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Clinical research

Analysis of whole blood using triple quadrupole inductively coupled plasma mass spectrometry (ICP-MS)

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Keywords

Biological samples, occupational exposure, clinical research, essential elements, quality control, toxic elements, triple quadrupole, TQ-O_2 mode, whole blood

Goal

To demonstrate a simple, fast, robust, and accurate analytical method for the determination of essential and toxic elements in whole blood using triple quadrupole ICP-MS.

Introduction

Essential and trace element analysis of biological samples provides significant information to support clinical research and forensic toxicology. For example, the exposure to toxic metals is a known risk factor for several diseases, whereas other elements, when present at appropriate levels, support regular biological function. Concentrations of elements within the blood of a population of subjects can correlate elemental exposure to geographical area, lifestyle, and socio-demographic factors.[1]

Inductively coupled plasma mass spectrometry (ICP-MS) is a highly sensitive technique that can work with low sample volumes while enabling high sample throughput and robust analysis even in the most demanding sample types. At the same time, it allows for the determination of a wide range of elements. These advantages make ICP-MS an attractive technique for the field of clinical research and occupational exposure analysis.

However, the analysis of samples containing higher levels of salts and biomolecules, such as proteins or metabolites is a known challenge in ICP-MS analytical techniques. The complexity of the sample matrix can significantly affect the sensitivity of the instrument, cause intensity fluctuation of the internal standard (suppression and drift), and lead to increased system maintenance with unwanted downtime due to obstruction of the interface cones, torch, and injector, or the nebulizer. In addition, the development of a multi-element method is challenging due to the wide concentration ranges that need to be covered across essential and toxic elements and the wide range of potential interferences from the sample matrix. These complex prerequisites often mean that triple quadrupole ICP-MS instruments are the best choice for analysis.

This application note focuses on the development of a fast, robust, and accurate method for the analysis of major, essential, and other trace elements in whole blood using the Thermo Scientific™ iCAP™ MTX ICP-MS. To demonstrate accuracy and precision, certified reference materials were analyzed together with a range of blood samples.

Experimental

Experimental optimization of the instrument parameters

An iCAP MTX ICP-MS, operated together with a Thermo Scientific™ iSC-65 Autosampler, was used for all analyses. The sample introduction system consisted of a Peltier-cooled (2.7 °C), baffled PFA cyclonic spray chamber (Savillex, Eden Prairie, MN, USA), PFA concentric nebulizer (Savillex), and PLUS torch with a 2.5 mm i.d. removable quartz injector. The built-in argon humidifier was used for moisturizing the nebulizer gas to prevent salt deposit on the nebulizer tip. To further increase uptime of the instrument, intelligent matrix handling was used, a unique feature of the Thermo Scientific™ iCAP™ MX Series ICP-MS instruments to reduce exposure of instrument components to sample matrix during sample uptake and wash.

In addition to the use of O_2 as a reactive gas in triple quadrupole mode for highly interfered analytes such as sulfur, phosphorous, arsenic, and selenium, the instrument was also operated in single quadrupole mode using helium and kinetic energy discrimination (KED) for interference-free analysis of other analytes over the full mass range. Table 1 summarizes the instrument configuration and analytical parameters.

The selection of the most appropriate isotopes per analyte, as well as the optimum analysis conditions (i.e., KED mode versus reactive gas, on mass mode versus mass shift reaction mode) was automatically recommended by the Reaction Finder Method Development Assistant available in the Thermo Scientific™ Qtegra™ Intelligent Scientific Data Solution™ (ISDS) Software. Measurement modes were optimized using the provided autotune procedures.

The iSC-65 autosampler allowed for the use of Step Ahead functionality to reduce the overall measurement time per sample and increase the productive time of the instrument.

Table 1. Instrument configuration and operating parameters

Parameter	Value (general analysis)
Nebulizer	PFA concentric nebulizer, 400 µL·min^{-1}
Peristaltic pump tubing	PVC orange-yellow tubing, 0.51 mm i.d.
Peristaltic pump speed	40 rpm
Humidifier	On
Spray chamber	PFA cyclonic, cooled at 2.7° C
Torch	PLUS torch
Injector	2.5 mm i.d., Quartz
Interface	Nickel sampler and skimmer cone
Plasma power	1,550 W
Nebulizer gas	0.998 L·min^{-1}

QCell setting	He KED	TQ-O_2
Qcell gas flow	100% He 4.2 mL·min^{-1}	100% O_2 0.32 mL·min^{-1}
CR bias	-21 V	-6.3 V
Q3 bias	-18 V	-12 V
Scan setting	0.1 s dwell time, 5 sweeps, 3 main runs	
Analysis time per sample	Total 3 min 14 s: including uptake (40 s) and wash out (30 s), Step Ahead (20 s)	

Sample preparation

Pre-cleaned (72 hours in 0.25% HNO_3 (Optima™ grade, Fisher Chemical™)) polypropylene bottles were used for the preparation of all blanks, standards, and samples.

