DOI: 10.1070/RCR4583

Inductively coupled plasma mass spectrometry in the analysis of biological samples and pharmaceutical drugs

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Inductively coupled plasma mass spectrometry (ICP-MS) is widely used in the analysis of biological samples (whole blood, serum, blood plasma, urine, tissues, *etc.*) and pharmaceutical drugs. The shortcomings of this method related to spectral and non-spectral interferences are manifested in full measure in determination of the target analytes in these complex samples strongly differing in composition. The spectral interferences are caused by similarity of masses of the target component and sample matrix components. Non-spectral interferences are related to the influence of sample matrix components on the physicochemical processes taking place during formation and transportation of liquid sample aerosols into the plasma, on the value and spatial distribution of plasma temperature and on the transmission of the ion beam from the interface to mass spectrometer detector. The review is devoted to analysis of different mechanisms of appearance of non-spectral interferences and to ways for their minimization or elimination. Special attention is paid to the techniques of biological sample preparation, which largely determine the mechanisms of the influence of sample composition on the results of element determination. The ways of lowering non-spectral interferences by instrumental parameter tuning and application of internal standards are considered.
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I. Introduction

The use of inductively coupled plasma mass spectrometry (ICP-MS) was started quite a long time ago in clinical laboratories engaged in the analysis of biological samples and development of new pharmacutical agents based on metal coordination compounds. However, the wide use of this method was limited due to high cost and complexity of the equipment. Only in 2007, it was suggested that ICP-MS could replace in the future flame and electrothermal atomic absorption spectrometries, which were the major methods in clinical practice at that time.[1] At present, ICP-MS holds a

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Received 29 June 2015
Translation: S.E.Boganov

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Table 1. The contents of various elements in biological fluids which can be determined using ICP-MS (according to the data of the independent laboratory INVITRO, http://www.invitro.ru).

Element	Concentration /μg litre^{-1}		
	blood	blood serum	urine
Al	–	–	0–40
P	200–500[a]	110–140[a]	400–1300[a]
Mn	7–15	1.5–4	0.75–3
Fe	–	–	5–300
Co	0.5–2.5	0.45–1	0.25–2
Ni	0–10	0–10	0–20
Cu	750–1500	750–1800	10–70
Zn	5500–9000	750–1500	200–1000
As	0–90	0–10	0–350
Se	75–200	70–120	15–60
Mo	–	0.4–1.5	–
Cd	0–5	0–0.15	0–1
Au	–	0–10	–
Hg	0–50	–	0–10
Tl	–	0–0.05	0–1
Pb	0–100	–	0–5

[a] Concentrations in mg litre^{-1}.

leading position in this field. It has been made possible owing to the availability and high throughput of modern equipment. Furthermore, the method retains the following obvious advantages:[2]

— uniquely low detection limits (at the level of nanograms or even pictograms per litre) for chemical elements and isotopes (according to the data presented in Table 1, such elements are Mn, Co, Ni, Mo, Cd, Au and Tl), which are necessary for analysis of highly diluted samples and for monitoring the excretion of drugs from a human body during a long period of time;

— the possibility of carrying out multielement analysis (see Table 1) and a wide range of analytes covering elements from Al to Pb;

— wide (up to 10 orders of magnitude) dynamic range of linearity of calibration curves; this is important in biomonitoring and screening of disease markers because of the necessity of determination of various elements with different contents in a single sample (according to Table 1, appropriate analytes are Tl, Cd and Zn, P);

— low level of instrument noise (0–10 pulses per second);

— relative simplicity of spectra and their interpretation;

— low consumption of a substance in analysis and possibility of analyzing samples of low volume (~0.1 ml) and mass (~0.1 mg).

However, like any other instrumental method, ICP-MS has its drawbacks, the major of which are so-called spectral and non-spectral matrix interferences.[2] Effects of these interferences on the results of analysis and the ways to minimize them depend on the sample type and sample preparation before analysis, and also on the class and design of the spectrometer.

A series of recent reviews published in the last 5 to 6 years were devoted to matrix effects in the ICP-MS analysis,[3] the use of ICP-MS for analysis of pharmaceuticals and biological substances[4,5] and to specific aspects of techniques and strategy of optimization of equipment operation.[6] The first-mentioned paper[3] surveyes virtually all possible mechanisms of influence of sample composition on the results of determination of target analytes and generally discusses the methods for taking such influence into account. Since consideration covers quite a number of types of complex matrices, in which matrix effects take place, only a minor part of the review deals with the problems of analysis of biological and pharmaceutical samples. The mechanisms of the impact of matrix composition in the samples of biological origin on the analytical signal were not considered in detail, little attention was paid to specific types of matrix effect depending on the sample preparation procedure. Two other reviews[4,5] describe methods of analysis of a large number of various samples, whereas the role of matrix effects in the accuracy of analysis results is not addressed. An important, although rather specific topic, *viz*., different ways of injection of a liquid sample into the plasma and accompanying interferences, is considered in the last-mentioned publication.[6]

The purpose of the present review is to analyze studies devoted to specific features of matrix effects and methods used to take them into account in order to obtain accurate results of analysis of biological specimens and pharmaceuticals. The results of several important studies that appeared after the publication of Agatemor and Beauchemin[3] are analyzed, the problems of the influence of non-spectral interferences on the results of determination of elemental composition of biological fluids and anticancer drugs using ICP-MS are considered in detail and specific matrix effects inherent in various sample preparation methods are discussed.

II. Application of inductively coupled plasma mass spectrometry to the analysis of biological fluids and in the development of pharmaceuticals

Two methods of sample preparation are mainly used in ICP-MS elemental analysis of biological fluids, namely, dilution[7–44] and oxidative mineralization.[45–74]

II.1. Analysis of biological fluids after dilution

Undoubtful advantages of the sample dilution method are experimental simplicity, high speed, low cost and minimum risk of further contamination of a sample. Obvious drawbacks are possibility of failure of flexible tubing for sample injection, blocking or chocking of the nebulizer, torch injector and even the sampler and skimmer, as well as increased effects of spectral and non-spectral interferences because of high contents of salts and organic compounds.[75] Nevertheless, despite these drawbacks, this method of sample preparation is rather often used in practice.[7–44]

The diluent composition is varied in different procedures (Table 2). Complex mixtures are used in preparation of whole blood samples.[7–25] Solutions acidified with nitric acid or ammonia solutions of 4-(1,1,3,3-tetramethylbutyl)-phenyl polyethylene glycol (Triton X-100, which will further be called Triton) without addition[8–12] or with addition of disodium ethylenediaminetetraacetate (Na-EDTA)[13–20,24] and/or butan-1-ol[15,16,19,23] are used most often. Blood serum and urine are typically diluted with nitric acid, the content of which amounts to a few percent by volume.[21,26–38] Each component in such mixtures plays a specific role. For instance, Triton preserves the nebulizer

Table 2. Examples of ICP-MS analysis of biological fluids after dilution.

Target elements	Sample dilution factor	Diluent	Internal standard	Calibration	Ref.
		Biological fluid: blood			
Cd, Hg, Pb	20	HNO_3 – Au	Ge, Tb, Y	No matrix matching	7
Cu, Zn	10	Triton – HNO_3	In	Matrix matching	8
As, Cd, Co, Cr, Cu, Mn, Pb, Se, Tl, V, Zn	50	Triton – HNO_3	Ir, Rh	The same	9
As, Ba, Be, Bi, Cd, Co, Cr, Cu, Hg, Mn, Mo, Ni, Pb, Pd, Pt, Rh, Sb, Se, Sr, Tl, V, Zn	20	Triton – HNO_3	Ge, In, Re, Sc	"	10
Cd, Hg, Pb	50	Triton – HNO_3 – Au	Ir, Rh	"	11
Ag, As, Au, B, Ba, Be, Bi, Cd, Ce, Co, Cs, Cu, Ga, Hf, Hg, In, La, Mn, Mo, Ni, Pb, Pd, Rb, Rh, Ru, Sb, Se, Sn, Sr, Te, Th, Tl, U, V, W, Y, Zr	10	Triton – NH_3	Tb	Standard addition method	12
Co, Cr	up to 50	Triton – Na-EDTA – NH_3	Sc	No matrix matching	13
Cr, Co, Mo, Ni	10	Triton – Na-EDTA – NH_3	Rh	The same	14
As, Cd, Hg, Mn, Pb, U	50	Triton – Na-EDTA, butan-1-ol – NH_3	Ge/Ir/Rh/Re/Tl	Matrix matching	15
Cd, Cu, Pb, Se, Zn	10	Triton – Na-EDTA, butan-1-ol – NH_3	–	The same	16
Cd, Hg, Pb	50	Triton – Na-EDTA – TMAH,[a] propan-2-ol	Ir	"	17
		Biological fluid: blood serum			
B, Ba, Bi, Cd, Cs, Hg, Li, Mo, Pb, Sb, Sn	5	HNO_3	Be, In, Tl	No matrix matching	26
Co, Cs, Cu, Fe, Mo, Rb, Zn	up to 10	HNO_3	Be, In, Tl	The same	27
Br, Ca, Cu, Mg, Rb, Sr, Zn	10	HNO_3	Rh, Te, Y	"	28
Al, Cd, Co, Cu, Li, Mn, Mo, Ni, Pb, Pt, Rb, Sb, Se, Zn	up to 50	HNO_3	Rh, Tl	Matrix matching	29
Se	10	Ethanol – HNO_3	In/Sc	The same	39
Al, Cd, Co, Cr, Cu, Fe, Hg, Mn, Ni, V, Zn	10	Na-EDTA – NH_3	Bi, Ge, In, Li, Sc, Tb, Y	No matrix matching	40
Al, As, B, Be, Cd, Co, Cu, Fe, Li, Mn, Mo, Ni, Rb, Se, Sr, Zn	10	Triton – AcOH	Ge, Rh	Matrix matching	41
		Biological fluid: urine			
Ag, As, Au, Ba, Be, Bi, Cd, Co, Cr, Cs, Cu, Ga, In, Li, Mn, Mo, Ni, Pb, Pd, Pt, Rb, Rh, Sb, Se, Sn, Tl, U, V, W, Zr	5	HNO_3	Tb	Standard addition method	30, 31
Ag, As, Bi, Cd, Co, Ge, Hg, Mo, Pb, Pt, Se, Sn, Te, Tl, Zn	10	HNO_3	Ga, In, Ir, Y	The same	32
Al, As, Co, Cr, Cu, Mn, Mo, Pb, V, Zn	10	HNO_3	In, Y	Matrix matching	33
As, Cd, Cu, Fe, Pb, Se, Zn	10	HNO_3	In, Rh, Tl, Y	No matrix matching	34
As, Cu, Mo, Ni, Pb, Se, Zn	16.5	HNO_3	Rh	Standard addition method	35
Bi, Cd, Hg, Pb, Pd, Pt, Sb, Sn, Te, Tl, W	1.1	HNO_3 – HCl	Ir, Rh	The same	42
Al, Ba, Be, Cd, Co, Cu, Cs, Mn, Ni, Pb, Pt, Sb, Se, Sn, Tl, U	20	Triton – HNO_3	Ir, Rh, Y	Matrix matching	43
As, Cd, Hg, Pb	20	Triton – NH_2SO_2OH, HNO_3 – Au	Ga, Ir, Rh, Y	The same	44
		Biological fluids: blood and blood serum			
Cd, Co, Cu, Ga, Hg, Mo, Ni, Rb, Rh, Pb, Pd, Pt, Sb, Se, Sn, Tl, W, Zn	10 and 5	Triton – Na-EDTA – NH_3	In, Sc	Matrix matching	18

Table 2 (continued).

