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Handling spectral interferences and matrix effects in DRC-ICPMS to assess elemental profile in human serum samples after dissolution with formic acid

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ABSTRACT

Inductively coupled plasma mass spectrometry instrumentation along with the dynamic reaction cell (DRC) technology has been increasingly used in the last decade for multielemental analysis of biological samples. This work reports the development of a method to assess concentration of Li, Be, B, Sc, Mn, Fe, Co, Ni, Cu, Zn, Ga, Ge, As, Se, Rb, Cd, Sr, Mo, Pd, Ag, Sb, Te, Cs, Ba, Os, Tl, Pb, and Bi in human serum samples treated with formic acid. This is a single-step procedure that minimizes sample handling avoiding contamination risks and analyte losses. To this aim, several experimental conditions such as sample pretreatment with formic acid and instrumental operating parameters were optimized. Interferences due to polyatomic ions were eliminated using DRC with oxygen as reaction gas through the formation of MO^+ ions. Our method involved low dilution factors, appropriate limits of detection in the low $\mu\text{g L}^{-1}$ range for all elements. The accuracy was evaluated through the analysis of a standard reference material (Inorganic Constituents in Animal Serum, NIST 1598a) and spiked samples, with satisfactory recoveries.

Introduction

The study and determination of essential and non-essential trace elements in biological samples have been linked with issues about the elimination of interferences due to the matrix of the sample and reagents for its preparation.¹ Attention has been paid to analytical methods improving or complementing clinical studies.² These methods are used to diagnose trace element deficiencies or to assess environmental or occupational exposure relying on the analysis of blood, serum/plasma, and/or urine specimens.³⁻¹¹ Up to date, inductively coupled plasma mass spectrometry (ICPMS) is by far the most effective method for multi-elemental determination due to its sensitivity and operational short times.¹

In most studies, sample preparation is limited to acid microwave digestion and direct introduction of the resulting aqueous solution into the plasma.⁴⁻¹³ In spite of the effectiveness of these approaches; they introduce high dilution factors and large sample manipulation which increase errors sources and loses in sensitivity. There are also some studies that suggest the use of organic solvents such as formic acid (FA) and tetramethylammonium hydroxide (TMAH), or dilution with ammonia, Triton X-100, and ethylenediaminetetraacetic acid (EDTA) for sample preparation for trace metal analysis.¹⁴ These reagents allow simplifying sample treatment, shortening times of work with a consequent increase in analysis frequency. TMAH was first used in the dissolution of biological samples by electrothermal atomic absorption spectrometry (ETAAS) and ICPMS.¹⁴⁻¹⁸ Formic acid has been introduced as an alternative for sample preparation combined with the analytical techniques before mentioned.¹⁹ Direct sample introduction into the plasma was possible replacing the conventional pneumatic nebulizer with a microconcentric one, which was able to generate a fine and stable aerosol at low flows, possessing high tolerance to dissolved solids.^{19,20}

One of the biggest challenges regarding multi-elemental determination by ICPMS is correcting for isobaric and polyatomic interferences. The development of the dynamic reaction cell (DRC) has been a very suitable alternative to solve spectral interferences.²¹⁻²⁵ The introduction of a second quadrupole between the ion lens system and the analyzing quadrupole allows overtaking interferences without modifying the standard working conditions. For eliminating these interferences, it has been proposed the use of several reaction gases such as CH₄ and H₂. For instance, it has been documented that they work efficiently in the case of Se isotopes, which are overlapped by the polyatomic interferences from plasma source ⁴⁰Ar⁴⁰Ar⁺, ⁴⁰Ar³⁸Ar⁺, and ⁴⁰Ar⁴⁰Ca⁺; and for ⁵¹V, which suffers from overlapping of the ions ³⁵Cl¹⁶O⁺, ³⁷Cl¹⁴N⁺, ⁴⁰Ar¹¹B⁺.²⁶⁻²⁹ In addition, there are also reports of the application of O₂ as a reaction gas to eliminate certain interferences related to As, Se, and Mo; specifically.²² On the other hand, there is still the problem of working with organic matrices, which depends mostly on the reagents used in sample treatment.

