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Advanced analytical methods and sample preparation for ion chromatography techniques

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Ion Chromatography (IC) has undergone a tremendous development and can be regarded today as one of the most versatile analytical methods for all kinds of ionic compounds. The IC technique offers an enormous range of possibilities for the selection of stationary and mobile phases, fabrication of novel separation modes, and hyphenation with different detection techniques, which has made IC eminently suitable for the rapid and simultaneous determination of numerous inorganic and organic anions and cations. In this paper, firstly, a general overview of the IC principle, including the IC methodology, development history, separation mechanism, apparatus and procedure, and application, is given as an introduction of this technology. Secondly, the significant role of sample preparation for IC is discussed, and various IC sample preparation methods are summarized. Finally, the currently practiced advanced IC techniques for complicated samples, critical analytical requirements and unique application are presented, which mainly focus on the two-dimensional IC technique (2D-IC), hyphenation technique of IC with mass spectrometry (IC-MS) and capillary IC technique (CIC).

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1. Introduction

In the past few decades, there are increasing demands for analytical science, especially for inorganic ion (cations and anions) determination, ionic organic compound quantification, and element content analysis.[1–5] A variety of methods have been used for analyzing inorganic ions, including rapid and sensitive spectroscopic methods like atomic absorption spectroscopy (AAS), inductively coupled plasma-atomic emission spectroscopy (ICP-AES), and inductively coupled plasma-mass spectrometry (ICP-MS), as well as electrochemical methods, such as polarography and stripping voltammetry.[1,3,5,6] Unfortunately, some of these methods suffer from spectral and chemical interferences, limited sensitivity, labor-intensity and problems with automating, and are unsuitable for direct trace analyses in complex matrices or for studies on metal speciation.[2,7,8] Ion chromatography (IC), one of the most powerful tools in element analysis, has grown to become the method of choice for the

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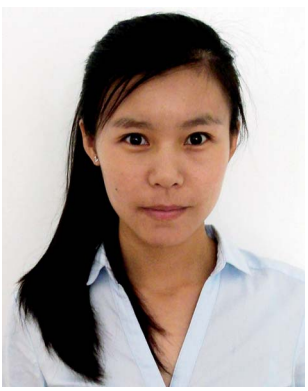

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determination of multiple cations and anions in solution, and is the most widely applied analytical method for the determination of the ion composition of aqueous samples. The main parameter, on which separation selectivity strongly depends, is the nature of the ion-exchange groups and the sorbent to which they are attached. IC offers several advantages over conventional methods, which make IC as the qualified and attractive analytical method, including short analysis time, small sample volume, high sensitivity (ppb level), simple water sample preparation, high selectivity and resolution, and simultaneous determination of anions and cations, or inorganic and organic ions.[6,7,9–17]

IC is an innovative analytical technique that has significantly improved analysis of ionic compounds in various complex samples. In the late 1950s, research team at the Dow Physical Research Laboratory (Midland, MI, USA) has foreseen the benefits of inorganic ion analysis by replacing many wet chemical methods with a single chromatographic technique. The first breakthrough came in the late 1971, when Hamish Small and his colleagues proposed and tested a chromatographic method that used ion exchange as the separation mode and conductivity detection.[18] Dow Chemicals patented suppressed conductivity and subsequently licensed it to Durrum Instruments, which later became Dionex (Thermo) for commercialization of IC.[18] In 1975, Small's group[9] initiatively reported a novel ion-exchange chromatographic method for the separation and conductometric detection of ionic species, in which a low-capacity ion-exchange stationary phase was employed for the separation of analyte ions, in conjunction with the second ion-exchange column and conductivity detector, capable for continuous monitoring of eluent. The milestones in the IC development are given in Fig. 1.

IC can be used for the determination of ionic solutes (Table 1) such as: inorganic cations, including alkali metals, alkaline earth metals, heavy metals, transition metals, and rare earth metals, carboxylic, phosphoric and sulfuric acids, detergents, carbohydrates, low molecular-weight organic bases, ionic metal complexes, and common inorganic anions, such as halide ions and acid ions.[7,8,19–28]

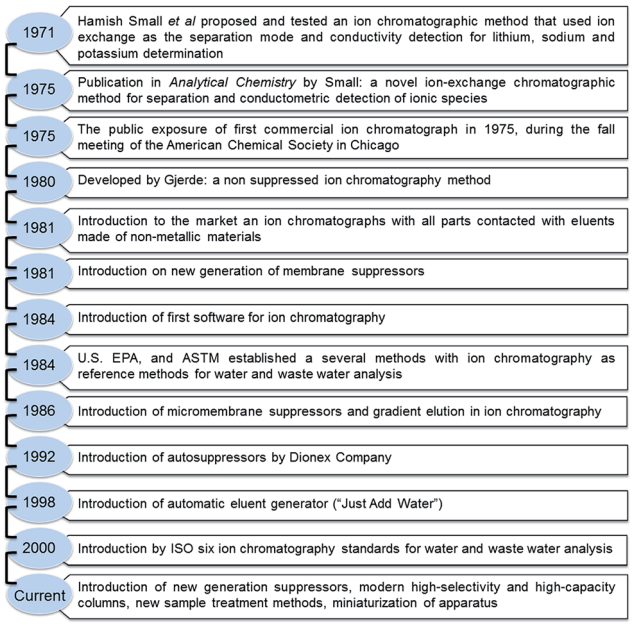

Fig. 1 The milestones in the IC development.

1.1 Mechanism

IC is designed to analyze individual components in a mixture, using a column packed with a specific material, normally an ion exchanger as a stationary phase and an eluent as a mobile phase. A test sample injected into the column is separated into individual components by flushing the eluent through the column, which is similar to the common liquid chromatography.[6,16] IC method utilizes the difference in ion-exchange capacity of individual components, and is applicable to liquids or substances that can be made into solutions, usually used for identification tests, purity tests, assays and other tests. IC can be used to reliably and effectively quantify the anions, cations, and polar substances throughout a wide concentration range and a whole variety of ions can be analyzed in a single determination with low-cost and time-consuming. IC

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Table 1 IC determination of ionic compounds

