Blaschke G and Chankvetadze B (2000) Enantiomer separation of drugs by capillary electrophoresis. *Journal of Chromatography A* 875: 3–25.

Blomberg LG and Wan H (2000) Determination of enantiomeric excess by capillary electrophoresis. *Electrophoresis* 21: 1940–1952.

Chen A, Nashabeh W, and Wehr T (2001) *CE in Biotechnology: Practical Applications for Protein and Peptide Analyses*. Wiesbaden, Germany: Vieweg.

Dolnik V, Liu S, and Javanovich S (2000) Capillary electrophoresis on microchip. *Electrophoresis* 21: 41–54.

Heegaard NHH and Kennedy RT (1999) Identification, quantitation, and characterization of biomolecules by capillary electrophoretic analysis of binding interactions. *Electrophoresis* 20: 3122–3133.

Hilhorst MJ, Somsen GW, and De Jong GJ (2001) Capillary electrokinetic separation techniques for profiling of drugs and related products. *Electrophoresis* 22: 2542–2564.

Nishi H (1999) Capillary electrophoresis of drugs: current status in the analysis of pharmaceuticals. *Electrophoresis* 20: 3237–3258.

Scriba GKE (2002) Selected fundamental aspects of chiral electromigration techniques and their application to pharmaceutical and biomedical analysis. *Journal of Pharmaceutical and Biomedical Analysis* 27: 373–399.

Shaw CJ and Guzman NA (2002) Applications of capillary electrophoresis technology in the pharmaceutical industry. In: Ohannesian L and Streeter AJ (eds.) *Handbook of Pharmaceutical Analysis*, pp. 313–386. New York: Dekker.

Thormann W (2002) Progress of capillary electrophoresis in therapeutic drug monitoring and clinical and forensic toxicology. *Therapeutic Drug Monitoring* 24: 222–231.

Thormann W, Way AB, Lurie IS, *et al.* (1999) Capillary electrophoresis in clinical and forensic analysis: Recent advances and breakthrough to routine applications. *Electrophoresis* 20: 3203–3236.

Wätzig H, Degenhardt M, and Kunkel A (1998) Strategies for capillary electrophoresis. Method development and validation for pharmaceutical and biological applications. *Electrophoresis* 19: 2695–2752.

Low-Molecular-Weight Ions

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Introduction

Low-molecular-weight (LMW) ions include both inorganic and organic compounds. The main application area of capillary electrophoresis lies in analyses for inorganic and organic anions and cations in environmental samples, in clinical chemistry, pulp and paper industry, process control, industrial applications, explosive residue analysis, biological samples, or drugs and drug intermediates. LMW organic acids are important intermediates or final metabolites of many biochemical pathways in living organisms, as well as degradative metabolites of amino acids, fats, and carbohydrates. LMW organic cations, e.g., quaternary ammonium compounds, are widely used in industry as antiseptic, antistatic, and antimicrobial agents.

In contrast to determinations of organic analytes, where the use of high-performance separations is almost inevitable in complex matrices, inorganic analysis has powerful tools in highly selective and sensitive spectroscopic methods and thus a separation step is often unnecessary. This is especially true for determination of inorganic cations. However, the selection of methods for determination of inorganic anions is much more limited.

The traditional approach to high-performance separations of LMW ions, ion chromatography (IC), is partially being replaced by capillary electrophoresis (CE) owing to the following main advantages of the CE: a higher separation efficiency caused by a flat local velocity profile in CE running buffers compared to parabolic profiles in IC; a higher speed of analysis caused by the absence of a partition process between the mobile and stationary phases (except for micellar electrokinetic chromatography (MEKC) where the analytes are distributed between a pseudostationary phase and the electrolyte, and capillary electrochromatography employing capillaries packed with stationary phase particles); very small amounts of sample required permit, e.g., an analysis for cations in a single small rat or mice eye lens or analysis for cations and anions present in a single rain drop; very low mass detection limits; low consumption of chemicals (low cost per analysis); relatively simple instrumentation, easy automation, and good tolerance to sample matrix, e.g., to high pH values.

The disadvantages of CE compared to IC include lower sensitivity, higher concentration detection limits, and somewhat poorer reproducibility of qualitative and quantitative data owing to instability of the electroosmotic flow (EOF). IC has so far been developed more extensively. Validated procedures and computer optimization approaches are available

Table 1 Equivalent ionic conductivities (Λ_{eq}) and ionic mobilities (m_i) of selected inorganic cations and anions

Analyte	Λ_{eq} ($cm^2\,\Omega^{-1}\,mol^{-1}$)	m_i ($10^{-4}\,cm^2\,V^{-1}\,s^{-1}$)[a]	m_i ($10^{-4}\,cm^2\,V^{-1}\,s^{-1}$)
NH_4^+	73.5	7.62	7.62
K^+	73.5	7.62	7.62
Ca^{2+}	59.5	6.17	6.17
Mg^{2+}	53.0	5.49	5.50
Na^+	50.1	5.19	5.19
SO_4^{2-}	80.0	8.29	8.29
Cl^-	76.3	7.91	7.91
NO_2^-	71.8	7.44	7.46
NO_3^-	71.4	7.40	7.41
PO_4^{3-}	69.0	7.15	7.15
F^-	55.4	5.74	5.74

[a] Calculated from the equivalent ionic conductivities.

in IC, while routine applications of CE are still less common. The selectivity range in CE is limited, as the selectivity can only be manipulated by the electrolyte composition. CE and IC are complementary rather than competing techniques and exhibit different selectivity; CE is used for separation of those mixtures of anions and cations that are difficult to separate by IC and vice versa.