The aim of this work was to develop and optimize a method for the multi-elemental analysis of serum samples by DRC-ICPMS, introducing a new sample treatment based on the use of formic acid and a highly-efficiency sample introduction system. The main experimental and instrumental conditions were carefully optimized. In addition, it was proposed the use of oxygen as single reaction gas to eliminate interferences in the DRC through the formation of MO⁺ ions. The recommended procedure was validated by means of the analysis of a standard reference material (SRM) and it was applied to the determination of Li, Be, B, Si, Sc, Mn, Fe, Co, Ni, Cu, Zn, Ga, Ge, As, Se, Rb, Sr, Cd, Mo, Pd, Ag, Sb, Te, Cs, Ba, Os, Hg, Tl, Pb, and Bi in real samples collected from healthy persons. Spiked samples were also analyzed.

2. Material and methods

2.1. Instrumentation

An Inductively Coupled Plasma Mass Spectrometer from Perkin-Elmer SCIEX, ELAN DRC-e (Thornhill, Canada) was used. The argon gas with purity of 99.996% was supplied by Air Liquide S.A. (Córdoba, Argentina). HF-resistant and high performance perfluoracetate (PFA) nebulizer model PFA-ST, coupled to a quartz cyclonic spray chamber with internal baffle and drain line, cooled with the PC³ system from ESI (Omaha - NE, USA) was used. Tygon black/black 40 cm length and 0.76 mm i.d. peristaltic pump tubings were used. The instrument settings are shown in **Table 1**.

2.2. Reagents and sample treatment

Ultrapure water (18.2 MΩ.cm) produced by an Easy pure RF system from Barnstead (Dubuque, IA, USA) was used. Nitric acid (65%, v/v) from Sigma-Aldrich (Germany), hydrogen peroxide (40%, v/v) from Parafarm (Argentina) and formic acid (98%, v/v) from Fisher Scientific (UK), were used throughout. Multi-element Calibration Standard 3 solution containing 10 mg L⁻¹ of Ag, Al, As, Ba, Be, Bi, Ca, Cd, Co, Cr, Cs, Fe, Ga, In, K, Li, Mg, Mn, Na, Ni, Pb, Rb, Se, Sr, Tl, U, V, and Zn in 5% (v/v) HNO₃, Multi-element Calibration Standard 5 Solution containing 10 mg L⁻¹ of B, Ge, Mo, Nb, P, Re, S, Si, Ta, Ti, W, and Zr in 5% (v/v) HNO₃, and a Setup/Mass resolution/Mass calibration solution containing 10 μg L⁻¹ of Ba and 1 μg L⁻¹ of Mg, Co, Fe, Be, In, Ce, Pb, U, and Th in 0.5 % (v/v) HNO₃ from Perkin Elmer Pure (Norwalk, USA), were used. The Inorganic Constituents in Animal Serum Standard Reference Material, NIST 1598a, (Gaithersburg, MD, USA) was thawed until reaching room temperature and used for validation purposes.

Venous blood (3–5 mL) was sampled from healthy subjects and serum was separated and stored at -20 °C until analysis. Exactly 200 μL serum samples were placed in a 15-mL polypropylene flask, then 800 μL of formic acid and 100 μL of nitric acid were added; the volume was made up to 10 mL with pure water and heated at 80 °C in a water bath for 30 minutes.

For calibration purposes aqueous standards prepared in 1.0% (v/v) nitric acid were measured. Additionally, standards in 8.0 % (v/v) formic acid and 1% (v/v) nitric acid were also prepared. The analytes' concentrations were 2.0, 5.0, 10.0, 20.0, 40.0, 80.0, and 100.0 $\mu\text{g L}^{-1}$.

3. Results and discussion

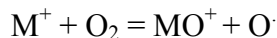
3.1 ICPMS operating conditions for formic acid matrix

The ICP operating conditions, namely radio frequency (RF) power and Ar gas flow rate, are parameters that may be handled in order to favor the ionization, but avoiding background contribution due to polyatomic ions, oxides, and/or double charged ions. The optimization was carried out with a 50 mL aqueous synthetic sample containing 4 mL of formic acid, 500 μL of nitric acid, and 300 μL of each multielemental standard solution. After the heating process in water bath, RF power and Ar gas flow rate parameters were optimized. Signals for each element were recorded modifying the RF power from 750 to 1400 W, and the Ar gas flow rate from 0.6 to 1.2 $\mu\text{L min}^{-1}$. Simultaneously, a blank solution was measured to compare and determine the best signal to background ratio value (SBR). Table 1 summarizes the optimized instrumental conditions.

