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Determination of alkali and alkaline earth metals in real samples by capillary ion analysis

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Abstract

Imidazole–H_2SO_4 background electrolyte was used to perform capillary ion analysis with indirect UV detection. Baseline separation of K, Na, Ca, Mg and Mn was achieved and the resolution could be enhanced by decreasing the pH of the electrolyte buffer. The electromigration dispersion for Na was smaller in the imidazole–H_2SO_4 buffer than in the background electrolyte containing UVCat1 (a UV-absorbing amine) and 2-hydroxyisobutyric acid. This therefore resulted in less Na peak broadening. As a consequence, large amounts of Na could be separated efficiently without interference with the other analyte cations. The method was validated for the quantitative analysis of pharmaceutical electrolyte solutions and beverages, and compared with flame atomic spectrometry for evaluation.

1. Introduction

Koberda *et al.* [1] tried to develop a capillary electrophoresis (CE) method to analyse parenteral electrolyte solutions quantitatively for Na, K, Ca and Mg simultaneously. Using UVCat1–2-hydroxyisobutyric acid (HIBA) as the background electrolyte (BGE), they found that Na, present in much higher concentrations than other ions, caused overlap between Na and the rest of the analyte cations. They therefore maximized the resolution by increasing the concentration of the complexing agent HIBA. Although they obtained an enhanced resolution, an increase in buffer conductivity and running current resulted in a significant increase in baseline noise and a marked decrease in the analyte peak response. Nevertheless, their method could not deal with the analysis of parenteral solutions owing to the presence of very high levels of Na.

The overlap is considered to result from the electromigration dispersion which causes a broad peak. The higher the concentration of the sample component in its zone, the more pronounced in this dispersion and therefore the broader is the peak [2]. There are two ways to suppress the electromigration broadening. The first is to keep the solute concentrations sufficiently lower than the concentration of BGE. This, however, will produce a negative effect on the sensitivity as a reduced amount of analyte is used. Another possibility is based on the selection of a co-ion with a mobility close to that of the analytes. In such a case the electromigration broadening of the analyte zones during the migration is negligible even if the concentration of solutes reaches the concentration of BGE.

Beck and Engelhardt [3] proposed a new

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background electrolyte system, imidazole–H_2SO_4, for the determination of alkali and alkaline earth metal cations by capillary ion analysis (CIA). In this buffer, positively charged imidazole ion was reported to have a mobility of 0.44 $cm^2\ kV^{-1}\ s^{-1}$, which is close to the mobility of Na (0.48 $cm^2\ kV^{-1}\ s^{-1}$). It was also found experimentally that Na had the highest separation efficiency in the pH range of 3–6. Although Beck and Engelhardt [3] applied this method to the quantitative analysis of mineral waters, so far work on the CIA of cations has mostly been focused on qualitative detection.

The main aim of this work was to investigate the applicability of CIA, by adapting Beck and Engelhardt's method, to the quantitative analysis of real complex mixtures. For this reason, a comparison with a well established metal analysis method, flame atomic spectrometry (FAS), was carried out in terms of sensitivity, limit of detection, linearity, accuracy and precision.

2. Experimental

2.1. Instrumentation

The CE instrument was a Waters Quanta 4000 capillary electrophoresis system with a twenty-sample carousel, a positive power supply and a zinc lamp detector (214 nm). Accusep fused-silica capillaries, 75 μm I.D. and 60 cm total length, were used in all analyses. A positive voltage of 20 kV was applied. The detector time constant was 0.3 s. The samples were introduced into the capillary by 20- or 30-s hydrostatic injections from a height of 10 cm, which corresponds to an injection volume of about 40 nl [4]. The electropherograms were recorded and treated with a Waters Model 810 data workstation equipped with a W51-watch-dog interface. Absolute peak areas (microvolts multiplied by seconds) were used in all calculations.

A Perkin-Elmer Model 373 flame atomic absorption spectrometer was used for the determination of Ca and Mg in the absorption mode (FAAS) and for Na and K in the emission mode (FAES). For Ca determinations, 1% (w/v) La was added to both standards and samples to eliminate possible interference from phosphate.

2.2. Temperature control for experiments

Temperature control was achieved by locating the instrument in a room with air conditioning where the temperature was set at 21.5°C. A temperature probe was inserted into the compartment where the capillary was situated in order to monitor the temperature inside the compartment. Within one day the temperature difference inside the compartment, as monitored by the temperature probe, was about 0.5°C at the end of all experiments.

2.3. Capillary preparation and cleaning

Every morning the capillary was cleaned and prepared according to the following procedure: washing for 2 min with 0.5 *M* KOH, for 5 min with Milli-Q-purified water and for 2 min with the BGE. Finally, the capillary was conditioned with the BGE for at least 15 min. At the end of the day the whole cleaning procedure was repeated, then the capillary was dried by sucking air through it for 5 min to prevent the formation of a gel layer inside the capillary overnight [5].

