates excellent performance in terms of its fast regeneration time ( $< 30$  min), low void volume ( $< 35 \mu\text{L}$ ), and low noise level (typically  $1\text{--}2 \text{ nS cm}^{-1}$ ). Since its operation is based on electrolytic mode, its regeneration is simultaneous during operation and there is no need to use chemical regeneration solution (such as strong acids or bases). As mentioned above, the use of IER bead provides a simple way to fabricate microscale devices. The dual-membrane  $\mu\text{-EDG}$  mentioned above can behave like a microscale suppressor with minor modification, *e.g.* it is an anion or cation suppressor



**Figure 3.** Chromatograms achieved with low capacitance  $C^4D$ .

when two CER or AER beads are respectively used to replace CER+AER beads used in dual-membrane  $\mu$ -EDG. Using a CER bead, Zhang *et al.* demonstrated an IER bead-based microscale electric suppressor [30]. This design was well suited with the CIC system due to low dead volume ( $\sim 600$  nL) and effective suppressed background (e.g. 10 mM KOH eluent could be suppressed to be  $\sim 3$   $\mu$ S  $cm^{-1}$ ). The drawbacks of the suppressor were limited suppression capacity and a still-higher electric resistor.

Generally, the fabrication of a microscale suppressor is still challenging and further study is needed to fabricate microscale suppressors with low dead volume and high dynamic suppression range.

## 2.4. Detector

Among the several key components of the CIC system, the detector is probably the only one that can be easily miniaturized. This is especially true for conductivity detectors (CD), which is the preferred detection mode for routine analysis in IC or CIC due to its universal and sensitive features. For CD, its signal magnitude is much less dependent on the flow cell scale which is always a barrier encountered for the miniaturized optical detector. The technology of miniaturized CD has been well explored with the development of capillary electrophoresis (CE), which can directly be transferred

to CIC. The nongalvanic CD (capacitively coupled contactless conductometric detector,  $C^4D$ ) introduced in 1998 has found widespread applications in CE or in CIC due to its robustness, minimal maintenance demands and low cost [31,32]. In the past decade, different designs and theoretical aspects of  $C^4D$  have been comprehensively investigated [33–35]. Commercial devices are now available by at least two companies (<http://www.istech.at/product.htm>; <http://www.edaq.com/products.php>). One of the latest reviews has mentioned, in detail, the progress of  $C^4D$  in micro-separation technologies [36]. Up to now, most of the applications of  $C^4D$  have been focused on CE and the reports for CIC have been very limited. In fact, for detecting inorganic anions when used in suppressed mode, the detection limit of  $C^4D$  was found to be comparable to that of galvanic CD [37]. It believes that  $C^4D$  will find more application of CIC due to the above mentioned advantages. To reduce the stray capacitance of flow cell, Kang *et al.* presented a way in which a piezoelectric quartz crystal resonator (PQCR) was in serial connected with  $C^4D$  [38]. The PQCR behaves to be an inductor and its induced impedance is inversed to that of a capacitor. At resonant frequency, the high capacitive impedance between two contactless electrodes was observed to be compensated by the inductive impedance from the PQCR, leading to minimum total system impedance and enhancement of signal-to-noise. Recent application of such detector in CIC was used for the analysis of alkaline cations at on-column mode, indicating much higher sensitivities compared to that of common  $C^4D$ . Direct comparison between two designs was shown in Fig. 3 [39]. One interesting extended application of  $C^4D$  for CIC presented by Gillespie *et al.* was for characterizing the homogeneity of monolithic stationary phase coatings [40]. The longitudinal homogeneity and stability of the internal capillary coating was investigated by measuring the detector response at different positions of the capillary column by sliding the  $C^4D$  cell along the length of the column. By using one commercially available integrated circuit chip that measures capacitance from floating sensors costing less than \$150, Dasgupta *et al.* fabricated a cheap contactless capacitance detector (CCD), which resembled common  $C^4D$  except that it responds to the change of capacitance between two electrodes other than conductivity [7]. By using this detector, an ideal electrostatic selectivity of tetraalkylammonium cations on a methacrylate-based sulfonate monolithic capillary column was observed [41]. The detailed information of the CCD was described in their later article [42]. CCD can essentially be used as a common  $C^4D$ , as further proved by their series of reports [7,12,23].