	Analyte groups	Examples of analytes	Separation mechanism	Detection mode
Inorganic	Alkali, alkaline earth metals and ammonia	Li^+, Na^+, K^+, NH_4^+, Rb^+, Cs^+, Mg^{2+}, Ca^{2+}, Ba^{2+}	Cation-exchange	Conductivity
	Halide ions, strong acid ions	F^-, Cl^-, Br^-; NO_3^-, SO_4^{2-}, SO_3^{2-}, PO_4^{3-}, PO_2^-, NO_2^-, ClO^-, ClO_2^-, ClO_3^-, $HCOO^-$, CH_3COO^-	Anion-exchange	Conductivity, UV/Vis
	Weak acid ions	BO_3^-, CO_3^{2-}, SiO_3^{2-}	Anion-exchange, ion-exclusion	Conductivity, UV/Vis
	Hydrophobic ions	CN^-, HS^-, BF_4^-, $S_2O_3^{2-}$, SCN^-, ClO_4^-, I^-	Anion-exchange, ion-exclusion, ion-pair	Conductivity, amperometric
	Heavy and transition metals	Cu^{2+}, Ni^{2+}, Zn^{2+}, Co^{2+}, Cd^{2+}, Pb^{2+}, Mn^{2+}, Fe^{2+}, Fe^{3+}, Sn^{2+}, Sn^{4+}, Cr^{3+}, V^{4+}, V^{5+}, UO^{2+}	Anion-exchange, ion-exclusion	UV/Vis, AAS, ICP-MS, ICP-AES
	Lanthanides, actinides	La^{3+}, Ce^{3+}, Pr^{3+}, Nd^{3+}, Sm^{3+}, Eu^{3+}, Gd^{3+}, Tb^{3+}, Dy^{3+}, Ho^{3+}, Er^{3+}, Tm^{3+}, Yb^{3+}, Lu^{3+}, Am^{3+}, Cm^{3+}	Anion-exchange, cation-exchange	UV/Vis, AAS, ICP-MS, ICP-AES
Organic	Fatty acid ($C < 5$)		Ion-exclusion	Conductivity
	Fatty acid ($C > 5$), aromatic acid		Anion-exchange ion-pair	Conductivity, UV/Vis
	Alkane sulfonate, aromatic sulfonic acid salt		Anion-exchange, ion-pair	Conductivity, UV/Vis
	Alcohol ($C < 6$)		Ion-exclusion	Amperometric
	Low molecular weight amines, alkylamines, mono-, di-, tri-, tetramethylamine, alkanolamines, monoethanolamine, diethanolamine		Cation-exchange, ion-pair	Conductivity
	High molecular weight amines alkylamines, aromatic amines, cyclohexamines, quaternary ammonium ions, polyamines		Cation-exchange, ion-pair	Conductivity, UV/Vis

incorporates three typical separation mechanisms for ion separation, including ion exchange, ion-pair and ion-exclusion, while the majority of methods are based on anion- or cation-exchange substrates.[16]

Ion exchange chromatography is based on a stoichiometric chemical reaction between ions in a solution and the oppositely charged functional groups on the column resin.[9] Ionizable chemical groups, interactive with target ions, are immobilized on a solid support such as cellulose or agarose maintained in the column. Molecules with opposite charge can bind to the column by electrostatic interaction while uncharged residues will pass through. Once bind to the column, molecules can be released with salt ions exchange. The salt ions compete for interaction for the column, and the molecule of interest is released. Molecules having different charges can be separated from one another by gradually increasing the salt concentration.[29] This is achieved with a gradient of increasing salt concentration in the solution being passed through the column. Lower charged molecules are released at low salt concentrations because they are weakly bound, while the higher charged molecules are more tightly bound and require higher salt concentration to release.[30] Thus molecules are released from the column according to the magnitude of their charge.[31–35] It is noted that the retention time of ion on the exchange resin is mainly dependent on the ion charge, ion radius, and ion hydrophobic.

The charged resin as stationary phase can be of two types: cation exchangers and anion exchangers, which bind the positively and negatively charged molecules, respectively.[36] The name of the resin refers to the molecules being exchanged, not the molecule bound to the resin. The exchangers are usually made of organic polymers, such as polyvinyl, polymethacrylate, styrene-divinylbenzene, and ethylvinylbenzene–diviniylbenzene.[15,36–38] The typical functional exchange groups are alkyl quaternary ammonium base or alkanol quaternary ammonium base for cation exchange, and sulfo group or carboxylic acid group for anion exchange, respectively.[10]

1.2 Apparatus and procedure

The common IC apparatus consists generally of a pump to move eluent, a sample injection device, a separation column, a detector, and a recording system.[14] The column is maintained at a constant temperature with equipment such as thermostat. The pump delivers the eluent into the column, the connection tubes and related devices at a constant flow rate. The detector detects components which are different in property from the eluent and gives signals in proportion to the concentration for a substance of a few micrograms or less. Conductivity, amperometric and potentiometric detection, UV-Vis absorbance, fluorescence and luminescence measurements, atomic spectroscopic detection and mass spectrometry (MS) have already been employed for IC detection.[14,39] The recording system records the intensities of the signals obtained by the detector.[7,8,40] When an electrical conductometer is used as the detector, a suppressor can be placed in front of the conductometer, which is able to significantly reduce the electric conductivity of the eluent and amplifies the ratio of the signals to the noises.[6]

With respect to the use of conductometric detection, two typical ion exchange chromatographic modes are defined: the

suppressed and non-suppressed IC.[6] In the suppressed IC, before detection, the eluent is driven through a suppressor device. Meantime, the background conductivity is greatly reduced so that the sensitivity, with which sample ions can be detected, is increased. Non-suppressed IC is performed without the use of the suppressor unit but with ion exchangers of low capacity and very diluted eluents so that the background conductivity is quite low. IC with suppressed conductivity detection is most widely used and generally offers the best performance to the target ionic compounds detection.[18]

Bicarbonate and hydroxide eluents have been used as the mainstay eluents in anion-exchange suppressed IC, especially the hydroxide, since after suppression it forms water that has virtually zero conductance, and therefore provides the perfect conductivity baseline.[17,41–43] However hydroxide eluent is difficult to use because it readily absorbs carbon dioxide and forms carbonate. Thus Dionex Company proposed the novel RFIC-ER (Reagent-Free IC with Eluent Regeneration) technique, which can provide extremely pure hydroxide eluent by ion-exchange membrane. The most popular eluents used in cations analysis are low concentration mineral acids such as: HCl, HNO_3, H_2SO_4 containing also organic modificators, like the ethylenediamine and 2,3-diaminopropionic acid.[8] Analyte ions are separated on the ion-exchange column and these ions together with the eluent move to the suppressor. In the suppressor, the conductance of the eluent is lowered and the conductance of the sample ions is increased, leading to a large increase in the signal-to-noise ratio of the detection signal.