3.2 Study of interferences

Working with organic matrices implies the appearance of polyatomic interferences with Ar, O, N and H due to C-containing ions. The major potential interferences³⁰ are shown in **Table 2**. The isotopes ⁷Li, ⁹Be, ¹¹B, ⁵⁵Mn, ⁵⁹Co, ⁶⁰Ni, ⁶³Cu, ⁶⁶Zn, ⁷⁴Ge, ⁸²Se, ⁸⁵Rb, ⁸⁸Sr, ⁹⁸Mo, ¹⁰⁶Pd, ¹⁰⁷Ag, ¹¹¹Cd, ¹¹⁸Sn, ¹³⁰Te, ¹³³Cs, ¹³⁸Ba, ¹⁹²Os, ²⁰⁵Tl, ²⁰⁸Pb, and ²⁰⁹Bi only required optimization of parameters such as the gas flow rate, radio frequency (RF) power and lens setting in standard mode. Additionally, mathematical equations to correct isobaric overlaps were used when applicable.

On the other hand, oxygen as reaction gas is proposed to eliminate isobaric interferences for ⁴⁵Sc, ⁷⁵As, ⁵⁶Fe and ⁶⁹Ga by modifying the analyte mass to charge ratio (m/z) as follows:



This reaction yields an analyte ion in a different position within the mass spectrum as oxide, having M+16 mass.

3.2.1 Tunable mass bandpass and DRC parameters optimization

Optimization of reaction gas flow rate, dwell time, and rejection parameter q (RPq) were performed by using pools of serum samples treated with formic acid diluted with water (1 + 9) and spiked with 60 µg L⁻¹ of As, Fe, Sc and Ga. As shown in **Fig. 1**, signal to background ratios (SBR) for the respective oxides (M+16) improved as the RPq increased up to values between 0.6 and 0.7 approximately. Above 0.7, signal decreased suddenly as a consequence of a poor ion transmission. Addressing selection of best reaction gas flow rate,

FeO⁺ and ScO⁺ oxides show relatively increased background signal above 0.5 mL min⁻¹, which is not the case of AsO⁺ and GaO⁺; these present good SBR from 0.5 to 2 mL min⁻¹, as seen in **Fig. 2**. It has been noticed that choosing different gas flow rates for each element produces data scattering. This fact is probably due to that the constant changes in the gas flow rate from analyte to analyte prevents the reaction cell from reaching certain stability in terms of oxygen concentration. As a result of these studies, the O₂ flow rate was set at two levels: 0.25 mL min⁻¹ for Fe and Ga, and 1.25 mL min⁻¹ for As and Ga.

Although the mentioned parameters were optimized, no satisfactory precision was achieved until higher dwell times were considered. Thus dwell time selection was carried out aiming to reduce the relative standard deviation (RSD) values for each oxide. The obtained outcomes indicated that most elements needed at least 100 ms dwell time to reach adequate precision (**Fig. 3**).

3.2.2 DRC oxides formation efficiency

Further insights of analytes behavior in the reaction cell was performed assessing the metal-oxide (MO⁺) to metal (M⁺) signals ratios versus the oxygen gas flow rate input (**Fig. 4**). In the case of Ga and As, the MO⁺/M⁺ ratio decreased as long as the oxygen flow incremented, but GaO⁺ presence remains stronger than AsO⁺ from 0.5 L min⁻¹ ahead though. Ratios lower than 1 were observed for Fe in the conditions under study. In spite of this last, it was preferred using MO⁺ instead of M⁺ considering the SBR values obtained for all analytes.

3.3 Analytical figures of merits

The analytical performance was evaluated for the proposed method. Limits of detection (LOD) were calculated as three times the standard deviation of ten replicate lectures of the blank. Both LOD values and correlation coefficients (R^2) are summarized in **Table 3**.