Target elements	Sample dilution factor	Diluent	Internal standard	Calibration	Ref.
		Biological fluids: blood and blood serum			
Al, As, Cd, Co, Cr, Cu, Fe, K, Mg, Mn, Mo, Na, Ni, Pb, Sb, Se, V, Zn	20	Triton – Na-EDTA, butan-1-ol – NH_3	Ge, In, Rh, Sc, Tl	Standard addition method	19
Se	15	Triton – Na-EDTA, butan-1-ol – NH_3	In	Matrix matching	20
		Biological fluids are blood and urine			
As, Cd, Pb, Tl	10	HNO_3	Bi, Ga, Rh	No matrix matching	21
Cd, Hg, Pb, Tl	20 and 10	2-Methylpropan-2-ol – HCl – Au	Bi, Ga, Rh	Matrix matching	22
		Biological fluids: blood serum and urine			
Al, As, Co, Cr, Cu, Ga, Ge, Mn, Ni, Sc, Se, Si, Ti, V, Zn	20	HNO_3	Bi, In	No matrix matching	36
Al, As, Bi, Cd, Co, Cs, Cu, Mn, Mo, Ni, Rb, Pb, Sb, Se, Sn, Sr, W, Zn	5	HNO_3	Be, Ga, In, Ir	No matrix matching/ standard addition method	37
Cu, Zn	20 and 10	HNO_3	Y	No matrix matching	38
		Biological fluids: blood, blood serum and urine			
Ag, Al, As, B, Ba, Be, Bi, Cd, Co, Cr, Cu, Ga, Ge, Hg, Li, Mn, Mo, Ni, Pb, Pd, Pt, Rb, Sb, Se, Sn, Sr, Tl, U, V, W, Zn	10	Triton – butan-1-ol – HNO_3	Rh	Standard addition method	23
Co, Cr, Mo, Ni	20	Triton – Na-EDTA – NH_3	In	Matrix matching	24
Al, As, Bi, Cd, Co, Cr, Cu, Fe, Mn, Mo, Ni, Pb, Sb, Se, Tl, V, Zn	50	TMAH [a] – HCl	Rh	No matrix matching	25

[a] Tetramethylammonium hydroxide.

and the torch injector from plugging; however a positive effect is achieved only if its concentration is >0.01 vol.%.[9] Na-EDTA prevents precipitation and absorption of elements on the vial walls. Butan-1-ol promotes elimination of polyatomic argon-containing interference with selenium isotopes due to predominant formation of the ArC^+ ion.[15, 20, 23] and the increase in the general sensitivity of analysis (the same effect can be achieved by additing any other organic compound to the analyte solution).[17, 22, 39, 41] Ammonia destroys the erythrocytes, while nitric acid stabilizes the forms in which elements exist in solutions, although proteins can precipitate if nitric acid concentration is >0.5 vol.%.[9] It is recommended in this case to centrifuge solutions before analysis.[16, 21, 23, 37] Sometimes, tetramethylammonium hydroxide (TMAH) is used to destroy the organic matrix.[17, 25]

The dilution factor can also significantly vary (see Table 2). Whole blood, the most complex biological fluid, is usually more highly diluted (10 – 50-fold). Most often, samples are diluted by a factor of ten.[8, 12, 14, 16, 18, 21 – 23, 27, 28, 32 – 34, 38 – 41] Higher dilution (20 – 50-fold) is used to reduce the loading of the input system and interface with organic substances and salts and also to level off the matrix effects. Clearly, this particular method of sample preparation makes it possible to apply calibration solutions without matching the matrix.[7, 13, 25, 36, 38] However, it is necessary to note that a high dilution factor makes determination of elements with significantly different concentrations in a single sample problematic.

Negative effects of components of biological fluid matrices on the sampling system can be reduced not only by using Triton X-100 and dilution of samples, but also by application of torch injectors with larger inner diameters [2.0 mm (Refs 9, 11, 20) or 2.5 mm (Refs 12, 13, 19, 30, 31)] as compared with those used most often (1.0 – 1.5 mm). For the same purpose, diluted samples are sometimes fed to plasma using continuous flow (flow-injection) systems.[14, 18, 35] To prevent plugging of the cones with soot, oxygen can be introduced into the Ar flow according to recommendations of mass spectrometer manufacturers.[76]

Spectral matrix interferences emerging in analysis of diluted samples can be taken into account and eliminated by several means. Spectrometers equipped with collision or reaction cells are used in the majority of cases for this purpose.[9, 10, 12, 13, 16, 17, 19, 22, 30, 31, 43, 44] High-resolution mass spectrometers are used less often because of their high cost.[14, 24, 25, 36, 39] The influence of spectral interferences on the results of analysis can be evaluated with the use of solutions that model the sample composition.

As noted above, one of the methods for reduction of effects of non-spectral interferences consists in sample dilution sufficient to level off these effects. However, standard addition calibration [12, 19, 23, 30 – 32, 35, 37, 42] and matrix

matching for calibration solutions (similar to the sample matrix) [8 – 11, 15 – 18, 20, 22, 24, 29, 33, 39, 41, 43, 44] are used more frequently. In this case, human [10, 16 – 18, 22, 33, 39, 43, 44] or animal [9, 11, 20] biological fluids can be used for calibration. The content of elements to be analyzed is relatively low as a rule. An artificial matrix simulating salt and/or organic composition of the sample is prepared for the same purpose in some cases.[8, 15, 29]

Nonetheless, irrespective of the method used to prepare calibration solutions, the internal standard technique is additionally used to eliminate non-spectral interferences, with the internal standard containing single [8, 12 – 15, 17, 20, 23 – 25, 30, 31, 35, 38, 39] or several elements [7, 9 – 11, 18, 19, 21, 22, 26 – 29, 32 – 34, 36, 37, 40 – 44] (see Table 2). A single internal standard is used if matrix-matched calibration solutions or standard addition calibration is used,[12, 15, 17, 23, 24, 30, 31, 35] and also when no more than two elements are determined.[8, 13, 20, 38, 39] If calibration solutions are prepared without matrix matching, a single internal standard can be used only in the case of high (50-fold) dilution of samples [13, 25] or if samples are fed to the mass spectrometer through a continuous flow system.[14] Several internal standards are used in all other cases.[7, 21, 26 – 28, 34, 36, 37, 40] The use of several standards seems to be undue with matrix-matched calibration solutions or standard addition calibration.[9 – 11, 18, 19, 22, 29, 32, 33, 41 – 44] The criteria for selection of internal standard elements (see the second and fifth columns in Table 2) are not entirely clear, though it was explicitly indicated in some cases that the selection was based on the similarity of atomic masses [26, 29, 37] and/or the first ionization potentials [10, 17, 19, 28] of the internal standard and the analyte. Alimonty *et al.*[29] noted that this criterion is not always applicable since Rh is used as an internal standard when Li or Al are determined, although its atomic mass is much higher than those of the analytes.

The possibility of decreasing non-spectral matrix interferences in the analysis of diluted biological fluids by the instrumental means, *viz.*, by selection of robust operating parameters, was mentioned only in several publications.[17, 20, 25, 26, 28, 33, 40] The necessity of decreasing the argon flow velocity through the nebulizer was also emphasized.[26, 28] The use of enhanced generator power to achieve more efficient digestion of organic matrix and ionization of elements in the plasma was reported.[17, 20] The tuning of all intrument parameters using any diluted sample was recommended in several studies,[25, 33, 40] while in other cases, the instrument is tuned using standard solutions. It is worth to note that several internal standards are used even when working under robust operating conditions. Some authors [17, 25] used one internal standard, which was possibly due to higher dilution of samples. The possibility of using only one internal standard, which can actually be any standard, in combination with robust operating conditions for practically complete elimination of non-spectral interferences in the analysis of biological samples using a quadrupole mass spectrometer was demonstrated recently.[77, 78]

A variety of nebulizer types have been used in the above-mentioned publications: cross-flow,[7, 11, 14, 20, 22, 35, 37, 38, 42] concentric [9, 10, 13, 15 – 17, 19, 24 – 28, 32 – 34, 36, 39, 40, 43] or Babington[7, 12, 30, 31] nebulizers.

II.2. Analysis of biological fluids after mineralization

Oxidative mineralization of biological fluids,[45 – 74] particularly, whole blood [45 – 62, 70 – 72, 74] is widely used in elemental analysis owing to the possibility to destroy the complex organic matrix and reduce biological hazard in the work with such objects. However, this type of sample preparation is characterized by relative complexity of procedures, large time consumption, relatively high cost and, of course, potential possibility of sample contamination and loss of some elements in the form of volatile compounds.

Concentrated nitric acid usually serves as the oxidizing agent (Table 3). It gives much less spectral interferences than $HClO_4$ or H_2SO_4, which are responsible for appearance of polyatomic ClO^+ and SO^+ ions in the plasma.[75] It was shown [79, 80] that treatment of various biological samples

Table 3. Examples of ICP-MS analysis of biological fluids after oxidative mineralization.