2.4. Reagents and standards

Water used for the preparation of all solutions was obtained from a Milli-Q water purification system (Millipore, Bedford, MA, USA) and contained no detectable analyte cations. Standards containing Na, K, Mg, Ca and Mn were prepared by mixing and diluting different Titrisol concentrates of 1000 μg/ml of these elements (Merck, Darmstadt, Germany). H_2SO_4 was of Suprapur grade and imidazole was of analytical-reagent grade (Merck). BGE containing 5 m*M* imidazole was prepared by dissolving 0.034 g of imidazole in a 100-ml plastic volumetric flask and then the pH was adjusted by titration first with 5 *M* and then 0.5 *M* H_2SO_4. The solution was kept in a refrigerator. Just before use it was filtered through a 0.45-μm syringe filter (Millipore, Molsheim, France).

2.5. Samples

Pharmaceutical NaCl, KH_2PO_4, $MgSO_4 \cdot 7H_2O$, calcium gluconate used for the preparation of a simulated concentrate and multiple electrolyte solutions for parenteral use were commercially available. Glucose, mixtures of various amino acids, intralipid and a mixture of trace elements Zn, Cu, Fe, Cr, Se, Mn, F and I, used for preparing real multiple electrolyte solutions were also commercially available. They were used in the hospital to prepare the electrolyte solutions for parenteral use. In this work, two test solutions (1 and 2) were obtained from the hospital and diluted 100-fold (1 ml in 100 ml) with Milli-Q-purified water for quantitative analysis.

The simulated electrolyte concentrate was prepared in the laboratory by mixing the aforementioned four electrolyte salts. The prepared electrolyte contained 178.4 μg/ml of Na, 468.5 μg/ml of K, 180.6 μg/ml of Ca and 43.9 μg/ml of Mg. In order to obtain the solutions at two concentration levels for each cation, the concentrated solution was diluted 25-fold (1 ml in 25 ml) and 50-fold (1 ml in 50 ml), respectively.

Apple juice and orange juice samples were purchased at a local supermarket and diluted 50-fold for Na, Ca and Mg determinations and 100-fold for K determination. Because pulp was present in the orange juice, the diluted orange juice was filtered through a 0.45-μm syringe filter.

3. Results and discussion

3.1. Effect of pH of the background electrolyte

A decrease in the pH of BGE results in an increase in the difference of the migration times between two neighbouring cations, Δt (min): changing pH affects the selectivity. When the pH decreases from 6 to 3, Δt increases from 0.4 to 0.8 for the K–Na pair, from 0.1 to 0.3 for the Na–Ca pair, from 0.08 to 0.1 for the Ca–Mg pair and from 0.07 to 0.15 for the Mg–Mn pair.

The pH effect could result from the following factors. First, the electroosmosis flow (EOF) decreases with a decrease in pH owing to a reduced dissociation of surface silanol groups. The effect of the EOF on the selectivity of separation can be derived from the following equation for Δt:

$$\Delta t = \frac{l}{E} \cdot \frac{\mu_1 - \mu_2}{(\mu_1 + \mu_{eof})(\mu_2 + \mu_{eof})} \quad (\mu_1 > \mu_2) \qquad (1)$$

where μ_1 and μ_2 are the electrophoretic mobilities of two neighbouring cations and μ_{eof} is the electroosmotic mobility, l is the distance from the injector to the detector and E is the electric field strength. When l and E are kept constant, decreasing the pH of the electrolyte buffer will decrease μ_{eof} and therefore increase Δt, except when $\mu_1 = \mu_2$. In that case another separation mechanism such as complexation and/or solvation must be included to maximize the resolution [6].

Second, when basic imidazole is neutralized by H_2SO_4, the ionic strength of the BGE increases owing to the addition of SO_4^{2-}, which results in a decreased μ_{eof} and electrophoretic mobilities of the analyte cations. Issaq *et al.* [7] have theoretically and experimentally confirmed that as the buffer concentration is increased, the μ_{eof} and ionic electrophoretic mobilities μ_1 and μ_2 are both reduced. The migration times of the solutes increase and the resolution improves with increasing concentration of the electrolyte buffer.