The routine IC analysis follows the procedures: condition the IC system previously, adjust the eluent, the column, the detector, the eluent flow rate to the operating conditions, equilibrize the column at a specified temperature. Inject the test solution into the sample injection device using a microsylinge or sample valve. Detect the separated components using the detector, and record the chromatogram on the recorder.[36,44] Identification of the substance is carried out by confirming that the same retention time as for the standard solution is obtained, or that the retention time does not change nor does the peak width widen when the standard sample is added. Quantification is usually performed by the peak height or peak area, using internal standard method or absolute calibration curve method.[18]

1.3 Application

There have been many important fields of application today for IC, such as the routine investigation effluents and rain water; analysis of ions in chemical products, foods, cosmetics, pharmaceuticals; ultra-trace analysis in the semi-conductor and power industry.[6–8] The emphasis of ion chromatographic application of inorganic anions/cations determination is mostly on the following areas: environmental analysis, power plant chemistry, semiconductor industry, metal processing, pharmaceutics, biotechnology, mining, agriculture, food and beverages, electroplating, and the pulp and paper industry.[31–35,45–51] In spite of the strong competition from atomic spectrometric techniques, the IC of metal cations is now well established as a relatively cheap method with ease of automation and on-line capability; it is particularly attractive in a wide variety of routine trace analysis.[23,24,26,27,32,33] Compared with the traditional spectroscopic methods, IC offers the advantage of providing information on metal speciation, which can distinguish different metal oxidation states such as Cr(III)/Cr(VI), Fe(II)/

Table 2 Typical IC methods for ion analysis recommended by Dionex

Method number	Method name	Analytes	Sample matrix
AN 4	Analysis of engine coolants by IC	Na^+, NH_4^+, K^+, Mg^{2+}, Ca^{2+}	Coolants
AN 25	Determination of inorganic ions and organic acids in non-alcoholic carbonated beverages	Na^+, NH_4^+, K^+, Mg^{2+}, Ca^{2+}	Non-alcoholic drinks
AN 69	Determination of aluminum in complex matrices using chelation IC	Al^{3+}	Water
AN 73	Determination of trace transition metals in reagent-Grade acids, bases, and salts using IC/inductively coupled argon plasma spectroscopy	Cd^{2+}, Co^{2+}, Cu^{2+}, Pb^{2+}, Ni^{2+}, Mn^{2+}, Zn^{2+}, Al^{3+}	Water solutions of: acid, base and their salts
AN 86	Determination of trace Cations in power plant waters containing Morpholine	Na^+, NH_4^+, K^+, Mg^{2+}, Ca^{2+}	Reagent water
AN 94	Determination of trace cations in concentrated acids using autoneutralization pretreatment/IC	Li^+, Na^+, NH_4^+, K^+, Mg^{2+}, Ca^{2+}	Concentrated acids
TN 23	IC of lanthanide metals	La^{3+}, Nd^{3+}, Pr^{3+}, Ce^{3+}, Gd^{3+}, Tb^{3+}, Dy^{3+}, Ho^{3+}, Tm^{3+}, Yb^{3+}	Wastewater
TN 24	Determination of chromium by IC	Cr^{3+}, CrO_4^{2-}	Wastewater
TN 44	The determination of trace anions in concentrated phosphoric acid	F^-, Cl^-, SO_4^{2-}, CO_3^{2-}, Br^-, NO_3^-, PO_4^{3-}	Acid
TN 46	Determination of trace anions in concentrated glycolic acid	F^-, Cl^-, SO_4^{2-}, CO_3^{2-}, Br^-, NO_3^-, PO_4^{3-}	Acid
TN 48	Determination of trace anions in high-purity water by high-volume direct injection with the EG40	F^-, $HCOO^-$, Cl^-, Br^-, SO_4^{2-}, CO_3^{2-}, NO_2^-, NO_3^-, PO_4^{3-}, CH_3COO^-,$C_2O_4^{2-}$	Water
TN 50	Determination of the amino acid content of peptides by AAA-direct	Amino acids	Peptide

Table 3 Typical IC methods for ion analysis recommended by metrohm

Method number	Method name	Analytes	Sample matrix
C-1	Sodium, potassium, calcium and magnesium in drinking water	Na+, K+, Mg^{2+}, Ca^{2+}	Drinking water
C-2	Sodium, potassium, calcium and magnesium in cooling water	Na^{+}, K^{+}, Mg^{2+}, Ca^{2+}	Coolants
C-14	Sodium, ammonium, potassium, calcium and magnesium in wastewater	Na^{+}, NH_4^{+}, K^{+}, Mg^{2+}, Ca^{2+}	Wastewater
C-18	Determination of lithium, sodium, ammonium, potassium, manganese, calcium, magnesium and strontium in sewage sludge after digestion with HNO_3	Li^{+}, Na^{+}, NH_4^{+}, K^{+}, Mg^{2+}, Ca^{2+}, Mn^{2+}, Sr^{2+}	Sewage sludge
C-19	Determination of sodium, ammonium, potassium, calcium and magnesium in rain water	Na^{+}, NH_4^{+}, K^{+}, Mg^{2+}, Ca^{2+}	Rain water
C-23	Determination of sodium, ammonium, diethanolamine, diglycolamine and potassium in wastewater	Na^{+}, NH_4^{+}	Wastewater
C-44	Determination of cations in tap water	Li^{+}, Na^{+}, NH_4^{+}, K^{+}, Mg^{2+}, Ca^{2+}	Drinking water
C-55	Determination of lead, zinc, indium, cadmium, cobalt, ammonium, potassium, manganese, magnesium and calcium	Zn^{2+}, In^{2+}, Co^{2+}, Cd^{2+}, Na^{+}, NH_4^{+}, K^{+}, Mg^{2+}, Ca^{2+}	Wastewater
C-69	Zinc, sodium, calcium and magnesium in an industrial bath	Zn^{2+}, Na^{+}, Mg^{2+}, Ca^{2+}	Wastewater
C-79	Nickel, zinc, cobalt, iron(II) and manganese in LiBr using post-column reaction	Zn^{2+}, Ni^{2+}, Co^{2+}, Fe^{3+}, Mn^{2+}, Li^{+}	LiBr
C-97	Cations in ethanol used as biofuel	Li^{+}, Na^{+}, NH_4^{+}, K^{+}, Mg^{2+}, Ca^{2+}	Ethanol
C-98	Lanthanides by IC applying non-suppressed conductivity detection	La^{3+}, Pr^{3+}, Ce^{3+}, Gd^{3+}, Tb^{3+}, Dy^{3+}, Tm^{3+}, Yb^{3+}	Solid samples
C-103	Standard cations in lake water on the Metrosep C3-250 column	Na^{+}, NH_4^{+}, K^{+}, Mg^{2+}, Ca^{2+}	Lake water
U-24	Vanadium speciation applying IC with UV/VIS detection	V^{3+}, V^{5+}	Solid samples

Fe(III), or As(III)/As(V).[16] Moreover, IC has also been used to determine stable metal complexes. A further advantage of IC over AAS is its relatively wide dynamic range, enabling IC to effectively determine low concentration analytes in the presence of high levels of other species, which would tend to cause problems in the nebulizers used in atomic spectrometry.[7,8] Recently, IC became well established as a regulatory method for the analysis of ions in various samples. There have been many ion chromatographic methods recommended by ISO, US EPA, and American Society for Testing and Materials (ASTM) for environmental samples in the range of inorganic ions. The IC procedures worked out by the world-leader IC manufacturers Dionex and Metrohm are listed in Tables 2 and 3, respectively.