The certified reference materials (Seronorm™ Trace Elements in Whole blood L-1, L-2 and L-3, SERO, Norway) and three different types of whole blood, collected from a healthy human volunteer, a horse, and a pig were gravimetrically diluted 50-fold with 0.01% Triton™ X-100, (Laboratory grade, Sigma-Aldrich), 0.05% NH_4OH, (Optima™ grade, Fisher Chemical™), 0.02% EDTA, (99.995% Ethylenediaminetetraacetic acid, Sigma-Aldrich) and 0.5% m/m nitric acid (Optima™ grade, Fisher Chemical™). A calibration blank, a series of standards, and a quality control (QC) sample were prepared using the same procedure.

The elements and final concentrations are shown in Table 2. All samples and standards were spiked with an internal standard mix (100 µg·L^{-1} Sc, Ge, and 10 µg·L^{-1} Y, Rh, and Ir), and 1,000 µg·L^{-1} gold was spiked for the amalgamation with mercury to prevent volatilization and to avoid carry over and memory effects.

Table 2. Summary of the concentration details of the standard calibration, CCV (continuing calibration verification. All numbers are shown in $\mu g \cdot L^{-1}$.

Standard group	STD-1	STD-2	STD-3	STD-4	STD-5	STD-6	STD-7	QC (CCV)
Al, As, Ag, Ba, Bi, Co, Cr, Ni, V, U, Pb, Mn, Ga, Tl, Se, Cd, In	0.002	0.025	0.05	0.2	1	10	50	0.2
Na, Mg, Fe, Si, P, K, Ca, S	200	1,000	10,000	50,000	-	-	-	1,000
Mo, Nb, Re, Ta, Ti, Ze, W	0.02	0.1	1	5	10	-	-	0.1
Sn, Sb, Pt	0.01	0.05	0.1	-	-	-	-	0.05
Hg, B, Li, Be	0.1	0.5	1	-	-	-	-	0.5
Cu, Zn, Rb, Sr	0.05	0.2	1	10	50	200	-	10

Results and discussion

Sensitivity and linearity

Table 3 summarizes the analysis conditions, instrument detection limits (IDLs), method detection limits (MDL) obtained, together with the coefficient of determination (R^2) for all 43 elements analyzed in this study. The correlation coefficients (R^2) obtained for all analytes were found to be greater than 0.9995, which suggests excellent linear response for the established concentration range for each analyte. The IDLs were calculated as three times the standard deviation of ten replicate measurements of the calibration blank. MDLs for all 43 elements measured are based on the instrumental detection limits summarized above but include the dilution factor 50, incurred during the sample preparation process.

Table 3 (part 1). Summary of analysis mode, and calibration results, R^2, LODs, and MDLs for all analytes. All numbers are shown in $\mu g \cdot L^{-1}$.

