JAAS FULL PAPER
www.rsc.org/jaas

Determination of sodium in blood serum by inductively coupled plasma mass spectrometry

Stephen E. Long* and Thomas W. Vetter

Analytical Chemistry Division, Chemical Science and Technology Laboratory, National Institute of Standards and Technology, 100 Bureau Drive, Stop 8391, Gaithersburg, Maryland 20899, USA. E-mail: selong@nist.gov

Received 27th August 2002, Accepted 21st October 2002
First published as an Advance Article on the web 28th October 2002

Owing to its importance as a serum electrolyte, sodium is determined routinely in clinical laboratories. In the United States, the accuracy of these measurements is assessed through a number of proficiency testing programs. Clinical measurements are supported by the National Institute of Standards and Technology through the production of serum matrix Standard Reference Materials® (909 and 956 series). For reference material certification, a gravimetric primary method has traditionally been used, but this method is time consuming. In this work, an alternative method has been developed in which sodium is determined by inductively coupled plasma mass spectrometry (ICP-MS) using a procedure, which is a cross between internal standardization and isotope dilution analysis. Diluted serum is spiked with ^{26}Mg enriched isotope and the isotope ratio ^{23}Na/^{26}Mg measured in analog detection mode. The ratios are standardized by measuring a sodium primary standard (SRM 919a) spiked with ^{26}Mg. As a relatively high concentration of sodium is measured, the sodium background from the ICP-MS instrument is comparatively small. The method has been successfully applied to the determination of sodium in SRM 909b (Human Serum), SRM 956a (Electrolytes in Frozen Human Serum) and serum pools from the College of American Pathologists.

Introduction

The normal concentration range for sodium in blood serum or plasma is 136–146 mmol L^{-1}, constituting approximately 90% of the total cationic species present.[1] Sodium ions play a pivotal role in the regulation of osmotic pressure and the distribution of water within the extra-cellular fluid compartments of the body, the concentration gradient being controlled by various ion channel proteins. Sodium is therefore an analyte that is determined routinely in the clinical laboratory to support diagnoses of circulatory, renal and nervous system function. The National Institute of Standards and Technology (NIST) supports these measurements through the provision of clinical Standard Reference Materials® (SRMs), and historically by certification of pooled proficiency testing materials in conjunction with the College of American Pathologists (CAP).

Several analytical techniques have been employed for the determination of sodium in blood serum. In routine use for clinical diagnostics, the most commonly used technique is potentiometry using ion selective electrodes (ISE). ISE technology offers rapid sample throughput, the capability for total automation and simplicity of use. Early studies involving comparison with established reference methods, such as flame photometry, indicated that equivalent measurement data could be obtained using this approach.[2–4] For example, Fuchs *et al.*[2] compared the performance of a glass membrane ISE system with flame photometry obtaining a correlation coefficient better than 0.98. Numerous other studies have been reported using ISE systems,[5–18] which generally fall into two categories, one involving a direct method where no dilution of the sample takes place and an indirect method where the sample is mixed with a diluent prior to the measurement. ISE measurements are subject to several errors. One of the main errors is an electrolyte exclusion effect if abnormal concentrations of protein are present in the sample. Recommendations and conventions for measurement of sodium in undiluted blood have been proposed by Burnett *et al.*[17]

Several optical methods have been developed for the determination of sodium in serum. Hisamoto and coworkers[19] reported the use of a disposable ion sensing probe based on ion pair extraction with a lipophilic anionic dye. The selectivity was sufficient to determine Na^+ in diluted serum samples. Gunnlaugsson *et al.* investigated the use of two high selectivity chemosensors,[20] one an anthracene based fluorescent sensor and the other based on an azo dye, which showed large changes in molecular absorption on addition of Na^+. Enzymatic methods have been proposed[21–27] which feature simplified measurement equipment, minimal endogenous interferences and a linear range that encompasses physiological and pathophysiological ranges in serum. However, the measurement precision is often poorer than that of ISE and flame photometric measurements, and lipemic samples can produce inconsistent results. Atomic spectrometry has been a popular method for serum sodium measurements owing to its high sensitivity and selectivity. Classical flame photometry[28–32] is still used routinely. Schaffer *et al.*[29] reported on a multi-laboratory evaluated reference method based on flame atomic emission spectrometry (FAES) in which good agreement was obtained with a gravimetric primary method on serum pools. Methods based on the direct current plasma,[33] ICP emission spectrometry,[34] and flow-injection atomic absorption spectrophotometry[35] have also been reported.

