Journal of Chromatography, 602 (1992) 235–240
Elsevier Science Publishers B.V., Amsterdam

CHROMSYMP. 2505

Capillary electrophoretic determination of alkali and alkaline-earth cations in various multiple electrolyte solutions for parenteral use

Michael Koberda*, Mary Konkowski and Paula Youngberg

I.V. Systems Division of Baxter Healthcare Corporation, Round Lake, IL 60073 (USA)

William R. Jones and Andrea Weston

Waters Chromatography Division of Millipore Corporation, Milford, MA 01757 (USA)

ABSTRACT

Simultaneous quantitation of sodium, potassium, calcium and magnesium in parenteral solutions is reported. A weakly complexing α-hydroxyisobutyric acid added to the carrier electrolyte aids in electrophoretic separation of cations. The cations are visualized indirectly at 214 nm using a strongly absorbing electrolyte co-ion, UV-Cat I. The method was optimized to enhance resolution between peaks, and limits of quantitation were determined. Effects of high sodium content on quantitation of other ions present at ppm levels are investigated.

INTRODUCTION

The earliest report of electrophoretic separations of inorganic cations appeared in 1967 [1]. In 1981 Nukatsuka *et al.* [2] described the use of α-hydroxyisobutyric acid (HIBA) as a complexing agent in isotachophoretic separation of lanthanides. Complex-forming equilibria between lanthanides, HIBA and acetic acid were studied by Hirokawa *et al.* [3]. In 1990 Foret *et al.* [4] reported separation of rare earth metals, and lithium, sodium, potassium and magnesium by capillary zone electrophoresis using HIBA as the complexing co-ion and a creatinine-acetate buffer allowing for indirect photometric detection of analytes. In 1991 Waters researchers applied a similar principle to the separation of alkali and alkaline-earth cations and presented their findings at two symposia [5,6]. A comprehensive paper was published recently [7].

This paper describes our attempt to develop a practical capillary electrophoresis (CE) method to analyze various parenteral solutions for sodium, potassium, magnesium and calcium simultaneously. Such solutions are currently analyzed by flame photometry for sodium and potassium, by atomic absorption for calcium and magnesium or by ion chromatography.

EXPERIMENTAL

Apparatus

Waters Quanta 4000 capillary electrophoresis system with a 20 sample carousel, positive power supply and a Zinc lamp detector (214 nm) was used in all analyses. Accusep fused-silica capillaries, 60 cm × 75 μm, were also supplied by Waters. Data were collected by Hewlett-Packard LAS 3357 at a rate of 16 Hz.

Materials

"UV-Cat 1", the carrier electrolyte co-ion was obtained from Waters. HIBA was purchased from

0021-9673/92/$05.00

Aldrich, Milwaukee, WI, USA. Test articles were prepared from analytical-reagent grade chemicals from various sources. Water used was distilled and deionized on Barnstead NANOpure II system. Standard solutions were prepared by diluting 1000 ppm atomic absorption standards obtained from Ricca (Arlington, TX, USA).

Methods

Carrier electrolyte contained 5 m*M* UV-Cat 1 and from 6.5 to 40 m*M* HIBA, pH 4.4, adjusted with N,N-diethylethanolamine purchased from Aldrich. Samples were introduced hydrostatically, 10 cm height for 30 s. Positive voltage of 20 kV was applied and the current was from 5.4 to 27 μA depending on HIBA concentration. Detector time constant was either 0.3 or 1 s (see below).

RESULTS AND DISCUSSION

Resolution optimization

Fig. 1 shows a typical separation of potassium, calcium, sodium and magnesium under conditions described in ref. 7. Some solutions which we intended to analyze contained 150 times as much sodium as any other cation, which could potentially