	Mode	Q3 analyte	Q1 Resolution	Q3 Resolution	Internal standard	R^2	LOD	MDL
^{7}Li	TQ-O_2	^{7}Li	High	Normal	Sc	>0.9999	0.009	0.43
^{9}Be	TQ-O_2	^{9}Be	High	Normal	Sc	>0.9999	0.014	0.71
^{11}B	TQ-O_2	^{11}B	High	Normal	Sc	0.9999	0.068	3.41
^{23}Na	He KED	-	-	Normal	Sc	>0.9999	0.635	31.8
^{24}Mg	He KED	-	-	Normal	Sc	>0.9999	0.049	2.43
^{27}Al	TQ-O_2	^{27}Al	iMS	Normal	Sc	0.9999	0.016	0.81
^{28}Si	TQ-O_2	$^{28}Si.^{16}O$	High	High	Sc	>0.9999	0.173	8.65
^{31}P	TQ-O_2	$^{31}P.^{16}O$	High	High	Sc	0.9999	0.270	13.5
^{33}S	TQ-O_2	$^{33}S.^{16}O$	High	High	Sc	0.9999	7.223	361.2
^{39}K	TQ-O_2	^{39}K	iMS	Normal	Sc	>0.9999	0.102	5.10
^{45}Sc	He KED	-	-	Normal	Internal standard			
^{45}Sc	TQ-O_2	$^{15}Sc.^{16}O$	High	High	Internal standard			
^{44}Ca	He KED	-	-	Normal	Sc	0.9999	1.6	79.6
^{49}Ti	TQ-O_2	$^{49}Ti.^{16}O$	High	Normal	Sc	0.9998	0.008	0.52
^{51}V	TQ-O_2	$^{51}V.^{16}O$	High	Normal	Sc	>0.9999	0.001	0.04
^{52}Cr	TQ-O_2	$^{52}Cr.^{16}O$	High	Normal	Sc	0.9998	0.013	0.66
^{55}Mn	TQ-O_2	^{55}Mn	High	Normal	Sc	0.9995	0.004	0.20
^{57}Fe	He KED	-	-	Normal	Sc	>0.9999	2.4	118.0
^{59}Co	TQ-O_2	^{59}Co	High	Normal	Ge	>0.9999	0.001	0.03
^{60}Ni	He KED	-	-	Normal	Ge	>0.9999	0.006	0.32
^{63}Cu	TQ-O_2	^{63}Cu	iMS	Normal	Ge	>0.9999	0.009	0.47
^{66}Zn	TQ-O_2	^{66}Zn	iMS	Normal	Ge	0.9999	0.035	1.76
^{71}Ga	He KED	-	-	Normal	Ge	>0.9999	0.005	0.24
^{72}Ge	He KED	-	-	Normal	Internal standard			
^{72}Ge	TQ-O_2	^{72}Ge	iMS	Normal	Internal standard			
^{75}As	TQ-O_2	$^{75}As.^{16}O$	High	Normal	Ge	0.9994	0.010	0.48
^{80}Se	TQ-O_2	$^{80}Se.^{16}O$	iMS	Normal	Ge	>0.9999	0.010	0.50

Table 3 (part 2). Summary of analysis mode, and calibration results, R^2, LODs, and MDLs for all analytes. All numbers are shown in $\mu g \cdot L^{-1}$.

	Mode	Q3 analyte	Q1 Resolution	Q3 Resolution	Internal standard	R^2	LOD	MDL
^{85}Rb	TQ-O_2	^{85}Rb	iMS	Normal	Y	0.9997	0.001	0.03
^{88}Sr	He KED	-	-	Normal	Y	>0.9999	0.003	0.14
^{89}Y	He KED	-	-	Normal	Internal standard			
^{89}Y	TQ-O_2	$^{89}Y.^{16}O$	iMS	Normal	Internal standard			
^{90}Zr	TQ-O_2	$^{90}Zr.^{16}O$	iMS	Normal	Y	0.9999	0.002	0.12
^{93}Nb	He KED	-	-	Normal	Y	0.9998	0.000	0.02
^{95}Mo	He KED	-	-	Normal	Y	0.9999	0.008	0.42
^{103}Rh	He KED	-	-	Normal	Internal standard			
^{103}Rh	TQ-O_2	^{103}Rh	iMS	Normal	Internal standard			
^{107}Ag	TQ-O_2	^{107}Ag	iMS	Normal	Rh	>0.9999	0.002	0.12
^{111}Cd	TQ-O_2	^{111}Cd	iMS	Normal	Rh	>0.9999	0.009	0.43
^{115}In	He KED	-	-	Normal	Rh	0.9999	0.001	0.06
^{115}In	TQ-O_2	^{115}In	iMS	Normal	Rh	>0.9999	0.001	0.05
^{118}Sn	TQ-O_2	^{118}Sn	iMS	Normal	Rh	>0.9999	0.001	0.07
^{121}Sb	TQ-O_2	^{121}Sb	iMS	Normal	Rh	0.9988	0.004	0.20
^{137}Ba	He KED	-	-	Normal	Rh	>0.9999	0.008	0.40
^{181}Ta	He KED	-	-	Normal	Ir	0.9996	0.000	0.01
^{182}W	He KED	-	-	Normal	Ir	0.9999	0.000	0.02
^{185}Re	He KED	-	-	Normal	Ir	0.9998	0.000	0.02
^{193}Ir	He KED	-	-	Normal	Internal standard			
^{193}Ir	TQ-O_2	^{193}Ir	iMS	Normal	Internal standard			
^{195}Pt	TQ-O_2	^{195}Pt	iMS	Normal	Ir	0.9998	0.002	0.12
^{202}Hg	He KED	-	-	Normal	Ir	0.9999	0.002	0.12
^{205}Tl	He KED	-	-	Normal	Ir	0.9997	0.001	0.04
^{208}Pb	He KED	-	-	Normal	Ir	>0.9999	0.001	0.05
^{209}Bi	He KED	-	-	Normal	Ir	>0.9999	0.001	0.03
^{238}U	He KED	-	-	Normal	Ir	>0.9999	0.000	0.02

