

Optimization of ICP-MS Analysis for Studying Matrix Effects in Biological Fluids

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This study examines the influence of matrix effects on the detection limits of individual components in inductively coupled plasma mass spectrometry (ICP-MS) analysis. A comparative evaluation of sample preparation techniques, including dilution and mineralization, was conducted to assess their effectiveness in mitigating matrix-related interferences. The investigation considered multiple elements in analytical solutions, revealing that a reduction in throughput within certain parts of the analyzer is associated with the narrowing of sampler and skimmer orifices due to the presence of organic solvents. To minimize the impact of organic components on analytical accuracy, two strategies were explored: microwave digestion and conventional digestion. While simple dilution offers specific advantages, oxidative mineralization was found to be the most effective approach for biological fluids such as whole blood, as it efficiently eliminates complex organic matrices and reduces biological hazards. Additionally, the potential application of internal standards for correcting results and mitigating matrix effects is discussed. These findings contribute to improving the accuracy and reliability of elemental analysis in complex matrices, benefiting both experimental analysts seeking enhanced data precision and medical professionals involved in restoring essential elements in patients undergoing dialysis.

Keywords: biological fluid, ICP-MS, spectral and non-spectral matrix effects, internal standard

Introduction

There is an increasing interest in medicine regarding the role of trace elements in the human body. An excess of toxic trace elements, along with a deficiency of essential trace elements in the diet, can lead to the development of various diseases [1]. These elements play a key role in enzymatic systems and are components of many proteins involved in regulating vital metabolic processes in the body.

Modern medical diagnostic methods, including inductively coupled plasma mass spectrometry (ICP-MS), actively investigate the relationship between the levels of trace elements in human tissues and biological fluids, as well as their role in increasing the risk of developing various diseases [2]. Due to its high sensitivity and ability to conduct multi-element analysis across a wide range of concentrations, ICP-MS currently holds a leading position in the field of elemental analysis of biological materials.

The method of inductively coupled plasma mass spectrometry (ICP-MS) is recognized as one of the most reliable analytical tools for addressing complex analytical challenges. Its main advantages include [3,4]. Over the past 10-15 years, numerous publications have emerged dedicated to the

development of analytical methodologies for various biological samples using ICP-MS [5,6]. Despite the existence of general methodological approaches for many types of samples, working with specific samples presents unique challenges related to both their composition and the conditions of their collection and preparation. For instance, the analysis of blood and urine from patients with renal failure, which is a focus of part of this work, is often complicated by difficulties in reproducible sample collection and the small volume of biological material.

The scientific novelty of this study lies in the proposal of new approaches to the analysis of matrix effects in biological fluids using ICP-MS. In contrast to traditional methods, this study showed that the use of a helium collision cell and optimization of sample preparation methods such as mineralization and simple dilution can significantly reduce spectral and non-spectral matrix interferences, improving the accuracy and reproducibility of the results.

Comparative analysis of different sample preparation methods (mineralization vs. dilution) and the use of an internal standard such as rubidium to correct for instability are important aspects that have not been sufficiently investigated in previous studies. For example, studies [5,6] demonstrated

the effectiveness of mineralization for blood analysis, but did not consider the effect of collision cells on improving accuracy at high concentrations of organic substances. In contrast to these works, our study focuses on the combined application of these methods to improve the quality of analysis in the complex matrices of biological fluids. In addition, this study also investigated the effect of oxygen addition on the analysis results, which have not been previously considered in such studies [7,8]. This discovery will allow optimization of ICP-MS methods for more accurate determination of trace elements in biological samples, which is important for medical diagnostics and monitoring of patient's health.

This article presents methodologies for determining chemical elements in concentration ranges from ng/L (ppb) to hundreds of µg/L (ppm) in biologically complex samples using ICP-MS. Various approaches to sample preparation, such as dilution and mineralization, are also discussed, along with measures to account for and eliminate matrix effects that may influence both the samples and the results of elemental analysis.

Experimental part

Measurements were performed on an Agilent Technologies 7700 inductively coupled plasma mass spectrometer (USA). The experiments were conducted in a stable operating mode of the instrument, as specified in Table 1 [9-12].

Table 1. Experimental mode.