Although CD is the preferred detection mode in IC, there are other detection modes that can find useful applications in CIC. Direct absorbance detectors that are a widely used mode in CE is only useful for measuring some inorganic anions with strong UV absorption (such as  $\text{BrO}_3^-$ ,  $\text{Br}^-$ ,  $\text{NO}_2^-$ ,  $\text{NO}_3^-$ ,  $\text{SCN}^-$ ,  $\text{IO}_3^-$ ,  $\text{I}^-$ ) although the achieved detection limits are much higher than that of suppressed CD. Actually, this mode has always been used for the evaluation of some homemade new capillary ion exchange columns [43,44]. As a very cheap miniaturized optical source, light-emitting diodes (LED) have found widespread applications in photometric and fluorescent detection [45]. LED-based indirect photometric detectors have been used to determine common inorganic anions separated by CE [46]. This mode can also be useful for CIC if suitable background adsorbing reagent is chosen. By the post-column derivatization method, LED-based photometric detection would probably provide a rather sensitive approach for the determination of transition metals [47,48]. One direct approach to increase the detection sensitivity of LED-based photometric detectors is to increase its optical path length. Mishra et al. reported multi-reflection flow cell-based capillary scale absorbance detectors, in which the optical path length was extended via silver coating [48]. For the tested capillary flow cell (180  $\mu\text{m}$  i.d.) with ~2-cm apparent optical length, 50-fold gain of signal-to-noise was achieved.

As a novel detection mode, charge detector (CHD) will be useful for suppressed CIC. When measuring the current-voltage curve of the above dual-membrane IER bead-based  $\mu$ -EDG, Yang *et al.* found that the curve was much similar to the behavior of the doped p-n junction. It is known that the doped p-n junction behaves LED at forward bias voltage and photodiode at reverse bias voltage respectively [7]. According to this analogy, they found that  $\mu$ -EDG could behave like a detector which responded to the total charge of the injected electrolyte. Its working principle has been clearly described previously [49]. A distinct feature of CHD is its identical response to the analytes if their total charges are the same, regardless of ionic valence. This is much different with common CD. For example, if  $\text{HNO}_3$  and  $\text{NaNO}_3$  solutions are the same concentration,  $\text{HNO}_3$  has a much higher response on CD due to the greatest ionic mobility of  $\text{H}^+$  relative to  $\text{Na}^+$ , while these two analytes have almost the same response on CHD

due to their same total charges. This feature allows identical calibration curves for all strong electrolyte samples to be possible, thus obviating individual calibration. In addition, it was found that CHD has higher sensitivity to weak electrolyte compared to common CD. CHD will probably be a good alternative to CD for the determination of ionic samples for CIC. An extended application of CHD is serving as a desalter, which is very useful for online coupling with mass spectrometers (MS) for the determination of biologic samples. The salts contained in the biological sample (e.g. proteins) are detrimental to MS and need to be removed prior to entering the MS. Chen *et al.* demonstrated this concept by using ion exchange membrane sheet-based CHD [50]. Four common proteins in the presence of up to 154 mequiv  $\text{L}^{-1}$  NaCl solution and smaller concentrations of citrate and phosphate buffers were used as model analytes and >99.8% salt removal and < 20% sample loss for the tested samples were achieved. Considering the large cell volume of the membrane sheet-based CHD, fabrication of an IER bead-based CHD should be a better choice for fabricating a microscale desalter that matches with CIC-MS.

### 3. Conclusion

This review summarizes the recent development of CIC in the last 5 years. Although CIC setup has been commercially available, it is still evolving and some key components need to be further developed. For the analysis of inorganic ions, CIC will be more competitive than CE due to its high reliability and stability. In addition, the distinct feature of CIC would also provide a potential alternative for capillary LC systems for bio-analysis because the aqueous eluent used in CIC is much more compatible with the aqueous system than capillary LC. Presently, CIC has been far from popular compared to its conventional counterpart; it needs more time in order to be widely accepted.

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