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Multispecies calibration: A novel application for inductively coupled plasma tandem mass spectrometry

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Abstract

Inductively coupled plasma tandem mass spectrometry (ICP-MS/MS) has significantly expanded the reach of analytical atomic spectrometry. In this work, we take advantage of the gas-phase chemistry available in ICP-MS/MS to propose a novel method of calibration. Rather than employing several standard solutions and a single mass-to-charge ratio, multispecies calibration (MSC) uses only one standard reference concentration and several chemical species of a monoisotopic element for calibration. In this work, multiple oxide and ammonia species generated in an ICP-MS/MS collision/reaction cell are used to determine As, Co and Mn in rice and liver samples. Only two calibration solutions are required per sample: S1 is a 1:1 mixture of sample and standard solution; S2 has the same 1:1 volume ratio of sample and blank. They are run separately, and the analytical calibration curve is built by plotting signal intensities from several ions containing the analyte. S1 and S2 signals are plotted on the *x*-axis and *y*-axis, respectively, and each point in the calibration plot corresponds to a different analyte species. The instrumental limits of detection calculated for As, Co and Mn were 0.07, 0.03, and 0.07 μg L^{-1}, with RSDs estimated as 7.8, 3.1 and 1.8 %, respectively (n = 10). Certified and MSC-determined values of As, Co and Mn in Tomato Leaves (NIST 1573a) and Bovine Liver (NIST 1577b) presented no statistically significant differences (Student's *t*-test, 95 % confidence level, n = 3). The MSC results were comparable and sometimes better than values determined by the traditional external standard, internal standard and standard additions calibration methods.

Introduction

Calibration in Analytical Chemistry involves the determination of a functional relationship between measured values and analytical quantities.[1] Most calibration models take advantage of a correlation between instrument response and analyte concentration, for which functional parameters are determined by linear regression based on least squares fitting. Among all calibration strategies used in instrumental analytical spectrochemistry, the external standard method is the most common and straightforward. Analytical signals from a few calibration standards of known concentration are used to estimate the linear function parameters, which are then used to predict the unknown analyte concentration in a sample.[2] Although efficient and adequate for most applications, external standard calibration (EC) assumes, for example, that matrix effects are negligible, which is rarely the case when analyzing complex-matrix samples. Concomitant components in the sample are usually absent in the standard solutions, which may result in severe signal bias and inaccurate results.

An alternative to overcome the limitations of EC is matrix matching.[3,4] However, as one would expect, the more complex the sample matrix the more time-consuming and expensive it is to identify all concomitants and reproduce the sample's chemical constitution when preparing standard solutions. Among the traditional calibration methods, standard additions (SA) may be the most successful at eliminating the matrix effects associated with EC.[5,6] In SA, the sample itself is used to prepare the standard solutions. Therefore, every solution has the same matrix, and no effect on the analytical signal due to differences in concomitant constitution should be observed.[7,8] Although providing superior accuracy, especially in complex-matrix applications, SA is time-consuming since a calibration curve with a few standard solutions is required for each individual sample. Another traditional calibration strategy with broad application is the internal

standard method (IS). It is especially popular in techniques with sequentially-collected analytical signals, such as inductively coupled plasma mass spectrometry (ICP-MS), because it can minimize variations in sample/ion transport and other instrument-related fluctuations.[9-12] However, it usually is ineffective at minimizing some severe matrix effects. In addition, identifying the most adequate internal standard for a specific application may be a challenging task, and a suite of internal standard elements, covering a wide range of mass-to-charge ratios (m/z), is required.[9]

Several calibration methods have been described to improve accuracy in quantitative analysis and minimize the limitations of EC and SA. Some of the new strategies involve multiple analytical signals,[13-15] gradient dilution combined with matrix matching,[16-23] and multivariate calibration.[24-29] Among the non-conventional calibration methods recently proposed, multi-energy calibration (MEC)[30] and multi-isotope calibration (MICal)[31] may be the only ones based on a dimension other than the traditional instrument response and analyte concentration. Rather than employing several standard solutions with increasing analyte concentrations and monitoring a single analytical wavelength or mass-to-charge ratio (m/z), MEC and MICal use only one standard reference concentration and many energy transitions or several isotopes for calibration. The analyte concentration in the sample is then determined by taking advantage of the linear relationship between instrument responses from multiple channels recorded from two calibration solutions containing the same matrix.