Theoretical Consideration

The electrophoretic mobility of an ion, $\mu_{ep(ion)}$, can be related to the limiting ionic equivalent conductivity, λ_{eq}, by

$$\mu_{ep(ion)} = \lambda_{eq}/F = q_i/6\pi\eta r_i \qquad [1]$$

where F is the Faraday constant ($F = 9.6487 \times 10^4\,A\,s\,mol^{-1}$); λ_{eq} ($cm^2\,mol^{-1}\,\Omega^{-1}$) is related, by the Stokes law, to the charge of the hydrated ion, q_i, to the dynamic viscosity of the electrolyte, η ($g\,cm^2\,s^{-1}$), and to the radius of the hydrated ion, r_i (cm).

The $\mu_{ep(ion)}$ values can be calculated from the experimental data, the apparent mobility of the ion, $\mu_{app(ion)}$, and the mobility of the EOF, μ_{eo}, according to

$$\begin{aligned}\mu_{ep(ion)} &= \mu_{app(ion)} - \mu_{eo} \\ &= (1/t_{m(ion)} - 1/t_{m(eo)})(L_T L_d/V)\end{aligned} \qquad [2]$$

where $t_{m(ion)}$ and $t_{m(eo)}$ (both in seconds) are the migration times of the ion, and of an EOF marker (an uncharged solute), respectively; L_T and L_D (both in centimeters) are the overall capillary length and the length of the capillary to the detector, respectively; V is the voltage (in volts).

The limiting ionic conductivities and the experimental and calculated electrophoretic mobilities of some anions and cations are compared in **Table 1**. The electrophoretic mobilities derived from the limiting ionic equivalent conductivity differ somewhat from the experimentally measured values that are dependent on the composition of the background electrolyte and its pH. Differences in the ionic mobilities as small as $0.1 \times 10^{-9}\,m^2\,V^{-1}\,s^{-1}$ are sufficient for the separation of ionic species, provided that the separation is highly efficient. As follows from **Table 1**, all the ions can be separated except for K^+ and NH_4^+ whose mobilities are identical.

Optimization of Separation

The running buffer composition is of primary importance to CE selectivity optimization. The buffer contains at least one anion and one cation, and one of these ions should have an adequate buffering capacity. If possible, the EOF should have the same direction as the migration of the analytes to shorten the analysis. The co-ion should have a similar mobility as the analyte to ensure a good peak shape.

The separation is optimized by changing the composition and concentration of the running buffer and by adjusting its pH. As follows from eqn [1], the electrophoretic mobility of ions depends on their charge-to-mass ratio. For weak acids and bases this ratio can be changed by changing the pH in the vicinity of the analyte pK_a. The effect of the pH on the separation of weak acids can be demonstrated on an example of separation of a high concentration of phosphate (more than $800\,\mu g\,l^{-1}$) from a low concentration of fluoride ($1\,\mu g\,l^{-1}$). Protonation of hydrogenphosphate at a pH of 7 results in its slower migration and leads to an improved separation from fluoride. Another example is a very fast separation of nitrate and nitrite within 10 s at pH 2.5.

An addition of organic solvent to the background electrolyte changes the separation selectivity. This

can be explained by changes in the relative hydration of ions. The organic solvent destroys the hydrated layer and thus changes the effective mass of the ions. Ions such as iodide and chloride, which are difficult to separate in an electrolyte consisting of pyromellitic acid and hexamethonium hydroxide, can be separated after addition of methanol. Organic solvents added to the running electrolyte decrease the EOF; they increase the viscosity and decrease the pK_a of the silanol groups on the capillary wall and improve the reproducibility of the migration times, with a less noisy baseline. The temperature also affects the selectivity, as it influences both the mobilities and the EOF through a change in the solution viscosity.

Cations – Direct Analysis

Inorganic cations are smaller and thus have higher charge densities (q_i/r_i ratios) than most organic ions; therefore, as follows from eqn [1], their electrophoretic mobilities are higher. The problems connected with CE analysis of inorganic cations are caused by small differences in their migration rates (see **Table 1**), and, similar to the CE analysis of inorganic anions, by their low absorption of ultraviolet (UV) radiation, which complicates detection.