Vindevogel and Sandra [8] found that adjusting the pH of the buffer has two effects, namely a pure pH effect and an ionic strength effect. The two effects can be either cooperative or contradictory with respect to the influence on the EOF. In a strong acid–weak base type of electrolyte buffer as in our case, the pH effect and the ionic strength effect are cooperative, therefore resulting in a strong pH dependence of the EOF. Fig. 1 shows a plot of the number of theoretical plates (N) as a function of pH. The number of theoretical plates was calculated using the expression [7]

$$N = 5.545\left(\frac{t_m}{W_{1/2}}\right)^2 \qquad (2)$$

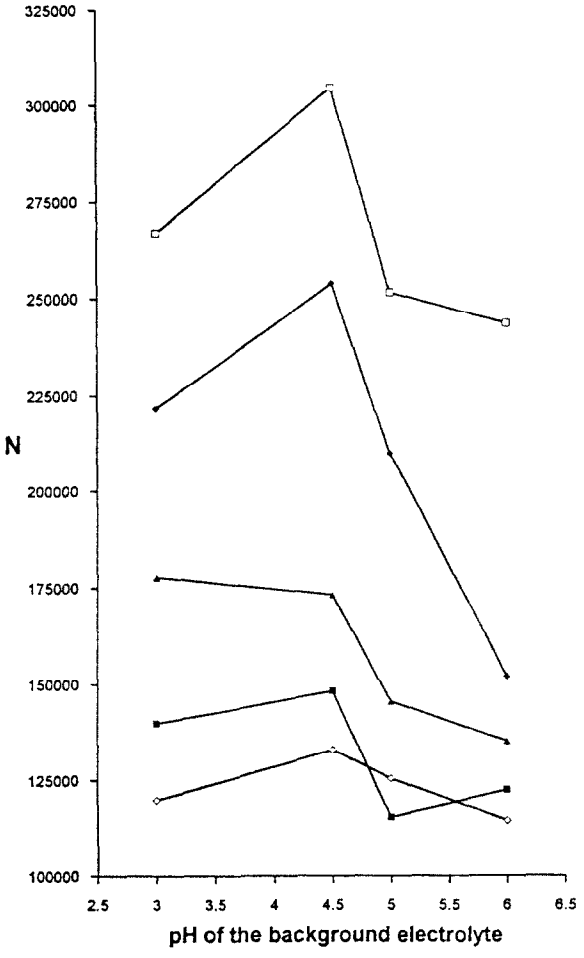

Fig. 1. Dependence of the number of theoretical plates (N) on the pH of the BGE. BGE, 5 mM imidazole–H_2SO_4; applied voltage, +20 kV; hydrostatic injection, 30 s from 10 cm. K, Na, Ca, Mg and Mn concentrations, 1 μg/ml each. ■ = K; □ = Na; ◆ = Ca; ◇ = Mg; ▲ = Mn.

where t_m is the migration time of the corresponding cation and $W_{1/2}$ is the peak width at half-height. With increasing pH, N for K, Na, Ca and Mg first increases and reaches a maximum at pH 4.5 and then decreases when the pH is increased further. Therefore, at pH 4.5, the largest peak height and consequently the highest detectability for these cations are obtained. The measurement of N is affected by the asymmetry of the peak and the asymmetry changes with pH. It is well known that the form of peaks in indirect detection is influenced by many parameters, but the theory of indirect detection and its influence on peak form are not well established and need further research. Na has the highest N value, about 300 000, because its electrophoretic mobility is close to that of ionic imidazole. The order of N as such Na > Ca > Mn > K > Mg can be explained by the order of the electrophoretic mobilities of these cations except for Mg. The exception is possibly due to the fact that Mg has a much higher displacement ratio than the other ions. This causes a higher peak and a larger peak width at half-height. As described in Eq. 2, the peak width is adversely proportional to N. To avoid this influence one should consider the use of peaks with equal height.

Fig. 2 is a plot of resolution (R_s) as a function

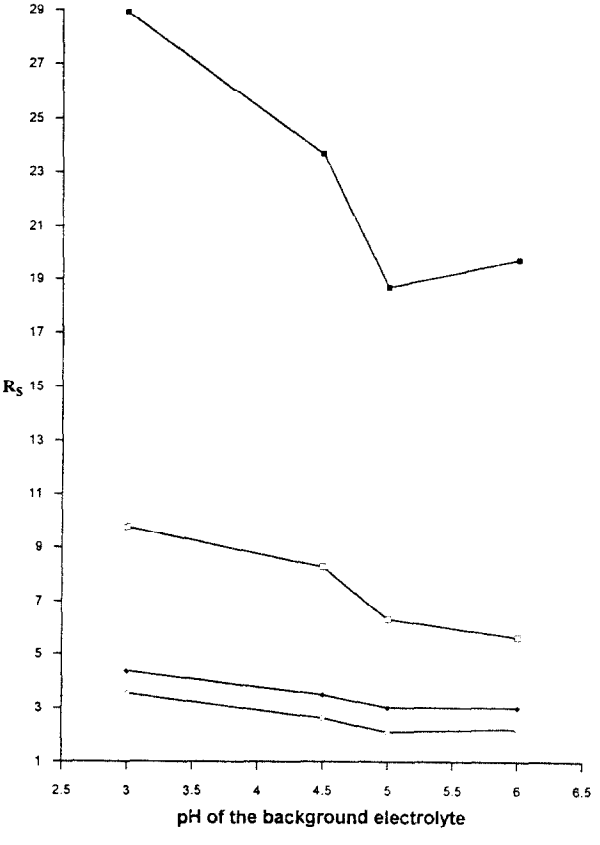

Fig. 2. Dependence of resolution (R_s) on the pH of the BGE. Experimental conditions as in Fig. 1. ■ = K–Na; □ = Ca–Na; ◆ = Ca–Mg; ◇ = Mg–Mn.