Although not a significant issue for MEC, the requirement of several instrument responses from the same analyte is a major limitation of MICal, *i.e.* in practice, it cannot be applied to monoisotopic analytes.[31] In the present work, we describe a calibration method based on the same principles of MEC and MICal, which can be used in combination with inductively

coupled plasma tandem mass spectrometry (ICP-MS/MS) to determine monoisotopic analytes such as As, Co and Mn. By generating multiple oxide and ammonia cluster species from the same analyte in an ICP-MS/MS instrument,[32,33] the multispecies calibration method (MSC) described here can overcome MICal's main limitation. Similar to MEC and MICal, only two calibration solutions are required in MSC: S1 is a 1:1 mixture of sample and a standard solution, and S2 has the same constitution as S1 with blank replacing the standard solution. These solutions are run separately, and the analytical calibration curve is built by plotting signal intensities from several ions containing the analyte. S1 and S2 signals are plotted on the *x*-axis and *y*-axis, respectively, and each point in the calibration plot corresponds to a different analyte species.

The parameters of the functional relationship associated with instrument responses from multiple channels recorded for each calibration solution are determined as follows. Consider the relationships for S1 and S2 as represented in eqn (1) and eqn (2), respectively:

$$S(M_iX_j)_{Sample+Standard} = m\,[C(M)_{Sample} + C(M)_{Standard}] \quad (1)$$

$$S(M_iX_j)_{Sample} = m\,C(M)_{Sample} \quad (2)$$

where S is the instrument response, M represents a monoisotopic analyte, X is the oxygen or ammonia derivate, *i* and *j* represent the number of ligands in the molecular species, m is a proportionality constant, and C is the concentration of analyte in the sample, or the standard

solution used to prepare S1. If instrumental conditions and sample matrix present negligible variation (both S1 and S2 contain the same amount of sample), eqn (1) and (2) can be combined and rearranged (eqn (3) and (4)):

$$\frac{S(M_iX_j)_{Sample}}{C(M)_{Sample}} = \frac{S(M_iX_j)_{Samle+Standard}}{C(M)_{Sample}+C(M)_{Standard}} \quad (3)$$

$$S(M_iX_j)_{Sample} = S(M_iX_j)_{Samle+Standard}\left[\frac{C(M)_{Sample}}{C(M)_{Sample}+C(M)_{Standard}}\right] \quad (4).$$

The analyte concentration in the sample, $C(M)_{Sample}$, can then be determined from the slope of a plot of $S(M_iX_j)_{Sample}$ (from S2) *vs.* $S(M_iX_j)_{Sample+Standard}$ (from S1), as shown in eqn (6) and eqn (7) below:

$$Slope = \frac{C(M)_{Sample}}{C(M)_{Sample}+C(M)_{Standard}} \quad (6)$$

$$C(M)_{Sample} = \frac{Slope \cdot C(M)_{Standard}}{(1-Slope)} \quad (7).$$

Experimental

Instrumentation

The ions used for MSC were generated in a collision/reaction cell of an ICP-MS/MS instrument (8800 ICP-MS/MS, Agilent, Tokyo, Japan). All determinations were carried out in MS/MS mode with O_2 (99.999% purity, Airgas, Colfax, NC, USA) or NH_3 (10 % v/v NH_3 in 90 % He - NH_3 99.999% pure, Air Liquide, Durham, NC, USA) serving as reaction gases. High purity He (99.999% purity, Airgas, Colfax, NC, USA) was also used in the NH_3 mode. The ICP-MS/MS instrument is composed of two quadrupoles (Q1 and Q2), and a third generation octopole reaction system (ORS3) positioned between Q1 and Q2. An SPS 4 automatic sampler, a Scott-type double pass spray chamber operated at 2 ^{o}C, and a Micromist concentric nebulizer comprise the sample introduction system. Additional details on the instrumental operating conditions used in this work are shown in Table 1.