Accuracy and polyatomic interference removal for the analysis of whole blood

The process of interference removal using oxygen is shown in Figure 1 using arsenic and titanium as examples. The analyte of interest reacts with oxygen and forms a molecular ion with a new mass-to-charge ratio (referred to as a mass-shift reaction), and the previously isobaric (i.e., having the same nominal mass) interference does not react in a similar way and can therefore be eliminated using the third quadrupole of the system. The first quadrupole provides an additional mass filtration before the collision/reaction cell, so that unwanted side reactions with other components present in the ion beam are effectively suppressed.

One element often analyzed in patients' samples is titanium, which is monitored to track potential degradation of titanium-based orthopedic and dental implants. Following recent research on the possible carcinogenic effects of titanium dioxide, the fate of titanium in the human body has become a growing area of clinical research focus. Due to the high concentrations of calcium in biological samples, the main isotope of titanium (^{48}Ti, 73.7% abundant in nature) has an isobaric interference with ^{48}Ca. To detect titanium at relevant levels, often a mass shift reaction using NH_3 is applied, which selectively forms $^{48}TiNH(NH_3)_3$, detectable at *m/z* 114, whereas ^{48}Ca does not react. The use of NH_3, however, is not always possible due to safety restrictions within the laboratory. In this study, a less abundant isotope of titanium was monitored (^{49}Ti, 5.41% abundant in nature) using TQ-O_2 mode. This allowed comparable detection limits to be achieved.[3]

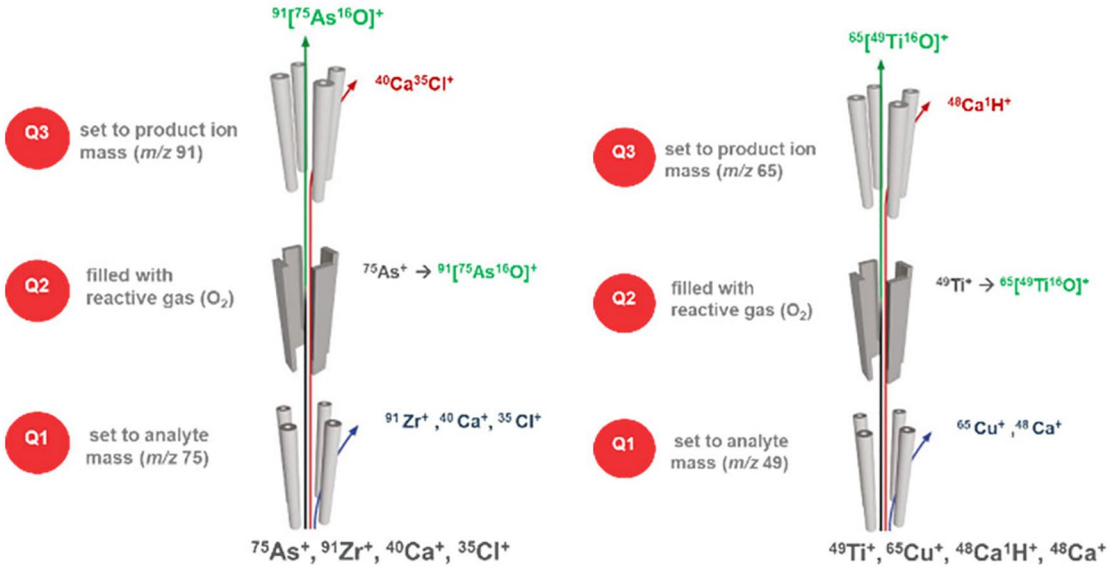

Figure 1. Schematic showing the use of TQ-O_2 mode and a mass shift reaction for interference free detection of arsenic (As) and titanium (Ti)

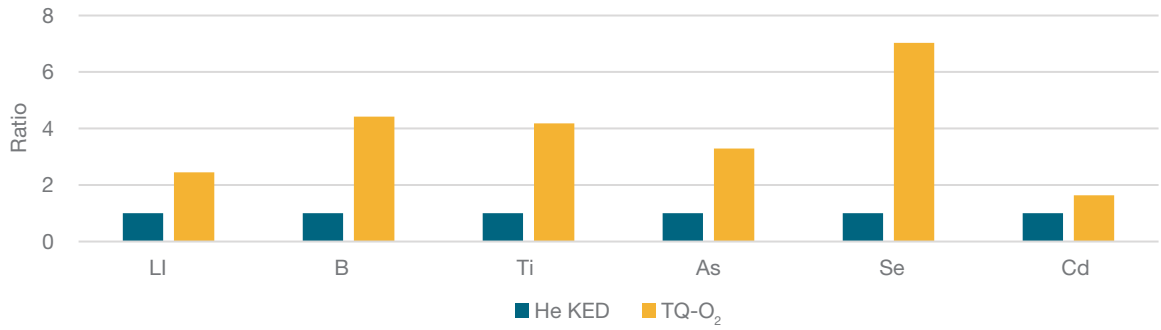

Figure 2. Sensitivity comparison between He KED (normalized as 1) and TQ-O_2 mode for selected analytes