Plasma, generator power, W	1450
Argon flow rate, l/min	1.2
Sample supply rate, l/min	1
Mass-spectrometer resolution, Da	0.2
Vacuum without plasma, Torr	$4 \cdot 10^{-4}$
Dynamic cells, gas	Helium
Time of measurement, s	0.1–0.5

Metrological characteristics of the proposed methodology: Detection Limit: 0.05 µg/L for copper, 0.1 µg/L for zinc. Linearity: Correlation $R^2 > 0.999$ in the range of 0.1 to 100 µg/L. Reproducibility: Relative standard deviation (RSD) of less than 3%. Detailed Metrological Characteristics: Quantification Limits (LOQ): 0.1 µg/L for copper, 0.2 µg/L for zinc. Linearity Test Conditions: Standard solutions at concentrations of 0.1, 1, 10, 50, and 100 µg/L. Reproducibility Verification Methods: Five independent measurements for each concentration with an RSD of less than 3%. Accuracy Verification: Analysis of a standard drinking water sample with a deviation of less than 2% from nominal value.

For sample mineralization, a microwave system "Speedwave Xpert" (Germany) was used, which allows for temperature control during operation and is equipped with small-volume vessels for working

with micro-samples. The system provides microwave radiation power of up to 2000 W (2×1000 W) and ensures uniform and precise heating according to the specified decomposition program, thanks to the use of two continuously adjustable magnetrons with a frequency of 2.45 GHz. In the study, dispensers with volumes of 100-1000 µl and 1-10 mL from manufacturers pipet4u and Eppendorf (Germany) were used, along with disposable tips and polypropylene tubes with volumes of 15 and 50 mL.

Comparative solutions were prepared by sequentially diluting a stock solution. The base standards used were solutions containing 68 elements at a concentration of 10 mg/L (produced by High Purity Standards, USA). To study the influence of matrix components, standard single-element solutions of Na, K, Ca, Mg, S, P, and Cl were employed. Internal standards were prepared based on standard solutions of Rh, In, Sc, and Ge (High Purity Standards, USA) at a concentration of 1 mg/L.

Sample mineralization and the preparation of calibration solutions were carried out using 65% nitric acid (HNO_3) and 30% hydrogen peroxide (H_2O_2) Suprapure (Merck, Germany). All solutions were diluted with deionized water with a specific resistance of 18.2 MΩ·cm. The accuracy of the instrument calibration was verified by analyzing a standard sample of drinking water.

Blood and urine samples were collected from patients aged 30 to 40 years suffering from kidney failure and regularly undergoing hemodialysis procedures. Disposable low-density polyethylene tubes were used for sample collection. Urine samples were preserved by adding nitric acid (HNO_3) at a ratio of 0.4 mL per 20 mL sample. The whole blood, being one of the most complex biological fluids, contains many both organic and inorganic compounds. A mixture of EDTA and nitric acid (HNO_3) was used for its preservation. Urine and blood samples were analyzed within a few days after collecting them. The dialysis solutions were prepared in 0.2% nitric acid.

Blood (0.5-1 mL) and urine (1-2 mL) samples were subjected to mineralization in a microwave using concentrated HNO_3 and H_2O_2 . The mineralization parameters are indicated in Table 2. Internal standards with element concentrations in the range of 20-50 µg/L were added to the prepared solutions intended for measurement.

Results and discussion

This study analyzed the content of several important elements in the initial dialysis solutions, as well as in the solutions obtained after dialysis from several patients. Using inductively coupled plasma mass spectrometry (ICP-MS), it was found that there are a number of limitations on the content of organic compounds in the samples. This is due to the deposition of salts or oxides from the matrix of the analyzed solution on the surface of the cones and ion optics of the mass

spectrometer, leading to a reduction in the throughput of these components of the instrument concerning the analyte, primarily due to a decrease in the diameter of the apertures. Moreover, excessive introduction of organic solvents (above 0.2%) can significantly alter the thermal characteristics of the plasma, mainly lowering its temperature, as additional energy is consumed for the evaporation and dissociation of these substances.

Table 2. Mineralization parameters for blood and urine samples.

