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Determination of potassium, sodium, calcium and magnesium in total parenteral nutrition formulations by capillary electrophoresis with contactless conductivity detection

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ABSTRACT

A simple method based on capillary electrophoresis with a capacitively coupled contactless conductivity detector (CE-C^{4}D) was developed for the determination of potassium, sodium, calcium and magnesium in parenteral nutrition formulations. A hydro-organic mixture, consisting of 100 mM Tris-acetate buffer at pH 4.5 and acetonitrile (80:20, v/v), was selected as the background electrolyte. The applied voltage was 30 kV, and sample injection was performed in hydrodynamic mode. All analyses were carried out in a fused silica capillary with an internal diameter of 50 μm and a total length of 64.5 cm. Under these conditions, complete separation between all cations was achieved in less than 4 min. The CE-C^{4}D method was validated, and trueness values between 98.6% and 101.8% were obtained with repeatability and intermediate precision values of 0.4–1.3% and 0.8–1.8%, respectively. Therefore, this method was found to be appropriate for controlling potassium, sodium, calcium and magnesium in parenteral nutrition formulations and successfully applied in daily quality control at the Geneva University Hospitals.

1. Introduction

Total parenteral nutrition (TPN) is the practice of feeding a person intravenously using nutritional formulas containing essential nutrients such as electrolytes, glucose, amino acids, trace elements and vitamins (see Table 1). These nutritional solutions are prepared daily at the pharmacy of the Geneva University Hospitals (HUG) for paediatric patients. Errors in the concentrations of electrolytes present increased risks for patients, especially for neonates. Therefore, TPN preparations are submitted to quality control before patient administration. Currently, sodium, potassium and calcium are checked at the HUG pharmacy using flame photometry or absorption spectrometry methods in control solutions without amino acids or vitamins. The constituents of real TPN samples (with increased concentrations of glucose, amino acids and vitamins) can interfere with the analysis of ions and contaminate the analytical system. Therefore, other analytical techniques are required.

Capillary electrophoresis (CE) coupled with indirect UV detection was developed for the analysis of inorganic cations [1–7], particularly sodium, potassium, calcium and magnesium, in TPN preparations [8,9]. These methods have been compared with flame atomic spectrometry and ion chromatography [1,9] and were found to be an acceptable alternative. However, UV-absorbing buffer additives and more complex buffer systems were needed to facilitate indirect absorbance detection [10], and weaker quantitative performance was achieved [1,9]. During the past few years, contactless conductivity detection has been recognized as an attractive alternative to optical detection techniques in CE because of its low cost, lack of maintenance requirements, easy handling and simple method development. Among the developed capacitively coupled contactless conductivity detectors (C^{4}D), we only consider in this paper the instrument used by Zemann [11,12]. The latter presents two metal tube electrodes, placed around the capillary. An oscillation frequency between 75 and 300 kHz is applied to one of the electrodes, and a signal is produced when an analyte zone with a different conductivity passes through the retention gap [2].

Numerous papers have described the analysis of inorganic cations (*e.g.*, sodium, potassium, calcium, magnesium) by CE-C^{4}D [2–4,10–23]. A buffer based on 2-(N-morpholino)ethanesulfonic

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Abbreviations: BGE, background electrolyte; CS, calibration standard; C^{4}D, capacitively coupled contactless conductivity detector; EOF, electroosmotic flow; HIBA, α-hydroxyisobutyric acid; His, Histidine; HUG, Geneva University Hospitals; IS, internal standard; MES, 2-(N-morpholino)ethanesulfonic acid; SFSTP, Société Française des Sciences et Techniques Pharmaceutiques; TPN, total parenteral nutrition; Tris, tris(hydroxymethyl)-aminoethane; VS, validation standard.

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Table 1
Composition of TPN at HUG.