Achieving high sensitivity is important especially when analyzing toxic elements in the diluted whole blood samples, in which these elements are often present in ultra-trace amounts. The use of collision cell technology is often associated with a loss of sensitivity in the low mass range, which is often the reason for measuring analytes such as lithium or beryllium using “No gas” or “Standard” mode. However, as opposed to the use of KED mode, reactive modes generally apply a negative bias potential at the outlet of the collision/reaction cell (CRC), so that some of the ion losses caused by collisions with gas molecules can be overcome.

The absolute sensitivity is typically not negatively affected, or even may be significantly enhanced when using TQ-O_2 mode, so that low mass analytes detection limits in the sub ng·L^{-1} range can be achieved (Figure 2).

The accuracy and precision of the analytical method was assessed by analyzing commercially available certified reference materials (CRMs) with different elemental concentration levels. The exact concentrations in each level are summarized in Table 4. The results obtained show that the calculated concentrations of the target elements matched the certified values, demonstrating the accuracy of method. For all reference materials, nine individual samples were measured so that the method was also demonstrated to deliver excellent precision (Table 4). In addition to the CRMs, three different blood samples were analyzed as technical replicates to assess the repeatability of the results over longer analysis times.

Table 4. Quantitative results obtained for the CRM whole blood samples. Analyte concentrations are reported as $\mu g \cdot L^{-1}$. All numbers annotated with * are known reference values (expected values).