Seven species of As (As^+, AsO^+, $As(NH_2)^+$, $As(NH_3)(NH_2)^+$, $As(NH_3)_2^+$, $As(NH_3)_2(NH_2)^+$, and $As(NH_3)_3^+$), 6 of Co (Co^+, CoO^+, CoO_2^+, $Co(NH_3)^+$, $Co(NH_3)_2^+$, and $Co(NH_3)_3^+$), and 7 of Mn (Mn^+, MnO^+, MnO_2^+, $Mn(NH_2)^+$, $Mn(NH_3)^+$, $Mn(NH_3)_2^+$, $Mn(NH_3)_3^+$) were used in MSC. The m/z monitored in O_2 mode (Q2) were 75 and 91 (As, Q1 = 75); 59, 75 and 91 (Co, Q1 = 59); and 55, 71 and 87 (Mn, Q1 = 55). In NH_3 mode, the m/z monitored (Q2) were 91, 108, 109, 125 and 126 (As, Q1 = 75); 59, 76, 93 and 110 (Co, Q1 = 59); and 55, 71, 72, 89 and 106 (Mn, Q1 = 55). Both oxide and ammonia cluster species were used to build the MSC curve for each analyte.

For comparison, certified reference materials were analyzed using MSC and the traditional EC, IS and SA calibration methods. The general operating conditions used in EC, IS

and SA determinations were optimized using the instrument's *Auto Tune* feature. Arsenic was determined in mass shift MS/MS mode, with O_2 gas flowing at 0.2 mL min^{-1} (30 %). For Co and Mn, operating conditions included single quadrupole, and on mass MS/MS modes, respectively, with He gas (4.0 mL min^{-1}) used for Co, and H_2 gas (1.8 mL min^{-1}) used for Mn. Other collision/reaction cell conditions included octopole bias, octopole radio frequency and energy discrimination values of -5, 200 and -7 V for As; -18, 190 and 5 V for Co; and -18, 160 and 0 V for Mn.

All samples were digested using a microwave-assisted digestion system (Ethos UP, Milestone, Sorisole, Italy).

Reagents, standard solutions and samples

Trace-metal-grade nitric acid (Fisher, Pittsburgh, PA, USA) and distilled-deionized water (18 MΩ cm, Milli-Q®, Millipore, Bedford, MA, USA) were used to prepare all analytical solutions. Sample digestions were carried out with trace-metal-grade HNO_3 (Fisher) and trace-analysis-grade H_2O_2 (30 % v/v, Sigma Aldrich, Atlanta, GA, USA). Single-element stock solutions of As, Co and Mn (10 mg L^{-1}, High-Purity Standards, Charleston, SC, USA) were used to prepare the standard solutions. S1 was prepared by mixing 3.00 mL of sample and 3.00 mL of a standard solution containing 20.0 μg L^{-1} of As, Co and Mn each in 4 % v/v HNO_3. S2 was prepared with 3.00 mL of sample and 3.00 mL of 4 % v/v HNO_3.

Certified reference materials (CRMs) of Tomato Leaves (NIST 1573a) and Bovine Liver (NIST 1577b), obtained from the National Institute of Standards and Technology (NIST, Gaithersburg, MD, USA), were used to evaluate MSC's accuracy. The same CRMs were

analyzed by the traditional EC, IS and SA calibration methods for comparison. The MSC method was also applied to the determination of As, Co and Mn in rice, and pork and bovine liver samples purchased in the local market.

Sample preparation

Sample aliquots of approximately 0.2 g were accurately weighed and transferred to polytetrafluoroethylene (PTFE) digestion vessels. One milliliter of concentrated HNO_3 (*ca.* 14 mol/L) was then added to the sample and a pre-digestion period of 20 min was observed before adding 6.0 mL of distilled-deionized H_2O and 3.0 mL of H_2O_2 30 % v/v to the mixture. The digestion vessels were closed and submitted to microwave-assisted digestion according to the following heating program: (*i*) 15 min ramp, at a maximum applied power of 1800 W, to reach 200 ^oC; (*ii*) 15 min hold at 200 ^oC, with maximum applied power of 1800 W; and (*iii*) a 15 min cooling period. All samples were then transferred to polypropylene tubes (Fisher Scientific, Suwanee, GA, USA) and diluted to 25.0 mL with distilled-deionized water.