The use of chromatography has been investigated. Thienpont and coworkers proposed the use of ion chromatography[36,37] as a candidate reference method, while Bohrer *et al.*[38] used high performance liquid chromatography. Isotachophoresis has also been examined as a candidate reference method.[39]

Inductively coupled plasma mass spectrometry (ICP-MS) has not been extensively used for the determination of sodium in blood serum. The main challenge with the use of this technique is the relatively high instrumental background, which originates from sodium contamination, and which severely limits the dynamic range when using pulse counting ion detection. Some general success has been obtained with the use of cold-plasma conditions. Tanner and coworkers[40] determined several elements, including sodium, at ng L^{-1}

This journal is © The Royal Society of Chemistry 2002

levels. Wollenweber *et al.* also determined sodium and five other elements using cold-plasma conditions,[41] however, neither of these studies was applied to serum sodium measurements.

The primary method employed at NIST for the certification of sodium in blood serum is a classical gravimetric method,[42,43] but this is extremely tedious and requires a relatively high degree of skill to obtain accurate results. The conventional alternative to gravimetry is a reference method using flame photometry, but the attainable accuracy is somewhat limited and the determination is prone to interferences from glucose, protein and urea components in the serum.

In this work, an alternative method was developed using ICP-MS, the object of which was to provide a much more rapid method than gravimetry, but also having the potential for very high accuracy. In this method, sodium is determined by diluting the serum, adding a ^{26}Mg enriched isotope and measuring the ^{23}Na/^{26}Mg isotope ratio in a manner similar to that used for stable isotope dilution mass spectrometry (IDMS). By measuring the isotope ratio in analog mode, the effect of instrumental sodium contamination is negligible. The performance of the new method has been investigated using NIST SRM 909b (Human Serum) and SRM 956a (Electrolytes in Frozen Human Serum). The results for these materials are compared with the primary gravimetric method, which was used to certify the reference materials. Additional measurements have been made on some performance testing materials from the College of American Pathologists (CAP) Surveys Program. The results are compared with the consensus values compiled by CAP in the Participant Summary.

Experimental

Reagents

High-purity nitric acid, hydrochloric acid and sulfuric acid were prepared at NIST[44] using a sub-boiling distillation apparatus and stored in double-bagged Teflon bottles. High purity, de-ionized, distilled water was prepared in-house by sub-boiling distillation using a conditioned quartz still. Hydrogen peroxide was reagent grade, ammonium carbonate was puriss grade (Fluka, Buchs, Switzerland). Reagent grade nitric acid (Baker Analyzed®, J.T. Baker, Phillipsburg, New Jersey, USA) and high purity de-ionized water from an in-house purification plant were used for cleaning all materials and containers.

Isotopic spike and calibration materials

The ^{26}Mg enriched spike material (99.6% atom fraction ^{26}Mg, lot number 217301) was purchased from Oak Ridge National Laboratory (Oak Ridge, Tennessee, USA) as solid magnesium oxide. A stock solution of the spike was prepared by dissolution in a small quantity of high-purity nitric acid and dilution to yield a concentration of approximately 0.12 mol L^{-1} in 0.16 mol L^{-1} nitric acid. The isotopic composition of the spike was verified by dilution of an aliquot of the stock and measurement by ICP-MS.

Instrument calibrations were made using SRM 919a Sodium Chloride (Clinical) primary standard, having a certified purity of 99.89 $\pm$ 0.03% by weight. Before use, the standard was dried for 3 h in a convection oven at 110 °C.

Serum materials and preparation

SRM 909b and SRM 956a were used for method validation. Details of the source and certification of SRM 909b, which is a two-level, lyophilized human serum material, have been published previously.[43] Bottles of each level of the material were kept refrigerated until use, and reconstituted by adding 10.00 mL of the diluent water provided with the SRM. The bottles were swirled gently to mix the contents, and allowed to stand for 2 h to ensure complete dissolution of the contents. SRM 956a is a three-level frozen human serum prepared by the Diagnostics Group, Bayer Corporation, Middletown, Virginia, USA, consisting of 2 mL aliquots of serum in flame-sealed glass ampoules. Ampoules from each level were stored frozen at −80 °C until use, thawed to room temperature for several hours, and the contents mixed thoroughly before opening and sub-sampling. Further validation of the method was made by comparing measurements on proficiency testing serum pools provided by the CAP (Northfield, Illinois, USA). The materials, from the 1993 Chemistry Series 1 and 2 Survey, were lyophilized materials, which were reconstituted with the provided diluent in the same manner as for SRM 909b. Prior to making measurements on all of the serum materials, the density of each material was measured using a calibrated 10 mL borosilicate glass pycnometer. The density information was used to convert the sodium analytical data from a mass basis to a volume basis.