	MDL	CRM L1 values	Measured L1 (n=9)	L1 RSD (%)	CRM L2 values	Measured L2 (n=9)	L2 RSD (%)	CRM L3 values	Measured L3 (n=9)	L3 RSD (%)
^{7}Li	0.43	0.37	0.45	14.3	11.00	11.49	4.0	0.73*	0.57	8.0
^{9}Be	0.71	<0.02	<MDL	N.D.	5.50	5.49	15.1	10.10	10.84	10.6
^{11}B	3.41	-	87.4	1.2	-	44.1	4.4	-	321.1	1.1
^{23}Na	31.8	1,598,000*	1,609,898	1.1	1,618,000*	1,582,356	0.7	1,512,000*	1,545,066	1.0
^{24}Mg	2.43	152,000	16,210	0.7	41,000	41,838	0.3	136,000*	14,737	0.5
^{27}Al	0.81	10.40	13.76	1.8	57.00	52.72	0.4	88.00	89.53	1.3
^{28}Si	8.65	-	1701	2.0	-	1,841	4.3	-	2,626	2.8
^{31}P	13.5	203,000*	201,616	0.7	200,000*	194,496	0.2	187,000*	192,525	1.2
^{33}S	361.2	957,000*	990,933	0.8	984,000*	978,749	0.4	921,000*	916,908	1.4
^{39}K	5.10	1,089,000*	1,153,957	1.4	1,078,000*	1,121,154	1.0	1,037,000*	1,098,131	2.0
^{44}Ca	79.6	158,000	17,205	1.2	56,000	58,192	0.6	141,000*	16182	0.6
^{49}Ti	0.52	-	5.34	6.9	-	3.33	4.7	-	14.96	3.8
^{51}V	0.04	0.26	0.26	1.5	3.10	3.34	1.1	4.40	4.53	1.7
^{52}Cr	0.66	0.77	0.81	4.9	10.00	9.71	4.9	35.50	34.65	1.2
^{55}Mn	0.20	19.70	21.10	0.8	24.20	21.62	0.3	33.30	31.49	1.4
^{57}Fe	118.0	334,000*	327,397	0.7	335,000*	326,225	0.6	300,000*	288,596	0.8
^{59}Co	0.03	0.22	0.31	3.8	5.00	4.87	0.3	10.30	10.22	0.6
^{60}Ni	0.32	2.13	3.58	2.5	9.20	8.50	2.0	11.00	11.48	1.0
^{63}Cu	0.47	640	601	0.3	940	842	0.2	2,080	1,938	0.1
^{66}Zn	1.76	4,600	4,307	0.3	5,800	5,202	0.3	8,360	7,519	0.2
^{71}Ga	0.24	0.05*	<MDL	N.D.	0.04*	<MDL	N.D.	0.04*	<MDL	N.D.
^{75}As	0.48	2.1	2.2	0.9	12.2	12.2	0.8	27.3	29.0	0.8
^{80}Se	0.50	69	67	0.1	144	126	0.1	198	223	0.0
^{85}Rb	0.03	1,420*	1,443	0.7	1,460*	1,406	0.3	1180*	1275	0.4
^{88}Sr	0.14	41.00	39.66	4.7	75.00	68.82	28.4	37.00	39.13	5.0
^{90}Zr	0.12	0.41*	0.34	15.2	0.28*	0.17	13.6	0.28*	0.33	12.8
^{93}Nb	0.02	0.03*	0.01	8.4	0.03*	0.02	2.4	0.04*	0.04	3.1
^{95}Mo	0.42	0.37	0.38	29.6	4.50	4.46	0.9	6.90	6.59	1.6
^{107}Ag	0.12	0.10	0.42	5.7	9.70	10.26	1.4	0.08	0.50	1.5
^{111}Cd	0.43	0.28	0.26	16.0	5.10	4.63	3.8	9.90	9.81	1.6
^{115}In	0.05	-	<MDL	2.0	-	0.03	0.4	-	0.07	0.6
^{118}Sn	0.07	0.2	0.2	3.0	4.7	4.0	0.6	9.9	9.5	0.3
^{121}Sb	0.20	3.3	2.8	0.3	22.3	18.9	1.0	21.9	18.4	0.3
^{137}Ba	0.40	427*	458	0.8	145*	153	1.6	557*	581	1.1
^{181}Ta	0.01	<0.001*	<MDL	N.D.	<0.001*	<MDL	N.D.	<0.001	<MDL	N.D.
^{182}W	0.02	-	<MDL	N.D.	-	<MDL	N.D.	-	<MDL	N.D.
^{185}Re	0.02	0.001*	<MDL	N.D.	0.0015	<MDL	N.D.	<0.001	<MDL	N.D.
^{195}Pt	0.12	0.004*	<MDL	N.D.	0.003*	<MDL	N.D.	0.01	<MDL	N.D.
^{202}Hg	0.12	1.57	1.57	1.8	16.60	14.79	1.3	25.80	22.0	1.4
^{205}Tl	0.04	0.01	<MDL	0.5	10.10	8.04	0.4	25.20	21.57	0.4
^{208}Pb	0.05	10.00	8.99	6.0	303	273	0.9	389	321	0.4
^{209}Bi	0.03	0.01	<MDL	1.8	4.90	4.69	1.8	47.00	41.54	2.2
^{238}U	0.02	0.13*	0.18	4.5	0.20*	0.25	5.2	0.12*	0.22	8.4

Some of the essential elements are found in high concentrations, however other commonly present metals such as vanadium, chromium, cobalt, arsenic, and selenium are typically found only in concentrations below 10 µg·L^{-1} in whole blood. However, there are many complex spectral interferences from the matrix, formed from elements such as sodium, magnesium, phosphorus, sulfur, potassium, calcium, and iron. These major elements generate different types of interferences, including oxides, isobaric interferences, or peak tailing for the target analyte. Thus, complete removal of these interferences is a key prerequisite to a successful method and was accomplished by using the TQ-O_2 mode, as demonstrated by the results.

Table 5 (next page) shows the results obtained for the three different whole blood samples and provides detailed information on the concentrations for both toxic and essential elements. Some analytes showed significant variation in the concentrations of toxic or essential elements between them. The capability of ICP-MS to provide fast and accurate data in a true multi-element analysis could significantly advance further research, for example in larger studies to assess biological variation or occupational health.

Evaluation of long-term robustness

To simulate high-throughput analysis of a large number of samples, a batch of samples containing the 50-fold diluted whole blood sample solutions previously analyzed were scheduled for analysis (Figure 3).

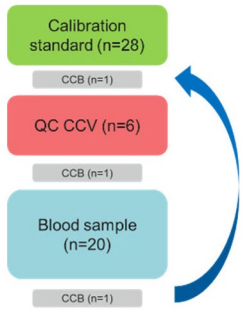

Figure 3. Schematic overview of the batch analyzed for testing the long-term performance of the proposed method. Nine blocks, containing 20 whole blood samples each, were analyzed.