of pH. R_s is calculated by the following equation [7]:

$$R_s = 1.177 \cdot \frac{(t_{m_2} - t_{m_1})}{(W_{1/2})_1 + (W_{1/2})_2} \quad (3)$$

The effect of pH on R_s is largest for the K–Na and Na–Ca pairs and is less pronounced for the Ca–Mg and Mg–Mn pairs. Hence, decreasing the pH of the BGE improves the separation.

Fig. 3a and b show the electropherograms of 1 μg/ml each of K, Ca, Mg, Mn and 20 μg/ml of Na at pH 4.5 and 3.0. The resolution is enhanced when the pH changes from 4.5 to 3.0. Even at pH 4.5 as much as 20 μg/ml of Na do not cause any overlap with the rest of the cations and baseline separation is achieved. At pH 3.0 even 40 μg/ml of Na are well separated from K, Ca and Mg. With UVCat1–HIBA BGE, however, even 10 μg/ml of Na led to very broad Na peaks [1]. Hence the electromigration dispersion for Na is smaller in the imidazole–H_2SO_4 BGE than in the UVCat1–HIBA BGE.

In Fig. 4, a decrease in pH results in an increase in peak area, although it is less pronounced for K. The increased peak responses are caused by a decreased migration velocity of the sample zone through the detector because peak area is inversely related to the migration velocity [9]. At pH 3.0 the largest peak response,

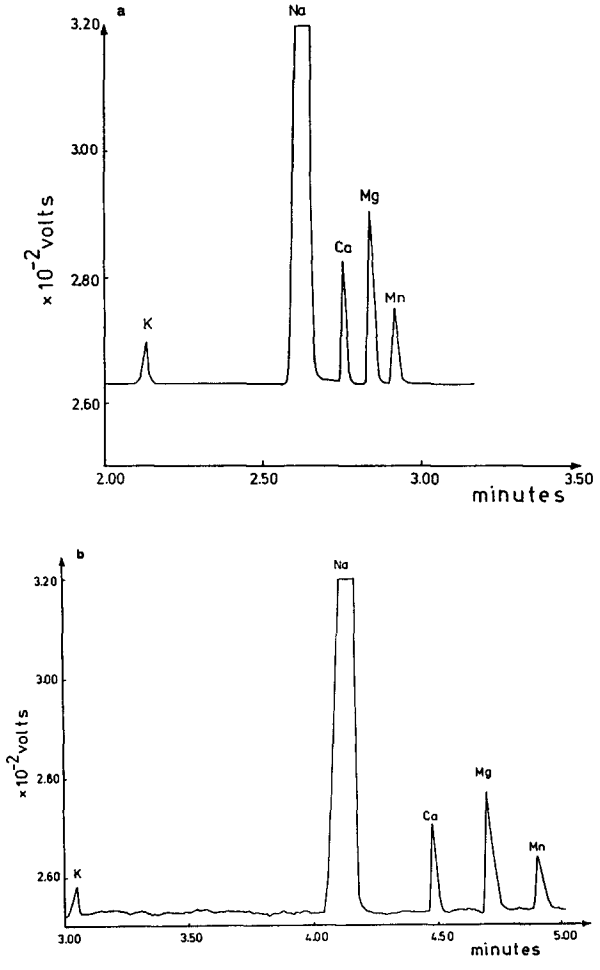

Fig. 3. Separation of 1 μg/ml each of K, Ca, Mg and Mn and 20 μg/ml of Na at (a) pH 4.5 and (b) pH 3.0. Experimental conditions as in Fig. 1.

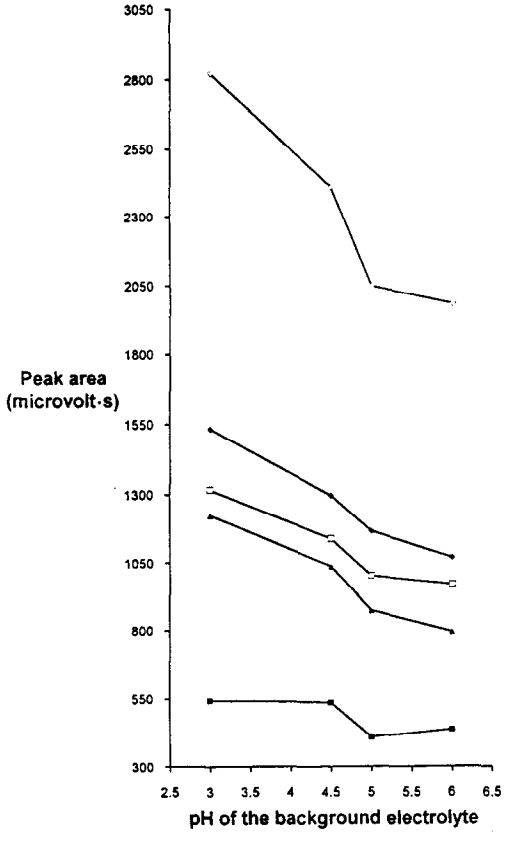

Fig. 4. Dependence of peak areas on the pH of the BGE. Experimental conditions and symbols as in Fig. 1.

and consequently the highest sensitivity, are obtained for all the cations.