All sample preparation was carried out in a Class 10 clean environment with the use of protective clothing and gloves. Serum sub-samples ranging from 0.8–1.0 g were accurately weighed into clean 60 mL low density polyethylene (LDPE) sample bottles. The samples were acidified with 0.08 mol L^{-1} nitric acid such that the final concentration of sodium was in the range 40–50 μg mL^{-1} (1.74–2.17 mmol L^{-1}) with a total sample volume of approximately 60 mL. The nitric acid concentration did not exceed 0.08 mol L^{-1} in order to limit any precipitation of serum proteins. At this point, the samples were found to be stable at room temperature for several days and no further sample processing was necessary. All samples were spiked gravimetrically with an aliquot of ^{26}Mg enriched isotope. Calibration solutions were prepared from SRM 919a (Sodium Chloride Clinical Standard) primary standard at concentrations of 40 and 60 μg mL^{-1} (1.74 and 2.61 mmol L^{-1}). The calibration solutions were spiked from the same stock of ^{26}Mg isotope and were used to generate a calibration response curve for the instrument. As a precaution, all sodium determinations were completed within two days of sample preparation. Control materials, consisting of SRM 909 or 909a Human Serum were also prepared in the same manner as the samples as an additional check on the accuracy of the determinations.

Instrumentation and isotope ratio measurements

Isotopic measurements were made on a PlasmaQuad 1 ICP-MS system (VG Elemental, Winsford, Cheshire, UK). The instrument was operated in a standard hardware configuration with the exception of the vacuum diffusion pumps, which were replaced with turbo pumps (Pfeiffer-Balzers, Asslar, Germany). A Meinhard TR-30 C0.5 concentric nebulizer and a double-pass Scott spray chamber were used for sample introduction. The operating parameters used for the measurements are listed in Table 1. The instrument was optimized for maximum ion

Table 1 ICP-MS instrument operating parameters

Parameter	
Plasma forward power	1.35 kW
Coolant gas flow rate	14 L min^{-1}
Auxiliary gas flow rate	0.6 L min^{-1}
Nebulizer flow rate	0.78 L min^{-1}
Solution uptake rate	0.4 mL min^{-1}
Spray chamber temperature	4 °C
Cone materials, sampler/skimmer	Ni/Ni
Data acquisition	
Detector mode	Analog peak jumping at low resolution
Dwell time	10 ms
Points per peak	3
Number of ratio sets	7

transmission at *m/z* 23 by nebulizing a standard solution of sodium and adjustment of ion lens voltages, plasma gas flows and rf forward power.

For each sample, seven replicate blocks of $^{23}Na/^{26}Mg$ and $^{24}Mg/^{26}Mg$ isotope ratios were measured using an integration time per block of 60 s. All ratios were acquired in peak jumping mode. Owing to the relatively poor stability of the quadrupole system power supply, it was necessary to use three measurement points per peak in order to reduce effects associated with peak drift. The instrument was also operated in a low-resolution mode to broaden the top of the peak profiles. An approach was used which was similar to conventional isotope ratio measurements for isotope dilution analysis, in that the dwell time was kept relatively short in order to optimize the isotope ratio measurement repeatability. Instrument calibration was carried out after every second sample to minimize the effects of instrument mass discrimination drift and to maintain measurement accuracy. The instrumental mass discrimination for the $^{24}Mg/^{26}Mg$ isotope ratio was determined using a magnesium isotopic standard. The measured factor (approximately 3.8%) was used to correct all $^{24}Mg/^{26}Mg$ serum ratios.

Gravimetry

The procedure was similar to that used for other serum samples.[42,43] Nominal 10 g sub-samples of each serum material were weighed into 100 mL Teflon® microwave digestion vessels. A mixture of 10 mL nitric acid and 2 mL hydrogen peroxide was added and the samples wet-ashed in a MLS Mega 1200 microwave oven (Milestone Inc., Bergamo, Italy). The samples were transferred, with rinsings of 0.16 mol L^{-1} nitric acid, to 125 mL Teflon® beakers and evaporated to near dryness on a hot plate. The residues were reconstituted in approximately 30 mL of water. The resulting solutions were loaded onto polycarbonate ion exchange columns containing AG 50W-X8 (100–200 mesh) cation exchange resin and the sodium eluted using 0.4 mol L^{-1} hydrochloric acid. The sodium fraction from each sample was collected in a 125 mL Teflon® beaker. All of the fractions eluting before and after the sodium were collected and transferred to clean LDPE bottles for later sodium determination by FAES. However, the total sodium in these fractions always amounted to less than 0.02% of the total sodium. Each sodium fraction was treated with 1 mL of 2.5 mol L^{-1} sulfuric acid and evaporated on a hot plate to a volume of approximately 8 mL. The sample and rinsings were transferred quantitatively to a previously ignited and weighed platinum crucible. The solution was evaporated on a hot plate to fumes of sulfur trioxide and finally to dryness. Brown residue in the crucible resulted from small amounts of dissolved resin and undigested organics eluting with the sample. After the samples had cooled, 0.4 g of ammonium carbonate was added to convert bisulfate to sulfate. The crucibles were covered and heated in an oven at 100 °C to volatilize ammonia. To remove the organics, the samples were heated slowly to 450 °C, then to 600 °C and finally 800 °C. At each point the temperature was held for 2 h. The samples then were heated rapidly at 900 °C to form sodium sulfate, removed to a desiccator to cool for at least 3 h, and weighed. A small amount of water was added to wet each sample and the samples were again heated to 800 °C for 2 h, ignited at 900 °C, cooled in a desiccator and weighed as before. The ignition was repeated, if necessary, to constant mass. Sample masses were corrected for the blank. The difference in mass between the sample and the empty platinum crucible was taken as the mass of sodium sulfate, and this mass was divided by a gravimetric factor of 3.08927[45] to determine the mass of sodium. The gravimetric mass of sodium was added to the FAES-determined sodium to calculate the total sodium.