The calibration strategy was also evaluated. It was experimentally corroborated that despite aqueous calibration could be applied for the majority of the analytes, the best recoveries were obtained when samples were compared with calibration standards prepared with formic acid (matrix matching approach).

3.4 Validation and application to real samples

In order to check the accuracy, the proposed method was applied to a serum standard reference material, and the results are presented in **Table 4**. Good agreement with Mn, Mo, Cd, Co, Cu, Zn, Se, Rb, Cs, As certified levels was achieved. Regarding Li, Be, B, Ge, Sr, Pd, Ag, Sn, Te, Ba, Os, Sc, Ga, Pb, and Bi neither reference values nor reported concentration have been informed in the SRM.

In addition, the proposed methodology was applied to a series of pooled serum samples where normal values for each analyte were expected. This study was performed to evaluate those analytes which reference values were not available. Spiked samples were thus analyzed with and the recoveries were calculated. The results are summarized in **Table 5**.

4. Conclusions

A large set of elements was determined in human serum by DRC-ICPMS. This was carried out through a novel strategy of sample treatment with formic acid. The optimization of serum preparation enabled its direct introduction and quantification via calibration with aqueous standards. The proposed method showed a satisfactory performance of the

dynamic reaction cell eliminating spectral interferences by using only oxygen as reaction gas to form elemental oxides.

In addition to the above mentioned advantages, further insights are operational short times and small amount of sample needed, facts that make this method as a valuable tool in fields of elemental research related to human physiology.

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Table1 Instrument settings and data acquisition parameters for DRC-ICPMS

Sample uptake rate ($\mu\text{L min}^{-1}$)	1000
Sample introduction	nebulizer model PFA-ST, coupled to a quartz cyclonic spray chamber with internal baffle and drain line, cooled with the PC ³ system from ESI (Omaha – NE, USA)
RF power (W)	1100
Gas flow rates (L min^{-1})	Plasma, 13.5; auxiliary, 1.2; nebulizer, 0.85
Interface	Ni cones (sampler and skimmer)
Cell gas A	$^{45}\text{Sc}^{16}\text{O}$, $^{69}\text{Ga}^{16}\text{O}$, $^{75}\text{As}^{16}\text{O}$, $^{57}\text{Fe}^{16}\text{O}$; reaction gas O_2
Standard mode	^7Li , ^9Be , ^{11}B , ^{55}Mn , ^{59}Co , ^{60}Ni , ^{63}Cu , ^{66}Zn , ^{74}Ge , ^{82}Se , ^{85}Rb , ^{88}Sr , ^{98}Mo , ^{106}Pd , ^{107}Ag , ^{111}Cd , ^{118}Sn , ^{130}Te , ^{133}Cs , ^{138}Ba , ^{192}Os , ^{205}Tl , ^{208}Pb , ^{209}Bi
Scanning mode	Peak hopping
Dwell time (ms)	30 in standard mode
Number of replicate	10

Table 2 Isotopes and major potential interferences

Isotope	Interferences
^{45}Sc	$^{29}\text{Si}^{16}\text{O}$, $^{13}\text{C}^{16}\text{O}^{16}\text{O}$, $^{12}\text{C}^{16}\text{O}^{16}\text{O}^1\text{H}$, $^{15}\text{N}^{14}\text{N}^{16}\text{O}$
^{75}As	$^{59}\text{Co}^{16}\text{O}$, $^{35}\text{Cl}^{40}\text{Ar}$, $^{39}\text{K}^{36}\text{Ar}$
^{56}Fe	$^{40}\text{Ar}^{16}\text{O}$, $^{40}\text{Ca}^{16}\text{O}$
^{69}Ga	$^{53}\text{Cr}^{16}\text{O}$, $^{29}\text{Si}^{40}\text{Ar}$, $^{51}\text{V}^{18}\text{O}$

Table 3. Figures of merit for the trace elements determination in serum samples treated with formic acid.