Target elements	Sample dilution factor	Mineralization conditions	Internal standard	Calibration	Ref.
		Biological fluid: blood			
Al, As, Cd, Cr, Co, Cu, Hg, Mn, Ni, Pb, Sb, Se, Tl, Zn	10	1 ml sample – 1 ml HNO_3, 10 h, 180 °C	Ir, Rh, Sc	No matrix matching	45
Ca, Cu, Fe, Mg, Mn, Pb, Zn	20	1 ml sample – 2 ml HNO_3, 1 h, ~100 °C	In, Ir, Lu	The same	46
Al, Ba, Be, Bi, Ca, Cd, Co, Cr, Cu, Fe, Hg, Li, Mg, Mn, Mo, Ni, Pb, Sb, Si, Sn, Sr, Tl, V, W, Zn, Zr	15	1 ml sample – 2 ml HNO_3, 5 h, 80 °C	In, Pt, Sc	Standard addition method	47
Se, Cu, Mn	25	0.5 ml sample – (HNO_3 + H_2O_2), heating to 95 °C and evaporation	Ge, In	No matrix matching	48
Al, As, Ba, Cd, Co, Cu, Li, Fe, Mn, Ni, Pb, Sb, Se, Sn, Tl, U, V, Zn	15	1 ml sample – (HNO_3 + H_2O_2), heating to 95 °C and evaporation	Ge, Lu, Rh, Sc	The same	49
Cd, Hg, Pb	10	1 ml sample – (2 ml HNO_3 + 1 ml H_2O_2), 3 h, 60 °C	Rh	Standard addition method	50, 51
As, Cd, Hg, Pb, Se, Tl	10	0.75 ml of the sample – 1.5 ml HNO_3, MW: 25 min up to 1000 W, 230 °C	Ge, Ir, Rh	The same	52

Table 3 (continued).

Target elements	Sample dilution factor	Mineralization conditions	Internal standard	Calibration	Ref.
		Biological fluid: blood			
As, Co, Cr, Cu, Mn, Pb, Se, Zn	25	1 ml sample – (2 ml HNO_3 + 3 ml H_2O_2), ~3 h, up to 95 °C	Bi, Ge, Te	Matrix matching	53
Ag, Al, As, Au, B, Ba, Be, Bi, Br, Cd, Co, Cr, Cs, Cu, Ga, Ge, Hf, Hg, I, Li, Mn, Mo, Nb, Ni, Rb, Re, Pb, Sb, Sc, Se, Si, Sn, Sr, Ta, Te, Th, Ti, Tl, U, V, W, Y, Zn, Zr, lanthanides, platinum group metals	10	1 ml sample – 1.5 ml HNO_3 (1 : 2), MW: 30 min, 300 W	In	The same	54
Cu, Mn, Se, Zn	15	1 ml sample – 2 ml HNO_3, MW: 4 h, 100 °C	Ga, In	"	55
Al, As, Ba, Cd, Co, Cr, Li, Mn, Mo, Ni, Pb, Sb, Se, Sn, Sr, V, Zr	10	1 ml sample – 2 ml HNO_3, MW: 5 h, 90 °C	Ga, Rh	Standard addition method	56
Ag, Al, Au, B, Ba, Be, Bi, Br, Cd, Ce, Co, Cr, Cs, Cu, Fe, Ga, Hf, Hg, I, La, Mn, Mo, Nb, Ni, Rb, Re, P, Pb, Sb, Se, Si, Sn, Sr, Ta, Te, Th, Ti, Tl, U, V, W, Y, Zn, Zr, platinum group metals	20	1 ml sample – 1 ml HNO_3, MW: 1 h, 600 W	In, Lu, Sc	No matrix matching/ matrix matching (Bi, Cd, Sb, Zn)	57
Al, As, B, Be, Cd, Co, Cu, Fe, Li, Mn, Mo, Ni, Pb, Rb, Se, Sr, Zn	15	0.5 ml sample – (1.5 ml HNO_3 + 1 ml H_2O_2), MW: 23 min, up to 900 W, 190 °C	Rh	Matrix matching	58
Al, Be, Cd, Co, Cr, Mn, Mo, Ni, Pd, Pb, Pt, Sn, V	20	0.5 ml sample – (2 ml HNO_3 + 1 ml H_2O_2), MW: up to 180 °C	Y	No matrix matching	59
Cr, Ni	50	1 ml sample – (2 ml HNO_3 + 2 ml H_2O_2), MW: 32 min, up to 800 W	Rh	The same	60
Ag, Al, As, Ba, Be, Cd, Co, Cr, Cs, Cu, Fe, Mn, Ni, Pb, Se, Sr, Tl, U, V, Zn	50	0.5 ml sample – (2 ml HNO_3 + 6 ml H_2O_2), MW: 25 min, 950 W, 190 °C	Y	Matrix matching	61
Au, Ir, Pd, Pt	~7	1 ml sample – (4 ml 0.5% HNO_3 + 1.6 ml H_2O_2), UV: 60 min, 1000 W	–	Standard addition method	62
		Biological fluid: blood serum			
Ag, Cs, Mo, Rb, Se, Sr	10	0.5 ml sample – 1 ml HNO_3, 5 h, 110 °C and evaporation	Ge, Re, Rh	No matrix matching	63
Cd, Co, Cu, Fe, Mg, Mn, Pb, Zn	20	0.15 ml sample – (0.15 ml HNO_3 + 0.1 ml H_2O_2, ~2.5 min, 96 °C	Bi, Ga, In, Sc, Y	Matrix matching	64
Ti, Zr	–	2 ml sample – (1.5 ml HNO_3 + 0.5 ml HF), autoclave 8 h, up to 180 °C	Rh	The same	65
Cd, Co, Cr, Cu, Fe, Mn, Mo, Ni, Pb, Sr, Zn	20 and more	0.5 ml sample – (1 ml HNO_3 + 0.5 ml H_2O_2 + 0.2 ml HF), MW: 22 min, to 300 W, 180 °C	Rh	"	66
		Biological fluid: urine			
U	2	5 ml sample – 5 ml HNO_3 MW: 20 min, 180 °C	–	Standard addition method	67
Pd, Pt, Rh	20	5 ml sample – (1 ml HNO_3 + 2 ml H_2O_2), UV: 90 min, 500 W	In	Matrix matching	68
Cd, Co, Cr, Ni, Pb, Rb, Sb, Se, V	20	5 ml sample – (1 ml HNO_3 + 2 ml H_2O_2), UV: 90 min, 500 W	Y	The same	69

Table 3 (continued).

Target elements	Sample dilution factor	Mineralization conditions	Internal standard	Calibration	Ref.
		Biological fluids: blood and blood serum			
Al, B, Cr, Cu, Fe, Li, Mg, Rb, Sc, Sr, Ti, Zn	10	0.5 ml sample – 1 or 0.5 ml HNO_3, 3 h, 95 °C	Rh	Standard addition method	70
Cu, Fe, Ni, Pb, Zn	–	0.5 ml sample – (0.4 ml HNO_3 + 0.4 ml H_2O_2), MW: 2 min, 300 W	–	No matrix matching	71
Ca, Cu, K, Mg, Rb, Sr, Zn	10	1 ml sample – (1.5 ml HNO_3 + 0.5 ml H_2O_2), MW: 27.5 min, up to 1000 W	Ga, In, Re	The same	72
		Biological fluids: blood serum and urine			
Al, Cd, Co, Cr, Cu, Fe, Mn, Ni, Pb, Pt, Tl, V, Zn	10 and 2	0.5 ml sample – (2 ml 1% HNO_3 + 40 μl HNO_3 + 0.5 ml H_2O_2), 5 ml sample – 0.6 ml H_2O_2, UV: 40 – 45 min, to 1000 W	–	Standard addition method	73
		Biological fluids: blood, blood serum and urine			
Al, Bi, Cd, Co, Cr, Hg, Mn, Mo, Ni, Tl, Pb	10, 5 and 5	1 ml sample – 2 ml/1 ml/ 0.5 ml HNO_3, MW: 40 min up to 130/80/60 °C	In, Pt, Sc	The same	74

Note. The following designations are used: MW is microwave radiation, UV is ultraviolet radiation.

with concentrated nitric acid at 180 °C under a pressure of up to 25 bar for 3 h results in practically complete mineralization of the organic matrices. Amino acids (phenylalanine, histidine, tryptophan, methionine) and unsaturated fatty acids (linoleic acid derivatives) can predominantly be found in the residue or in the solution after this treatment. In some cases, hydrogen peroxide is additionally introduced into the reaction mixture [48 – 51, 53, 58 – 62, 64, 66, 68, 69, 71 – 73] to reduce the formation of nitrogen dioxide vapour and accelerate mineralization by the temperature rise.[52] Other acids such as HF are used more rarely.[65, 66]

Along with mineralization by heating in an open beaker or a special block,[45 – 51, 53, 63, 64, 70] microwave radiation is widely used [52, 54 – 61, 66, 67, 71, 72, 74] to intensify the process. This not only shortens the sample preparation time (on average, from several hours to a half an hour) and diminishes the possibility of sample contamination (if closed beakers are used) but also makes it possible to control the whole decomposition process by programming the power and temperature.[52, 58 – 60, 66, 72, 74] The disadvantages of commercially available microwave ovens with standard accessories consist in impossibility of carrying out mineralization of more than 10 – 12 samples simultaneously and relatively large volumes of mineralization beakers.[74] Note that modern microwave systems are equipped with special vessels [Mars (CEM Corporation, USA) and Ethos (Milestone S.r.I., Italy) microwave ovens] or micro-inserts for standard beakers (Ethos microwave ovens) to increase the performance of sample preparation process owing to the increase in the number of samples treated in a single cycle. Additional advantage of the use of micro-inserts consists in the possibility of treatment of low volume samples, which is important in clinical trials. Examples of the use of UV radiation to accelerate the degradation of organic matrix are rare.[62, 68, 69, 73] Quite low detection limits are achieved with this decomposition method due to the utilization of low amounts of oxidizing agents. However, the latter fact restricts the application of UV mineralization, and this method is mainly used in the case of samples such as blood serum or urine with relatively simple matrices.