Results and discussion

Method design

Sodium has not commonly been measured by pulse counting detection ICP-MS because of high residual background contamination, which comprises a substantial fraction of the total dynamic range. Because of the relatively high concentration of sodium in serum, however, it is possible to measure sodium using analog ion detection. This approach offers the advantages of a much more effective dynamic range as well as immunity to detector dead-time effects and the limitations of counting statistics. Since sodium is monoisotopic, it is not possible to use isotope dilution approaches. However, a hybrid measurement strategy was adopted by using a ^{26}Mg enriched isotope as an internal standard and measurement of $^{23}Na/^{26}Mg$ isotope ratios for each sample. Magnesium was selected for the internal standard on the basis of proximity in mass to that of sodium and similarity in ionization and analytical behaviour. The ^{26}Mg enriched isotope was used because the serum materials also contain a small amount of magnesium and the contribution from this was minimized by the use of ^{26}Mg as the internal standard rather than natural magnesium, which is predominantly ^{24}Mg. All of the $^{23}Na/^{26}Mg$ ratios were internally corrected by concurrent measurement of the $^{24}Mg/^{26}Mg$ ratio and subtracting out the contribution from the serum ^{26}Mg component according to the following equations:

$$^{26}I_{meas} = {}^{26}I_{true} + C_{nat}{}^{24}I_{serum} \quad (1)$$

where, $^{26}I_{meas}$ is the measured signal intensity at *m/z* 26, $^{26}I_{true}$ is the true signal intensity for ^{26}Mg spike, $^{24}I_{serum}$ is the signal intensity for serum ^{24}Mg and C_{nat} is the ratio correction for the natural isotopic composition $^{24}Mg/^{26}Mg$

$$^{24}I_{serum} = {}^{24}I_{meas} - C_{spk}{}^{26}I_{true} \quad (2)$$

where, $^{24}I_{meas}$ is the measured signal intensity at *m/z* 24, and C_{spk} is the ratio correction for the spike composition $^{24}Mg/^{26}Mg$

$$^{26}I_{meas} = {}^{26}I_{true} + C_{nat}({}^{24}I_{meas} - C_{spk}{}^{26}I_{true}) \quad (3)$$

$$^{26}I_{meas} = (1 - C_{nat}C_{spk}){}^{26}I_{true} + C_{nat}{}^{24}I_{meas} \quad (4)$$

$$^{26}I_{true} = ({}^{26}I_{meas} - C_{nat}{}^{24}I_{meas})(1 - C_{nat}C_{spk})^{-1} \quad (5)$$

The magnitude of this correction process, however, was extremely small, amounting to approximately 0.08% for a sodium concentration in the region of 140 mmol L^{-1}.

A scanned ICP-MS mass spectrum at unit resolution for a typical spiked serum sample is shown in Fig. 1. The isotopes at

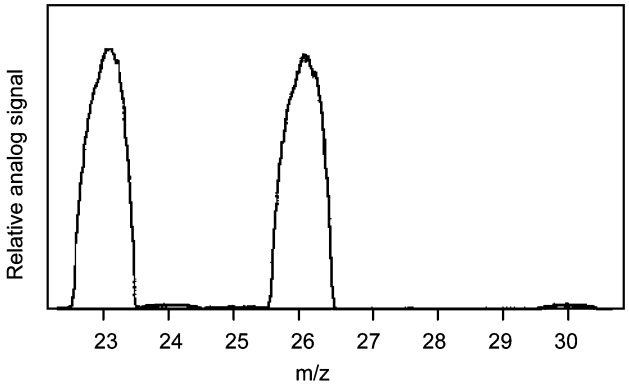

Fig. 1 Analog mass spectrum for a typical serum sample spiked with ^{26}Mg. The peak at *m/z* 30 is a mixture of background polyatomic ions.

Table 2 Typical isotope ratios and measurement repeatability for sodium in analog mode

Run	$^{24}Mg/^{26}Mg$	$^{23}Na/^{26}Mg$
1	0.00878	1.01920
2	0.00879	1.01725
3	0.00876	1.01572
4	0.00878	1.01782
5	0.00880	1.01824
6	0.00878	1.01769
7	0.00879	1.01884
Mean ($n = 7$)	0.00878	1.01782
Standard deviation	0.00001	0.00115
RSD (%)	0.133	0.113

m/z 24 and 25, originating in part from magnesium in the serum, are just visible. The isotope appearing at *m/z* 30 is most likely due to a mixture of $^{15}N_2^+$, $^{14}N^{15}NH$, $^{14}NO^+$ and ^{30}Si ions. A separate study on an unspiked serum showed no evidence of C_2^+ or CN^+ interferences on the magnesium isotopes. Likewise there are no realistic interferences possible at *m/z* 23, for the matrix components normally found in blood serum.