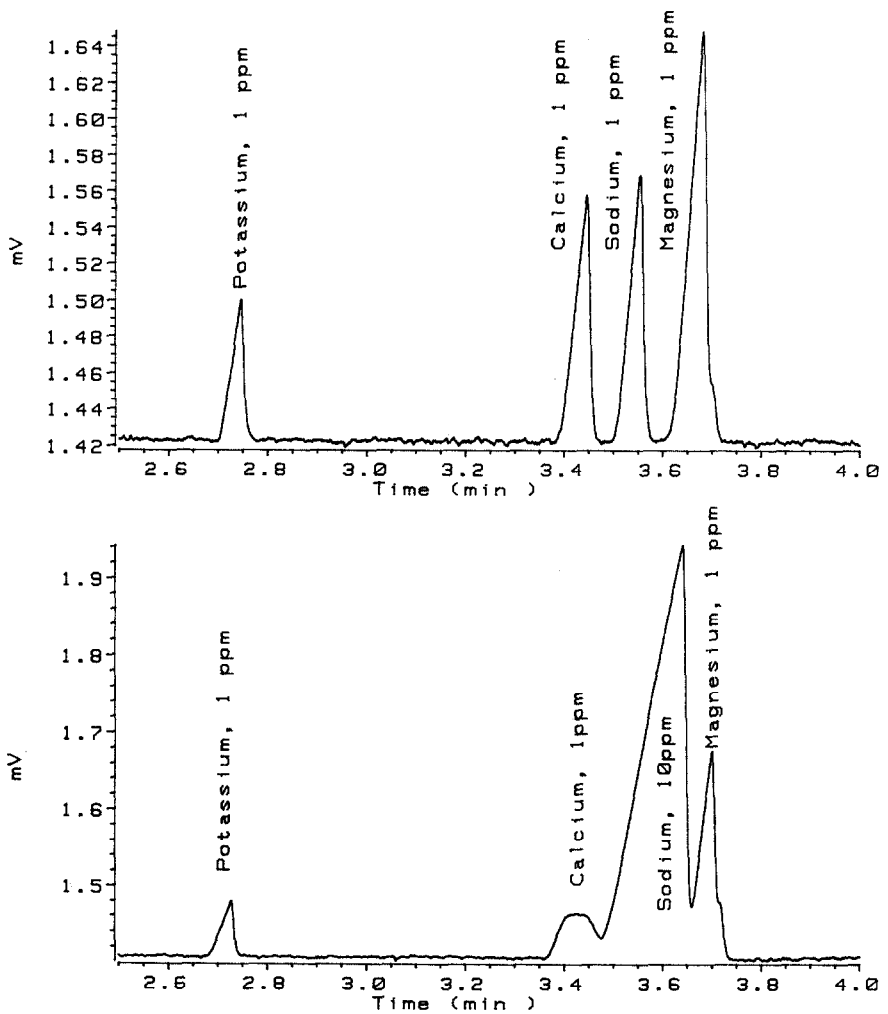

Fig. 1. Electropherograms of solutions containing potassium (1 ppm), calcium (1 ppm), magnesium (1 ppm) and sodium [1 ppm (top) or 10 ppm (bottom)]. Electrolyte: 5 m*M* UV-Cat 1, 6.5 m*M* HIBA, pH 4.4. Hydrostatic injection, 10 cm for 30 s. Time constant: 0.3 s.

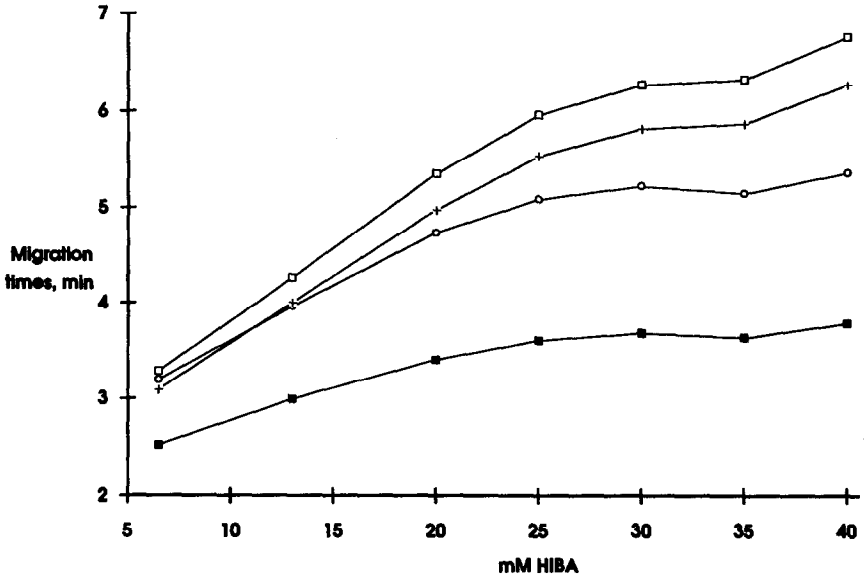

Fig. 2. Cation migration times *versus* HIBA concentration in carrier electrolyte. Other conditions as in Fig. 1. ■ = Potassium; ○ = sodium; + = calcium; □ = magnesium.

cause interference between sodium and other analytes. Our first experiments were designed to maximize resolution between sodium, calcium and magnesium.