Only the alkali metal ions exhibit large differences in their mobilities and thus can easily be separated within very short times (less than 2 min), if the directions of the EOF and of the cation migration are the same, toward the cathode. Exceptional is the separation of K^+ and NH_4^+ ions whose mobilities are identical at a slightly acidic pH. Their separation can be attained in alkaline buffers as the ammonium ions are less protonated and their mobility decreases while the K^+ ion mobility is not affected by the pH. Quaternary ammonium ions can be separated in coelectroosmotic mode. However, to have a sufficiently large separation window, the EOF has to be decreased, e.g., by addition of organic solvents.

Cations – Separation of Complexes

Complexation with auxiliary ligands is used to promote cation separation. Different degrees of complexation lead to different migration times. The migration can thus be influenced by the type and the concentration of the complexing agent, pH, ionic strength, viscosity, etc.

Several complexing agents have been proposed and successfully tested in analyses of cations. Weak complexing agents, such as lactate, phthalate, tartrate, or hydroxyisobutyric acid (for separation of lanthanoids), have been used. For example, 19 alkali, alkaline earth, and rare earth metal ions can be separated in very short time (less than 2 min), using hydroxyisobutyric acid as a complexing agent and an indirect UV detection method (**Figure 1**). Other complexing agents, such as ethylenediaminetetraacetic acid (EDTA), diaminocyclohexanetetraacetic acid, and 18-crown-6, have also been used.

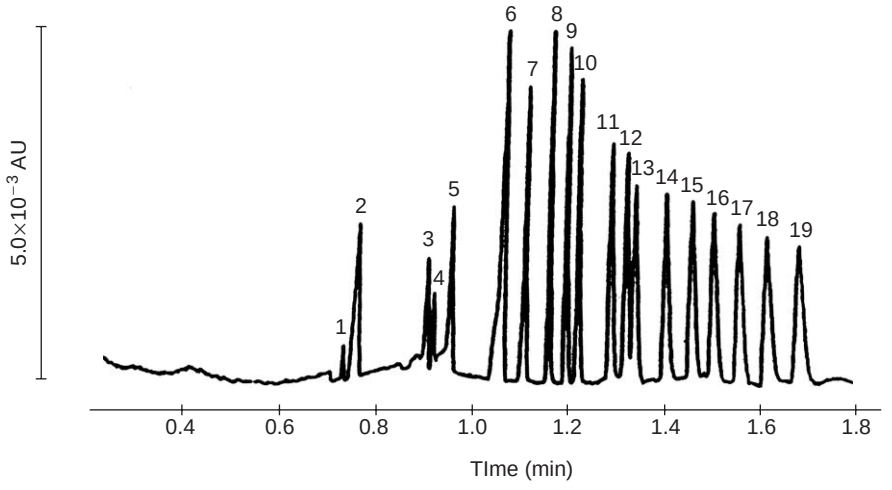

Figure 1 Electropherogram of the separation of alkali, alkaline earth, and lanthanide metal ions. Capillary, 36.5 cm, 75 μm ID, fused silica; running electrolyte, 10 mmol l^{-1} UV-Cat-1, 4.0 mmol l^{-1} HIBA, pH 4.4; separation voltage, 30 kV; detection, indirect UV at 214 nm. Peaks (mg l^{-1}): 1, Rb (2); 2, K^+ (5); 3, Ca^{2+} (2); 4, Na^+ (1); 5, Mg^{2+} (1); 6, Li^+ (1); 7, La^{3+} (5); 8, Ce^{3+} (5); 9, Pr^{3+} (5); 10, Nd^{3+} (5); 11, Sm^{3+} (5); 12, Eu^{3+} (5); 13, Gd^{3+} (5), 14, Tb^{3+} (5); 15, Dy^{3+} (5); 16, Ho^{3+} (5); 17, Er^{3+} (5); 18, Tm^{3+} (5); 19, Yb^{3+} (5). (Reproduced with permission from Weston A, Brown PR, Jandik P, Jones WR, and Heckenberg AL (1992) *Journal of Chromatography* 593: 289–295.)

In principle, two experimental approaches are taken in the CE analysis of cations, an offline preparation of complexes, prior to the CE analysis, and online complexation in the separation capillary. Their application depends on the stability of the complexes formed.

If weak complexes are rapidly formed, on-capillary partial complexation can be used. A ligand is added to the running electrolyte and a rapid equilibrium between the free metal ions and their complexes is established, with most of the ions present in the free form. Owing to different complexation degrees with various charges on the complexes, the ions have different migration rates. The capillary zone electrophoresis (CZE) mode and an indirect UV photometric detection method are usually employed in this case, as only a small fraction of the cations is complexed.

If the complexes of metal ions with ligands are sufficiently stable under the CE conditions, then off-capillary complexation is preferred. An excess of a strongly complexing agent is added to the sample prior to the CE analysis. On-column UV photometric detection is possible as the fraction of the complexed ions is large. If there is a danger of the dissociation of the complex during the CE analysis, the complexation agent is added to the running buffer in a high concentration. Poor peak shapes can be caused by slow attainment of complexation equilibria in the capillary.