Parameter	Value
Sample type	Blood (0.5-1 mL) / Urine (1-2 mL)
Reagents	Concentrated HNO_3 and H_2O_2
Microwave power	1500 W
Temperature	180°C
Mineralization time	20 minutes
Vessel volume	10-20 mL
Reagent volume added	2 mL HNO_3 , 1 mL H_2O_2
Internal standard concentration	20-50 $\mu\text{g/L}$ for each element

In this regard, two methods were investigated to reduce the impact of organic components on the results of element determinations in the analyzed solutions: microwave mineralization and simple dilution with 2% nitric acid. Simple dilution has several undeniable advantages, such as ease of execution, speed, cost-effectiveness, and minimal risk of additional sample contamination. However, among its drawbacks, one can note the possibility of failure of the sample delivery hoses, as well as the risk of blockage and clogging of the nebulizer, injector, and the apertures of the sampler

and skimmer. Furthermore, high concentrations of salts and organic substances can exacerbate spectral and non-spectral matrix interferences. Despite these drawbacks, this sample preparation method is widely used in practical research [12-14].

Oxidative mineralization is also widely used in the elemental analysis of biological fluids, especially whole blood. This is due to its ability to effectively remove complex organic matrices and reduce biological risks when working with such samples. At the same time, the method is characterized by relative complexity, greater time and financial costs, as well as an increased risk of additional sample contamination and loss of volatile elements. The results of the analysis of the dialysate are presented in Figure 1.

As shown in Figure 1, the results of element determinations using both sample preparation methods for dialysates coincide. However, when analyzing dialysates obtained from patients, changes in the contents of Cu, Zn, and Sr were observed with simple dilution compared to the data obtained from microwave mineralization. In some cases, the concentration of copper increased by more than 2 times, zinc by more than 1.6 times, and strontium by 2 times (Figure 1a). This can be explained by the presence of spectral matrix interferences affecting the accuracy of the analysis. The signals of neighboring ions with high intensity, for example, from matrix elements, significantly distort the analytical signal due to the overlapping of "tails" on closely located peaks.

The sample preparation method significantly impacts the obtained analytical results. The values of element concentrations determined by the dilution method are usually higher than those obtained using mineralization. This difference is due to matrix effects, particularly spectral interferences arising from the superposition of matrix ion signals on analytical peaks. Such effects are most noticeable during analysis without a collision cell.

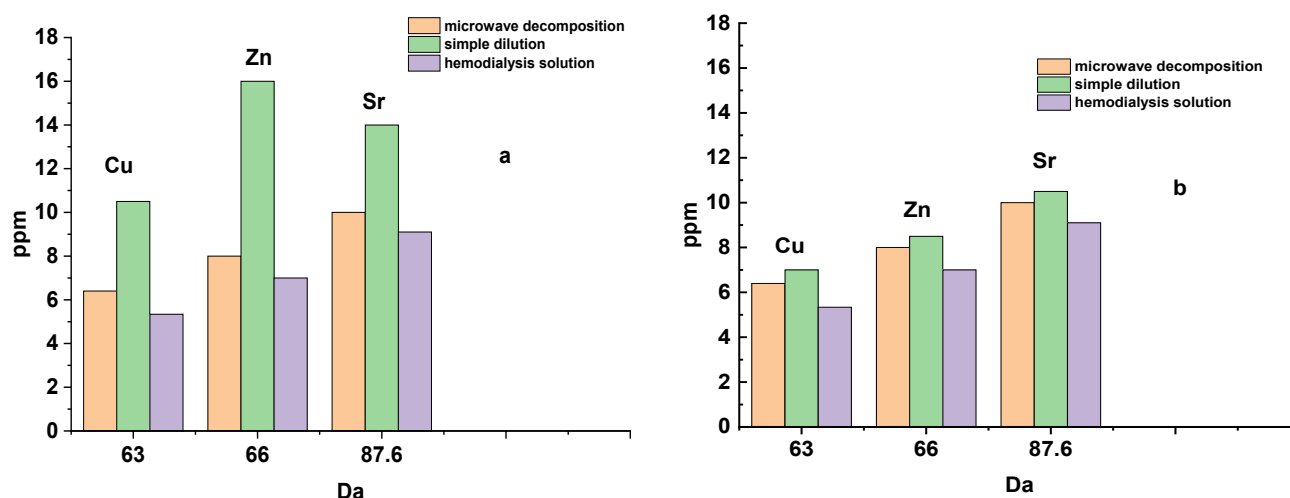


Figure 1. Change in element concentrations in dialysates depending on sample preparation conditions. a - without using a collision cell; b - with the use of a collision cell.