Since a concentrated acid is most often used in the sample preparation, degraded samples are additionally diluted before ICP-MS analysis. The dilution factor is chosen proceeding not only from the requirement to decrease the whole acidity of the solution down to the level acceptable for its subsequent introduction into plasma, but also taking into account the content of elements to be analyzed and salts in the sample. Increased concentration of nitric acid (which is usually the main reagent in the dilution process) may result not only in fast corrosion of interface nickel cones, but also in suppression of the analyte signal. Some authors [72, 75] assert that it is desirable to introduce nitric acid solutions with concentration of <2 M (15 vol.%) into the mass spectrometer. However, this recommendation is not fulfilled in some cases.[50 – 52, 56, 58, 59, 67, 71, 74] Clearly, platinum sampler and skimmer[51, 52, 74] or continuous flow system for the introduction of samples of a limited volume [67, 71] should be used in these cases. As a whole, the dilution factor varies depending on the particular procedure (see Table 3), although tenfold dilution prevails. A more drastic method of decreasing the sample acidity is evaporation of mineralized samples with subsequent dissolution of the residues in a solvent of a particular composition.[48, 49, 63] Note that dissolution is applied more rarely in modern practice because of high chance of contamination of sample and increase in the analysis duration.

As in the case of direct dilution, spectral matrix interferences are eliminated by using quadrupole mass spectrometers with collision or reaction cells,[46, 48 – 51, 53, 56, 59, 60, 66, 70] as well as by using high resolution mass spectrometers.[45 – 47, 54, 55, 57, 61, 62, 64, 68, 69, 73, 74]

To take into account the possible non-spectral interferences (suppression of signals of elements due to the presence of acid and various salts in the solution), the standard addition method is used[47, 50–52, 56, 62, 67, 70, 73, 74] or the matrix for the calibration solutions is selected to match the composition of the sample.[53–55, 57, 58, 61, 64–66, 68, 69] Only the content of the acid is typically simulated in this case[53, 58, 61, 64, 66] because in the given examples, the effects of salts are decreased due to the use of high dilutions (20–50-fold). The method of simple external calibration with standard solutions on the basis of HNO_3 (1 vol.%)[45, 46, 48, 49, 57, 59, 60, 63, 71, 72] is also used, although its application is sometimes associated with additional technical difficulties. For example, evaporation of mineralized samples to remove excess acid can precede the analysis.[48, 49, 63]

It was suggested[71] to introduce the samples into the mass spectrometer *via* a flow injection system after preliminary separation of the matrix elements (Na, K, Ca, Mg, Cl, P and S) on an iminodiacetate resin. A high (50-fold) dilution of the samples was used.[60] Additionally, this calibration method can lead to systematic errors in determination of the elements such as Bi, Cd, Sb and Zn,[57] Cd, Se, Zn,[59] Be, Bi, Cd, Hg.[72] The authors of these studies noticed that the results of determination of these elements were underestimated and attributed this to the difference in the nitric acid concentrations in the analyzed and calibration solutions. However, in other studies,[45, 46] no underestimation of analytical signals was observed, although the nitric acid concentrations in the sample and calibration solutions were also different. These discrepancies may be attributable to the fact that a high-resolution mass spectrometer was used in one of these studies,[45] and in the other one,[46] analytes with high first ionization potentials were not determined.

Along with the above-considered ways of reducing non-spectral interferences, the method of internal standard is additionally used in most cases (see Table 3). However, in some studies,[62, 67, 71, 73] no internal standard was applied. In our opinion, the neglect of using internal standards is not substantiated since this would provide, at least, a control over the instrumental drift. A single internal standard is typically used to control the instrumental drift both in calibration by adding an internal standard[50, 51, 70] and in matrix matching for calibration solutions.[54, 58, 61, 65, 66, 68, 69] Note that several internal standards were used for the same purpose in some papers.[47, 52, 53, 55, 56, 64, 74] The reasons behind the different approaches to the use of internal standards were not explained in the publications cited.

Several internal standards are usually employed when external calibration is used. As can be seen from the data of Table 3, several internal standards were used in most publications,[45, 46, 48, 49, 57, 63, 72] while only one standard was used only in two papers.[59, 60] This may be responsible for the underestimation of determination results of some elements reported by Griesel *et al.*[59] In the other study,[60] one internal standard was used because the sample was highly diluted, and this resulted in a substantial weakening of the matrix effects. It is noteworthy that the criteria for choosing the type and number of internal standards by the authors of different publications are not completely evident. The reasons for the choice were substantiated only in some cases.[45, 53, 54, 57, 60, 72, 74] Selection of an internal standard considering the similarity of the atomic masses of elements has been recommended.[45, 53, 72, 74] Alimonty *et al.*[60] emphasized the importance of similarity of not only the masses but also the first ionization potentials of the internal standards and analytes.

The necessity of special tuning of mass spectrometers before determination of elements in the mineralized sample matrices was mentioned only in two papers.[57, 58] In most cases, this tuning is done with the Autotune standard solution included in the spectrometer kit.

The vast majority of employed nebulizers are concentric.[45, 47, 50, 51, 53, 54, 57, 59, 61, 62, 64, 66, 72–74] Only in rare cases, cross-flow,[60] ultrasonic[65, 68, 69] or Babington[67] nebulizers are used.

II.3. Development of pharmaceuticals

As follows from the above consideration, ICP-MS is widely used in elemental analysis of biological fluids with the aim of biomonitoring and screening of markers of various diseases. However, the role of this method in the clinical practice is not limited to this application. ICP-MS is actively used in the development of new pharmaceuticals.

Most of active substances in drugs are organic compounds. A separate class in pharmacology is represented by coordination compounds of metals, which are of special therapeutic value.[81] They include antitumour (based on Pt, Ru, Ga, Au, Sn, *etc.*), anti-inflammatory (Cu-based), antirheumatic (Au-based), antidiabetic (based on Zn, V) drugs as well as diagnostic agents for magnetic resonance imaging (Gd-based) and radionuclide diagnostics (based on Co and Tc). The ICP-MS method is indispensable in the development of such pharmaceuticals. It can be employed both as an independent analytical method for determination of the analyte total content and in combination with suitable separation methods such as high-performance liquid chromatography or capillary electrophoresis[5, 82] for determination of forms in which the target element is present. Below we dwell in detail on examples of applications of ICP-MS as an independent method in the development of antitumour agents and problems arising in these applications.

Before preclinical and clinical trials, drug candidates are studied in detail *in vitro*. The properties such as solubility, stability with time, lipophilicity (indicating the compound ability to penetrate through cell membrane), ability to associate with the transport proteins of blood plasma can be tested directly using ICP-MS. This method also finds wide use in preclinical and clinical trials of new drugs.

Irrespective of the method of administration into the human body (oral or intravenous), the solubility of a drug should be sufficient to ensure high bioavailability. The solubility can easily be determined by ICP-MS. As a rule, saturated solutions of pharmaceuticals are diluted with nitric acid (1 vol.%), first of all, to avoid spectral interferences caused by the presence of polyatomic ions, the composition of which depends on the solvent nature.[5, 83]

To investigate the drug stability in time, ICP-MS is rarely used without being combined with separation. There are only several publications concerning this issue. Particularly, mass spectrometric study of the release of a platinum-based agent from a polymer micelle[84] and partial transformations of platinum nanoparticles isolated from a tumour[85] were reported.

The logarithm of the partition constant of a pharmaceutical in the octan-1-ol–water system ($\log P$) is used in medicine to characterize lipophilicity of pharmaceutical

agents. The so called shake-flask method is used most often to determine $\log P$ in the range from -2 to 4.[86] In this method, equilibrium distribution of the agent between two phases is attained, and the content of an element in these phases is determined by spectrophotometry, gas or high-performance liquid chromatography, atomic absorption spectroscopy or inductively coupled plasma atomic emission spectroscopy (ICP-AES). The application of mass spectrometry is rational only in boundary cases when the concentration of the compound in one phase is utterly low and cannot be determined by the listed methods. Since it is undesirable to introduce ocatan-1-ol (either pure or diluted with some organic solvent) into the instrument, the content of the substance in the organic phase is usually determined by spectrophotometry[87] or found as the difference between its contents in the aqueous phase before and after the partition.[83, 88 – 90]

The direct use of ICP-MS in the analysis of interactions of pharmaceuticals with blood plasma proteins is possible only after physical separation of protein-associated and non-associated fractions of the compound. The separation is achieved by ultracentrifugation[91 – 93] or ultrafiltration.[94 – 101] Ultracentrifugation is applied rarely and only for qualitative estimations. It is used sometimes together with co-precipitation of proteins using ethanol or acetonitrile.[82] In contrast, plasma ultrafiltrates are subjected to ICP-MS quantitative analysis. They are usually obtained by centrifugation of blood plasma through concentrators with a cutoff threshold of 10 kDa[95, 98, 100, 101] or 30 kDa.[94, 96, 97, 99, 101 – 103] The major drawback of this phase separation method consists in the possibility of non-specific association of a drug or its adducts with proteins on the membrane or other plastic parts of the filter. Mass balance should always be checked in order to avoid errors.[5]

ICP-MS is also often utilized in *in vivo* studies at the stage of preclinical and clinical trials to determine the distribution of a pharmaceutical in biological fluids and tissues after administration. Owing to high sensitivity of the method, the distribution can be detected even within a considerable time after administration and, hence, the drug excretion can be monitored.

Some examples of determination of the total platinum content in biological fluids of humans and animals treated with widespread antitumour agents are summarized in Table 4. As in the case of simple screening of elements in such substrates with the use of ICP-MS, the samples are, as a rule, diluted before analysis[91 – 101, 104 – 110, 112, 116, 117] or, which is less often, mineralized and then diluted.[104, 111, 113 – 115] Deionized water,[96 – 99, 101, 104, 111, 115] nitric acid (1 vol.%),[91 – 94, 100, 104 – 108, 110, 112] as well as mixtures such as Triton – Na-EDTA – NH_3,[95, 117] Triton – butan-1-ol – HNO_3[109, 114] can be used as diluents. After mineralization, samples are diluted with hydrochloric acid (1 vol.% – 3 vol.%)[113, 114] to eliminate the memory effects (which are

Table 4. Examples of ICP-MS determination of platinum in antitumour drugs and biological fluids.