The equilibria of complexation reactions with weakly acidic or basic ligands are influenced by the pH of the running buffer and by the concentration of the complexing agent. The optimum pH for the separation is around the pK_a of the monoprotic acid. With di- and triprotic acids, the pH must lie between $pK_{a,1}$ and $pK_{a,2}$ (pK_{a3}).

The complexing agent must contain suitable binding groups (e.g., carboxyl, hydroxyl), its dissociating sites should not interfere with the complexation equilibrium (they should be located far from the binding groups), and the agent should absorb radiation at wavelengths different from that of the complex.

Cationic, anionic, or neutral metal complexes can be formed offline. In dependence on their structure and charge, they can be separated by CZE or MEKC. An advantage of cationic complexes lies in rapid analyses in CZE due to coelectroosmotic migration. However, the number of metals that can be separated in this mode is limited by a narrow migration window and/or by their similar mobilities. When using MEKC, the polarity can be reversed by an addition of a cationic surfactant to the electrolyte and thus the separation can be improved. Anionic metal complexes, such as those with cyanide, move, during CZE in uncoated capillaries, to the cathode against the EOF and are detected within an acceptable time due to their rapid migration caused by their small size and/or high charge. Complexes with large ligands move very slowly or not at all. It is then necessary to suppress or reverse the EOF by adding a cationic surfactant or by a suitable coating of the capillary. Neutral complexes can be separated by MEKC.

Separation of cations can be influenced by their interaction with crown ethers, which depends on the sizes of the cation and the crown ether cavity. The concentration of a crown ether in the running buffer also plays a role. The best results have been obtained with 18-crown-6-ether where the selectivity changes were largest. The use of crown ethers makes it possible to separate, e.g., potassium from ammonium. Electrolyte containing 4 mmol l^{-1} 18-crown-6, 4 mmol l^{-1} copper sulfate, and 4 mmol l^{-1} formic acid was successfully applied to complete separation of all alkali and alkaline earth cations including ammonium (**Figure 2**).

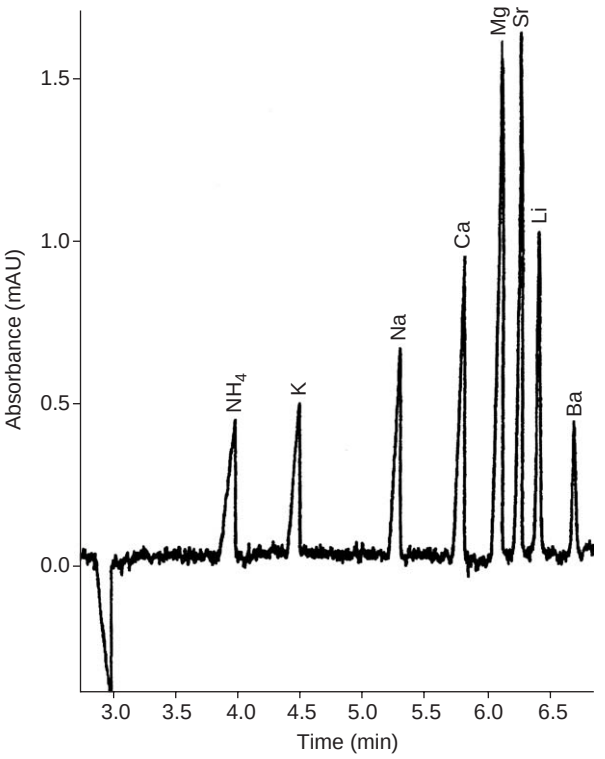

Figure 2 Electropherogram of a mixture of alkali and alkali earth metal ions. Capillary, 58.5 cm, 75 μm ID, fused silica; running electrolyte, 4 mmol l^{-1} 18-crown-6, 4 mmol l^{-1} copper sulfate, and 4 mmol l^{-1} formic acid, pH 4.4; separation voltage, 20 kV; detection, indirect UV at 215 nm. Peaks (mg l^{-1}): NH_4^+ (20); K^+ (19.5); Na^+ (11.5); Ca^{2+} (20); Mg^{2+} (12.2); Sr^{2+} (43.8); Li^+ (3.5); Ba^{2+} (68.7). (Reproduced with permission from Havel J, Janoš P, and Jandik P (1996) *Journal of Chromatography A* 745: 127–134.)

Anions

While cations can be analyzed directly in CE, the elution of anions in bare silica capillaries requires reversion of the EOF. The EOF can be changed by addition of cationic additives to the running electrolyte, by changing the concentration of the running electrolyte, or by a chemical modification of the capillary walls. Cationic surfactants are mostly added to reverse the EOF in analyses of anions. At concentrations below the critical micelle concentration, hemicelles are formed at the capillary wall that reverses the EOF. If anions interact with a monomeric surfactant present in the electrolyte, then their electrophoretic mobilities are influenced through ion association. The most common cationic surfactants used are, e.g., tetrabutylammonium, dodecyltrimethylammonium, tetradecyltrimethylammonium, and cetyltrimethylammonium (CTA) bromides or hydroxides, hexadimethrine, and hexamethonium hydroxides. Higher concentrations of additives lead to longer migration times owing to the formation of equilibrium ion-pairs. Differences in the selectivity allow complex samples to be analyzed by properly selecting the EOF modifier concentration and thus increasing the weak acid anion migration times.