Results and discussion

Advantages and limitations of the MSC method

Similar to the standard additions method, one of the main advantages of MSC is its matrix-matching capabilities. Because both calibration solutions (*i.e.* S1 and S2) contain the same amount of sample, matrix effects become negligible. However, MSC is faster and more

straightforward than a typical multiple-calibration-solution SA determination. On the other hand, MSC has a lower sample throughput than EC.

Although more easily applied when using a 1:1 volume ratio between sample and standard solution, or sample and blank, the MSC method presents the possibility of employing any other proportion. As long as the same amount of sample is present in S1 and S2, one could adopt a 10 % sample / 90 % standard (or 90 % blank) mix, for example, to minimize matrix effects even further. On the other hand, an 80 % sample / 20 % standard (or 20 % blank) mix, for example, may be used to improve sensitivity. In these cases, the only caveat is that a dilution correction factor must be included in eqn (7), as shown in eqn (8), where $V_{Standard}$ and V_{Sample} correspond to the volumes of standard solution and sample used to prepare S1 and S2. Note that eqn (8) becomes eqn (7) when the 1:1 volume ratio is used, *i.e.* $V_{Standard} = V_{Sample}$.

$$C(M)_{Sample} = \frac{Slope \cdot C(M)_{Standard} \cdot V_{Standard}}{(1-Slope) \cdot V_{Sample}} \quad (8)$$

Another distinctive advantage of methods such as MEC, MICal and MSC when compared with traditional calibration strategies is the possibility of more easily identifying interferences specific to an analytical wavelength or m/z. Each point in the MSC plot corresponds to a different species. Therefore, any interfering effect may be readily detected as a lack of linearity caused by the species under interference (*i.e.* by a point showing outside the calibration curve line). Typical MSC calibration plots are shown in Fig. 1.

On the other hand, MSC may be more prone to systematic errors during solution preparation. Because it relies on a single $C(M)_{Standard}$ value (eqn (7)), any error in that concentration will lead to inaccurate results. Obviously, this is less of an issue when employing multiple standard solutions with a conventional calibration method such as EC.

MSC analytical performance

The method's accuracy was evaluated by determining As, Co and Mn in certified reference materials (CRM) of Tomato Leaves (NIST 1573a) and Bovine Liver (NIST 1577b). No statistically significant differences were observed between certified and MSC-determined values by applying a Student's *t*-test at the 95 % confidence level (Table 2). As discussed in a previously published work describing the MICal method,[31] a MSC slope close to 1 may provide inaccurate results because the standard solution concentration becomes negligible compared to the analyte concentration in the sample. Thus, considering the high concentrations of Mn in Tomato Leaves, the digested samples were diluted 100-fold before analysis. The MSC plots shown in Fig. 1 were built with signals from undiluted solutions of Tomato Leaves for As and Co, and the 100-fold diluted sample solution for Mn. As shown in Table 2, the MSC results are comparable and sometimes better than the values determined with the traditional calibration methods of EC, IS and SA.

The instrumental limits of detection (LOD) for MSC determination of As, Co and Mn were calculated according IUPAC recommendations as 3 times the standard deviation (S) of the concentration found in the blank (C_B), *i.e.* LOD = 3 SC_B. To determine C_B, a 1% v/v HNO_3 solution was considered the "sample", as well as blank. Therefore, S1 was prepared by mixing

3.00 mL of 1% v/v HNO_3 and 3.00 mL of a standard solution containing 20.0 μg L^{-1} of each analyte. S2 was simply 1% v/v HNO_3. The LODs (n = 10) for As, Co and Mn were then calculated as 0.07, 0.03 and 0.07 μg L^{-1}, respectively. The instrumental limits of quantification (LOQ) were calculated as LOQ = 10 SC_B, with values of 0.2, 0.1 and 0.2 μg L^{-1} for As, Co and Mn, respectively. Additional details on LOD calculations for MSC can be found in the Electronic Supplementary Information (ESI).