Measurement repeatability and linearity

The isotope ratios and the isotope ratio measurement repeatability for a typical spiked serum sample are shown in Table 2. It is evident that the measurement repeatability obtainable for $^{24}Mg/^{26}Mg$ is much better than could be attained by pulse counting ion detection, where counting statistics would limit this to approximately 2%. The measurement repeatability averaged across all of the serum samples used in this study was 0.114% for $^{24}Mg/^{26}Mg$ and 0.138% for $^{23}Na/^{26}Mg$.

As with pulse counting detection, analog mode detection is also subject to non-linearity at higher concentrations. To test the linearity of this system, four sodium calibration standards covering the range 20–75 μg mL^{-1} were spiked with a constant amount of natural Mg and the ratio $^{23}Na/^{24}Mg$ was measured as a function of the sodium concentration. The resulting calibration curve was fitted through zero and clearly indicated that the measurement system is linear ($r = 0.999995$) up to this limit. However, all of the measurement data in this work were obtained using a concentration range spanning 40–60 μg mL^{-1} (1.74–2.61 mmol L^{-1}).

Instrument background and procedural blank

The use of analog mode ion detection dramatically reduced the measured instrument background. The magnitude of background corrections to the measurement data was approximately 0.25%, which was considered to be very acceptable, especially as the background was found to be extremely stable throughout the work.

The sodium blank originating from the procedure was assessed by adding a small amount of ^{26}Mg spike to clean LDPE sample bottles and processing through the preparation and measurement protocol in a manner identical to the samples. The average blank ($n = 7$) was 403 ng (1 SD = 69 ng), which amounted to approximately a 0.01% correction to the sample data. This was therefore a negligible source of uncertainty.

Determination of sodium in SRM 909b

The ICP-MS method was initially tested during the certification of SRM 909b. Nine statistically selected bottles of SRM 909b Level 1 were tested using the method. Four separate bottles were tested by gravimetry, which was being used as the primary definitive method for certification of the material. In addition, six bottles of the Level 2 material were tested by the ICP-MS method and five separate bottles were tested by gravimetry. The analytical data obtained by both methods are compiled in Table 3, together with the expanded uncertainties and the final certified values listed on the Certificate of Analysis.[46] The expanded analytical uncertainties for each set were composed of Type A and Type B uncertainties, which were combined according to ISO guidelines.[47] For the ICP-MS method, Type A components consisted of the standard uncertainties of the sample determinations and the correction for the blank. Type B components consisted of the purity of the SRM 919a primary calibrant, uncertainty of the density correction, variability in the ICP-MS instrument mass discrimination during the analysis sequence and weighing uncertainty. For the gravimetric method, Type A components were based on corrections for the blank, measurement repeatability and analyte stoichiometry, while Type B components were based on estimates of mechanical loss, the uncertainty in the sample volume (which was calculated by adding the uncertainties of the mass and density in quadrature), uncertainty of the ignited mass of sodium sulfate and corrections by FAES. Coverage factors were determined from the effective degrees of freedom using the Welch–Satterthwaite formula.[47] Excellent agreement between the methods was obtained. For Level 1, the relative difference between the arithmetic means of the methods was 0.14%, and for Level 2 the relative difference was 0.07%. In both cases the means of the two methods were within the calculated expanded uncertainties of each method.

Table 3 ICP-MS and gravimetric data for sodium in SRM 909b

	Level 1/mmol L^{-1}		Level 2/mmol L^{-1}	
Sample	ICP-MS	Gravimetry	ICP-MS	Gravimetry
1	120.73	120.75	141.13	141.21
2	121.31	120.90	140.92	140.95
3	120.94	120.53	141.61	141.02
4	120.97	120.83	140.41	140.94
5	120.74	—	141.23	141.08
6	120.76	—	141.55	—
7	121.27	—	—	—
8	120.84	—	—	—
9	120.73	—	—	—
Mean	120.92	120.75	141.14	141.04
Standard deviation	0.23	0.16	0.44	0.11
RSD (%)	0.19	0.13	0.31	0.08
Expanded uncertainty[a]	0.45	0.31	0.62	0.26
Certified value[b]	120.76 ± 0.92		141.0 ± 1.3	

[a]Expanded uncertainty calculated at a 95% confidence interval. [b]NIST certificate value and expanded uncertainty for a 95% statistical tolerance interval reflecting the effects of measurement uncertainty and variability in the mass of dry serum fill mass.

Several controls, consisting of SRM 909 and SRM 909a Human Serum, were analyzed by the method and by gravimetry, as a check on the accuracy of the analytical data. All of the control data for both methods were within the uncertainty of the certified values.