Another possibility for EOF modification is coating of the capillary walls with cationic-soluble polymers. A net positive charge is then formed at the capillary walls. Reducing the EOF, e.g., by coating the capillary walls with silane, is sufficient for attaining sufficiently short analysis times for some anions. The EOF can also be modified by using capillaries made of materials other than fused silica, e.g., of polypropylene.

Detection Modes

Detection in CE takes place directly on the separation column. The UV/Vis photometric detection is most common in capillary electrophoresis, as it is simple and reliable. The problems connected with the detection of LMW ions are caused by their low absorption in the UV region. Therefore, direct UV detection is only applicable to a few inorganic anions, e.g., to nitrate, sulfide, nitrite, iodide, bromide, and thiocyanate (for example, a detection limit of $10\,\mu g\,l^{-1}$ has been attained for sulfide in waste water using direct UV detection at 229 nm). LMW carboxylic acids can be detected at low wavelengths (200 nm and below).

Direct UV/Vis or fluorescence detection is often employed in analyses of cations after their complexation, provided that the ligand contains a chromophore or a fluorophore. Several metal ions, e.g., Fe^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Cd^{2+}, form complexes with cyanide. Analogously, Fe^{2+} and Fe^{3+} form complexes with *o*-phenanthroline in the presence of EDTA and Au^{3+} with chloride and these complexes can be detected spectrophotometrically. 8-Hydroxyquinoline-5-sulfonic acid forms fluorescing complexes with metals. Dithizone sulfonate complexes have been used in determination of traces of inorganic mercury. 4-2-(Pyridylazo)resorcinol (PAR) forms colored complexes with Cu^{2+}, Pb^{2+}, Ni^{2+}, Cd^{2+}, Fe^{2+}, and Fe^{3+}, arsenazo I forms complexes with Ba^{2+}, Sr^{2+}, Ca^{2+}, and Mg^{2+}, arsenazo III has been recommended for separation of the lanthanoids and U^{6+}, sulfonoazo III for the determination of Ba^{2+} and Sr^{2+}. Detection limits of $10^{-7}\,mol\,l^{-1}$ have been

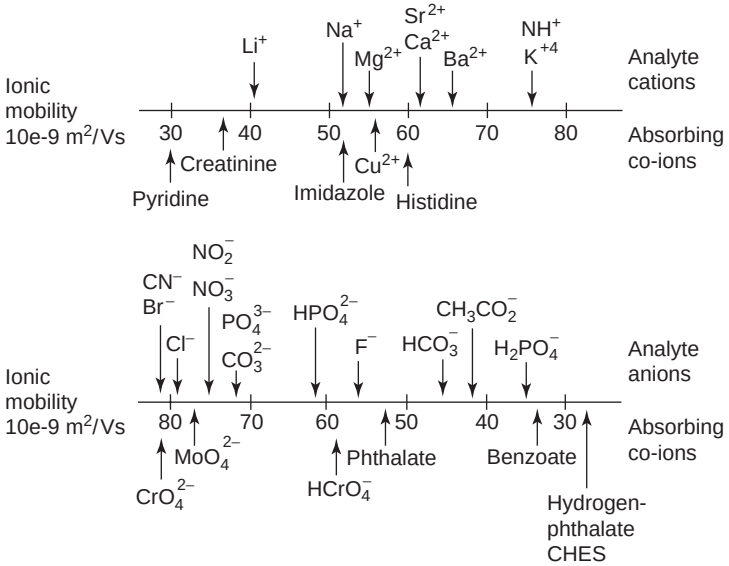

Figure 3 Ionic mobilities of analytes and absorbing co-ions.

attained, using PAR complexes with the transition metals.

Indirect UV or fluorescence detection, based on charge displacement of an absorbing co-ion, is nearly universal. A disadvantage of indirect detection is a high background absorbance and thus a high noise and a limited linear dynamic range. UV absorbing anions or cations are added to the running electrolyte. For indirect UV detection, the co-ion should strongly absorb in the UV region and should have a mobility similar to those of the analytes to ensure optimum separation and peak shape. The EOF should have the same direction as the analyte migration to improve the speed of analyses. Cupric sulfate, imidazole, histidine, 4-methylbenzylamine, or creatinine are employed in analyses of cations while chromate, pyromellitic acid, phthalate, *p*-aminobenzoate, or molybdate in analyses of anions. **Figure 3** helps in the selection of a suitable UV-absorbing ion for indirect analysis of cations and anions. The chromate anion matches the mobilities of small anions while phthalate or benzoate is suitable for large anions. Molybdate has been shown to be a better visualization agent than chromate, yielding improved peak shapes because the molar absorptivity of molybdate is higher than that of chromate. Detection limits in ppb region have been obtained using a running electrolyte containing chromate, with a time of analysis of 3 min. *p*-Aminobenzoate has been found useful for simultaneous determination of low mobility organic and high mobility inorganic anions. The separation has been facilitated by an addition of a barium salt. So far the best separation of anions with indirect UV detection has been attained in the IonPhor PMA electrolyte buffer consisting of 2.5 mmol l^{-1} pyromellitic acid, 6.5 mmol l^{-1} NaOH, 0.75 mmol l^{-1} hexamethonium hydroxide, and 1.6 mmol l^{-1} triethanolamine, with a pH of 7.7. Anionic chromophores (benzoate, anisate) and cationic buffers (Tris, ethanolamine) have been tested for simultaneous detection of nonabsorbing anions and cations.