2. IC sample preparation

The enormous performance of modern IC with respect to chromatographic resolution, simultaneity, sensitivity and speed can be demonstrated best by the analysis of standard solutions.[10,37,52–56] However, in practice the operator normally encounters real samples whose composition may vary considerably and which in many cases can only be analyzed by IC after suitable sample preparation procedure. The sample preparation methods for the wide range of problems to be solved are very numerous and the apparatus and time required for sample preparation differ enormously. Sample preparation is one of the key steps for sample analysis, and also the important segment for an effective analytical method. As the stringency of requirements for higher sensitivity, selectivity, accuracy, precision, and the number of samples to be processed has escalated, the corresponding increases in speed and sophistication of data collection and analysis have outpaced improvement in the many traditional techniques of sample collection and preparation. By some estimates, 75–80% of the work activity and operating cost in a contemporary analytical lab is spent processing and preparing samples for introduction or injection into an analytical separation and/or measurement device. Clearly, efforts directed and products designed to streamline sample preparation protocols are essential to future progress in analytical science. The suitable and effective sample preparation method could greatly contribute to the accuracy, sensitivity and reproducibility. Thus development of suitable sample preparation method as to the corresponding analytical instrument and different type of samples is quite necessary and of high value.[57]

There are three key issues that often arise that necessitate of sample preparation prior to analysis: (1) the sample in the unsuitable physical state for the analysis method cannot be direct sample injection; (2) the sample has significant

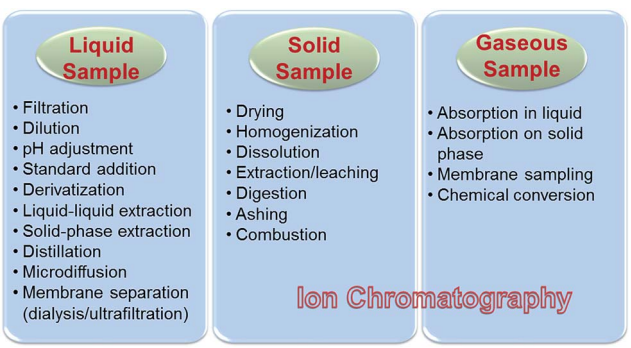

Fig. 2 List of common used sample preparation methods for IC technique.

interfering matrix components that may give either a false positive or negative reading in the measurement; (3) the analyte concentration is out of the detection ability of the corresponding apparatus or methods.[57] Thus successful sample preparation for most analytical techniques has a threefold objective: to provide the sample component of interest in solution free from interfering matrix elements at the concentration appropriate for detection or measurement. A wide variety of sample preparation methods have been used in combination with IC, including dissolution, homogenization, extraction (liquid or solid phase), filtration, concentration, evaporation, separation, chemical derivation, and standardization.[58] Fig. 2 lists the common sample preparation methods used on IC separation and the typical application in elemental analysis.

2.1 Filtration

Within the context of IC analysis, filtration is generally recommended so that blockages in the injection valve, in the capillary connection and in the column head frits can be avoided. Filtration is indispensable for samples containing particles, and membrane filters with a pore size of 0.45 μm are normally used. For biologically active samples, the use of sterile filters with a pore size of 0.2 μm is advisable as these also retain microorganisms and therefore prevent the conversion of certain analytes by microbial oxidation or reduction. When carrying out membrane filtration with commercially available disposable filters, the risk of contamination as well as the loss of analyte resulting from adsorption on the filter should be put into consideration. Therefore, it is recommended to thoroughly rinse the filter with ultrapure water before use and to reject the first milliliters of the sample filtrate as they could still contain the rinsing liquid.

2.2 Solid phase extraction

Solid-phase extraction is particularly suitable for the isolation and preconcentration of analyte ions from the interfering matrix components. The general procedure is passing the sample solution through the solid phase cartridge that is filled with the sorbent material suitable for the separation, which either retains the analyte ions or retains the interfering matrix components. In the case of analyte preconcentration, the analyte ions are eluted from the column in a subsequent step and the eluate is then analyzed by the corresponding IC method. If matrix components are retained on the solid phase, the determination is carried out on the solution leaving the column. For the practical performance of solid-phase extraction, many manufacturers offer ready-to-use cartridges filled with sorbent materials (Table 4) as well as devices for passing the sample solution through the sorbent bed either manually, semi-automatically or fully automatically.[59–61]

There are great demands for the trace analysis in many scientific disciplines, requiring correspondingly sensitive methods to improve IC detection performance. With the currently available instrument configurations in IC technique, numerous ions can be routinely determined without any great difficulty even in concentration ranges below 1 mg L^{-1}. Large volume injection can improve the sensitivity by up to one to two orders of magnitude, but only for samples with low ionic strength.[62–65] By preconcentration of the ions to be determined in a pre-chromatographic step, it is possible to achieve considerable improvements in the sensitivity and better matrix elimination.[65] Whereas in individual cases, it is more important to selective preconcentration of individual ion in the presence of great amount of other ions and selective multi-component preconcentration from complex matrix.[63] The use of solid-phase extraction with appropriate sorbents is very versatile and is by far the mostly frequently used method for preconcentration.

2.3 Dissolution and extraction

Complete or partial dissolution followed by extraction is the simple and practical method of sample preparation for the determination of ionic constituents in solid samples by IC. This method does not require special apparatus, and can be performed in all common plastic vessels and glass containers. Dissolution of the sample or extraction of the ions to be determined is normally carried out at room temperature, but can also be accelerated by gentle heating, vigorous shaking, string and ultrasonic treatment. Due to its high polarity, ultrapure water is often very suitable as the extraction solvent for ionic compounds in solid samples. It is noted that the extraction

Table 4 Typical commercialized solid phase cartridges for IC sample preparation

Ions removed	Chemistry	Example of commercial product
Cations	Sulfonic acid, H-form	OnGuard H and InGuard H (Thermo) IC-H (Alltech & Metrohm)
Cations	Sulfonic acid, Na-form	OnGuard Na and InGuard Na (Thermo) IC-Na (Alltech & Metrohm)
Transaction metals	Iminodiacetate	OnGuard M (Thermo Scientific) IC-Chelate (Alltech)
Halides	Sulfonic acid, Ag-form	OnGuard Ag and InGuard Ag (Thermo) IC-Ag (Alltech & Metrohm)
Sulfate	Sulfonic acid, Ba-form	OnGuard Ba (Thermo) IC-Ba (Alltech)
Halides and cations	Sulfonic acid, Ag- and H-form, two layer	OnGuard Ag/H (Thermo)
Anions	Quaternary ammonium, OH-form	IC-OH (Alltech)
Anions	Quaternary ammonium, bicarbonate form	OnGuard A (Thermo)
Halides, sulfate, and cations	Sulfonic acid, Ag-, Ba-, and H-forms	OnGuard Ba/Ag/H (Thermo)
Hydrophobic species	Styrene-divinylbenzene	OnGuard RP (Thermo) IC-RP (Alltech & Metrohm)
Hydrophobic species	Styrene-divinylbenzene, hydrophilic	InGuard HRP (Thermo)
Hydrophobic species	Octadecyislane	IC-C18 (Alltech & Metrohm)

efficiency is critical for the accuracy of the final IC quantification of the target analytes, thus usually need recovery test to verify the extraction.