Determination of sodium in SRM 956a

Additional measurements using the new method were made on SRM 956a. Five measurements from separate ampoules were made for each of the three concentration levels. Gravimetric measurements were used to certify the sodium concentrations, and were made independently on six ampoules of concentration Levels 1 and 2 and five ampoules of concentration Level 3. Analytical data obtained by both methods are summarized in Table 4, together with the expanded uncertainties and the assigned certificate values.[48] Expanded uncertainties were calculated on a similar basis to those for SRM 909b. Again excellent agreement was obtained between the two methods for all of the concentration levels. The difference between the two methods was 0.16%, 0.05% and 0.13% respectively for Levels 1,

Table 4 ICP-MS and gravimetric data for sodium in SRM 956a

Sample	Level 1/mmol L^{-1}		Level 2/mmol L^{-1}		Level 3/mmol L^{-1}	
	ICP-MS	Gravimetry	ICP-MS	Gravimetry	ICP-MS	Gravimetry
1	121.51	121.45	140.51	141.00	160.07	161.10
2	120.64	121.59	141.24	141.05	160.09	160.83
3	120.95	121.46	141.08	140.91	161.40	160.88
4	121.42	121.40	140.61	141.02	161.12	160.89
5	121.59	121.35	141.41	141.36	160.73	160.75
6	—	121.22	—	140.89	—	—
Mean	121.22	121.41	140.97	141.04	160.68	160.89
Standard deviation	0.41	0.12	0.39	0.17	0.60	0.13
RSD (%)	0.34	0.10	0.28	0.12	0.37	0.08
Expanded uncertainty[a]	0.59	0.31	0.62	0.29	0.82	0.30
Certified value[b]	121.4 ± 0.3		141.0 ± 0.3		160.9 ± 0.4	

[a]Expanded uncertainty calculated at a 95% confidence interval. [b]NIST certificate value and expanded uncertainty for a 95% statistical confidence interval.

2 and 3. Again, for all three levels, the means of the two methods were within the calculated expanded uncertainties of each method.

In general, the analytical measurement repeatability tends to be slightly higher (approximately 2.5 times higher) for the ICP-MS method relative to gravimetry, but is considered to be very acceptable for an instrumentally based method. The expanded uncertainties are also typically higher (approximately 2 times higher) for the ICP-MS method, largely as a result of the slightly higher measurement repeatability.

CAP proficiency testing specimens

The method was used to measure the sodium concentrations in a range of CAP Survey proficiency specimens. Seven different specimen materials were analyzed and measurements were made in duplicate on each material. The expanded uncertainties for each specimen were calculated in the same manner as SRM 909b and SRM 956a, except that the Type A sample replication uncertainty was distributed across all of the duplicates by averaging the variances of each set of duplicates, calculating a distributed standard deviation by dividing by the square root of the average, and dividing the resulting distributed relative standard deviation by the square root of the total number of duplicates ($n = 7$). The relative expanded uncertainty from combined Type A and Type B components was then scaled to generate a specific expanded uncertainty for each specimen mean. Data from each duplicate measurement are summarized in Table 5 together with the arithmetic mean and expanded uncertainty. Data from the CAP Chemistry Survey compilation are also listed in Table 5. Two sets of data are included, one (column 5) consisting of the mean of a selected set of methods, which comprise colorimetry, flame photometry and ISE diluted serum ($n \approx 3200$ laboratories), and the other (column 6) which is the mean of all the methods including ISE undiluted serum ($n \approx 6600$ laboratories). The data obtained by the ICP-MS method agree remarkably well with the overall consensus means of the selected method group, but the means from all methods are slightly higher as they tend to be biased high by the ISE (undiluted) data. This disparity is well known and ISE undiluted methods are usually compared as a separate peer group.

Conclusions

The use of analog detection ICP-MS provides an elegant, rapid and accurate method for the determination of sodium in blood serum. Measurements can be completed on a dozen samples in less than one day, while gravimetry, takes one to two weeks and is therefore not suited to routine use. Comparative measurements on reference materials by classical gravimetry clearly demonstrate that this method is capable of providing accurate and precise data. Excellent agreement is obtained between the two methods. For all of the materials tested, the means of the two methods agree within the expanded uncertainties of each method. In general, the expanded uncertainty of the ICP-MS measurements is slightly higher than that of gravimetry, largely because of the higher measurement repeatability obtained from the early generation instrumentation used in the study. The use of current ICP-MS instrumentation, particularly multi-collector systems employing Faraday cup detection, would enhance the performance of the method further. The simplicity of the method, which involves minimal sample preparation, the ubiquity of ICP-MS instrumentation and freedom from both