Pharmaceutical	Sample preparation [a]	Internal standard	Calibration	Ref.
	Biological fluids: ultracentrifugable material and plasma			
Cisplatin	7 and 20 (HNO_3, 1 vol.%)	Eu	Matrix matching	91
Oxaliplatin	10 and 20 (HNO_3, 1 vol.%)	Eu	The same	92
	Biological fluids: ultracentrifugable material, ultrafiltrate and plasma			
Oxaliplatin	10 and 20 (HNO_3, 1 vol.%)	Eu	"	93
	Biological fluid: ultrafiltrate			
Cisplatin, carboplatin, oxaliplatin	100 (HNO_3, 1 vol.%)	Ir	"	94
Cisplatin	167 (Triton – Na-EDTA – NH_3)	In, Tl	"	95
	Biological fluids: ultrafiltrate, plasma and blood			
Satraplatin	25 (H_2O)	–	No matrix matching	101
Oxaliplatin	18 (HNO_3, 1 vol.%)/oxidative mineralization,		Matrix matching	
	100 and 50 (H_2O)	Ir		104
	Biological fluids: ultrafiltrate and plasma			
Cisplatin	7 and 20 (HNO_3, 1 vol.%)	Eu	The same	105
	Biological fluids: ultrafiltrate and blood serum			
Cisplatin, carboplatin	100 (HNO_3, 1 vol.%)	Bi	"	106
	Biological fluids: ultrafiltrate, plasma and urine			
Oxaliplatin	30, 100 and 200 (H_2O)	–	No matrix matching	96
	60, 250 and 400 (H_2O)	Ir	The same	97
BBR3464	10 – 100 (H_2O)	–	Matrix matching	98
JM216	10 – 100 (H_2O)	Ir	The same	99
Satraplatin	30 and 50 (HNO_3, 1 vol.%)	Ir	"	107
	100 and 50 (HNO_3, 1 vol.%)	In	"	108
–	30 and 50 (HNO_3, 1 vol.%)	Ir	"	100

Table 4 (continued).

Pharmaceutical	Sample preparation [a]	Internal standard	Calibration	Ref.
	Biological fluid: plasma			
Dicycloplatin	40 times (Triton – butan-1-ol – HNO_3)	Re	Matrix matching	109
	Biological fluid: blood serum			
Cisplatin	20 (HNO_3, 1 vol.%)	Au	No matrix matching	110
Carboplatin	Oxidative mineralization, 100 (H_2O)	Tb	The same	111
	Biological fluid: urine			
	3 or 10 (HNO_3, 1 vol.%)	Ir	Standard addition method	112
	Biological fluids: plasma and urine			
Cisplatin	Oxidative mineralization, evaporation, 10 (HCl, 1 vol.%)	In (Au)	No matrix matching	113
	Biological fluids: blood serum and urine			
Carboplatin	Oxidative mineralization, 40 (H_2O)/ oxidative mineralization, evaporation, 5 (HCl, 3 vol.%)	In, Re	The same	114
	Biological fluid is blood			
Cisplatin	Oxidative mineralization, evaporation, 10 (H_2O)	Au	Matrix matching	115
	Biological fluids: blood and urine			
Cisplatin	20 (Triton – butan-1-ol – HNO_3)	Rh	No matrix matching	116
	Biological fluids: plasma and blood			
Cisplatin, carboplatin, oxaliplatin, satraplatin, ormaplatin	24 (Triton – Na-EDTA – NH_3)	–	Calibration in HCl (10 vol.%)	117

[a] The numbers are dilution factors, the solvent is given in parentheses.

observed when 1 vol.% platinum solutions in nitric acid are used) owing to the formation of metal chloride complexes. The choice of the dilution factor is a trade-off between the requirement not to go beyond the detection limit of the element and the necessity of minimizing the matrix interferences; therefore, if the compound content in the sample is high, the dilution can also be quite high (100-fold or more).[94 – 98, 106, 108, 111] The contribution of spectral interferences to the determination error is usually evaluated by analyzing matrix-matched solutions.

Collision or reaction cell instruments [112] or high-resolution mass spectrometers [112, 114] are used less often to eliminate the interferences.

The calibration solutions for the analysis of pharmaceuticals are usually prepared in the same matrix as the samples.[91 – 95, 98 – 100, 104 – 107, 109, 115, 117] The standard addition method is seldom used because of consumption of large amounts of samples and long analysis time;[112] the internal standard method is applied additionally almost in all cases. The use of internal standard makes it possible not only to level off the possible interferences but also to take into account the instrumental drift. However, the choice of internal standards is ambiguous even in the case of a single analyte. As can be seen from the data of Table 4, elements differing from platinum by both atomic masses (Eu, In, Rh, Tb) and first ionization potentials (Bi, Eu, In, Rh, Re, Tb, Tl) can be used as internal standards. However, elements with both characteristics close to those of platinum such as Ir [94, 97, 99, 100, 104, 107, 112] and Au [110, 113, 115] are used most often, although the injection of gold into the mass spectrometer is complicated by memory effects.

As in the case of analysis of biological fluids, concentric nebulizers are mainly used in the analysis of pharmaceuticals,[91, 92, 94, 104, 112] while cross-flow [96, 105] and ultrasonic [114] nebulizers are used less often.

In recent decades, the problem of spectral interferences has been studied fairly comprehensively and many methods for eliminating these interferences have been worked out. The most efficient method of decreasing spectral interferences is the use of high-resolution mass spectrometers (double-focusing mass spectrometers). A less expensive method consists in the use of various cells in which complexes interfering with the analyte ions are removed from the flow upon collisions with neutral atoms added in the cell, *e.g.*, helium atoms. Much less attention has been paid to the analysis of non-spectral interferences emerging at different stages (during introduction of liquid samples into the nebulizer or aerosol formation) and related to changes in plasma parameters such as temperature or electron density, depending on the matrix composition and the conditions of ion beam propagation through the mass filter.

The effects of non-spectral interferences on the results of ICP-MS determination of elemental composition of biological fluids and antitumour drugs are considered below.

III. Mechanisms of non-spectral interferences

The effect of sample composition on the results of analysis of biological and pharmaceutical samples can formally be divided into effects of acids (first of all, of nitric acid added for mineralization), accompanying elements (elements of dissolved inorganic salts) and organic substances (both solvents and sample components).

III.1. Effects of acids

Two types of acid effects are usually distinguished.[118] The so called steady state effects consist, most often, in suppression of signals of determined elements when solutions with high acidity are analyzed.[119] The reasons of the suppression are changes in sample uptake processes, aerosol production, transport of solvent and analyte, as well as in ionization processes in the plasma. The degree of the suppression depends on the concentration and nature of the acid. Along with the steady state effects, transient acid effects are observed [120] when consecutive analysis of samples with different acid contents is carried out. In this case, either sharp decrease or increase in the signals (up to 50%) caused by changes in the physicochemical properties of the matrix may be detected for 5–25 min.

As noted above, the steady state acid effects may affect various processes occurring in the course of analysis, which can be divided into two groups:[121]

— processes which depend on physical characteristics of the solution (supply of the sample to the nebulizer, aerosol formation, transport of the solvent and the analyte);

— processes occurring directly in the plasma (not only ionization, but also the preceding desolvation, evaporation and atomization).

Certainly, physical properties of solutions of acids may significantly differ from those of water. Of particular note are the properties that are most important for the analysis, that is, viscosity, surface tension, density and volatility. Some physical characteristics of solutions of nitric and hydrochloric acids of various concentrations are given in Table 5. Clearly, the viscosity and the density largely determine changes in the solution behaviour.

The dependence of the sample uptake rate on the acid content may appear if the most common pneumatic nebulizers operate only in the free aspiration mode. It is a typical mode for concentric nebulizers, which are often used in clinical laboratories. The whole process of sample uptake can be described in this case by one modified Poiseuille equation, from which it follows that with an increase in the sample viscosity, the rate of its uptake is reduced. The latter fact may result in suppression of analyte signals due to decrease in the analyte amount entering the instrument.[121, 122] The solution viscosity is higher for solutions with increased acidity, as can be seen from the data of Table 5. If a sample is fed by a pump, such as a syringe or peristaltic pump, this effect is partially or completely eliminated as has been demonstrated, for instance, in studies using ICP-AES.[122–124]

Table 5. Physical characteristics of solutions of nitric and hydrochloric acids at 25 °C: acid concentration (c), viscosity relative to water (η), surface tension (σ) and density (ρ).[121]

c (mass %)	η	σ /mN m^{-1}	ρ /g cm^{-3}
	HNO_3 *solution*		
4	1.014	72.15	1.022
30	1.397	68.75	1.180
	HCl *solution*		
4	1.057	72.45	1.017
30	1.896	65.75	1.149

The acid effect on the Sauter mean diameter ($D_{3,2}$), which is one of the most important characteristics of primary aerosols, in the case of application of pneumatic nebulizers can be roughly estimated by the Nukiyama–Tanasawa equation, which relates $D_{3,2}$ to the physical characteristics of the sprayed solution. However, the equation holds only for certain ranges of viscosity, surface tension and density, and also when nebulizers with impactors are used; incorrect theoretical estimates are obtained in other cases.[121] It has been shown experimentally that the acid effect on the size distribution of primary aerosol droplets is different for different sample uptake modes.[124] If the solution is transported by a carrier gas flow, an increase in the nitric or hydrochloric acid concentration in the solution leads to a finer aerosol. This is due to the fact that with increasing sample viscosity and, hence, decreasing nebulizer load at a constant gas flow rate, the kinetic energy of argon per unit volume of the liquid sample becomes higher. However, when pumping is used, higher acid content leads to the formation of aerosols enriched with large- and medium-size droplets. For acids with lower viscosity (such as nitric or hydrochloric acid), the difference between the mean diameters of droplets formed from diluted and more concentrated solutions is not substantial.[118, 124]

The effect of the presence of acid on the tertiary aerosol (discharged from the spray chamber) is more unambiguous: the higher the acid concentration in the solution, the finer the aerosol.[124, 125] This effect is more pronounced in the free aspiration mode. A possible explanation of this regularity consists in the lower probability for larger droplets to leave the spray chamber at a higher density of the solution they consist of, because of their higher inertia. Another important characteristic serving as a sort of indication of the acid effect on the solution transport through a spray chamber, namely, the aerosol volume concentration (VC), does not change at all or slightly increases upon a slight increase in the acid concentration.[124] It was also noted that the VC value depends on the design of the spray chamber.[126] When a cyclonic chamber was employed, VC was not changed on going from water to 3 M HNO_3, whereas a twofold increase in the VC was observed in this case with a double-pass chamber. Additionally, it was demonstrated [118] that one more quantity, *viz.*, the total volume of droplets passing through cross-section in a given direction per unit time, decreases with an increase in the nitric acid concentration from 2 vol.% to 25 vol.%. However, the appearance of this effect depends not only on the design of the whole spraying system, but also on the argon flow rate: the higher the rate, the more pronounced this effect.