For comparison, the instrumental LODs for As, Co and Mn calculated using the EC method were 0.05, 0.05 and 0.02, respectively. It is worth noting that the operating conditions were not optimized for MSC in this proof-of-concept study. LODs may improve by optimization of the reaction cell gas flow rate and other instrumental parameters such as octopole bias and energy discrimination. In addition, analyte species with relatively low sensitivities are used in MSC, which may negatively affect the method's overall LODs. Thus, MSC LODs may be slightly higher than typical ICP-MS values for some elements. This main disadvantage may be compensated by two distinct advantages: (*i*) the larger the number of analyte species, the larger the number of calibration points, which contributes to higher precisions and accuracies; and (*ii*) by using analytical signals from multiple sources, one avoids the preparation of several calibration standards, which results in higher sample throughputs when compared with the SA method. Although the LODs reported here are in the parts-per-trillion range, which is adequate for most applications, in some cases the MSC method may be suitable to applications more concerned with accuracy than sensitivity.

The method's precision was estimated using a 10 μg L^{-1} solution as "sample", and a 20.0 μg L^{-1} reference standard. Relative standard deviation (RSD) values of 7.8, 3.1 and 1.8% were calculated for As, Co and Mn, respectively (n = 10). The sources of random errors in MSC may

be mainly associated to the formation of analyte complexes in the collision/reaction cell. As discussed before for LODs, precision may be improved by optimizing instrumental conditions and conducting a more strict selection of analyte species.

Application to rice and liver samples

The MSC method was applied to the determination of As, Co and Mn in white and brown rice, and bovine and pork liver samples to evaluate the method when applied to commercial samples. The results are shown in Table 3. As expected, relatively low levels of these elements were found, with some concentrations below the LOQs.

Conclusions

Inductively coupled plasma tandem mass spectrometry has significantly expanded the reach of analytical atomic spectrometry. With higher sensitivities and fewer spectral interferences, it has enabled many new applications in several fields. This proof-of-concept work demonstrates that ICP-MS/MS allows not only for new applications, but also for novel approaches to calibration. The MSC method may be an efficient strategy to minimize matrix effects and ensure accuracy in complex-matrix analyses. Although more prone to systematic errors during solution preparation, and limited by the type of instrumentation required, it presents both higher sample throughput than SA, and matrix-matching capabilities absent in EC. Similar to other single-standard-concentration, multichannel calibration methods such as MEC and MICal, one of MSC's most distinctive advantages is the possibility of visually identifying interfering effects on a specific species during calibration.

Conflicts of Interest

There are no conflicts of interest to declare.

Acknowledgements

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Table 1. ICP-MS/MS operating conditions for MSC applications using O_2 and NH_3 as reaction gases.

Instrumental parameter	**Operating condition**
Radio frequency (RF) applied power (W)	1550
Sampling depth (mm)	10.0
Carrier gas flow rate (L min^{-1})	1.05
Integration time (s)	0.1
Extraction lens 1 (V)	0
Extraction lens 2 (V)	-180
Omega lens bias (V)	-80
Q1 entrance (V)	-6
Q1 exit (V)	0
Q1 bias (V)	0
Q1 pre-filter bias (V)	-38
Q1 post-filter bias (V)	-14
Cell focus (V)	0

Cell entrance (V)	-40
Cell exit (V)	-90
Octopole RF (V)	180
Energy discrimination (V)	-8
Plate bias (V)	-100
Specific to O_2 mode	
Cell gas flow rate (mL min^{-1})	0.2 (20 %)[a]
Omega lens (V)	7.1
Deflect lens (V)	-4
Octopole bias (V)	-18
Specific to NH_3 mode	
Cell gas flow rate (mL min^{-1})	1.4 (14 %)[a]
He gas flow rate (mL min^{-1})	1.0
Omega lens (V)	7.9
Deflect lens (V)	3
Octopole bias (V)	-8

[a]The instrument software shows gas cell flows as percent of the maximum flow rate for O_2 and NH_3.

Table 2. Determination of As, Co and Mn in certified reference materials by ICP-MS/MS and MSC, and comparison with EC, IS and SA. Results are the mean ± 1 standard deviation of concentrations in mg kg^{-1} (n = 3).