A CE method with indirect UV detection has been validated for eight anions and two electrolyte systems: pyromellitic acid + hexamethonium hydroxide and chromate + TTAB. The detection limits are between 1 and 3 mg l^{-1}, the repeatability and reproducibility of the measurement differ for different compounds and amounts to 5%, except for fluoride and phosphate. Linear calibration curves have been obtained within a concentration range between 1 and 10 mg l^{-1}.

Conductivity detection (CD) is a nearly universal bulk property detection mode for small ions and, similar to detection in IC, both nonsuppressed and suppressed CDs are used. There are more options for the selection of the running electrolyte in combination with CD. The co-ion must have a substantially different conductivity. In nonsuppressed

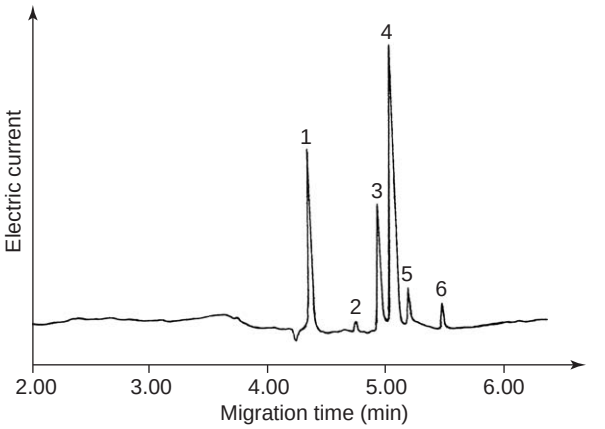

Figure 4 Electropherogram of the analysis of cationic impurities in drug Carbetocin with conductivity detector. Capillary, 70.0 cm, 50 μm, fused silica; running electrolyte, 30 mmol l^{-1} histidine, 30 mmol l^{-1} 2-morpholinoethan-sulfonic acid; separation voltage, 30 kV; injection, hydrodynamic, 20 mbar for 6 s; detection, conductometric. Peaks: 1, K^+; 2, Ba^{2+}; 3, Ca^{2+}; 4, Mg^{2+}; 5, Na^+; 6, Li^+. (Kindly provided by Dr. I. Jelínek from our Department.)

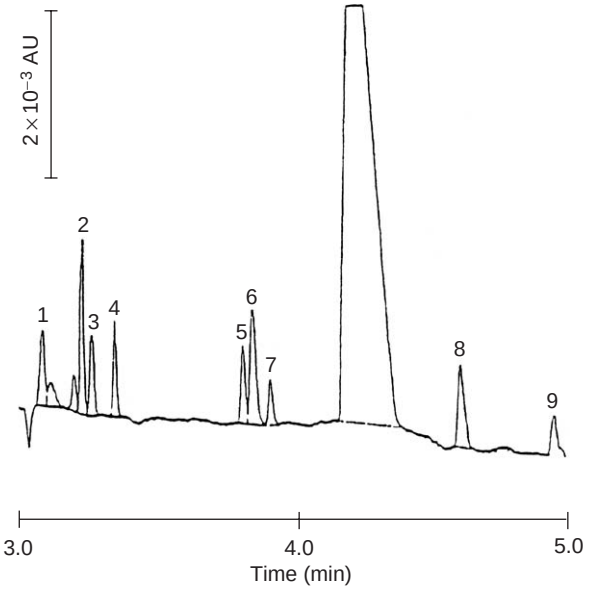

Figure 5 Trace determination of inorganic and organic anions in pure water, after an electrophoretic enrichment at 5 kV for 45 s with an addition of 75 μmol l^{-1} octanesulfonate to the sample. Capillary, 60 cm, 75 μm, fused silica; running electrolyte, 10 mmol l^{-1} sodium chromate and 0.5 mmol l^{-1}, pH 8, UV detection at 254 nm. Anions (concentration in mg l^{-1}); 1, chloride (3.5); 2, sulfate (4.8); 3, nitrate (6.2); 4, oxalate (5); 5, fluoride (1.9); 6, formate (5); 7, phosphate (3.2); 8, acetate (5); 9, propionate (5). (Reproduced with permission from Bondoux G, Jandik P, and Jones WR (1992) *Journal of Chromatography* 602: 79–88.)