The overall acid effect on the mass transfer in the solution can be estimated by measuring the total transportation velocities of the solvent (S_{tot}) and the analyte (W_{tot}). The latter characteristic is more important, as the analytical signal should be proportional to the mass of the analyte that has been injected into the plasma. The difference between the S_{tot} values for water and HNO_3 and HCl solutions is not so critical as in the case of more viscous

mineral acids like H_2SO_4 and H_3PO_4.[127] It was already noted above that primary and tertiary aerosols of HNO_3 and HCl are rather fine irrespective of the sample intake mode. In addition, high volatility of solutions of these acids also promotes minor if any changes in the S_{tot}. In the first approximation, W_{tot} decreases if a solution contains an acid,[121] a stronger decrease in the analyte transport velocity occurring for solutions of viscous acids introduced in the free aspiration mode. In the case of HNO_3 or HCl, significant changes in W_{tot} can be observed only if the acid contentration in the solution is high (>30 mass %).[124] In the free aspiration mode, W_{tot} depends on the amount of sprayed fluid, while in the case of pumping, it depends on the size distribution of aerosol droplets. It was also established that the W_{tot} value can be affected by the flow rate of the carrier gas through the nebulizer[118] and by design features of the spray chamber.[126] The higher the rate of argon flow, the less noticeable the W_{tot} decrease. The use of a cyclonic chamber proved more preferable than the use of a double-pass chamber.

The acid effect on the processes occurring in the plasma depends strongly on the operating parameters of the instrument, first of all, on the argon flow rate through the nebulizer and/or generator power.[119] The use of the standard mode in the case where the maximum sensitivity of the mass spectrometer has been adjusted using a special solution containing elements with different atomic masses and 2 vol.% of HNO_3 always results in suppression of signals of more acidic samples. This can be explained by less effective ionization of elements, especially those with high first ionization potentials, under these conditions due to higher load of plasma with nitric acid and, as a result, lowering its local temperature.

The point is that the plasma energy consumed for evaporation and atomization of HNO_3 molecules is much higher than in the case of H_2O molecules and the contribution of nitric acid decomposition products (having higher thermal conductivity than argon) to the energy transfer to the central channel is much lower than the contribution of water decomposition products.[119] In addition, at lower plasma temperature, the transmission of ion optics for charged particles with lower average kinetic energy decreases.

In the robust operating mode, in which the argon flow rate is decreased in comparison with the standard characteristcs, while the same or increased generator power is used, the signal suppression is eliminated owing to higher efficiency of desolvation, evaporation, atomization and ionization processes. This is related to two factors that increase the residence time of the sprayed solutions in the high-temperature zone. First, aerosol moves more slowly from the tip of the torch injector to the plasma when the argon flow rate decreases; second, the region of sharp temperature difference (from 100 to several thousand degrees) is displaced to the injector tip.[118] It was also noted that optimization of the instrument operating parameters for sampling depths of <15 mm results in lower argon flow rates and higher power being established, which allows more efficient levelling off of the acid effect.

Nevertheless, since the argon flow rate through the nebulizer affects also the processes depending on the physical properties of the sample, it is often impossible to determine reliably the reasons for signal changes and find out a way of elimination of the influence. In other words, there is no univocal criterion for the choice of robust parameters in ICP-MS (in contrast to ICP-AES).[119]

It has already been mentioned above that the acid effect depends on the design of the sample spraying system or, more exactly, on the nebulizer and spray chamber types.[121] However, no clearly marked regularity has been revealed in this connection. The only indubitable conclusion is that application of cyclonic spray chambers is more reasonable.

Apart fom the methods which are widely used in clinical laboratories such as matrix matching, standard addition and internal standard methods, as well as robust operating conditions, purely instrumental methods can also be used to reduce the acid effect. One of them consists in refusal of the application of spray chambers and injection of samples into the plasma through a direct injection nebulizer.[128–130] Another way is the use of desolvation systems promoting vaporization of a large fraction of the solvent present in the primary aerosol and subsequent elimination of the vapour using a condenser or a membrane.[131, 132] Electrothermal vaporization as a sample injection technique can also be efficient.[133–135] In this case, the acid is also preliminarily vaporized. Besides, application of mixed $Ar-CH_4$ plasma can also be suitable for the same purpose.[136]

The transient effect mentioned above appears when one solution is changed for another with higher or lower acidity. For example, if a solution with 10 vol.% of HNO_3 is initially supplied into the sample spray system for a while and then it is quickly replaced by a solution containing 2 vol.% of HNO_3, the analyte signal intensities sharply increase up to a value higher than the value attained upon long-term supply of the less concentrated solution (which corresponds to a constant influence of the 2 vol.% HNO_3 solution on the signals). This effect disappears in several minutes and the equilibrium value corresponding to the new constant acid concentration is achieved for the signals. A similar pattern is observed in the opposite case: a temporary decrease in the signal intensities also takes place if the acid concentration is increased from 2 vol.% to 10 vol.% (Fig. 1).

It is important to note that the signal intensity change and the relaxation time depend on the acid nature and concentration. The larger the difference between the acidities of solutions, the sharper the change in the signal

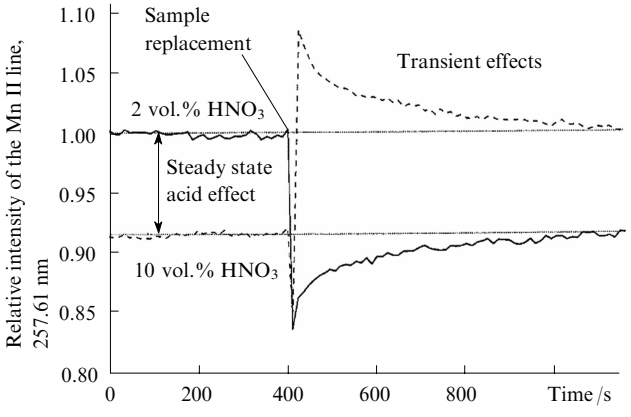


Figure 1. Example of appearance of the transient effect in the ICP-AES determination of manganese (1 mg litre^{-1}) in nitric acid solutions (2 vol.% and 10 vol.%).[120]

intensity. The effect is more pronounced at reduced sample uptake rates and lower nebulizer argon flow rates, which is possibly associated with the aerosol residence time in the spray chamber. Varying the generator power virtually does not affect elimination of this effect, although the temporal effect of nitric acid on elements with different first ionization potentials is levelled off at higher power. All the considered trends are the same for different pneumatic nebulizers and generators.[120]

In our opinion, the transient effect is caused by the change in the intensity of aerosol vaporization in the spray chamber. Water vapour appears in the chamber as a result of vaporization of both the preceding sample remaining on the chamber walls and aerosol droplets of a new sample supplied to the instrument, and these vaporization processes compete in some way. The relative contribution of each of these processes to the formation of water vapour depends on the acidity of the solutions. Water vapour pressure is known to decrease with an increase in the acid content in the sample. If the system was conditioned with a solution with a high acid concentration before introduction of the test sample, relative content of water vapour in the spray chamber decreases. If an aerosol formed from a solution with a lower acid content is introduced into this relatively dry atmosphere, its vaporization should be more intense. Therefore, the amount of the analyte injected into the plasma should increase as a result of transportation of smaller droplets containing higher analyte concentration. The situation should be inversed on going from a solution with low acidity to a more acidic one.

In order to avoid the transient acid effect, matrices of control and calibration solutions should be chosen in accordance with the acidities of test samples and deionized water should be never used for washing; otherwise, for obtaining accurate results, it would be necessary to condition the system between successive samples for a long time (up to 25 min). This effect can also be eliminated by instrumental means: as noted above, with an increase in the sample uptake rate or the nebulizer argon flow rate, the time required to reach the equilibrium state corresponding to the new steady state acid effect usually decreases; application of direct injection nebulizers and heating the spray chamber walls are also efficient.[120]

III.2. Sample composition effects

Two types of effect of sample composition on the results of ICP-MS analysis are usually distinguished.[137] The so-called reversible effect results in a change in the analytical signal only during sample supply into the spectrometer, irreversible effects are characterized by gradual decrease in the signal intensity and persist even after sample injection has been completed. This is related to deposition of salts and oxides of the sample matrix elements on the surfaces of cones and ion optics of the mass spectrometer, thus lowering the throughput of the spectrometer for the analyte, mainly due to decrease in the cone tip diameters. In addition, it was indicated[120] that an effect analogous to the transient acid effect can appear in the analysis of solutions with different contents of salts since the origin of such effects is universal and not inherent in particularly acid matrices.

On the whole, high concentration of matrix elements in the solution may bring about either suppression[127, 138–147] or increase in analytical signals, or none of these effects.[148–150] It was shown experimentally[149] that all of these options were involved in determination of Ge, As and Se in solutions of matrix components (1 mass %) depending on their nature, *viz.*, signal was suppressed in Na or K solutions, increased in Cl, S or C solutions and did not change in N or P solutions. Similarly, suppression of Cr, Fe, Mn, Ni, Cu, Zn, As, Ag, Cd, Sn, Hg and Pb signals was observed in 0.01 M solutions of B, Al and U, growth of these signals occurred in solutions of Na, K, Mg and Ca and no effect was observed in a Li solution of the same concentration.[150] It is interesting that in Ref. 149, supression of As signals by Na and K was observed, whereas in Ref. 150, these signals, conversely, increased. In addition, the effect of accompanying elements may be manifested as a change in the background current. Upon an increase in concentrations of Bi or matrix elements with the first ionization potentials of >6 eV, the intensities of signals of argon-containing ions (Ar^+, ArH^+, ArO^+ and Ar_2^+) decrease, while an increase in the content of Na or elements with ionization potentials of <6 eV lead to the opposite result.[142] As can be seen from these examples, this sort of non-spectral matrix interferences is rather complicated; therefore, it is reasonable to start with discussion of its possible mechanisms in more detail.

The effect of matrix components, first of all, of easily ionizable elements begins to emerge in a spray chamber. While excessive presence of some components in the solution virtually does not affect the properties of primary aerosol irrespective of the nebulizer used,[127] the tertiary aerosol characteristics substantially change. The reason is that the droplets formed by a pneumatic system carry an electric charge on their surfaces, and the larger the salt content in the solution, the higher the charge. Owing to a higher frequency of fission of these charged droplets, a finer tertiary aerosol is formed.[151] At the same time, the solvent transport rate, S_{tot}, remains invariable as in the case of acid effect and, possibly, due to the analogous reasons.[127] The W_{tot} value usually decreases, probably, because of redistribution of hydrated ions in the aerosol [aerosol ionic redistribution (AIR)] due to their different ability (depending on their size) to migrate towards the electrical double layer at the droplet/air interface.[152] Since the analytical signal is proportional to the amount of the element entering the plasma, the W_{tot} decrease can result in a signal intensity decrease.