2.4 Wet-chemical digestion

Wet-chemical digestion is often chosen for treating the sample, for which the aqueous extraction is not capable of releasing the components to be analyzed. The advantage of the digestion method is that it can help IC to provide the total quantification information of the sample. The major process is treating the solid samples with strong acid, such as concentrated HNO_3, HCl, H_2SO_4, HF, and aqua regia, carried out in either an open system or a closed system under certain temperature.[66] Open digestion can be carried out relatively simply in heat resistant vessels on a hotplate. Digestions under pressure require special vessels and the necessary safety precautions must be observed. On the other hand, microwave ovens have proved to be outstandingly suitable for heating the samples. However, wet-chemical digestion now is not a popular method for IC sample preparation, mainly because the digested sample solutions usually are not suitable for direct injection to IC system. Involvement of strong acids for digestion leads to incompatibility with the subsequent IC analysis, as the low pH of the digestion solution may damage the separation column, and influence the equilibration on the separation column, which can cause large retention time displacements and unstable baseline. In addition, the presence of the added acid anions may produce severe interference for the quantification of the other anions, which should be overcome by advanced IC technique, like the multi-dimensional IC.

2.5 Dry ashing and combustion

For special samples hard to be digested, dry ashing using air as the oxidizing agent or combustion in an atmosphere of pure oxygen is the ideal choice, which is particularly used for biological samples, pharmaceutical preparations, polymerized substances, coal and fuels with high organic matrix content. Ashing the dry and homogenized sample is mineralized in a crucible or combustion boat by heating it in a muffle furnace for several hours at a temperature of typically 300–800 °C. Then the ashes are dissolved in water or in a diluted mineral acid. Dry ashing is particularly useful for the determination of cations, in particular those of the transition metals, as sample preparation is easy to carry out and the absence of acids and other additives means no interference to the IC analysis.[67]

Combustion analysis can be carried out in various ways.[68–70] The Schoeniger digestion method is widely used: the sample is burned in a closed glass or quartz flask in pure oxygen and the released combustion gases are taken up in an absorption solution placed in the flask. Combustion is simple, rapid and favorably priced, but only relatively small amounts (~0.1 g) of the sample can be burned, strictly limiting the method sensitivity. As an alternative, combustion can also be carried out at high pressure in an oxygen bomb, with the pressure up to 40 bar that allows sample weight over 1 g.[68]

2.6 Ultrafiltration

Ultrafiltration is regarded as a filtration technique in which the membranes have pore sizes that are much smaller than those used in membrane filtration. In all cases, transfer of the solvent and the dissolved fraction through the filter are affected by the pressure gradient. Depending on the pore size of the filter or the ultrafiltration membrane, colloidal fractions and dissolved molecules with a high molecular weight are also retained.[71,72] The characteristic value for the filtration effect is the pore size and the molecular separation limit, which refers to the molecular weight of a substance that can just or just not pass through the membrane, requiring much higher pressure gradients, higher cost and more labor and time. However, in the light of its extraordinary good matrix elimination a great potential can also be recognized for other applications.

2.7 Dialysis

Familiar with ultrafiltration, dialysis is a membrane-based sample preparation technique. The basic procedure is using membrane to separate the sample solution from an acceptor solution that takes up the substances transported through the membrane. There is a great variety in the geometric arrangement of the dialysis cells, in the dimensions of the liquid compartments as well as in the operating procedures used in the various dialysis techniques.[58,73,74] Compared with ultrafiltration, dialysis is much easier to carry out continuously and to automate, while the continuously operating flow-through dialyzers and miniaturized disposable dialyzers are already commercially available.[58]

2.8 Liquid–liquid extraction

Liquid–liquid extraction is one of the most powerful tools for isolating a desired component from a mixture. Selective partitioning of the compound of interest into one of two immiscible phases occurs by the proper choice of extraction solvents. However, liquid–liquid extraction is limited used in the sample preparation for IC analysis, because the transfer of the analyte to the organic solvent phase means the remove of the solvent before separation by IC should be carried out. The working steps associated with this require a great deal of expenditure on both work and time and even suffer from the great risks of contamination and loss of analyte.[75]

2.9 Fusion method

Fusion is an alternative to the wet chemistry treatment of solid samples with strong acids under alkaline conditions. The solid sample is mixed with a suitable fluxing agent and heated in a crucible until it melts. After cooling down, the fused mass is treated with a suitable solvent and the ions are determined in the solution. In consideration of the compatibility of the fusion solution and the IC analysis, the fluxing agents frequently used in the fusion process such as sodium hydroxide and sodium carbonate are also the components of the mobile phase frequently used in an IC, normally just need some dilution before carrying out the final IC analysis.[76,77] While for cation

determination, the fusion method is strictly limited owing to the high alkali metal ion content from the fluxing agent. Fusion is particularly used for the analysis of geological material as well as glasses. The procedure is usually effort-intensive, time-consuming, and holds high risks of contamination and loss of analyte, therefore not much suitable for trace analysis.

In summary, the sample preparation is often an indispensable step when determining ions by IC. The variety of sample preparation methods is great and it is not always easy to find a suitable method for the problem to be solved. For one and the same problem there are often several versions so that the operator has to make a decision based on different criteria. Regardless of the choice of method, each of the working steps involved must be optimized again for each problem (with reference to the ions to be determined and the existing matrix). The risks of contamination and loss of analyte must always be kept in view as this is the only way in which the high quality of the analytical results can be ensured. The instrumental integration of sample preparation steps in the analytical procedure is not only interesting for automation reasons, but also opens up important analytical aspects concerning reliability, improved separation of traces, efficient matrix elimination and reduced risk of contamination.

3. Advanced IC technique

IC can now be defined as the typical expression of analytical chemistry, because IC represents not only a tool for solving analytical problems in all areas of interest, but also the equilibria, the core of analytical chemistry, which is the key factors for separation technique. Equilibria play the principal role in IC and can be modulated as a function of the nature of the analytes. Most of the IC development and innovation, such as new separation mode, new mobile phase, and new detection ability are strictly related to both good and highly selective separation and extremely low detection limit. As shown in Fig. 3, the advanced IC techniques, in combination with proper sample preparation, can be a powerful tool for solving complicated analytical problems through ionic compound determination. Herein, several typical advanced IC techniques are discussed, including the two-dimensional IC (2D-IC), IC-MS hyphenation technique, and capillary ion chromatography (CIC).