Using a collision cell with helium made it possible to minimize the influence of spectral interferences. As shown in Figure 1, with the addition of helium (optimal flow rate of 3 mL/min), the results for both sample preparation methods became more consistent. However, despite the possibility of correcting the results, the dilution method remains sensitive to the accumulation of matrix components on the interface elements of the device, which can reduce its reliability when working with biological fluids.

To demonstrate the advantages of the proposed approach, a comparative analysis was conducted with alternative methods described in the literature (Table 3). The methods considered include traditional techniques such as atomic absorption spectroscopy (AAS) and ICP-OES, as well as other ICP-MS-based approaches.

Most significant spectral matrix interferences in ICP-MS are caused by ions containing oxygen, in combination with elements present in the plasma-forming gas (Ar), as well as substances coming from the air and acids used during sample preparation. In particular, the signal for Cu^{60} is affected by interferents such as $^{23}\text{Na}^{40}\text{Ar}^+$, $^{25}\text{Mg}^{38}\text{Ar}^+$, and $^{27}\text{Al}^{36}\text{Ar}^+$; for Zn^{66} , the interferences are $^{26}\text{Mg}^{40}\text{Ar}^+$ and $^{28}\text{Si}^{38}\text{Ar}^+$; and for Sr^{88} , they include $^{50}\text{Cr}^{38}\text{Ar}^+$, $^{52}\text{Cr}^{36}\text{Ar}^+$, among others.

Spectral matrix interferences arising during the analysis of diluted samples can be accounted for or eliminated using various methods. Typically, instruments equipped with collision or reaction cells are used for this purpose. Figure 1b shows the results of the analysis of dialysate using a collision cell, with helium selected as the buffer. The optimal flow rate of helium was 3 mL/min. After introducing helium into the ICP-MS system, good agreement in results was obtained when applying both sample preparation methods (Figure 1a and b).

Thus, the choice between dilution and mineralization depends on the requirements for the accuracy of the analysis and the complexity of the sample matrix. For complex biological fluids such as whole blood, mineralization is the preferred method as it effectively removes organic components and minimizes biological risks.

It was also noted that there was a significant leaching of copper and zinc from patients' bodies during hemodialysis, which may lead to a deficiency of these elements in the blood. For example, a

deficiency of copper can cause anemia and weaken the immune system, while a lack of zinc is associated with neurological disorders, decreased visual acuity, and deterioration of skin condition [23]. The results obtained may assist doctors in replenishing the elements lost during dialysis in patients' bodies, which, in turn, helps avoid side effects associated with hemodialysis.

Urine is a highly concentrated saline solution with a noticeable content of organic acid salts. The study analyzed the necessity of mineralization and dilution of samples when analyzing urine. It was established that urine can be analyzed without prior mineralization. Urine samples were collected directly into disposable polypropylene tubes, after which they were immediately acidified with nitric acid and diluted tenfold with deionized water before analysis.

Among the disadvantages of simple dilution of biological fluids is the risk of clogging the nebulizer, torch injector, and the sample and skimmer holes with matrix components from the sample. In our practice, especially when determining elements in diluted urine samples, we observed contamination of the interface cones with soot resulting from the incomplete combustion of organic substances present in the solution. To prevent the formation of deposits on the surfaces of the cones and reduce their diameter, oxygen was added to the main gas flow. The presence of 1-5% O_2 in argon not only affected the condition of the cones but also increased signal intensity and helped minimize nonspectral interferences.

The results of this study confirm the feasibility of using this approach to extend the lifespan of the sampler and skimmer by adding just 1-2% oxygen to the argon plasma. Figure 2 shows the results of urine composition analysis for three patients before (Fig. 2a) and after (Fig. 2b) the gas introduction. As seen in the figure, after the addition of oxygen, the concentration of elements increased. This indicates a reduction in the number of organic substances on the surfaces of the cones, which creates a positive electric field and hinders the proper trajectory of ion movement.