Analyte	Isotope (a.m.u.) ^b	Limit of detection ($\mu\text{g L}^{-1}$) ^c	Correlation Coefficient (R^2)
Li	7.016	0.05	0.999828
Be	90.122	0.02	0.999821
B	11.0093	0.06	0.999543
Mn	54.9381	0.03	0.999905
Co	58.9332	0.004	0.999945
Ni	59.9332	0.02	0.999963
Cu	62.9298	0.08	0.999962
Zn	65.926	0.1	0.999821
Ge	73.9219	0.009	0.999817
Se	81.9167	0.06	0.999721
Rb	84.9117	0.005	0.999951
Sr	87.9056	0.01	0.999944
Mo	97.9055	0.01	0.999905
Pd	105.903	0.01	0.999801
Ag	106.905	0.007	0.999753
Cd	110.904	0.007	0.999805
Sn	117.902	1	0.999902
Te	129.907	10	0.999878
Cs	132.905	0.002	0.999944
Ba	137.905	0.02	0.999303
Os	191.962	0.002	0.999767
Tl	204.975	0.004	0.999935
Pb	207.977	0.005	0.99976
Bi	208.98	0.004	0.99973
Sc ^a	60.9559	0.06	0.999482
Ga ^a	84.9257	0.003	0.999933
As ^a	90.9165	0.08	0.999655
Fe ^a	71.9354	0.5	0.998181

^aMeasured at $M+16$ m/z (as MO^+)^bTaken from Coursey et.al.³⁴^c3 sigma criterion.

Table 4 Determined and certified values for SRM NIST 1598a (n=3) (sample treated with formic acid).

Element	Proposed method ($\mu\text{g L}^{-1}$)	Certified value ($\mu\text{g L}^{-1}$)
Li	2.20 ± 0.02	n.i.
Be	< LOD	n.i.
B	< LOD	n.i.
Mn	2.20 ± 0.01	1.78 ± 0.33
Co	1.150 ± 0.259	1.24 ± 0.07
Ni	< LOD	0.94 ± 0.18
Cu	1536.99 ± 11.46	1580 ± 90
Zn	859.8 ± 45.5	880 ± 24
Ge	0.025 ± 0.835	n.i.
Se	154.50 ± 20.74	134.4 ± 5.8
Rb	283.238 ± 9.765	274 ± 19
Sr	53.13 ± 1.97	n.i.
Mo	3.17 ± 0.01	5.5 ± 1.0
Pd	4.37 ± 0.04	n.i.
Ag	3.978 ± 0.020	n.i.
Cd	0.052 ± 0.014	0.048 ± 0.004
Sn	< LOD	n.i.
Te	2.63 ± 2.07	n.i.
Cs	0.74 ± 0.32	0.64 ± 0.10
Ba	< LOD	n.i.
Os	0.78 ± 0.01	n.i.
Tl ^a	< LOD	0.033
Pb	0.950 ± 0.003	n.i.
Bi	0.100 ± 0.001	n.i.
Sc	79.35 ± 0.29	n.i.
Ga	130.567 ± 0.221	n.i.
As ^a	0.37 ± 0.06	0.3
Fe	1590.0 ± 71.0	1680.0 ± 60.0