Since complexation with HIBA affects the mobilities of alkaline earths over that of the alkali metals, we investigated the effect of increasing its concentration in carrier electrolyte. As the HIBA concentration increases, two changes occur in the separation. The electroosmotic flow decreases [8] resulting in a net increase in the migration times for all the cations, and the mobility of magnesium and calcium decrease due to greater interaction with HIBA. At approximately 13 m*M* HIBA, calcium and sodium co-migrated. Increasing HIBA concentration further changed the order of migration to potassium, sodium, calcium and magnesium (Fig. 2).

Increasing HIBA concentration caused a rise in buffer conductivity, and the running current increased from 5.4 μA at 6.5 m*M* HIBA to 27 μA at 40 m*M*. Higher current caused significant increase in baseline noise due to additional Joule heating, and a marked decrease in analyte peak response. Detector time constant was changed from 0.3 to 1 s, which greatly improved baseline stability, but also slightly reduced peak responses. Carrier electrolyte containing 30 m*M* HIBA proved to be the best compromise between peak separation, acceptable baseline noise level and sensitivity (Fig. 3).

Precision and linearity of response

With the instrumental conditions established, solutions containing from 5 to 50 ppm of each cation were analyzed. Precision of peak area response was evaluated by computing its percent relative standard deviation for 10 replicate injections. As shown in Fig. 4, sodium, calcium and magnesium behaved similarly, but potassium, which has the lowest peak response of all analytes, was quantitated much less precisely. If a relative standard deviation (R.S.D.) of 2% is chosen as the limit of acceptable precision, sodium, calcium and magnesium can be quantitated at levels as low as approximately 5 ppm, and potassium as low as approximately 20 ppm. With increasing analyte concentrations resolution between peaks deteriorated. At 50 ppm each, resolution between sodium and calcium (USP method [9]) was 1.9 and 1.5 between calcium and magnesium. All peaks retained very sharply defined slopes, so even at the highest concentrations they were essentially baseline resolved. Acceptable linearity of peak response was obtained in the entire concentration