3.2. Effect of applied voltage

The relationship between the number of theoretical plates (N) and the applied voltage is as follows [7]:

$$N = \frac{\mu V}{2D} \quad (4)$$

where V is the applied voltage and D is the diffusion coefficient of the solute. N increases with increasing applied voltage and maximum separation efficiency is attained at the highest possible applied voltage. In practice there is a limit to the voltage that can be applied [7].

Fig. 5 shows a plot of the number of theoretical plates (N) for K, Na, Ca, Mg and Mn as a function of applied voltage. N first increases with increased voltage, reaches a plateau at a certain voltage and then drops as the applied voltage is increased further. This is in agreement with the observation of Issaq *et al.* [7] and was explained as the result of increased temperature and the formation of a radial temperature gradient inside the capillary. The higher temperatures result in increased buffer conductivity, solute diffusion coefficient and double-layer thickness and decreased buffer density and viscosity [10]. The net effect of these changes is an increase in solute mobility and a decrease in efficiency. As observed here, the voltage where N reaches a maximum value varies among the cations: 20 kV for K and Ca, 25 kV for Na and 15 kV for Mn. For Mg a larger N was observed at 10 kV. This may be due to the ratio of the electrophoretic mobility, μ, to the diffusion coefficient, D, being a solute-dependent parameter. The mechanism is not clearly understood. It is also observed that the number of theoretical plates is significantly higher for Na and Ca than for K, Mg and Mn, and again Na has the highest N, about 310 000. The explanation is the same as above.

Fig. 6 shows a plot of the resolution as a function of applied voltage. The resolution between K and Na and that between Na and Ca are much higher than the others. A change in the applied voltage has a slight effect on the resolution, as the resolutions between the neighbouring cation pairs change by less than 1 unit when the applied voltage changes from 10 to 30 kV. From the above considerations, a positive voltage of 20 kV was selected for all further experiments.

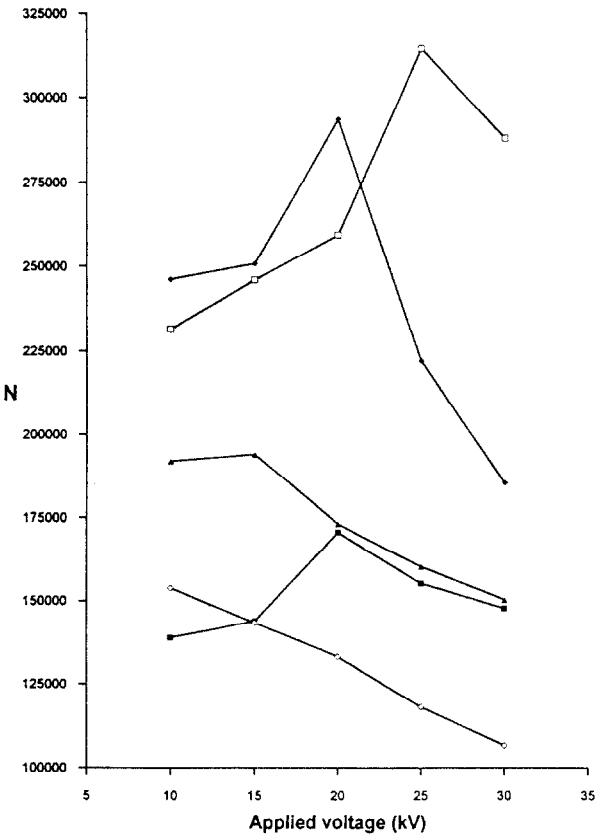

Fig. 5. Effect of applied voltage on the number of theoretical plates (N). BGE, 5 mM imidazole–H_2SO_4 (pH = 4.5); hydrostatic injection, 20 s from 10 cm. K, Na, Ca, Mg and Mn concentrations, 1 μg/ml each. Symbols as in Fig. 1.