There are much more mechanisms explaining the reversible effect of accompanying elements directly in the plasma, the interface or the ion optics. Usually, several possible mechanisms are proposed by the authors of the same study.

The simplest interpretation of the decrease in the signals of analytes with relatively high ionization potentials consists in suppression of their ionization in the presence of salts of more easily ionizable elements due to an increase in the efficiency of the ion–electron recombination with growth of the electron density in plasma.[138–141, 143, 146, 148]

There are several obvious reasons for the situation when the extent of signal decrease depends on the atomic mass. If heavier accompanying elements supress more strongly the signals of light analytes, this is attributable to scattering of the analyte upon collisions with the matrix component particles in the area of supersonic expansion between the sampler and the skimmer.[139–141] This effect can be most striking for lithium in a matrix containing uranium.[141]

However, it is not the only version for interpretation of this effect. It can also be associated with the appearance of the positive space charge in the high-vacuum part of the instrument directly downstream of the skimmer because of intense vacuum-induced withdrawal of electrons from the ion beam.[140, 142, 144, 145, 148] In the absence of accompanying components, the space charge is mainly formed by Ar^+ ions. With the increase in the concentration of matrix elements, their charges start to dominate in the space charge, thus increasing the charge density and, as a result, increasing scattering of the ion beam mainly for light isotopes (with masses < 80); the heavier the matrix ions, the more intense the scattering (Fig. 2).

If more substantial changes of analytical signals are observed for elements with higher atomic masses, the interferences are most possibly caused by changes in radial diffusion in plasma or by deposition of salts on the cone surface.[143, 146, 148] In fact, the increase in the electron density in the central plasma channel upon supply of solutions with high salt concentrations can result in appearance of so-called ambipolar diffusion, which more strongly affects light analytes. As a result, elements with lower atomic masses are accumulated in close vicinity of this channel. Since temperature in this area is higher, the degree of ionization of these elements is increased. The formation of a thin layer with lower thermal conductivity on the cone surface also enhances this effect. Indeed, because of salt deposition, the temperature near the sampler increases, which markedly reduces the ion–electron recombination, especially for light elements because of their high concentration in this area.

Taking into account the presence of a large number of explanations, researchers arrived at the consensus that the real effect results from a combination of the given interpretations. In addition, many researchers [140, 143, 145, 146] assert that the predominant mechanism, as well as the sign and the extent of the effect may be determined by the design of the mass spectrometer and its operating parameters. In particular, it was directly indicated [140, 143] that for every instrument, there is a specific parameter setting that minimizes the effect of accompanying elements (robust operating parameters), whereas discrepancies encountered in the literature result from different instrument configurations. Note also that the class of mass spectrometer also affects the intensity of interference.[127, 143] It is considered that the use of high-resolution instruments gives less significant non-spectral interferences than the use of quadrupole mass spectrometers. This is related to acceleration of ions up to higher energies in the former type of mass spectrometers.

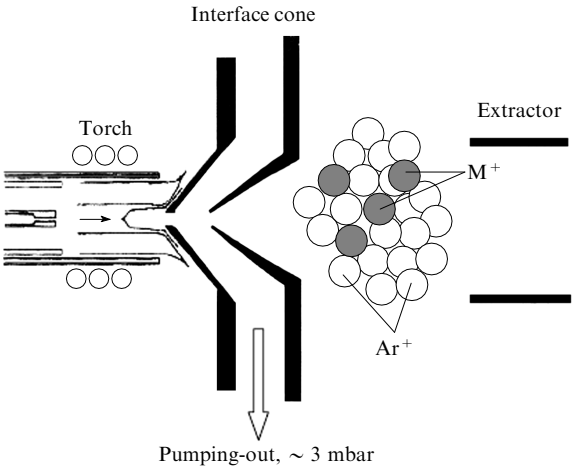


Figure 2. Schematic diagram of space charge formation in the mass spectrometer interface.[144]

Despite the complexity of the problem in question, the operating parameters play the key role in levelling off of these effects, the principal regularities being more or less universal. Among the settings, a special place is assigned to the argon flow rate through the nebulizer,[141–143, 145, 153] as in the case of acid effect. It was experimentally demonstrated that the decrease in the flow rate results in minimization of the effects of accompanying elements, while at high flow rates, not only substantial suppression, but also an increase of signals can occur.[141] Indeed, upon a decrease in the flow rate, the density of matrix ions forming the space charge decreases in comparison with the density of Ar^+ ions, resulting in a decrease in the interferences according to the mechanism discussed above. The plasma temperature and the sample residence time in the central channel also increase in this mode; this results in more efficient ionization of elements and suppression of the ion–electron recombination. However, since the detection sensitivity decreases $\sim$2–3-fold [153] in this operating mode, correct choice of the argon flow rate is based on a compromise between a low detection limit and minimized non-spectral interferences.[143]

The variation of other instrumental parameters relevant for this goal, such as the sample uptake rate, generator power, ion sampling depth and ion optics characteristics, is considered to be less efficient.[141, 143, 153] Nevertheless, it was established that the decrease in the sample uptake rate reduces the interferences.[153] Setting the generator power above the value corresponding to the maximum detection sensitivity leads to more efficient energy transfer from the periphery to the central channel in the plasma, which is beneficial for minimization of non-spectral interferences.[141–143, 145, 153] An increase in the fraction of doubly charged ions in the plasma is perhaps the only shortcoming of this procedure. There are different opinions on the influence of the ion sampling depth, which is the distance from the load coil to the sampler tip. It was indicated that this distance affects the appearance of the effects of accompanying elements.[139] At the same time, it was demonstrated [140] that an increase in the ion sampling depth, like sample dilution, favours elimination of interferences because of the lower load of plasma with matrix ions.[141, 145, 146] However, this contradicts the facts established by other researchers,[143, 146] indicating interference minimization upon a decrease in the distance between the coil and the sampler. The role of ion optics parameters is also ambiguous,[127, 139, 140, 145, 153–155] although some recommendations concerning setting the appropriate first extraction lens voltage are given in some publications.[140, 154, 155]

The inner diameters of sampler and skimmer orifices can sometimes be critical for minimization of non-spectral interferences caused by accompanying elements.[139, 155] In fact, if the skimmer orifice is larger than the sampler orifice, the matrix effects are more pronounced only for analytes with relatively high first ionization potentials. Otherwise, signals of all elements are suppressed, and the minimum

concentration of matrix elements that does not result in any changes decreases.[155]

The key point in the analysis of solutions with high contents of salts is the choice of the nebulizer. There are several types of nebulizers suitable for the analysis, *viz.*, Babington and Hildebrand nebulizers, V-groove and cone-spray nebulizers.[3] In contrast to these nebulizers, concentric and direct injection nebulizers, which are also often used, are prone to fast clogging. The same problem is also typical of ultrasonic nebulizers,[138] the use of which, apart from the irreversible effect of accompanying elements, induces also more pronounced reversible interferences because of a 3–10-fold increase in the amount of aerosol introduced into the plasma. If the possibility of clogging of the orifices of direct injection nebulizers is eliminated, the application of these nebulizers will reduce the influence of matrix components.[156]

Among other, not considered above, ways of elimination or minimization of non-spectral interferences of this type, note various methods of physical separation of the analyte and the matrix (precipitation, electrodeposition, co-precipitation, liquid–liquid extraction, sorption on ion exchange and chelating resins), the use of flow injection systems of sample supply to the mass spectrometer,[3, 127, 157] as well as addition of nitrogen to the argon plasma.[3, 147, 158] The last-mentioned approach is equivalent to robust operation mode.

III.3. Effects of organic compounds

The samples which are analysed using ICP-MS usually represent aqueous solutions of inorganic salts and acids. However, there are numerous examples of determination of elements in more complex mixtures. Indeed, as discussed above, biological fluids, which represent mixtures of organic substances, are often diluted with solutions comprising Triton, EDTA, TMAH and butan-1-ol or analogous alcohols. Another organic substance quite usual for clinical mass spectrometry is octan-1-ol, which is typically diluted with lower alcohols in view of its high viscosity and low solubility in water. It is applied in studies of lipophilicity of metal-containing drugs. Therefore, considering the effect of organic compounds, first of all, solvents because of their usually high content in the samples, is of high importance.

Like the acid effect, the effect of organic matrix can appear both in the sample injection system and in the plasma.[127]

The effect of organic solvents on the sample uptake system is most pronounced among the known non-spectral interferences because of significant changes in physical characteristics of solutions containing these solvents. Depending on the nature and concentration of the added solvent, a substantial decrease in the surface tension and significant change (typically, a decrease) in the viscosity of the dilute solution in comparison with the aqueous solution take place. As a first approximation, these changes lead to formation of a finer primary aerosol.[159–162] With time, the droplet size distribution in this aerosol can shift towards larger (although still smaller than in the aqueous solution) diameters because of virtually complete evaporation of small droplets owing to higher volatility of aqueous organic mixtures.[163, 164] In addition, the density of such solutions usually decreases, for example, as in the case of solutions of lower aliphatic alcohols or acetone.[127] The latter fact along with those specified above favours more efficient aerosol transport to the plasma. In other words, the presence of organic solvents in the samples implies higher S_{tot} and, what is more important, W_{tot}.[161, 162, 165, 166] This entails a growth of intensities of the analyte signals. However, the increase in the aerosol transport velocity may result in an excessive load of plasma with organic matrix components, which, in turn, can lead to increase in the signals of analytes with relatively high first ionization potentials owing to the charge transfer from C^+ to the analyte isotope. Meanwhile, signal decrease is also possible because of the decrease in the analyte ionization following lowering of the plasma local temperature.