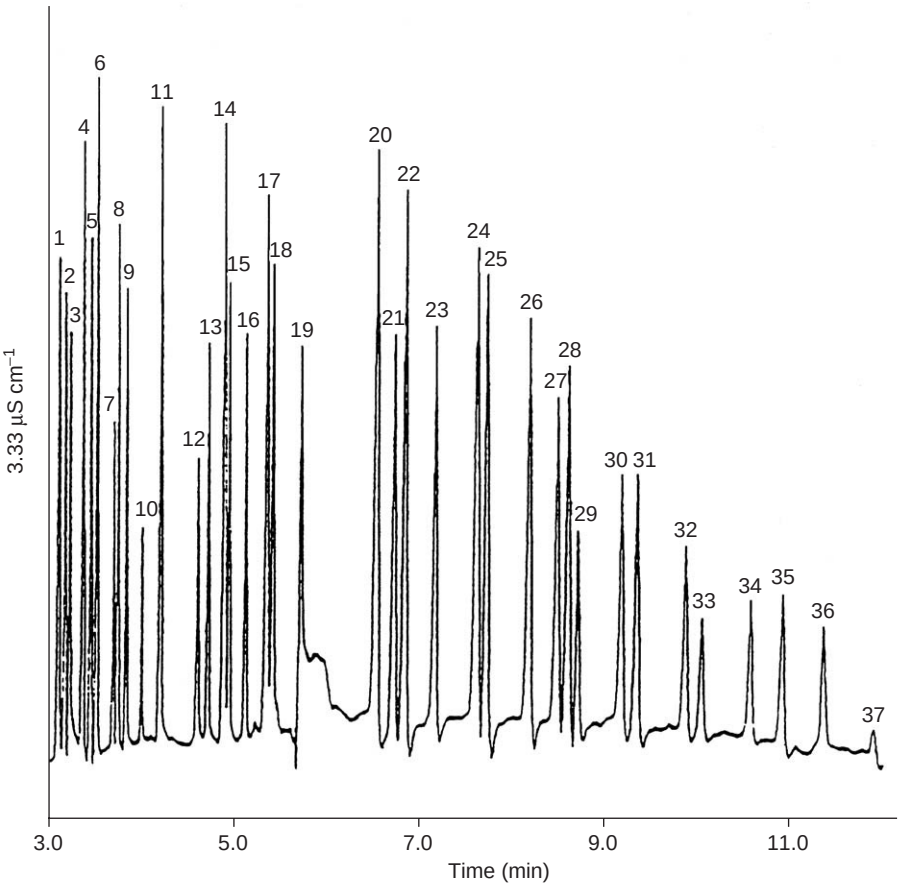

Figure 6 Determination of inorganic and organic anions with direct conductivity detection. Capillary, 60 cm, 50 μm, fused silica; running electrolyte, 50 mmol l^{-1} 2-*N*-cyclohexylamino-ethane-sulfonate, 20 mmol l^{-1} LiOH, 0.03% Triton X-100; separation voltage, 25 kV; injection, hydrodynamic, 25 mbar for 12 s; the EOF was modified by preflushing the capillary with a 1 mmol l^{-1} CTAB. Anions (concentration in mg l^{-1}): 1, bromide (4); 2, chloride (2); 3, hexacyanoferrate (7); 4, nitrite (4); 5, nitrate (4), 6, sulfate (4); 7, azide (2); 8, oxalate (3); 9, molybdate (5); 10, tungstate (6); 11, 1,2,4,5-tetracarboxylic acid (7); 12, fluoride (1); 13, tartrate (5); 14, selenite (10); 15, phosphate (4); 16, citraconate (5); 17, glutarate (10); 18, phthalate (10); 19, carbonate (4); 20, acetate (10); 21, chloroacetate (10); 22, ethanesulfonate (20); 23, dichloroacetate (15); 24, propionate (15); 25, propanesulfonate (20); 26, crotonate (15); 27, butanesulfonate (20); 28, butyrate (15); 29, toluenesulfonate (15); 30, penatenesulfonate (20); 31, valerate (15); 32, hexanesulfonate (20); 33, caproate (15); 34, heptanesulfonate (20); 35, morpholineethanesulfonate (35); 36, octanesulfonate (20); 37, D-gluconate (40).

CD, low mobility buffers with higher ionic strengths provide an extended linearity and improve preconcentration by sample stacking.

In comparison with indirect UV detection, the sensitivity of CD is ~10 times greater. The linear dynamic range extends over three concentration decades and the reproducibility of the migration times, peak area, and height is very good. A borate buffer (2 mmol l^{-1}, pH 9.2) combined with suppressed conductivity detection provides good peak shapes owing to a close match of the borate mobility with those of the separated anions and meeting the principal condition of suppressed CD, i.e., the suppression leads to a weakly conducting species. Additives, such as barium ions, decrease the EOF and the migration velocity of high mobility anions, so that they can be analyzed simultaneously with organic anions. Detection limits within a range of 1–10 ppb have been reported with suppressed conductivity detection.