3.3. Validation of the method

Limit of detection (LOD)

With hydrostatic injection for 30 s, at pH 4.5 the LOD was found to be 100 μg/l for K, Na, Ca and Mn and 50 μg/l for Mg, based on three times the baseline noise. With the UVCat1-HIBA BGE [11] the LOD was 135 μg/l for K,

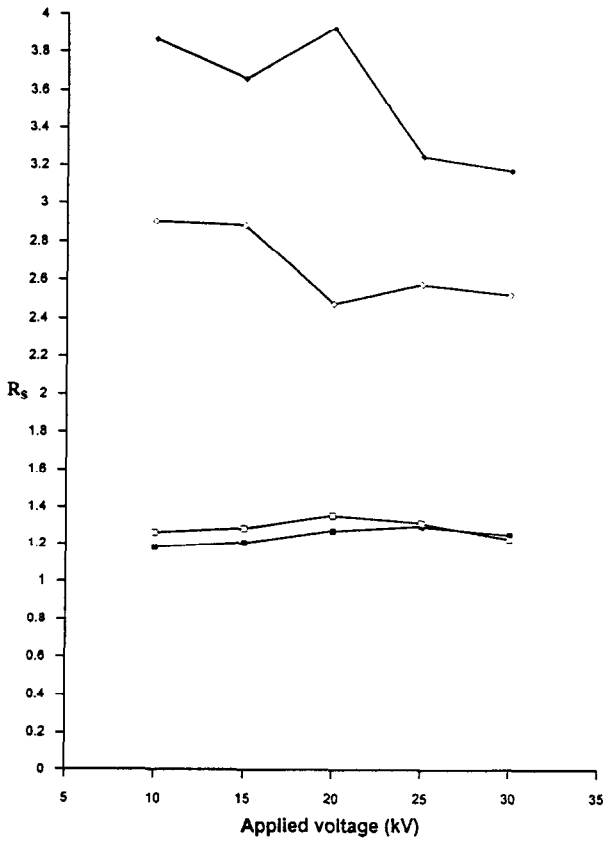

Fig. 6. Effect of applied voltage on the resolution (R_s). Experimental conditions as in Fig. 5. Symbols as in Fig. 2.

110 μg/l for Ca, 100 μg/l for Na, 60 μg/l for Mg and 120 μg/l for Mn. It is concluded that comparable LODs are obtained.

With FAAS, the LOD was 1 μg/l for Ca, 0.1 μg/l for Mg and 1 μg/l for Mn, and using FAES, 3 μg/l for K and 0.1 μg/l for Na [12]. In relative amounts (concentrations) CIA is much less sensitive. However, considering that at least 100 times more sample is needed in FAS than in CIA (in our experiment about a 40-nl sample volume), the minimum detectable absolute amounts are similar.

Linearity of the calibration line

Standard solutions containing 0.5, 1, 3, 5, 7, 10 and 20 μg/ml each of K, Na, Ca, Mg and Mn were prepared. Four injections were performed at each concentration level. Analytical calibration lines were calculated based on the measurement of the absolute peak areas. Analysis of variance (ANOVA) for lack of fit was used to check the linearity of the calibration lines estimated by the least-squares linear model. The regression equations are $y = 995x + 123$ (K), $y = 2367x + 104$ (Na), $y = 2569x + 245$ (Ca), $y = 4723x + 283$ (Mg) and $y = 2124x + 139$ (Mn), where x = concentration in μg/ml and y = peak area. In all instances, the calculated F value is smaller than the theoretical value, so that the null hypothesis is accepted, that is there is no lack-of-fit: the calibration lines are straight. At pH 3.0 the calibration lines were linear up to 20 μg/ml for K, Na, Ca and 10 μg/ml for Mg and Mn. At high concentrations peak distortion occurred owing to overloading, which caused insufficient selectivity of separation, so that the calibrations were no longer useful. At pH 4.5 the calibration line for Mn was linear only up to 6 μg/ml owing to the insufficient separation between Mn and Mg. In addition, the estimated calibration lines were subjected to statistical evaluation to determine whether or not the intercepts are different from zero [13]. No significant difference was found.

In FAS, owing to the restriction of the Lambert–Beer law, the calibration is linear up to 2 μg/ml for K, 1 μg/ml for Na, 0.5 μg/ml for Mg, 5 μg/ml for Ca and 3 μg/ml for Mn [14]. In this respect CIA is superior.

Precision and accuracy and analysis of multiple electrolyte solutions

The precision of the proposed method was evaluated within day (repeatability) and from day to day (reproducibility). The repeatability was determined first by analysing the two 25- and 50-fold dilutions of the simulated multiple electrolyte concentrate. For each dilution six replicate determinations was carried out. The concentrations were calculated from the same calibration line measured on the same day. Subsequently analysis was performed over 6 days to determine the reproducibility. Each day a new calibration line was measured. The results are given in Table 1. The relative standard deviations (R.S.D.) for the repeatability and repro-