After generating calibration standard curves, the batch contained several blocks of the whole blood samples together with the required QC checks. The total number of analyses was 287 (including 180 whole blood matrix samples and 28 calibrants and 54 QC checks), requiring a total analysis time of approximately 15 hours.

The regular CCV checks (n=9) indicated excellent recovery (within 88–124%) for all 43 elements. The iCAP MTX ICP-MS therefore allows for robust and reliable long-term analysis even for challenging matrix types like whole blood.

The response of the internal standards is shown in Figure 4. All internal standards showed reliable and predictable recovery (within approximately 75% to 112%) over the entire runtime of the batch, demonstrating robust analytical performance.

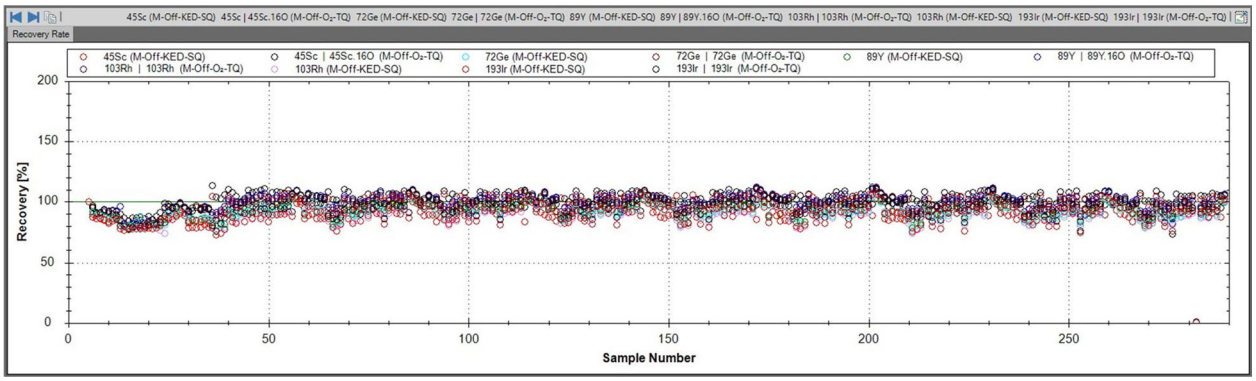

Figure 4. Response of the internal standards in a batch covering about ~15 hours of uninterrupted analysis of 287 samples

Table 5. Quantification results for different whole blood samples. All concentrations are reported as $\mu g \cdot L^{-1}$.

	MDL	Mean horse (n=9)	RSD (%)	Mean human (n=9)	RSD (%)	Mean pig n=9)	RSD (%)
^{7}Li	0.43	23.2	2.0	0.6	15.5	1.4	7.2
^{9}Be	0.71	<MDL	N.D.	<MDL	N.D.	<MDL	N.D.
^{11}B	3.41	56.8	8.8	37.7	5.2	47.8	2.5
^{23}Na	31.8	2,433,814	0.7	1,986,726	0.4	3,069,314	0.8
^{24}Mg	2.43	37,045	0.5	31,892	0.7	54,173	0.4
^{27}Al	0.81	5.0	11.3	5.0	4.7	8.4	5.2
^{28}Si	8.65	989.1	1.9	557.1	1.9	487.4	0.7
^{31}P	13.5	248,530	0.5	353,021.9	0.6	550,665	0.8
^{33}S	361.2	1,128,097	0.6	1,436,586	0.9	1,018,857	0.2
^{39}K	5.10	2,157,418	0.9	2,357,705	0.6	2,084,854	0.7
^{44}Ca	79.6	99,752	0.5	62,057	1.0	60,445	0.5
^{49}Ti	0.52	3.5	6.8	1.5	7.6	1.9	5.4
^{51}V	0.04	0.3	7.7	0.1	6.1	0.8	2.2
^{52}Cr	0.66	1.4	9.8	0.8	15.2	1.2	8.3
^{55}Mn	0.20	6.2	0.9	6.2	1.4	13.8	0.7
^{57}Fe	118.0	306,624	0.7	342,230	0.3	360,384	0.5
^{59}Co	0.03	0.6	2.2	0.6	1.2	0.2	5.7
^{60}Ni	0.32	0.9	11.4	2.7	3.6	<MDL	N.D.
^{63}Cu	0.47	787.5	0.3	1,127	0.3	1,061	0.4
^{66}Zn	1.76	1,998	0.3	4,476	0.3	3,089	0.3
^{71}Ga	0.24	<MDL	N.D.	<MDL	N.D.	<MDL	N.D.
^{75}As	0.48	0.6	0.5	5.0	1.0	<MDL	N.D.
^{80}Se	0.50	200.2	1.1	113.7	0.9	215.6	0.4
^{85}Rb	0.03	1,933	0.3	1,495	0.1	2,233	0.8
^{88}Sr	0.14	55.1	0.9	15.9	0.9	58.4	0.5
^{90}Zr	0.12	<MDL	N.D.	<MDL	N.D.	25.3	1.3
^{93}Nb	0.02	<MDL	N.D.	<MDL	N.D.	<MDL	N.D.
^{95}Mo	0.42	3.5	1.9	1.2	5.2	5.9	1.9
^{107}Ag	0.12	0.76	9.8	0.3	11.2	0.6	9.5
^{111}Cd	0.43	<MDL	N.D.	<MDL	N.D.	<MDL	N.D.
^{115}In	0.05	<MDL	N.D.	<MDL	N.D.	<MDL	N.D.
^{118}Sn	0.07	<MDL	N.D.	<MDL	N.D.	<MDL	N.D.
^{121}Sb	0.20	3.4	3.4	<MDL	N.D.	<MDL	N.D.
^{137}Ba	0.40	3.6	12.0	1.4	10.8	7.5	3.3
^{181}Ta	0.01	<MDL	N.D.	<MDL	N.D.	<MDL	N.D.
^{182}W	0.02	<MDL	N.D.	<MDL	N.D.	<MDL	N.D.
^{185}Re	0.02	<MDL	N.D.	<MDL	N.D.	<MDL	N.D.
^{195}Pt	0.12	<MDL	N.D.	<MDL	N.D.	<MDL	N.D.
^{202}Hg	0.12	0.5	3.8	1.1	2.3	0.5	2.4
^{205}Tl	0.04	<MDL	N.D.	<MDL	N.D.	<MDL	N.D.
^{208}Pb	0.05	2.9	5.5	5.7	0.9	1.5	3.5
^{209}Bi	0.03	<MDL	N.D.	<MDL	N.D.	<MDL	N.D.
^{238}U	0.02	<MDL	N.D.	<MDL	N.D.	0.1	7.7