Similar to CE analysis of anions, on- or end-column CD can be used for cations, with a sensitivity ~10 time greater than that of the indirect UV detection. CD is a nearly universal bulk property detection mode for small ions. Inorganic or organic buffers with low conductivities, e.g., borate or MES–histidine, and higher ionic strengths are used when employing conductivity detection. **Figure 4** depicts a determination of cationic impurities (K^+ Ba^{2+}, Ca^{2+}, Mg^{2+}, Na^+, and Li^+ ions) in the drug Carbetocin using a MES–histidine buffer with conductivity detection. Contactless conductivity detection has

been suggested for analysis of Rb^+, K^+, Na^+, Ca^{2+}, Mg^{2+}, Mn^{2+}, Cd^{2+}, and Li^+ cations, with a detection limit of $\sim 1 \times 10^{-4}$ mol l^{-1}. On-capillary cells combining contactless conductivity and UV/Vis detection improve the identification potential in separations of LMW ions.

CE–MS has been used in analyses of anions and cations as a method simultaneously providing positive identification and quantitation. CE–ESI MS is particularly well suited for analyses of quaternary ammonium salts. Speciation analysis of As can be carried out using a CE–ICP-MS. Problems in interfacing the ICP-MS detection to CE are associated with low flow rates and small samples analyzed. Detection limits in ppb region can be attained, using postcapillary hybridization prior to ICP-MS.

Preconcentration Techniques

Sample preconcentration is usually necessary for analyses of highly dilute solutions, e.g., for separations of anions in deionized water or their determination in the presence of a large excess of a matrix component.

Isotachophoretic enrichment by electrostacking at the sample–buffer interface can be used. The sample matrix can assist in the stacking process by functioning as the leading or terminating electrolyte. The co-ion of the running electrolyte has to be chosen so that the analyte mobilities are between those of the ions of the electrolyte and the matrix. Limits of detection lower than 50 nmol l^{-1} have been attained in the simultaneous analysis of inorganic and organic anions in rain water when enriching by sample stacking with a dynamic injection. This preconcentration method permits determination of inorganic anions in the presence of a fluoride matrix up to an analyte–matrix ratio of $1{:}6 \times 10^6$.

Preconcentration with the electrokinetic injection can be used for nonionic matrices. With long injection times, the ionic components are preconcentrated at the expense of the nonionic interferents. The EOF has the direction opposite to the migration of the analytes. The matrix effects caused by ionic components can be decreased by suppressing their dissociation by a pH change, thus enriching the analytes by up to two orders of magnitude. The choice of the amount injected is influenced by the analyte mobilities, the magnitude of the EOF, and the sample and buffer ionic strengths. The reproducibility of the electrokinetic injection is poorer than that of the dynamic pressure injection and strongly depends on the running electrolyte ionic strength. Internal standards are usually added to improve the accuracy and precision. A trace determination of some inorganic and organic anions in deionized water after electrokinetic enrichment with indirect UV detection is shown in **Figure 5**. A number of applications can be found in the references under Further Reading. An electropherogram of inorganic and organic anions with direct conductivity detection is given in **Figure 6**.

See also: **Ion Exchange**: Principles; Ion Chromatography Applications.

Further Reading

Fritz JS (1997) Determination of inorganic anions and metal cations. In: Camilleri P (ed.) *Capillary Electrophoresis Theory and Practice*, 2nd edn. Boca Raton, FL: CRC Press.

Haddad RP (ed.) (2003) Inorganic species and small organic ions (Paper Symposium). *Electrophoresis* 12–13.

Haddad RP, Macka M, Hilder EF, and Bogan DP (1997) Separation of metal ions and metal-containing species by micellar electrokinetic capillary chromatography, including utilization of metal ions in separations of other species. *Journal of Chromatography A* 780: 329–341.

Haddad PR (1997) Comparison of ion chromatography and capillary electrophoresis for the determination of inorganic ions. *Journal of Chromatography A* 770: 281–290.

Jandik P and Bonn B (1993) *Capillary Electrophoresis of Small Molecules and Ions*. New York: VCH.

Jones WR (1994) Electrophoretic capillary ion analysis. In: Landers JP (ed.) *Handbook of Capillary Electrophoresis*, pp. 209–232. Boca Raton, FL: CRC Press.

Macka M and Haddad PR (1997) Determination of metal ions by capillary electrophoresis. *Electrophoresis* 18: 2482–2501.

Okada T (1997) Micellar electrochromatography of inorganic compounds. *Journal of Chromatography A* 780: 343–360.

Pacáková V and Štulík K (1997) Capillary electrophoresis of inorganic anions and its comparison with ion chromatography. *Journal of Chromatography A* 789: 169–180.

Pacáková V, Coufal P, and Štulík K (1999) Capillary electrophoresis of inorganic cations. *Journal of Chromatography A* 834: 257–275.

Pacáková V, Coufal P, Štulík K, and Gaš B (2003) The importance of capillary electrophoresis, capillary electrochromatography and in chromatography in separations of inorganic ions. *Electrophoresis* 24: 1883–1891.

Timerbaev AR (1997) Strategies for selectivity control in capillary electrophoresis of metal species. *Journal of Chromatography A* 792: 495–518.