Sample	Analyte	Reference	MSC	EC	IS	SA
Tomato Leaves	As	0.112 ± 0.004	0.115 ± 0.008	0.109 ± 0.004	0.074 ± 0.002	0.073 ± 0.067
(NIST 1573a)	Co	0.57 ± 0.02	0.570 ± 0.015	0.482 ± 0.018	0.322 ± 0.016	0.428 ± 0.167
	Mn	246 ± 8	238 ± 8	255 ± 6	249 ± 6	242 ± 5
Bovine Liver	As	0.05	0.062 ± 0.007	0.058 ± 0.020	0.050 ± 0.009	0.060 ± 0.014
(NIST 1577b)	Co	0.25	0.249 ± 0.007	0.269 ± 0.049	0.239 ± 0.004	0.185 ± 0.023
	Mn	10.5 ± 1.7	11.96 ± 0.79	13.63 ± 2.46	12.16 ± 0.18	13.34 ± 4.96

Table 3. Determination of As, Co and Mn in rice and liver samples by ICP-MS/MS and MSC. Results are the mean ± 1 standard deviation of concentrations in mg kg^{-1} (n = 3).

Sample	Analyte	Analyte concentration
White rice	As	0.298 ± 0.031
	Co	0.019 ± 0.012
	Mn	24.41 ± 7.28
Brown rice	As	0.664 ± 0.131
	Co	0.032 ± 0.007
	Mn	43.11 ± 9.64
Bovine liver	As	< LOQ
	Co	0.145 ± 0.011
	Mn	5.97 ± 1.13
Pork liver	As	< LOQ
	Co	< LOQ
	Mn	0.629 ± 0.188

Figure captions

Fig. 1. Multispecies calibration plots used to determine As (**a**), Co (**b**), and Mn (**c**) in Tomato Leaves (NIST 1573a) by ICP-MS/MS.