Table 1
Repeatability and reproducibility

	Metal	Calculated (μg/ml)	Found[a] (μg/ml)	R.S.D.[b] (%)	Recovery[c] (%)
Repeatability					
(n = 6)					
50-fold	K	9.4	9.4	3.2	100
dilution	Na	3.6	3.5	2.2	98
	Ca	3.6	3.5	3.2	96
	Mg	0.9	0.8	2.4	95
25-fold	K	18.7	19.1	2.5	102
dilution	Na	7.1	7.3	1.2	102
	Ca	7.2	7.6	1.5	105
	Mg	1.8	1.8	2.3	103
Reproducibility					
(n = 6 days)					
50-fold	K	9.4	9.6	2.4	102
dilution	Na	3.6	3.6	2.9	99
	Ca	3.6	3.6	5.5	98
	Mg	0.9	0.8	5.4	93
25-fold	K	18.7	18.8	3.4	101
dilution	Na	7.1	7.2	4.9	101
	Ca	7.2	7.1	4.2	98
	Mg	1.8	1.7	3.0	98

Experimental conditions: BGE, 5 m*M* imidazole–H_2SO_4 (pH 4.5); applied voltage, +20 kV; hydrostatic injection, 30 s from 10 cm.
[a] Mean.
[b] Relative standard deviation.
[c] Result from CIA/calculated value.

ducibility are less than 3 and 6%, respectively. The recoveries range from 93 to 105%. One can conclude that reliable results can be obtained by CIA without the use of an internal standard.

In order to evaluate the precision of the method for real samples, the repeatability was determined for two real electrolyte solutions (see Section 2.5) and the reproducibility for one of them. The data are given in Table 2, where the R.S.D. values indicate that the repeatability is less than 3%. The repeatability for FAS is better than that for CIA. The R.S.D. values for the reproducibility in CIA are less than 4%.

Baseline separation for K, Na, Ca and Mg in a 100-fold dilution of the multiple electrolyte solution was achieved in the presence of amino acids and glucose. The concentrations of the four cations obtained by CIA and FAS are given in Table 2. The concentrations of K, Na and Mg obtained from both methods are comparable. With CIA, the Ca concentrations are slightly lower than those measured with FAAS. Probably some sample components such as amino acids interact with Ca, causing the deviation [15]. A similar observation was also made by Swaile and Sepaniak [16] in the detection of Zn in blood and was attributed to protein binding. Matrix interferences in CIA are therefore possible and the accurate determination of an element requires a single ionic form. The use of digestion

Table 2
Analysis of real multiple electrolyte solutions for parenteral use

Metal	Found by CIA (μg/ml)[a] (n = 6)	Repeatability[b] (%) (n = 6)	Reproducibility[b] (%) (n = 6 days)	Found by FAS[a] (μg/ml) (n = 6)	FAS Repeatability[b] (%) (n = 6)
Solution 1					
K	4.4	1.9		4.4	1.2
Na	5.1	0.4		5.3	0.4
Ca	3.1	3.3		3.5	0.3
Mg	0.5	2.5		0.5	0.0
Solution 2					
K	4.4	2.7	2.7	4.4	0.2
Na	2.6	0.9	2.2	2.6	0.4
Ca	1.8	2.2	2.9	2.0	0.3
Mg	0.4	3.3	4.3	0.4	1.0

Experimental conditions: BGE, 5 m*M* imidazole–H_2SO_4 (pH 4.5); applied voltage, +20 kV; hydrostatic injection, 30 s from 10 cm.
[a] Mean. The results are given as the concentrations of the 100-fold dilutions of original samples obtained from the hospital.
[b] R.S.D.

to destroy the matrix, extraction to separate the analyte ions from the matrix or perhaps the use of a stronger complexing reagent might solve the problem.

Analysis of beverages

To avoid clogging and contamination of the capillary, diluted orange juice was filtered before analysis. In order to be sure that no analyte elements were left inside the filter membrane and no contamination caused by the filtration, the results obtained with and without the treatment were compared. No significant difference was found.

Baseline separation of K, Na, Ca and Mg was obtained for apple and orange juice. Fig. 7 shows an electropherogram of a 50-fold dilution of orange juice. The repeatability and reproducibility were determined for orange juice and apple juice (Table 3). The repeatability shows R.S.D. values less than 5%. For FAS the repeatability is less than 2%. The R.S.D. values for the reproducibility in CIA are less than 6% for both juices.