n.i.: not informed

<LOD: below limits of detection

^aprecision data of SRM not available

Table 5 Recovery study of elements in human serum samples*

Element	Base ($\mu\text{g L}^{-1}$)	Added ($\mu\text{g L}^{-1}$)	Found ($\mu\text{g L}^{-1}$)	Recovery (%)
Li	0.04 ± 0.05	10	11.07 ± 0.78	110
Be	<LOD	10	10.29 ± 0.51	103
B	0.41 ± 0.59	10	11.67 ± 0.15	113
Mn	0.06 ± 0.04	10	9.66 ± 0.04	96
Co	<LOD	10	9.868 ± 0.154	99
Ni	<LOD	10	9.59 ± 0.19	96
Cu	30.05 ± 1.73	10	40.83 ± 0.75	108
Zn	21.5 ± 0.9	20	41.5 ± 0.2	100
Ge	<LOD	10	9.827 ± 0.193	98
Se	2.00 ± 0.66	10	13.11 ± 0.24	111
Rb	2.270 ± 0.092	10	13.523 ± 0.070	113
Sr	0.86 ± 0.07	10	12.17 ± 0.16	113
Mo	0.06 ± 0.04	20	21.38 ± 0.31	107
Pd	0.09 ± 0.12	20	22.08 ± 0.35	110
Ag	0.079 ± 0.070	20	21.198 ± 0.860	106
Cd	0.001 ± 0.011	10	9.886 ± 0.409	99
Sn	<LOD	5	4 ± 3	84
Te	<LOD	20	17 ± 14	83
Cs	0.018 ± 0.013	10	10.765 ± 0.124	107
Ba	<LOD	20	22.21 ± 0.74	111
Os	0.016 ± 0.008	10	10.639 ± 0.067	106
Tl	<LOD	20	19.515±0.515	98
Pb	0.019 ± 0.011	20	19.115±0.459	95
Bi	0.002 ± 0.004	20	19.048±0.290	95
Sc	1.59 ± 0.89	5	6.25±0.47	93
Ga	2.611 ± 0.662	5	9.055±0.442	129
As	0.01 ± 0.18	5	4.49 ± 0.88	90
Fe	18.6 ± 1.2	5	24.2 ± 1.6	111

*recovery = [(found - base) / added] *100

Figures captions

Fig. 1. Effect of RPq value on oxide ion formation.

Fig. 2. Effect of oxygen gas flow rate on oxide ion formation.

Fig. 3. Dependence of reading precision with dwell time.

Fig. 4. MO^+ to M^+ ratio in terms of oxygen gas flow rate.

Graphical Abstract caption

Development of a novel method for elemental profile assessment based on the formic acid dissolution of human blood serum and its direct introduction into the DRC-ICPMS system.