Figure 5 shows an image of the sample and skimmer cone after aspirating over 1,000 whole blood samples tested in this study. No deposition of material on the cone surface was observed; thus, this analysis configuration enables the analysis of whole blood solutions over longer periods.

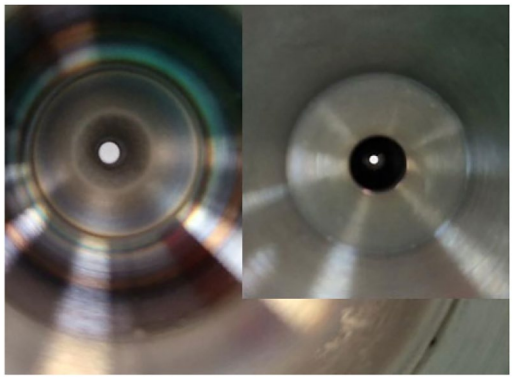

Figure 5. Sample (A) and skimmer (B) cone condition after running more than 1,000 whole blood samples

Conclusions

The iCAP MTX ICP-MS was employed to analyze 43 elements in whole blood samples. Among the analytes, several critical interferences can cause unexpected bias, which were investigated closely for effective and complete removal by means of selective collision / reaction cell reactions with oxygen. This analytical method was rigorously tested, and the results obtained clearly demonstrated the following analytical advantages:

- The combination of He KED and TQ-O_2 mode allows for high sensitivity analysis required for the accurate determination of the entire mass range (lithium to uranium), while effectively suppressing typical interferences.
- The developed method provides the required detection limits and a linear response for all analytes, which cover a concentration range of 8 orders of magnitude (from sub ng·L^{-1} to 50 mg·L^{-1}).
- The iSC-65 Autosampler equipped with the Step Ahead feature allowed for a 9% reduction of the total analysis time, and in combination with intelligent Matrix Handling, the analysis of whole blood could be carried out with improved productivity.
- The use of TQ-O_2 mode allowed removal of interferences of any kind, especially on key analytes such as common transition metals, and toxic/essential elements such as arsenic or selenium in the 50-fold diluted whole blood samples. This is proven by the excellent results obtained for the analysis of whole blood reference materials.
- The total analysis time was 3 min 14 s per sample (including uptake and wash time) for 43 elements (covering major, essential, and trace level analytes). This is specifically for large cohort studies, for example to screen exposure in a representative population. The analysis time could be further shortened with a discrete sampling valve.
- Robust and stable analytical performance was demonstrated over 15 hours of continuous acquisition of 287 samples by the iCAP MTX ICP-MS with excellent CCV results.

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