3.1 2D-IC technique

Ion determination in the wide range of samples occurring in the very different fields of application requires an adequate selection of separation conditions as well as the detection method. In the analysis of complex matrices, where different types of interference could occur, attempts should always be made to exhaust the separation performance of the chromatographic system and the selectivity of the detector used after suitable sample preparation. Application of IC for elemental analysis in specific sample, involving the detection of low-level anions in complicated matrix, demand suitable sample preparation method or advanced IC separation mode. The typical case is the detection of trace-level ion in complex solid sample, and the

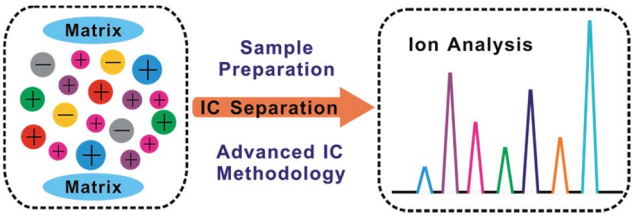

Fig. 3 Schematic protocol of advanced IC techniques and sample preparation for ion analysis.

acid digestion method should be first performed on the solid sample to get the fully digested solution, which contained trace-level analyte and great amount of interference. The basic principle of the 2D-IC technique is the utilization of column hyphenation and valve switch technology to cut off the sample zone containing matrix and the analyte.[78–89]

2D-IC separation with column switch technique can successfully separate the target analyte from the matrix. For the fabrication of 2D-IC method, two six-way valves, two IC columns, two eluent flow, one suppressor, and one detector were combined into the IC system. The sample containing the target analyte and matrix will be first pre-separated by the column 1, then the pre-separated sample zone will be cut-off into two parts by the valve switch. One part containing small portion of the matrix, as the target analyte, will be transferred into column 2 for further separation; the other part is the majority of the matrix, which will be left in the column 1. Through the column switch process, the target analyte can be easily analyzed by the column 2 and realized quantification by the suppressor and conductivity detector. Fig. 4 has demonstrated the process of the 2D-IC instrumentation and operation with column switch technique.

Step 1 (Fig. 4A) is the sample loading: sample was loaded into the loop by the autosampler, while on the other line, the eluent generator provided eluent with proper concentration for the balance of the whole 2D-IC system.

Step 2 (Fig. 4B) is the sample injection: the six-way valve 1 switched, and the sample in the loop was injected into the 2D-IC system by the eluent flushing. Then the sample will be pre-separated by the IC column 1 for the sample zone cut-off in the next step.

Step 3 (Fig. 4C) is the column switch: the six-way valve 2 switched, and the pre-separated sample zone would be cut-off into two parts. One part containing the target analyte and the small portion of the matrix will be transferred into column 2 for further separation; the other part containing the majority of the matrix will be left in the column 1, and flushed to the waste by another eluent flow. In this step, the target analyte would be quantified by the detector.

Step 4 (Fig. 4D) is the column switch back: the six-way valve 2 switched back, and the IC column 1 was reconnected into the 2D-IC system. Separation eluent will flush the two IC columns, and rebalance the whole 2D-IC system for next injection.

Through this novel 2D-IC column switch technology, the interference from the complicated matrix to the target analyte can be easily eliminated. For the set-up of 2D-IC method with

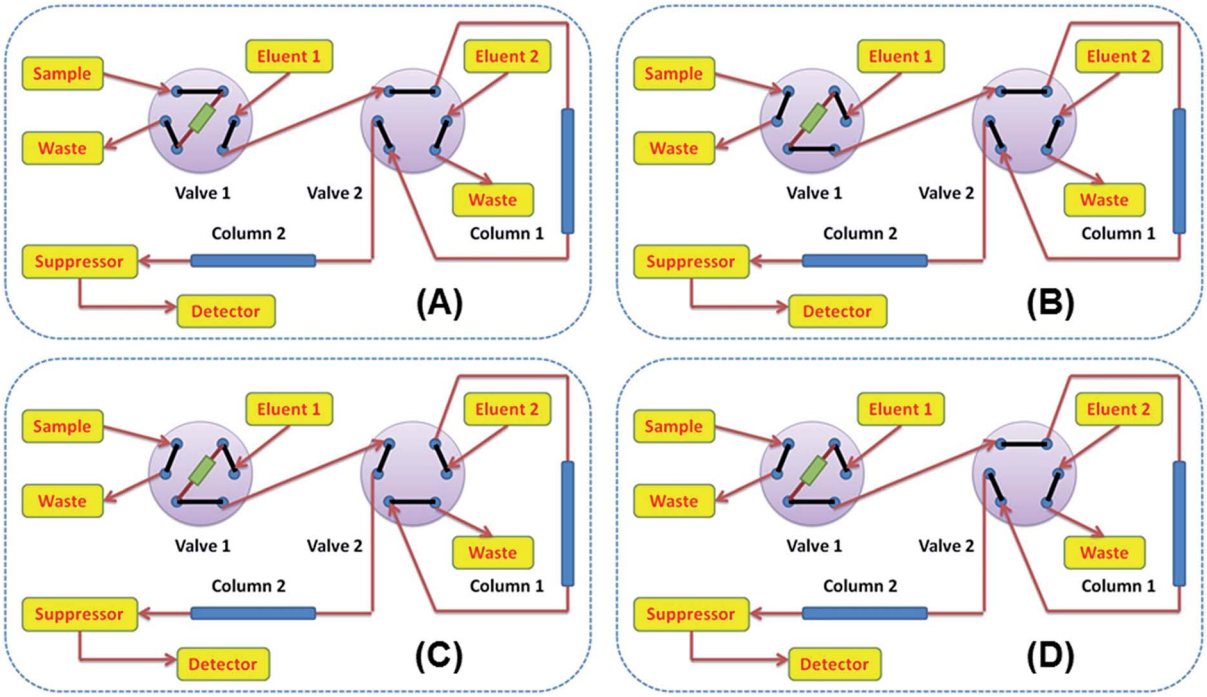

Fig. 4 Schematic illustration of 2D-IC technique: (A) sample Loading; (B) sample injection and pre-separation; (C) column switch and final separation; (D) column switch and rebalance.

optimal analytical performance, design optimization, reproducibility and recovery test have been fully investigated.

2D-IC methodology with advanced separation or detection ability has been extensively applied in complex sample analysis from biological, industrial, and food chemistry. Recently, a highly sensitive and reliable 2D matrix elimination IC method was developed by Li *et al.*[81] for simultaneous detection of bromate, chlorite and five haloacetic acids. This method combined the conventional IC in first dimension with capillary IC in the second dimension coupled with suppressed conductivity detection. The first dimension utilized a high capacity column to partially resolve matrix from target analytes. By optimizing the cut window, the target analytes were selectively cut and trapped in a trap column *via* a six-port valve, while the matrix were diverted to waste. The trapped target analytes were delivered on to the capillary column for further separation and detection. Temperature programming was used to improve selectivity in second dimension column to obtain complete resolution of the target analytes. Compared to the performance of one-dimensional IC, the 2D approach resulted in a significant increase in sensitivity for all target analytes and provided more reliable analysis due to the second column confirmation.

Dasgupta's group[83] reported an improved 2D-IC method that used sequential suppressed and nonsuppressed IC for the sensitive detection of both common anions and very weak acid anions. After suppressed conductometric detection of an electrolytically generated hydroxide eluent and an electrolytic suppressor, the eluent was passed into a membrane device where KOH is passively introduced into the eluent stream using Donnan forbidden leakage. A second conductivity detector then measured the conductivity of the stream. The background conductance of the second detector was typically maintained at a relatively low level. The weak acids were converted to potassium salts that were fully ionized and detected against a low KOH background as negative peaks.