The study found that when oxygen was added, the concentrations of the elements being determined increased. This confirms the hypothesis that organic substances deposited on the surface of the cones form a dielectric layer that creates a positive electric field. Such a field can change the trajectories of ions

Table 3. Comparison with other methods.

Method	Cu ($\mu\text{g/L}$)	Zn ($\mu\text{g/L}$)	Sr ($\mu\text{g/L}$)	Standard Deviation (%)	Time of Preparation (min)	Accuracy (%)	Contamination Risks
Proposed ICP-MS method	6.5	8.0	10.0	2.3	30-40	98.5	Low
ICP-OES method [5]	6.8	8.2	10.5	3.0	60	95.2	Moderate
AAS method [6]	7.0	8.5	11.0	3.5	90	93.0	High

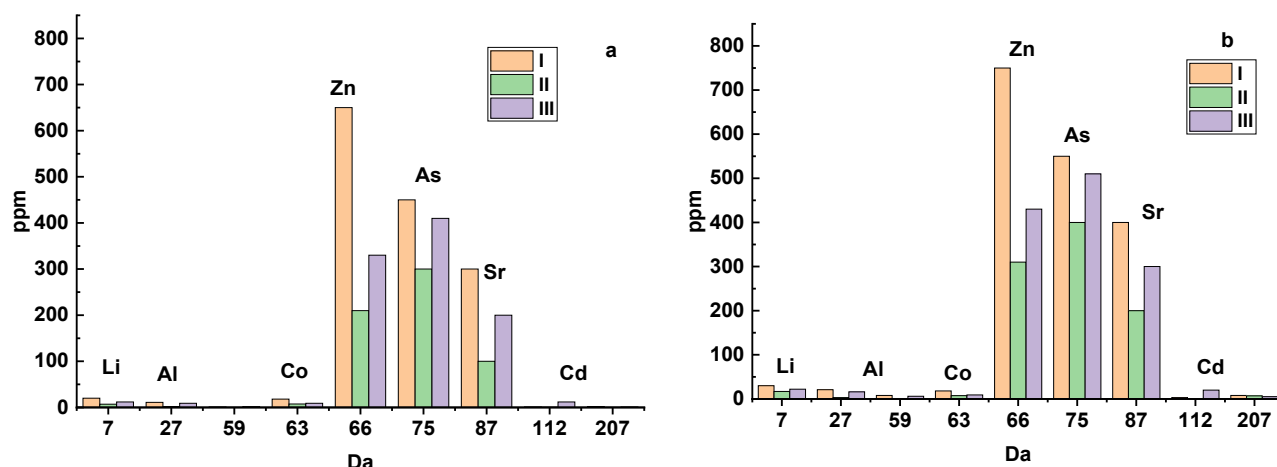


Figure 2. Results of urine composition analysis for three patients before (a) and after (b) the introduction of oxygen.

passing through the cone, which leads to a decrease in their registration in the mass spectrometer. The addition of oxygen facilitates the effective removal of organic contaminants from the surface of the cones, which eliminates this effect and improves the analysis results.

Traditionally, blood is a commonly used biomaterial in medical and biological research. Several methods for preparing blood for analysis are described in the literature [10, 22, 24]. Biological fluids consist of a conglomerate of organic compounds; therefore, the use of internal standards is essential to obtain reliable analytical results.

The method of internal standard (IS) is widely applied in inductively coupled plasma mass spectrometry (ICP-MS) to account for instrument instability, correct signal drift, and eliminate nonspectral matrix interferences [25]. The main requirements for the element serving as an internal standard include: its complete absence or minimal presence in the analyzed samples; the absence of spectral overlaps

that affect the signal of this isotope in the given matrix; the absence of spectral interferences caused by the internal standard on the analyzed elements; and similarity in physicochemical properties to the elements being determined.

Selecting an internal standard that functions effectively when analyzing biological fluids is a challenging task due to difficulties in accurately registering its signals. However, the decision to forgo the use of an internal standard when the sample is introduced via a flow-injection system is unjustifiable: at least one internal standard is essential to account for instrumental drift. In works [26, 27], a group of internal standards is used, which may cause spectral interferences for the isotopes being analyzed or contaminate the sample. Sometimes, polyatomic ions formed from the plasma-forming gas or the matrix of the analyzed solution are recommended as internal standards, such as Ar^{2+} , ArO^{+} , N_2^{+} , ClO^{+} , SO^{+} , MO^{+} , where M is the atom of the analyzed element (Fig. 3).