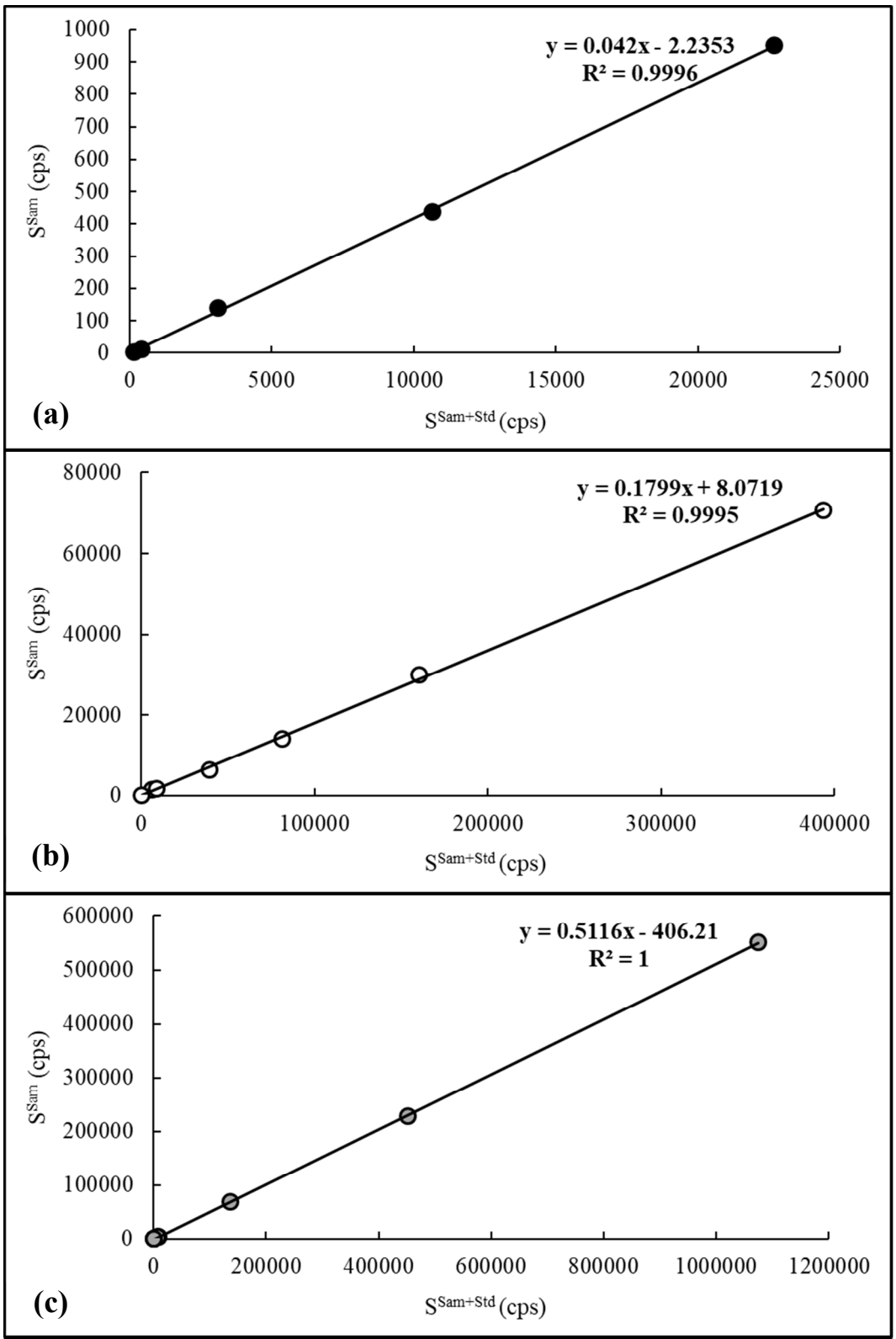

Fig. 1

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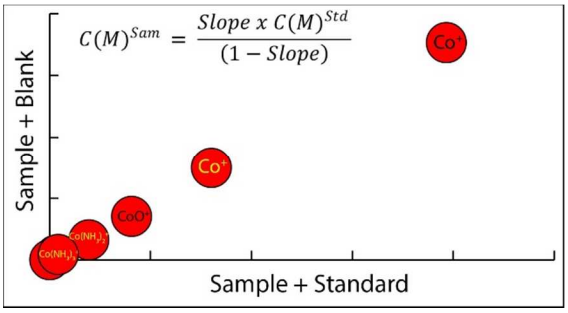
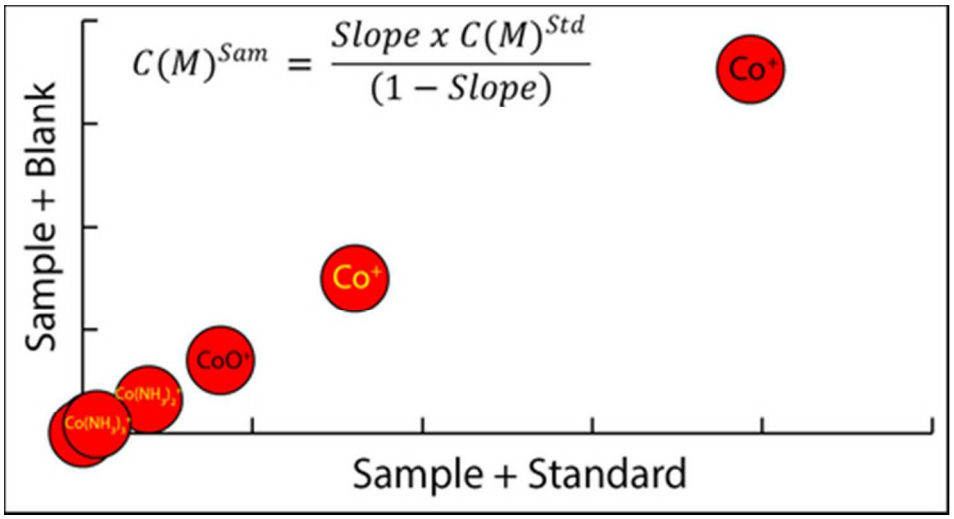


ICP-MS/MS is used to generate multiple oxide and ammonia species in a novel calibration method for As, Co and Mn.



Graphical abstract

39x21mm (300 x 300 DPI)