Table 5 ICP-MS data for sodium in CAP proficiency testing samples

Material	Replicate	Concentration/mmol L^{-1}	Mean[a]/mmol L^{-1}	Survey selected[b]/mmol L^{-1}	Survey all[c]/mmol L^{-1}
C-01	A	149.41	149.17 ± 0.44	149.3 ± 1.8	151.0 ± 2.8
	B	148.92			
C-02	A	127.89	127.68 ± 0.38	127.5 ± 1.6	128.8 ± 2.3
	B	127.47			
C-03	A	140.00	139.95 ± 0.42	139.5 ± 1.8	139.6 ± 2.0
	B	139.89			
C-05	A	147.28	146.92 ± 0.44	147.6 ± 1.8	149.0 ± 2.6
	B	146.56			
C-11	A	149.67	149.41 ± 0.44	149.7 ± 1.9	151.8 ± 2.9
	B	149.15			
C-12	A	128.83	128.64 ± 0.38	128.6 ± 1.6	130.1 ± 2.3
	B	128.46			
C-13	A	126.45	126.01 ± 0.37	125.9 ± 1.7	127.7 ± 2.6
	B	125.58			

[a]Arithmetic mean of replicates A and B and expanded uncertainty. [b]Grand mean (± 1 s) of selected group of CAP Survey data by colorimetric, flame photometric and ISE diluted methods. [c]Grand mean (± 1 s) of all CAP Survey data including those of ISE undiluted methods.

spectral and matrix interferences, mean that the method could easily be adapted to a more routine laboratory environment.

Acknowledgements

Part of this work was performed under a Cooperative Research and Development Award (CRADA) with the College of American Pathologists, Northfield, Illinois, 60093, USA. Sandi Larsen is acknowledged for providing the CAP Surveys participant data and for permission to include some of the data in the manuscript. The authors also acknowledge J. D. Fassett for helpful comments.

Appendix

Disclaimer

Certain commercial equipment, instruments or materials are identified in this work to specify adequately the experimental procedure. Such identification does not imply recommendation or endorsement by the National Institute of Standards and Technology, nor does it imply that the materials or equipment identified are necessarily the best available for this purpose.