Solution	Composition	Manufacturer
NaCl 11.7%	Sodium: 2 mmol mL^{-1}	Bichsel (Interlaken, CH)
Calcium gluco-bionate 10%	Calcium: 0.16 mmol mL^{-1}, lactobionate: 0.16 mmol mL^{-1}, glucobionate: 0.16 mmol mL^{-1}	Bichsel (Interlaken, CH)
Phocytan®	Phosphate: 0.33 mmol mL^{-1}, glucose: 0.33 mmol mL^{-1}, sodium: 0.66 mmol mL^{-1}	Aguettant (Lyon, F)
KCl 7.5%	Potassium: 1 mmol mL^{-1}	Sintetica-Bioren (Couvet, CH)
$MgSO_4$ 5%	Magnesium: 0.2 mmol mL^{-1}	Pharmacy HUG
Sodium acetate 16.4%	Acetate: 2 mmol mL^{-1} Sodium: 2 mmol mL^{-1}	Pharmacy HUG
Vitamins	Vitamin A: 0.4 mg mL^{-1}, D3 1.1 μg mL^{-1}, E 2.04 mg mL^{-1}, C 25 mg mL^{-1}, B1 0.7 mg mL^{-1}, B2 0.83 mg mL^{-1}, B6 0.91 mg mL^{-1}, B12 1.2 μg mL^{-1}, B9 82.5 μg mL^{-1}, B5 3.45 mg mL^{-1}, B8 13.8 μg mL^{-1}, PP 9.2 mg mL^{-1}	Baxter (Volketswil, CH)
Cernevit®		
Trace elements	Fe^{2+}: 0.1 mg mL^{-1}, Zn^{2+}: 0.16 mg mL^{-1}, Mn^{2+}: 27.2 μg mL^{-1}, Cu^{2+}: 38 μg mL^{-1}, Cr^{3+}: 0.5 μg mL^{-1}, Mo(VI): 0.5 μg mL^{-1}, Se(IV): 1 μg mL^{-1}, F^-: 28.5 μg mL^{-1}, I^-: 6.5 μg mL^{-1}, Na^+: 1.9 μmol mL^{-1}, K^+: 0.05 μmol mL^{-1}, Cl^-: 17 μmol mL^{-1}	BBraun (Sempach, CH)
Tracutil® diluted		Pharmacy HUG
Heparin	50 UI mL^{-1}	Pharmacy HUG
Amino acids	Alanine: 6.3 g L^{-1}, arginine: 4.1 g L^{-1}, asparagine acid: 4.1 g L^{-1}, cysteine: 1 g L^{-1}, glutamic acid: 7.1 g L^{-1}, glycine: 2.1 g L^{-1}, histidine: 2.1 g L^{-1}, isoleucine: 3.1 g, leucin: 7.0 g L^{-1}, lysine: 5.6 g L^{-1}, methionine: 1.3 g L^{-1}, phenylalanine: 2.7 g L^{-1}, proline: 5.6 g L^{-1}, serine: 3,8 g L^{-1}, taurine 0,3 g L^{-1}, threonine: 3.6 g L^{-1}, tryptophan: 1.4 g, tyrosine: 0.5 g L^{-1}, valine: 3.6 g L^{-1}	Fresenius Kabi (Stans, CH)
Vaminolact®		
Glucosteril	Glucose 70%	Fresenius (Stans, CH)
Injection water	Water ppi	Bichsel (Interlaken, CH)

acid and histidine (MES/His) has been widely used for the determination of alkali and alkaline earth metals and ammonium ions [2–4,11–20]. Other background electrolytes (BGE) composed of citric, lactic or acetic acids and His or maleic acid/arginine have also been successfully used for the separation of these cations [15,20].

Weak complexing agents have been added to the BGE to modify the separation of inorganic cations, such as α-hydroxyisobutyric acid (HIBA) [4,7,17]. An organic solvent was added (10% methanol) to modify the selectivity and to obtain a complete separation of sodium, calcium and magnesium in blood samples [20]. However, to our knowledge, a validated CE-C^{4}D for TPN has not yet been reported.