Vermeiren's group[80,82] proposed the novel 2D ion exclusion chromatography/IC (IEC-IC) method for the determination of trace anions in concentrated hydrofluoric acid. Electrolytically generated and purified hydroxide eluents in combination with a low noise electrochemical suppressor has been used to successfully achieve lower detection limits.

Wagner *et al.*[88] developed a selective method for the analysis of perchlorate in drinking waters at ng L^{-1} levels using 2D-IC with suppressed conductivity detection. In the first dimension, a large sample volume was injected onto a first separation column and the separated matrix ions were diverted to waste while the analyte of interest were selectively cut, trapped and concentrated in a concentrator column. The contents from the concentrator column were eluted onto a second analytical column for separation and quantitation of the analyte of interest. Incorporation of two columns with different affinities for the analyte in a single analysis could provide comparable selectivity and superior sensitivity to a method using second column confirmation in a second separate analysis step. The new 2D-IC method demonstrated excellent sensitivity, selectivity, precision, accuracy and robustness.

Another 2D-IC method with improved resolution of complex samples was presented by Haddad's group.[87] Two columns containing different stationary phases were connected *via* a tee-piece, which enabled an additional eluent flow and independent control of eluent concentration on each column. The resultant mixed eluent flow at the tee-piece could be varied to

produce a different eluent concentration on the second column. This allowed analytes strongly retained on the first column to be separated rapidly on the second column, whilst maintaining a highly efficient, well resolved separation of analytes retained weakly on the first column. Eighteen inorganic anions have been separated to demonstrate the utility of this approach, which provided separation of this mixture with resolution of all analytes greater than 1.3.

Brudin *et al.*[89] has further promoted the novelty of 2D-IC technique by developing a comprehensive 2D chromatography: IC × reversed-phase liquid chromatography (RPLC) for separation of low-molar-mass organic acids. IC was chosen for the first-dimension separation and RPLC was chosen for the second-dimension separation mode. The coupling of these modes was made possible by neutralizing the first-dimension effluent, containing KOH, prior to transfer to the second-dimension reversed-phase column. This method had been successfully used to analyze a mixture of 24 low-molar-mass organic acids and proved to be robust and suitable for the analysis of wine, orange juice and yogurt.

Matysik's group[85] has further extended the 2D-IC methodology by fabricating a novel hyphenation system of CIC × capillary electrophoresis-MS (CE-MS) to determine a model system consisting of nucleotides and cyclic nucleotides with data presented in a multidimensional contour plot. An ICS-5000 (Dionex, Thermo Scientific) IC system, consisting of a dual pump module with both capillary and analytical pump, an eluent generator module, an inline eluent degasser, a four-port injection valve, a column oven, an anion capillary eluent suppressor, and a conductivity detector, was employed for capillary-scale IC separation. For the nucleotides and their cyclic derivates, the separation efficiency and resolution could be enhanced in the CIC × CE-MS compared to the single techniques.

Among the technique innovation and development for advanced IC methods, the 2D-IC principle is a very promising research topic. Various separation columns (IC, LC, GPC, CE) and various detectors (conductivity, electrochemical detection, MS, UV-Vis, fluorescence, *etc.*) can be combined together to fabricate the multi-dimensional IC method[90] with suitable flow schematic design, which would produce a comprehensive detection capability for solving complicated analytical problems.

3.2 IC-MS hyphenation technique

Hyphenation of IC with a range of detection techniques including atomic absorption, atomic fluorescence or atomic emission has been a continuing theme in the development of IC, but in recent years MS has become the most practical instrumentation with high selectivity and sensitivity for trace analysis of molecular mass inorganic and organic anions. There are two major fields where MS plays an important role as a detection technique for IC. MS with ICP ionization serves as an element-selective detector with extremely low detection limit, whereas atmospheric pressure ionization, mostly in the form of electrospray ionization (ESI), is used for identification of compounds *via* determination of molecular mass or characteristic fragmentation of the analyte to obtain structural information on the analytes.[14,39,91–93]

ICP-MS with high element specificity, high sensitivity, wide dynamic range and simultaneous detection ability is compatible to hyphenate with IC separation that can employ totally aqueous phases. The most important application of IC-ICP-MS hyphenation technique is speciation analysis and metallomics study. Speciation analysis is defined as the identification and quantification of chemical species in environmental, biological or food samples. Metallomics focus on the study of metal species and their interactions, transformations, and functions in biological systems. IC-ICP-MS can provide selective detection of all species containing the element of interest, which make it a powerful tool for speciation analysis and metallomics.[94–98]

One of the most extensively developed areas in current speciation analysis is the investigation of arsenic-containing species in environmental and biological samples.[91] There are over 40 naturally occurring organoarsenicals that have been identified, such as methylated arsenic species, arsenobetaine, arsenocholine, various arsenic-containing ribosides, arsenic-containing propanoic and butanoic acid, and arsenolipids, most of them are ionic.[16] Schaeffer *et al.*[99] employed ion exchange chromatography hyphenated with ICP-MS for analyzing total arsenic and arsenic species in a range of freshwater samples (sediment, water, algae, plants, sponge, mussels, frog and fish species). Total arsenic concentrations were measured by ICP-MS and arsenic species were measured in aqueous extracts of the samples by IC-ICP-MS. In order to separately determine the efficiency of the extraction method and the column recovery, total arsenic concentrations in the extracts were obtained in three ways: (i) ICP-MS determination after acid digestion; (ii) flow injection analysis performed directly on the extract; (iii) the sum of arsenic species eluting from the IC column. Through this, IC-ICP-MS gave full quantitative and qualitative information for arsenic species in various environmental samples.

Another typical speciation application of IC-ICP-MS is the selenium analysis. Selenium acts both as a toxicant and an essential trace element, thus has attracted considerable interest in speciation research. Selenium exists in the form of selenoamino acids, the constituents of various peptides and proteins in various samples, such as foods, plants, and biological fluids. The significant progress that has been made in selenium speciation analysis using IC-MS was the identification of selenium metabolites in urine.[100] Both selenosugars and trimethylselenonium could be found in urine samples from persons after intake of low amounts of selenite, with trimethylselenonium showing a considerable individual variability from trace levels to being a significant or even major metabolite.