References

1 *Fundamentals of Clinical Chemistry*, ed. N. W. Tietz, 3rd edn., 1987, pp. 614–616.
2 C. Fuchs, D. Dorn and C. McIntosh, *Fresenius' J. Anal. Chem.*, 1976, **279**, 150.
3 C. Fuchs and C. J. Preusse, *J. Clin. Chem. Clin. Biochem.*, 1977, **15**, 154.
4 C. J. Preusse and C. Fuchs, *J. Clin. Chem. Clin. Biochem.*, 1979, **17**, 639–645.
5 D. S. Daniel, B. E. Babb, C. J. Battaglia, M. U. Bogdanowicz, J. C. Chang, S. H. Kim, T. R. Kissel, J. R. Sandifer, P. N. Schnipelsky, R. Searle and D. S. Secord, *Clin. Chem.*, 1980, **26**, 990.
6 S. E. Gross and H. Khayambashi, *Clin. Chem.*, 1982, **28**, 1629–1630.
7 H. Tamura, K. Kumami, K. Kimura and T. Shono, *Mikrochim. Acta*, 1983, **2**, 287–296.
8 P. Wilkes, L. P. Schnurr and E. D. Burgess, *Clin. Invest. Med.*, 1985, **8**, A68.
9 E. D. Burgess, L. P. Schnurr and P. Wilkes, *Ann. Intern. Med.*, 1985, **103**, 806.
10 G. J. Moody, B. B. Saad and J. D. R. Thomas, *Analyst*, 1989, **114**, 15–20.
11 P. R. Demko, R. Welch, L. Bellino, D. Griben, C. C. Young and H. Winarta, *Clin. Chem.*, 1989, **35**, 1091.
12 W. R. Kulpmann, *J. Clin. Chem. Clin. Biochem.*, 1989, **27**, 815–824.
13 K. Tohda, K. Suzuki, N. Kosuge, H. Nagashima, K. Watanabe, H. Inque and T. Shirai, *Anal. Sci.*, 1990, **6**, 227–232.
14 P. C. Gunaratna, W. F. Koch, R. C. Paule, A. D. Cormier, P. Dorazio, N. Greenberg, K. M. O'Connell, A. Malenfant, A. O. Okorodudu, R. Miller, D. M. Kus and G. N. Bowers, *Clin. Chem.*, 1992, **38**, 1459–1465.
15 G. Rumpf, U. Spichigerkeller, H. Buhler and W. Simon, *Anal. Sci.*, 1992, **8**, 553–559.
16 K. Dewitte, D. Stockl and L. M. Thienpont, *Clin. Chim. Acta*, 1999, **282**, 227–228.
17 R. W. Burnett, A. K. Covington, N. Fogh-Andersen, W. R. Kulpmann, A. Lewenstam, A. H. J. Maas, O. Muller-Plathe, C. Sachs, O. Siggaard-Andersen, A. L. VanKessel and W. G. Zijlstra, *Clin. Chem. Lab. Med.*, 2000, **38**, 1065–1071.
18 T. Lang, P. Prinsloo, A. F. Broughton, N. Lawson and C. B. Marenah, *Ann. Clin. Biochem.*, 2002, **39**, 66–67.
19 H. Hisamoto, N. Miyashita, K. Watanabe, A. E. Nakagawa, N. Yamamoto and K. Suzuki, *Sens. Actuators B*, 1995, **29**, 378–385.
20 T. Gunnlaugsson, M. Nieuwenhuyzen, L. Richard and V. Thoss, *J. Chem. Soc., Perkin Trans. 2*, 2002, 141–150.
21 M. N. Berry, R. D. Mazzachi, M. Pejakovic and M. J. Peake, *Clin. Chem.*, 1988, **34**, 2295–2298.
22 M. N. Berry, R. D. Mazzachi and M. J. Peake, *Wien. Klin. Wochenschr.*, 1992, **104**, 5–11.
23 R. Quiles, J. M. Fernandezromero, E. Fernandez, M. D. L. Decastro and M. Valcarcel, *Clin. Chem.*, 1993, **39**, 500–503.
24 W. Hubl, R. Wejbora, I. Shaftikeramat, A. Haider, P. Hajdusich and P. M. Bayer, *Clin. Chem.*, 1994, **40**, 1528–1531.
25 R. D. Mazzachi, B. C. Mazzachi and M. N. Berry, *Eur. J. Clin. Chem. Clin.*, 1994, **32**, 709–717.
26 J. Chalas, J. Francoual and A. Lindenbaum, *Ann. Biol. Clin. Paris*, 1994, **52**, 333–339.
27 H. L. Vader and C. L. J. Vink, *Clin. Chim. Acta*, 1975, **65**, 379–388.
28 J. Vanpelt, *Clin. Chem.*, 1994, **40**, 846–847.
29 R. Schaffer, R. A. Velapoldi, R. C. Paule, J. Mandel, G. N. Bowers, B. E. Copeland, D. O. Rodgerson and J. C. White, *Clin. Chem.*, 1981, **27**, 1824–1828.
30 G. N. Doku and V. P. Y. Gadzekpo, *Talanta*, 1996, **43**, 735–739.
31 J. F. Vanstaden, *Talanta*, 1991, **38**, 1033–1039.
32 H. Berndt, *Fresenius' J. Anal. Chem.*, 1979, **296**, 277–280.
33 H. Berndt and J. Messerschmidt, *Fresenius' J. Anal. Chem.*, 1980, **301**, 104–105.
34 P. Schramel and B. J. Klose, *Fresenius' J. Anal. Chem.*, 1981, **307**, 26–30.
35 J. L. Burguera, M. Burguera and M. Gallignani, *Ann. Acad. Bras. Cienc.*, 1983, **55**, 209–211.
36 L. M. Thienpont, J. E. VanNuwenborg and D. Stockl, *J. Chromatogr., A*, 1995, **706**, 443–450.
37 L. M. Thienpont, J. E. VanNuwenborg, H. Reinauer and D. Stockl, *Clin. Biochem.*, 1996, **29**, 501–508.
38 D. Bohrer, P. C. do Nascimento and J. K. A. Mendonca, *J. Chromatogr., B*, 2001, **750**, 61–69.
39 A. A. G. Lemmens, J. C. Reijenga, F. M. Everaerts, R. T. P. Janssen, J. A. R. J. Hulsman and C. A. M. Meijers, *J. Chromatogr.*, 1985, **320**, 193–197.
40 S. D. Tanner, M. Paul, S. A. Beres and E. R. Denoyer, *At. Spectrosc.*, 1995, **16**, 16–18.
41 D. Wollenweber, S. Strassburg and G. Wunsch, *Fresenius' J. Anal. Chem.*, 1999, **364**, 433–437.
42 J. R. Moody and T. W. Vetter, *J. Res. Natl. Inst. Stand. Technol.*, 1996, **101**, 155–164.
43 C. S. Phinney, K. E. Murphy, M. J. Welch, P. M. Ellerbe, S. E. Long, K. W. Pratt, S. B. Schiller, L. T. Sniegoski, M. S. Rearick, T. W. Vetter and R. D. Vocke, *Fresenius' J. Anal. Chem.*, 1998, **361**, 71–80.
44 J. R. Moody and E. S. Beary, *Talanta*, 1982, **29**, 1003–1010.
45 IUPAC Commission on Atomic Weights and Isotopic Abundances, *Pure Appl. Chem.*, 1992, **64**, 1522–1523.
46 NIST Certificate of Analysis, SRM 909b, Human Serum, October, 1997.
47 B. N. Taylor and C. E. Kuyatt, *Technical Note 1297*, NIST, Gaithersburg, MD, 1994.
48 NIST Certificate of Analysis, SRM 956a, Electrolytes in Frozen Human Serum, November, 1996.