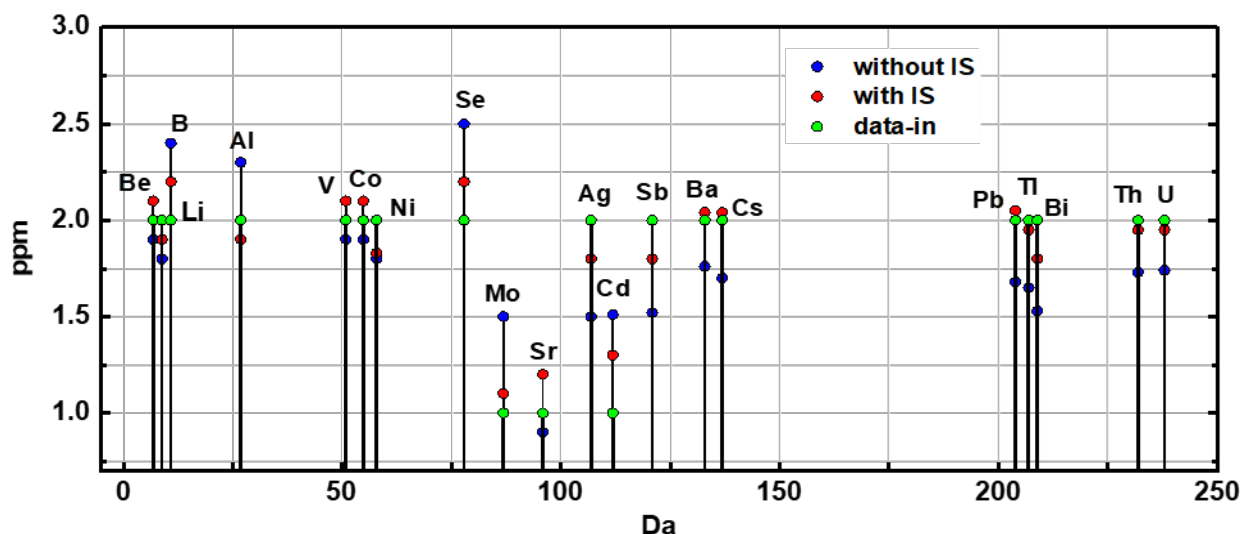


Figure 3. Metrological characteristics of measuring elements in blood: introduced and found values with (Rh) and without the use of internal standards.

To obtain accurate content for the added substance, two methods were applied. In the first method, sodium was added to the calibration solutions at concentrations corresponding to its blood levels, at around 100 mM. However, this approach did not yield positive results, and the amount of the addition was also underestimated. In the second method, the internal standard Rh (ruthenium) was introduced into the samples and comparison solutions. The use of the internal standard provided results close to the introduced concentration. These results can be explained by the fact that sodium alters the physicochemical properties of the solutions as well as plasma parameters such as temperature and electron concentration.

Conclusions

The analysis of the data highlights several key findings relevant to the accurate determination of elemental composition in biological fluids using ICP-MS. Spectral matrix interferences, which commonly arise during such analyses, can be effectively eliminated or mitigated by introducing helium into the plasma, ensuring consistency between results obtained via microwave digestion and simple dilution methods. Furthermore, the study confirms that the leaching of essential elements like copper and zinc during hemodialysis may contribute to immune system weakening, emphasizing the importance of monitoring and restoring these elements in patients. Additionally, urine samples can be analyzed without preliminary digestion, provided they are diluted tenfold with deionized water before measurement. Another crucial finding is that organic deposits accumulating on the surface of the instrument's cones generate an electric field that can alter ion trajectories, potentially affecting analytical accuracy. To minimize nonspectral matrix interferences, the introduction of 1–3% oxygen into the argon plasma has been demonstrated as an effective strategy. These findings contribute to the refinement of ICP-MS methodologies for clinical and biomedical applications, improving the reliability of elemental analysis in biological samples

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