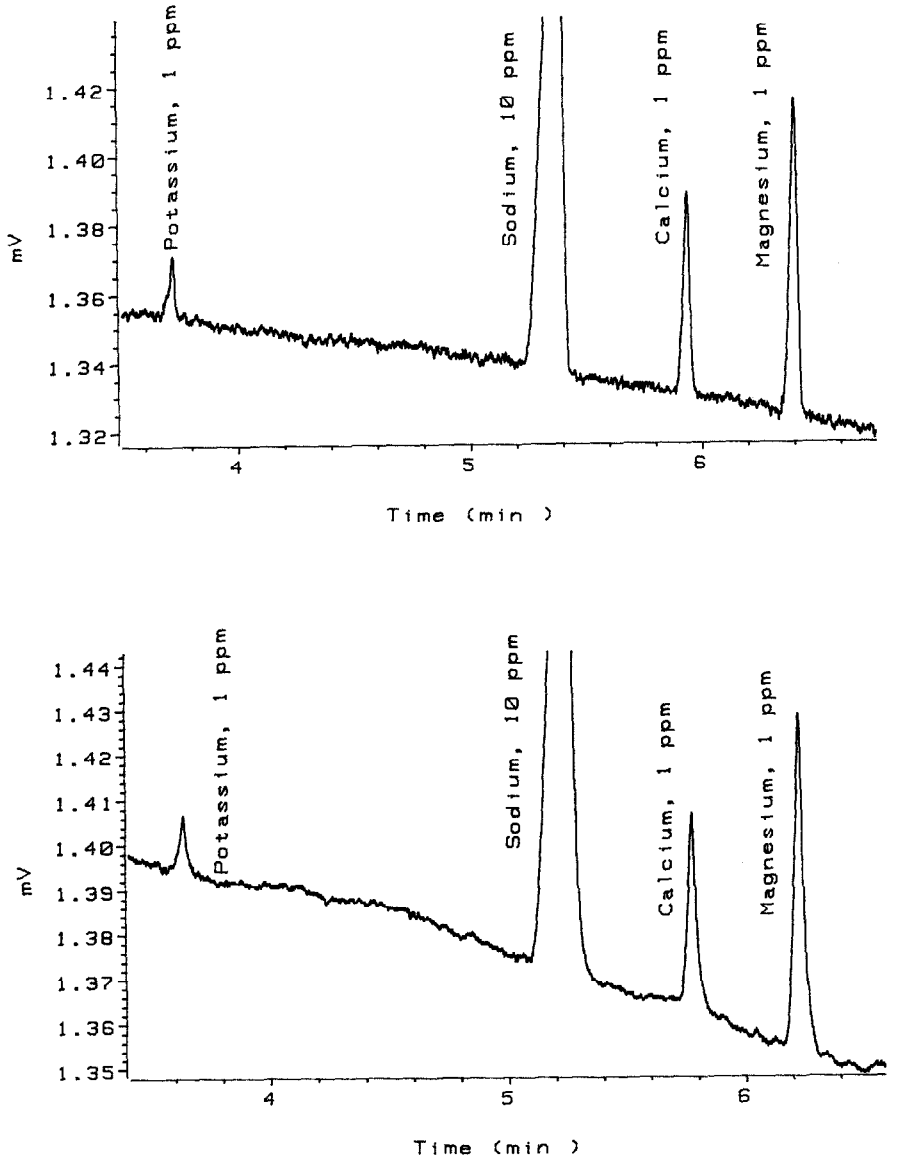

Fig. 3. Separations at 30 m*M* HIBA. Time constant: 0.3 s (top) and 1 s (bottom). Other conditions as in Fig. 1.

range with correlation coefficients (r^2) ranging from 0.997 to 0.9997.

Accuracy assessment

The solutions with highest ionic strength, usually containing high concentrations of sodium chloride, had seriously distorted potassium peaks, while the shapes of calcium and magnesium peaks were unaffected. An experiment was performed in which CE analysis was done on solutions containing constant amounts of potassium, calcium and magnesium, 40, 10 and 10 ppm, respectively, and from 60 to 400 ppm sodium. As shown in Table I, sodium levels of more than approximately 80 ppm caused decrease in potassium peak response.

Table II lists simulated parenteral solutions chosen

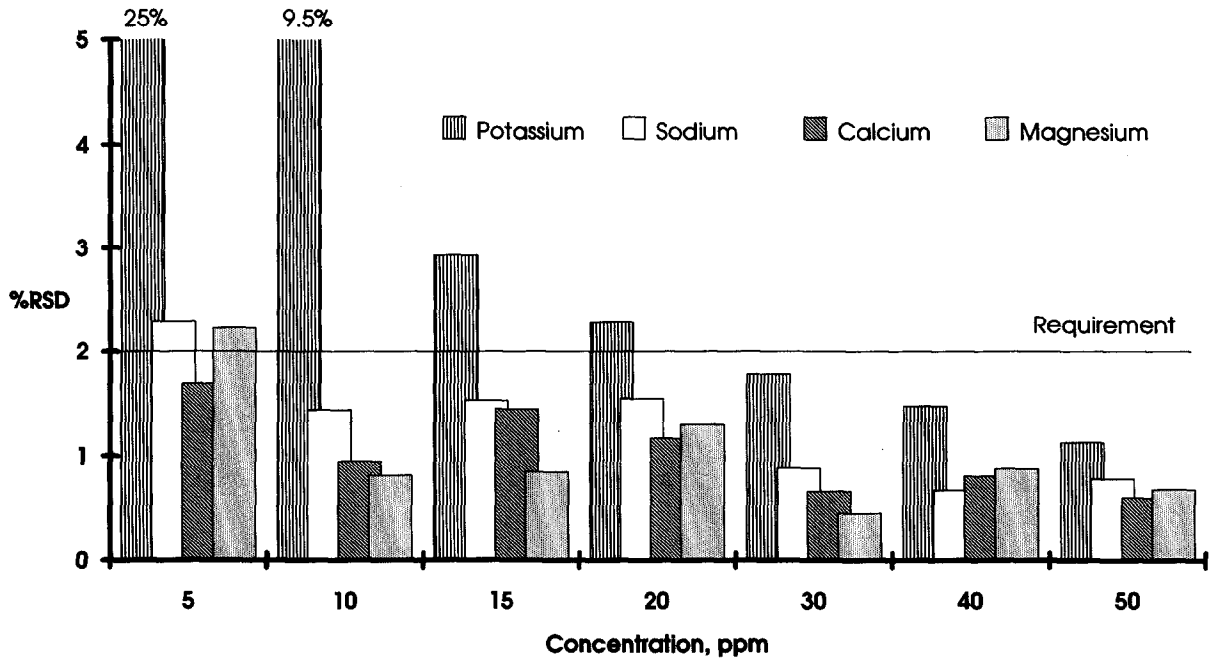

Fig. 4. Peak area response precision for ten replicates *versus* analyte concentration. Electrolyte: 5 m*M* UV-Cat 1, 30 m*M* HIBA, pH 4.4. Hydrostatic injection, 10 cm for 30 s. Time constant: 1 s.