FIGURE 1

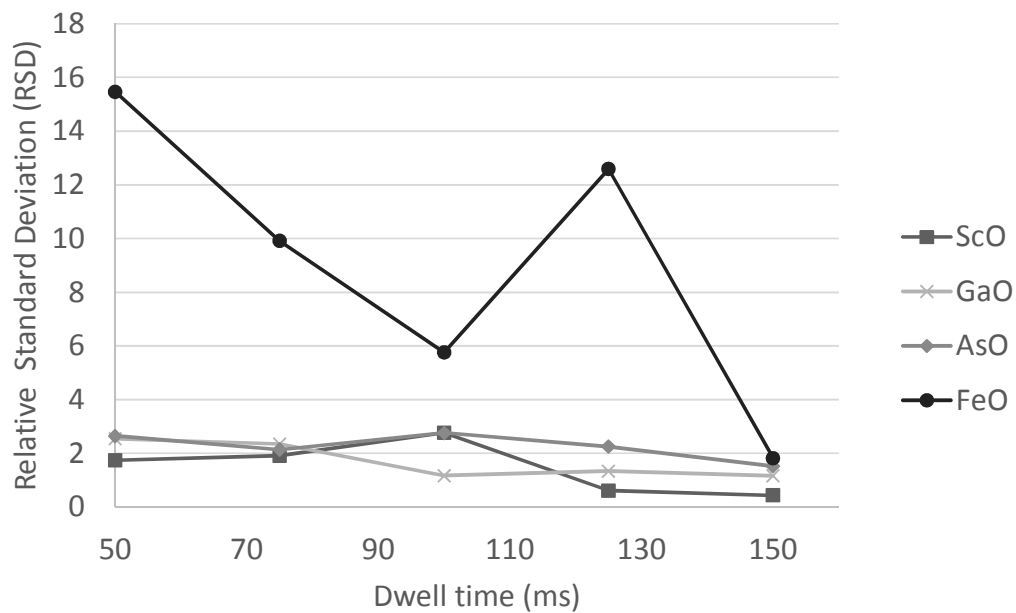


FIGURE 2

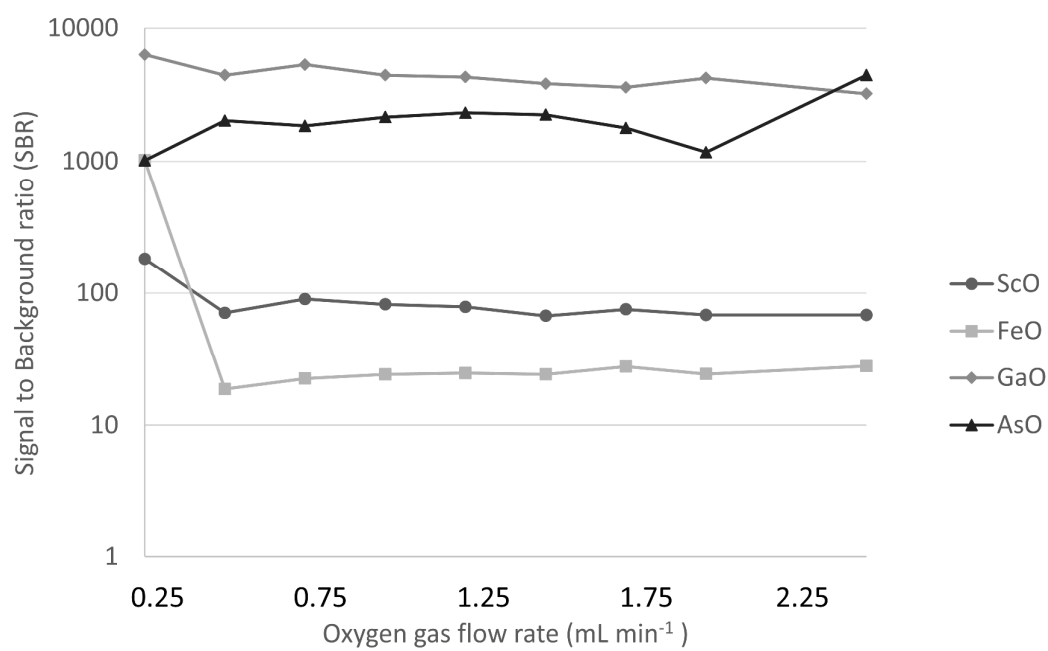


FIGURE 3

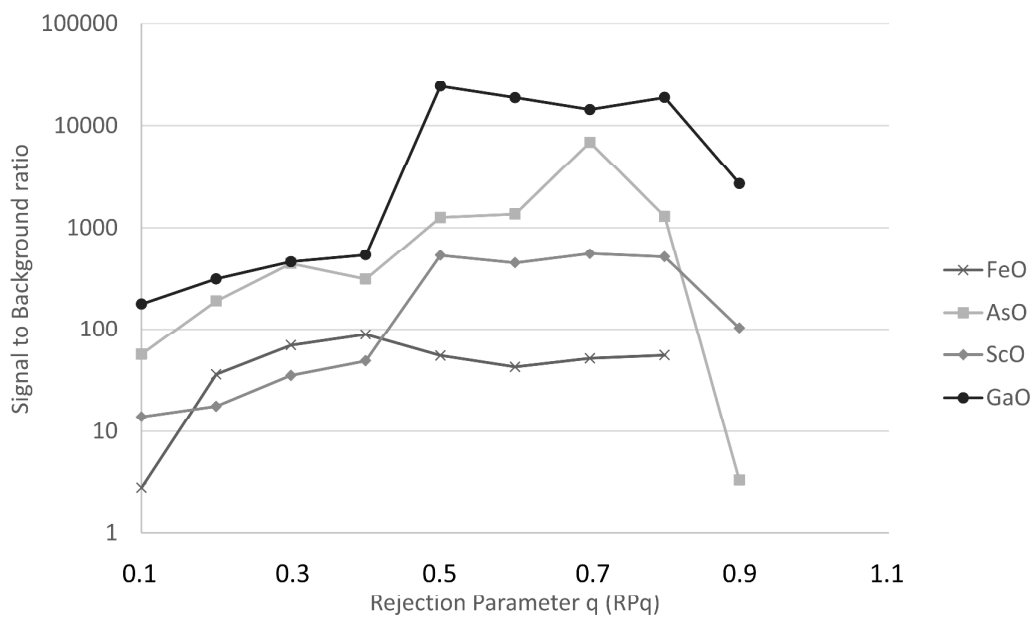