The results obtained with CIA and FAS are given in Table 3. The concentrations of K, Na, Ca and Mg obtained by both methods agree well

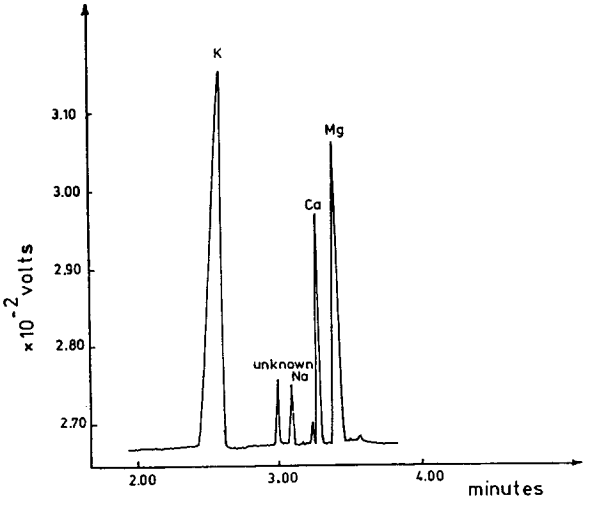

Fig. 7. Separation of a 50-fold dilution of orange juice. BGE, 5 m*M* imidazole–H_2SO_4 (pH 4.5); applied voltage, +20 kV; hydrostatic injection, 30 s from 10 cm.

Table 3
Analysis of orange juice and apple juice

Metal	Found by CIA[a] (μg/ml) ($n = 6$)	Repeatability[b] (%) ($n = 6$)	Reproducibility[b] (%) ($n = 6$ days)	Found by FAS[a] (μg/ml) ($n = 6$)	FAS Repeatability[b] (%) ($n = 6$)
Apple juice					
K	20.0	2.5	5.3	18.1	1.8
Na	0.5	3.1	5.5	0.5	1.4
Ca	2.3	1.6	1.2	2.5	1.9
Mg	1.1	3.6	5.5	1.1	1.9
Orange juice					
K	36.8	1.6	4.4	36.6	0.6
Na	0.7	0.7	5.4	0.7	1.1
Ca	2.7	1.4	3.9	2.8	1.3
Mg	2.3	3.4	2.0	2.4	0.2

Experimental conditions: BGE, 5 m*M* imidazole–H_2SO_4 (pH 4.5); applied voltage, +20 kV; hydrostatic injection, 30 s from 10 cm.
[a] Mean. The results are given as the concentrations of the 50-fold dilutions of commercial juices.
[b] R.S.D.

but the repeatability of FAS is better than that of CIA.

4. Conclusions

Imidazole was found to be suitable for performing indirect detection of inorganic cations by CIA. With the imidazole–H_2SO_4 BGE, Na shows smaller peak broadening, so that high concentrations of Na present in samples do not interfere with the other cations. The CIA method can be used in the separation of metal cations in complex samples.

The accuracy and precision of CIA with hydrostatic injection are acceptable but that of FAS is better. A wider linear range is obtained in CIA than in FAS. As expected, the limit of detection for CIA is poorer than that for FAS. As in most analytical techniques, matrix effects arise in CIA. The CE method is comparatively more susceptible to matrix interferences and a sample pretreatment may be necessary. However, it is possible in CIA to detect different elements simultaneously, but this is not the case in FAS, thus making the new approach very attractive. CIA may therefore be a promising technique for process analysis.

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References

[1] M. Koberda, M. Konkowski, P. Youngberg, W.R. Jones and A. Weston, *J. Chromatogr.*, 602 (1992) 235.
[2] F. Foret, S. Fanali, L. Ossicini and P. Boček, *J. Chromatogr.*, 470 (1989) 299.
[3] W. Beck and H. Engelhardt, *Chromatographia*, 33 (1992) 313.
[4] J.D. Olechno, J.M.Y. Tso, J. Thayer and A. Wainright, *Int. Lab*, May (1991) 42.
[5] C. Schwer and E. Kenndlew, *Anal. Chem.*, 63 (1991) 1801.
[6] Q. Yang, J. Smeyers-Verbeke and D.L. Massart, *J. Chromatogr. A*, submitted for publication.
[7] H.J. Issaq, I.J. Aamna, G.M. Muschik and G.M. Janini, *Chromatographia*, 32 (1991) 155.
[8] J. Vindevogel and P. Sandra, *J. Chromatogr.*, 541 (1991) 483.
[9] D.K. Altria, *LC · GC*, 6 (1993) 164.
[10] R.J. Wieme, *A Laboratory Handbook of Chromatography and Electrophoretic Methods*, Van Nostrand Reinhold, New York, 1975.

[11] A. Weston, P.R. Brown, P. Jandik, A.L. Heckenberg and W.R. Jones, *J. Chromatogr.*, 608 (1992) 395.
[12] B. Welz, *Atomic Absorption Spectrometry*, VCH, Weinheim, 1985.
[13] J.C. Miller and J.N. Miller, *Statistics for Analytical Chemistry*, Ellis Horwood, Chichester, 1984.
[14] *Instructions for Model 372 and Model 373 Atomic Absorption Spectrophotometers*, Perkin-Elmer, Norwalk, CT, 1977.
[15] O.A. Shpigun and Yu.A. Zolotov, *Ion Chromatography in Water Analysis*, Ellis Horwood, Chichester, 1988.
[16] D.F. Swaile and M.J. Sepaniak, *Anal. Chem.*, 63 (1991) 179.