for the study. These represent several worst cases with respect to the concentration ratio of sodium to other cations, as well as the presence of potentially interfering substances. As shown in Table II, sodium could be quantitated accurately in all tested solutions. However, in most cases, the sodium peak overlapped with the calcium and magnesium peaks at maximum practical dilutions, making their quantitation impossible.

TABLE I

QUANTITATION OF POTASSIUM, CALCIUM AND MAGNESIUM IN THE PRESENCE OF EXCESS SODIUM

Percent theoretical recovery.

	Na^+ (ppm)					
	60	80	100	200	300	400
K^+	97.3	97.8	91.0	85.9	77.3	71.1
Ca^{2+}	99.7	102.2	99.1	99.1	93.3	95.2
Mg^{2+}	98.3	103.1	97.4	97.0	96.9	98.4

Ammonium ion can co-migrate with potassium under these separation conditions. No solution tested here contained ammonium salts added intentionally, and absence of ammonia was also confirmed analytically. Amino acid blends did not interfere with the analysis.

CONCLUSIONS

The results of this work demonstrate that sodium, potassium, calcium and magnesium can be quantitated simultaneously as long as the sample can be diluted sufficiently so that the level of sodium is below approximately 80 ppm, while the other analyte concentrations remain above 5 ppm (20 ppm for potassium). However, the method described in this article was not practical for the parenteral solutions evaluated in this article due to very high levels of sodium in most of these solutions. We plan to continue to develop a workable CE method by extending the linear range of the method to accommodate higher levels of sodium. Initially, we will address the following to aid the accommodation of

TABLE II

ANALYTE RECOVERY FOR SIMULATED PARENTERAL SOLUTIONS

NQ = Not quantifiable: potassium, distorted peak; calcium or magnesium, sodium peak overlap.

No.	Sample components	Sodium		Potassium		Calcium		Magnesium		Dilution factors
		ppm	Recovery (%)	ppm	Recovery (%)	ppm	Recovery (%)	ppm	Recovery (%)	
1	Carbonate, citric acid	1856	102.1					2192	99.3	50
2	Chloride, dextrose	3386	100.9	163	NQ	94	93.6			80 (Na) 4 (K) 10 (Ca)
3	Chloride, lactate, dextrose	2971	99.4	158	NQ	55	NQ			80 (Na) 4 (K)
4	Chloride, lactate, acetate, dextrose	931	99.8	632	92.3	100	NQ	37	NQ	22 (Na) 17 (K) 0 (Mg)
5	Chloride, dextrose	1783	100.2	199	90.7					42 (Na) 5 (K)
6	Chloride, phosphate, sulphate	3169	99.2	212	NQ			20	NQ	83 (Na) 6 (K)

higher sodium levels in the sample: (1) investigate a stronger complexing agent to replace HIBA that will offer a different, perhaps better, selectivity; and (2) increase the ionic strength of the electrolyte to improve sample stacking.

REFERENCES

1 S. Hjertén, *Chromatogr. Rev.*, 9 (1967) 122.
2 I. Nukatsuka, M. Taga and H. Yoshida, *J. Chromatogr.*, 205 (1981) 95.
3 T. Hirokawa, N. Aoki and Y. Kiso, *J. Chromatogr.*, 312 (1984) 11.
4 F. Foret, S. Fanali, A. Nardi and P. Boček, *Electrophoresis*, 11 (1990) 780.
5 W. R. Jones, P. Jandik and A. Weston, presented at the *3rd International Symposium on High Performance Capillary Electrophoresis, San Diego, CA, February 1991*, abstract LT-9.
6 A. Weston, W. R. Jones and P. Jandik, presented at the *42nd Pittsburg Conference and Exposition, Chicago, IL, March 1991*, abstract 158.
7 P. Jandik, W. R. Jones, A. Weston and P. R. Brown, *LC · GC*, 9 (1991) 634.
8 R. Wallingford and A. Ewing, *Adv. Chromatogr.*, 29 (1989) 1.
9 *USP XXII, NF XVII*, United States Pharmacopeial Convention, Rockville, MD, 1990, p. 1565.