In this study, a simple CE-C^{4}D method was developed and validated to determine sodium, potassium, calcium and magnesium in TPN and was applied to the quantitation of these cations in daily quality control.

2. Experimental

2.1. Chemicals

Sodium chloride, potassium chloride, calcium chloride, magnesium chloride, lithium chloride and tris(hydroxymethyl)-aminoethane (Tris) were purchased from Fluka (Buchs, Switzerland). Water and NaCl (0.9%) used for pharmaceutical preparations were obtained from Bichsel Laboratories (Interlaken, Switzerland). Acetic acid (glacial, 100%), methanol and acetonitrile were obtained from Merck (Darmstadt, Germany).

Parenteral nutrition solutions were prepared at the HUG pharmacy using the automated compounding system BAXA MM12 (Baxa corporation, Englewood, CO, USA) with the following solutions: Calcium glucobionate (10%) and NaCl (11.7%) obtained from Bichsel Laboratories (Interlaken, Switzerland), KCl (7.5%) from Sintetica-Bioren SA (Couvet, Switzerland), Phocytan from Aguettant (Lyon, France), Aminosteril Hépa (8%), Glucosteril (70%), and Vaminolact from Fresenius Kabi (Stans, Switzerland; Bad Homburg, Germany). Tracutil was diluted in a 1:2 ratio (BBraun, Sempach, Switzerland) and Cernevit was obtained from Baxter (Volketswil, Switzerland). Sodium acetate (16.4%), heparin (50 UI/mL) and magnesium sulfate (5%) were produced by the HUG pharmacy.

2.2. BGE preparation

Different BGEs (phosphate pH 2 and 7, borate pH 9, MES/His pH 6.1, citrate pH 3.1 and pH 4.8, lactate and acetate/Tris pH 4.5) were prepared for the method development. The final BGE was composed of a hydro-organic buffer corresponding to a mixture of an aqueous BGE (100 mM Tris-acetate buffer at pH 4.5) and acetonitrile (80:20, v/v). The aqueous BGE was prepared by an adequate dilution of the concentrated acid solution, and a solution of Tris at 1 M was added to adjust the solution to pH 4.5. The solution was then diluted to the final volume with distilled water. The BGE was degassed in an ultrasonic bath for 10 min before use.

2.3. Instrumentation and capillaries

CE experiments were carried out with an HP^{3D}CE system (Agilent Technologies, Waldbronn, Germany) equipped with an autosampler and a power supply able to deliver up to 30 kV. HP^{3D}CE was coupled to a TraceDec detector (Innovative Sensor Technologies GmbH, Strasshof, Austria). The conductivity sensor consisted of two electrodes separated by a detection gap of 1 mm, positioned along the capillary by sliding it into the desired position (14.5 cm from the cathode). A CE ChemStation (Agilent) was used for CE control and data handling, and a C^{4}D Tracemon (Innovative Sensor Technologies, Austria) was used for conductivity detector control and data acquisition. Analyses were performed in uncoated fused silica capillaries from BGB Analytik AG (Böckten, Switzerland) with an internal diameter of 50 μm, an external diameter of 375 μm and a total length of 64.5 cm (effective length of 50 cm). All experiments were performed in the normal mode (cathode at the outlet end of the capillary). The capillary was thermostated at 25 °C in a high velocity air stream, and a voltage of 30 kV was applied. The generated current was between 5 and 50 μA depending on the buffer solution. Samples were kept at ambient temperature in the autosampler and injected in the hydrodynamic mode to fill approximately 1% of the effective capillary length (40 mbar for 10 s). The final configuration of the C^{4}D was set at an output frequency of 150 kHz, an output voltage of 40 Vpp, 50% gain and an offset of $\sim$30. The detector acquisition corresponded to the CE mode of 19.8 Hz. Before first use, capillaries were sequentially rinsed with methanol, 0.1 M NaOH, water, methanol, 0.1 M HCl, water and BGE for 5 min. A voltage of 30 kV was then applied for 60 min with the BGE. The