Since ICP is a destructive ionization mode, it cannot provide any information about the structure of the analyte. ESI/MS is capable for detection and identification of unknown species once hyphenation with IC separation, especially for molecular-mass anions where conductivity detection could not provide sufficient sensitivity and/or selectivity.[101–108] Krynitsky *et al.*[109] developed a rapid, sensitive, and specific IC-MS method for determining perchlorate anion in lettuce, cantaloupe, bottled

water, and milk. The $^{18}O_4$-labeled perchlorate internal standard was introduced to correct for matrix effects on measured signals. The labeled internal standard greatly simplified extract preparation and cleanup before IC-MS/MS analysis. There are several other typical current applications in the area of molecular-mass anions by IC-ESI/MS, including the quantification of phosphorus oxyanions in geothermal water samples,[110] detection of nitrite and nitrate in fresh and cured meat,[111] identification of organic acids as degradation products of chlorinated phenols,[112] trace analysis of haloacetic acids and oxyhalides in water and soil,[113] and determination of anion profiles in plasma of persons suffering from acidosis.[114]

IC-ESI/MS is also suitable to been applied for measurements of the isotopic distribution of specific element in molecular-mass ionic species. For example, IC-ESI/MS was proved to be important tool in metabolic-flux analysis, aiming to discover the steady-state conversion velocities of metabolites to each other through enzyme-catalyzed reactions in organisms. Information about the fluxes could be obtained by feeding the cell with a mixture of natural and ^{13}C-labeled substrates, followed by IC-MS measurements of the distribution of ^{13}C atoms in metabolites that were derived from the ^{13}C-labeled substrate.[115]

Organic trace analysis of low molecular mass analytes is another promising application area for IC-ESI/MS. Traditional LC-MS method was used for analyzing organic analytes in the molecular-mass range (100–1000) with reversed phase separation mode, but this method usually required the addition of ion-interaction reagent due to the presence of ionizable groups in the analytes, in which case commonly employed ion-interaction reagents were poorly compatible with electrospray ionization. IC-ESI/MS is an alternative method for organic trace analysis of low molecular mass analytes, which has been used successfully in the environmental analysis of residues of polar pesticides and polar pharmaceuticals,[116] and food analysis of biogenic amines.[117,118]

3.3 CIC technique

CIC is the IC system employing a separation column to be a capillary column with the inner diameter less than 1 mm. CIC has exhibited many advantages, such as low consumption of reagents, high separation efficiency and excellent compatibility with sensitive detectors like ICP/MS and ESI/MS.[119–125] CIC analytical method was first published by Rokushika *et al.* in 1983,[126] which presented a suppressed CIC technique using capillary column of 0.19 mm diameter and coupling these to a 0.2 × 10 mm Nafion® perfluorosulfonate hollow fiber suppressor. Through a surface agglomerated anion exchanger of 10 μm base particle size and sodium carbonate–bicarbonate as eluent, this method has been proved to be capable of separation and detection of several inorganic anions and organic acids at low ppm level, and successfully applied for real sample analysis, including river water and fruit juice. In the following work, UV-detection was involved into CIC technique to extend the application, and CIC-UV method demonstrated great potential for separation and analysis of UV-absorbing anions, including aminobenzoic acids, nucleotides and nucleobases, hydroxybenzoic acids and nitrophenols with carbonate–bicarbonate eluents.[127,128]

Takeuchi's group has further developed the CIC technique, and has made extensive investigation on the employing CIC for the ionic compound analysis by using packed fused silica capillary IC columns. Firstly, they proposed an indirect photometric detection method for mono-valent cations *via* post-suppressor ion replacement in microcolumn IC by using a cation exchange system (0.35 × 50 mm, packed with 10 μm particles) with HNO_3 as eluent.[129] Applying a 0.32 × 100 mm column packed with 3 μm octadecyl silica (ODS) microparticles coated with hexadecyltrimethylammonium bromide and mixed eluent containing 1 mM sodium salicylate with 5% acetonitrile, Takeuchi's group developed another CIC method for inorganic anions.[130]

Stationary phases coated with immobilized biological macromolecules, such as bovine serum albumin (BSA), has been introduced to the CIC technique innovation. The BSA molecule, immobilized on 5 μm ODS particles, was protonated at specific pH condition and affected the anionic analyte retention. Using 0.35 × 75–150 mm columns and an eluent containing NaI and tartaric acid, this method was successfully applied for indirect photometric detection of nitrite and bromide in tap water.[131]

Ionically coated ion exchanger is another promising way for fabrication of CIC technique, which means modifying ion exchangers onto polymers that contain ionizable groups.[132] The chondroitin sulfate possessing/with the sugar skeleton containing –COOH, $-CH_2OSO_3H$, and $-NHCOCH_3$ group was modified on the stationary phases, TSKgel IC-Anion-SW, in a 0.32 × 100 mm column format. It was found that retention of anions was not significantly affected by the eluent concentration after the chondroitin modification, and the analysis of common UV absorbing anions such as NO_3^-, I^-, and SCN^- using low concentrations (10 mM) of Na_2SO_4 as eluent and direct UV detection was realized.[133] Another polymer molecule with high charge density, heparin, which contains an amido-sulfonic acid group aside from carboxylate and sulfonate groups, has been chosen for the exchanger modification. Retention behavior of inorganic anions and cations on anion exchangers modified with heparin has been investigated. Retention of anions on the anion exchanger was remarkably reduced after the modification with heparin. The cations of the eluent affected the retention behavior of ions. The retention factor of anions decreased with decreasing eluent concentration when sodium sulfate and magnesium sulfate were used as the eluent, whereas it increased with eluent concentration decreasing when aluminum sulfate, copper sulfate and sulfuric acid were used as the eluent. When copper sulfate was used as the eluent, both anions and cations were retained on the modified stationary phase, and simultaneous separation of both anions and cations was achieved.[134]

MS is an attractive method for extending capillary IC to create a valuable technique for speciation and trace analysis.[135–139] Using an injection valve to couple CIC and MS was found to be the best method for hyphenation, since it constituted a flexible and dead-volume-free approach. Matysik's group

developed a CIC/sheath-flow-ESI-MS method, which featured no dead volume, fast transfer from IC to MS, only minimal peak-widening, high reproducibility, and the ability to fine-tune the ESI spray for higher sensitivity and stability by adjusting the composition of the sheath-liquid.[139]

Fluorescence detection can be easily hyphenated with CIC as well. Aluminum and magnesium were determined by fluorimetric detection *via* pre-column and/or in-column derivatization with 8-hydroxyquinoline (oxine) in the microcolumn format (0.32 × 100 mm, ODS packing). The incorporation of oxine in the eluent was found to produce substantially superior performance relative to post-column addition, with improved sensitivity for cations.[140]

Besides, on-column enrichment CIC,[141] open-tubular CIC,[142] monolithic column CIC,[135,143–145] and IC on a chip[146] are hot research areas for the scientists. CIC is an evolving field that is still very much in the making, and has been attracting more and more research interests worldwide.

4. Conclusions

In this paper, we presented a brief introduction of IC principles, summarized the common sample preparation methods for IC technique, and selectively introduced several advanced IC methods to demonstrate the rapid and diverse development of IC. IC, born as the special mode of liquid chromatography, has already exhibited great ability to be a powerful tool for elemental analysis and ionic compound quantification in various samples. Although this review has not fully covered all the IC technique development and novel methods, we are aiming to present the hot research topics and new-developed advanced IC methods that showed great potential for further progress and widely application. Cross-linked with other advanced separation techniques, detection techniques, and advanced materials for column packing, IC would demonstrate more and more applicability for scientific research.

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