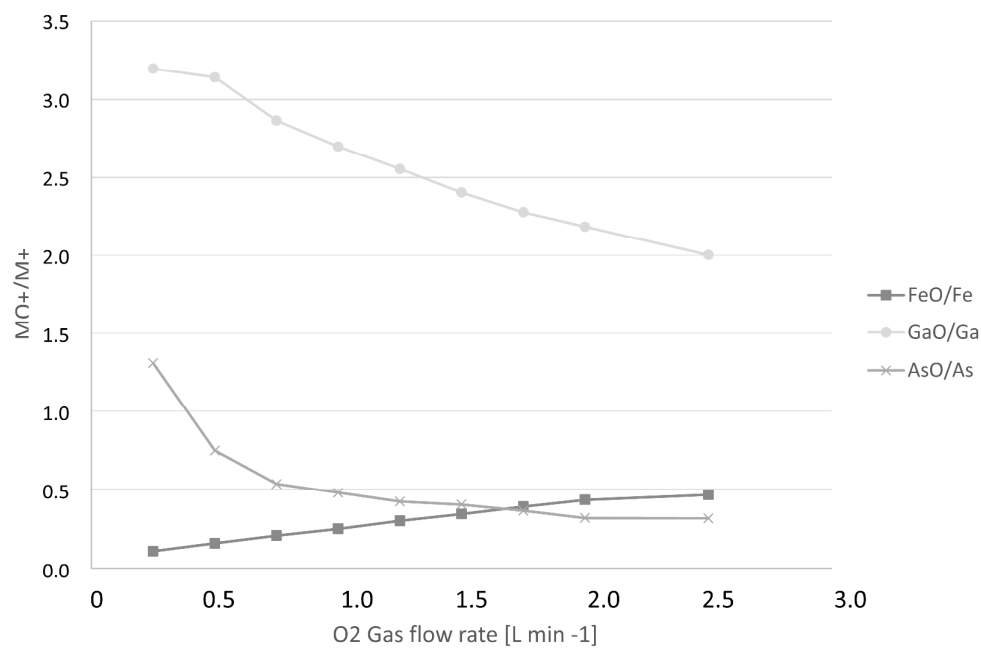
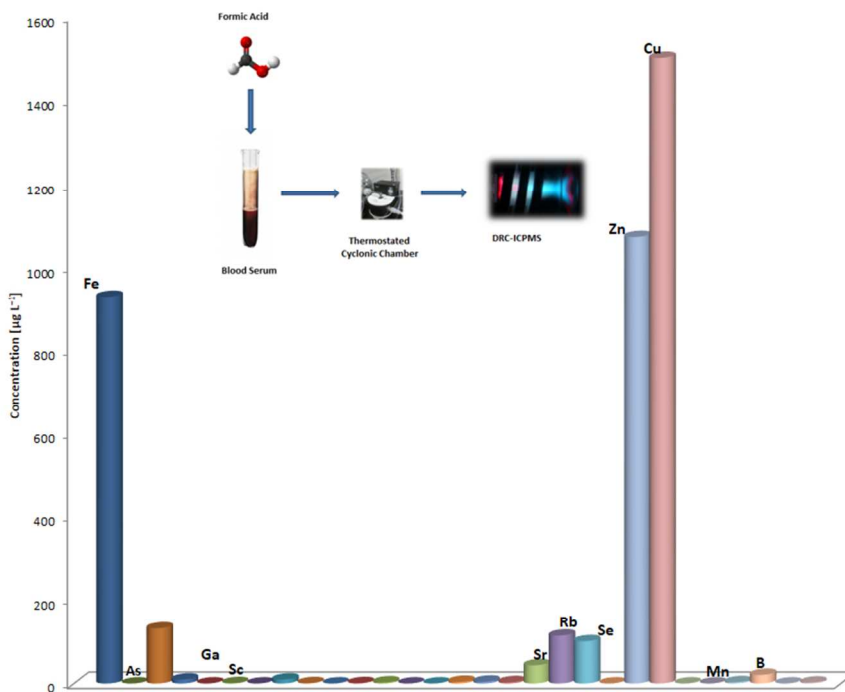


FIGURE 4





254x190mm (96 x 96 DPI)