Actually, an excessive supply of organic solvents into the plasma can significantly change its thermal characteristics, first of all, decrease its temperature because additional energy is required to vaporize and dissociate the solvents. As a result, a decrease in the intensities of analyte signals is possible, and this effect was repeatedly noticed in the ICP-AES analysis.[127] In the ICP-MS analysis, an increase in the signal intensities was predominantly observed, and this could not be always (or completely) attributed to processes occurring in the injection system. Among the mechanisms that account for this effect most adequately, note charge transfer from the C^+ ion to an analyte particle[161, 162, 165–172] and spatial shift of the plasma zone with a maximum density of analyte ions.[161, 162, 169, 170, 173, 174] Besides, an excess of organic matrix in solutions often causes non-robust operation of the analytical system due to formation of a deposit consisting of non-destroyed organic substance or soot on the inner surfaces of torch, injection tubing or interface cones (Fig. 3).[76, 165, 167, 168]

On the whole, both a decrease and increase in the signal intensities are possible, depending on the concentration of organic compounds, ionization potentials and atomic masses of analytes, as well as on the mass spectrometer operating parameters, which are inseparably linked with these characteristics.[149, 161, 162, 165, 166–174]

The content of organic matrix in the sample solution plays a key role in the appearance of non-spectral interferences.[161, 165, 169, 170] It was repeatedly emphasized in different studies that the increase in the signal intensities is observed only at low or moderate concentrations of organic compounds. The total dependence of signal changes on the

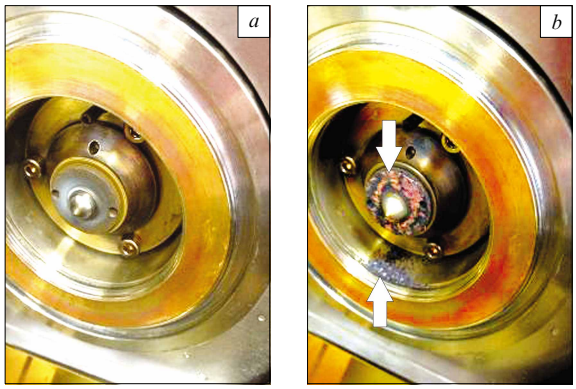


Figure 3. State of the skimmer before (*a*) and after (*b*) analysis of thirty samples of diluted whole blood. The arrows point to the deposit.

mass fraction of organic substances has a maximum, and high concentrations lead to a decrease rather than increase of signal intensities as compared with the intensities observed in aqueous solutions. This is associated with lowering of the plasma temperature upon injection of the non-aqueous matrix. As in the case of acid and accompanying element effects, this effect can be controlled by choosing robust operation mode of the instrument. Indeed, increasing the generator power and decreasing the argon flow rate through a nebulizer should result in the increase in the plasma temperature and the analyte and solvent residence times in the plasma, and, hence, in a decrease in the S_{tot} and W_{tot} values. Therefore, a compromise argon flow rate should be chosen.[127]

The quite frequent substantial (several-fold) increase in the signals of elements with relatively high first ionization potentials (from 9 to 11 eV) such as As, Au, Be, Hg, I, Se, Te and Zn[161, 162, 165–172] can be explained by the charge transfer from the carbon cation. The C^+ cation, formed in quite large amounts ($\sim$5%) even at standard operating parameters of the instrument, is able to add electrons from other atoms. An important condition is that the first ionization potential of this atom should be lower than that of carbon (11.26 eV). The most pronounced effect of the charge transfer is observed for analytes the ionization potentials of which differ from the carbon ionization potential by $\sim$1–2 eV (see the list of elements above). The effect of mass spectrometer settings is obvious in this case: a decrease in the generator power and increase in the argon flow rate (*i.e.*, deviation from the values of robust operating mode) should diminish the gain in signal intensity as a result of the decrease in the C^+ concentration caused by decreasing plasma temperature under these conditions.

To explain the sample composition effects on signals, a zonal model of the plasma was suggested.[173] This model accounts for the effects of organic solvents, as well as any other matrix on the signals of elements depending on their atomic masses and instrument operating parameters. According to this model, a zone corresponding to the maximum signal intensity for a given matrix exists for each element in the central channel of inductively coupled plasma, and the location of this zone is determined by the optimal argon flow rate. The latter depends on the atomic mass of the analyte: the heavier the element, the lower the flow rate. Therefore, for invariable instrument settings, elements occur under uneven conditions, except for the element for which the optimization was performed. On going to a different matrix (in the composition or concentration), the plasma zones with the maximum density of the analyte ions would shift,[161, 162, 169, 170, 173, 175] *i.e.*, the location of the zones with respect to the sampler orifice would change. This leads to either a decrease or increase (in comparison with the preceding matrix) in the analyte signals, including the element for which the optimal conditions were initially chosen, and the optimal rate for this element would also change (most often, the introduction of organic solvents decreases the rate).

In addition to the above approaches to elimination or minimization of organic solvent effects by optimal tuning of the instrument operating parameters, there are also other methods, which are purely instrumental. They are mainly aimed at lowering the load of the mass spectrometer with organic substances. For this purpose, one may use flow injection sample uptake,[162, 173] desolvation systems (the simplest of which is a cooled spray chamber)[127] or introduction of oxygen into the argon flow (up to 20%, although the best results are achieved upon the introduction of an amount stoichiometric to the amount of carbon contained in the sample, *i.e.*, an amount sufficient to burn all carbon).[76, 165, 173]

IV. Choice of internal standard for inductively coupled plasma mass spectrometry

Internal standards are often used in the ICP-MS analysis to check the robustness of instrument operation, correct signal drift and eliminate non-spectral matrix interferences.[3] The analyte serving as an internal standard should meet the following major requirements:[176, 177]

— complete absence or low (undetectable) content in the samples;

— absence of spectral overlaps affecting the signal of this isotope in a given matrix;

— absence of spectral interferences caused by the internal standard itself for the target elements;

— similarity of the physical and chemical characteristics of the standard and the target elements;

Whereas the first three requirements do not raise doubts, the requirement of similarity of the physical and chemical characteristics of the internal standard and the analyte is still debated.

Indeed, two firm, although somewhat contradictory, opinions were established back in the late 1980s–early 1990s. According to these opinions, the key criteria for selecting the internal standard were either the similarity of both the atomic masses and the first ionization potentials[176, 178–181] or only the atomic masses of the standard and the analyte.[182–184] The principal importance of the latter characteristics for correcting the lack of robustness of the instrument operation is explained, first of all, by the fact that in the scanning mode of measurements, two isotopes with similar masses are detected by the analyzer at approximately the same time, which mitigates the effect of random fluctuations on the signals. Some authors attempted more detailed analysis of this problem with the use of statistical approaches, or more precisely, various chemometric techniques: least squares method,[176, 181, 183, 185] cluster analysis[177] and principal component analysis.[185] Particularly, selection of the internal standard on the basis of differences in not only the first ionization potentials, but also kinetic energies of the ions formed in plasma, bond energies of the element in its oxide and hydride and also electronegativities has been reported.[177] Even a larger number of characteristics was investigated in another paper[186] where in addition to the atomic masses and first ionization potentials, attention was paid to the second ionization potentials, mobilities of ions, thermodynamic characteristics of the solutions under analysis and the total charges.

Undoubtedly, the operating parameters of the mass spectrometer should be taken into account, in addition to the analyte nature, in the selection of the internal standard. It is well known that in the case of ICP-AES in the robust operating mode, at least, in the case where the matrix effect (from a certain matrix but not a mixed one) on the plasma processes can be eliminated by the instrumental method, any single internal standard can be used.[127] This is due to the fact that the effects arising in the sample injection

system during the aerosol formation and transport are expected to equally appear in the analysis of any analytes irrespective of their physical or chemical properties. However, the latter statement is not completely true if one takes into account the AIR theory mentioned above, which implies some differentiation of elements in the course of tertiary aerosol formation. Since the non-spectral matrix interferences are typically stronger and more intricate in ICP-MS, first of all, due to the presence of an additional ion extraction and focusing unit and also because of the dependence of the matrix effect mechanisms on the instrument design and configuration, examples of application of one internal standard in the multielement analysis of matrices of complex composition are rare. The situation is aggravated by the fact that in contrast to ICP-AES, in ICP-MS, there is no exact definition of robust operating parameters. However, there are publications in which instrument tuning made it possible to simplify the matrix interferences to one particular mechanism and, hence, to reveal a single characteristic responsible for the selection of internal standard.[3]

On the whole, the simultaneous use of several internal standards selected on the basis of different criteria is more common in the multielement analysis. Of the above considered cases of ICP-MS determination of elements in biological fluids, a single internal standard is used only in the case of matrix-matched calibration solutions, standard addition calibration (mainly, to correct the instrumental drift and non-robust operation of the spectrometer)[12, 15, 17, 23, 24, 30, 31, 35, 50, 51, 54, 58, 61, 65, 68 – 72] and/or, which is trivial, in determination of one or two elements.[8, 13, 20, 38, 39, 91 – 94, 97, 99, 100, 104 – 112, 115, 116] If calibration solutions are prepared without matrix matching, one element can be used as an internal standard only if a substantial ($\sim$50-fold) dilution of samples is carried out[13, 25, 60] or if they are supplied into a mass spectrometer using a flow injection system,[14] which significantly mitigates the appearance of non-spectral interferences. Otherwise, understated data are obtained for some elements.[59]

If the source of spectral overlap with the analyte is the isotope of internal standard, it is sometimes recommended to use, as the standard, the polyatomic ions generated from the plasma-forming gas or the matrix of the analyte solution, such as Ar_2^+, ArO^+, N_2^+, ClO^+, SO^+ or MO^+, where M is an isotope of the target element.[179, 187] However, even in these studies, the application of this expedient is limited by the requirement of similarity of the atomic masses of the target elements. The difference between the mechanisms of formation and distribution in plasma of such ions and the analyte ions can also interfere with the use of this approach.[157]

A single internal standard can also be used if an additional mathematical correction of the measured signals is performed with so-called common analyte internal standardization (CAIS) technique.[188, 189] Indeed, according to CAIS, any element can be used as an internal standard irrespective of its physical and chemical characteristics both to take into account the instrumental drift of the mass spectrometer and to eliminate non-spectral matrix interferences. Note that at least two internal standards differing by their atomic masses and first ionization potentials are typically required for levelling off these two effects simultaneously. The method is based on preliminary finding of a linear mathematical function relating the analyte signal intensity correction coefficient to the change in the signal intensity of the internal standard in some matrix with respect to water. The authors of this approach claim that the procedure does not require substantial time and special mathematical knowledge; nonetheless, CAIS has not yet been extended to matrices more complex than river or ground waters. For certain, a significant increase in the number of control solutions and substantial complication of the used mathematical functions will be required on going to more complex systems.[3]

V. Conclusion

As follows from the above consideration, ICP-MS has a leading position in the field of element analysis of biological fluids and development of pharmaceuticals. Among the methods used to mitigate a major drawback of this method — matrix interferences — various types of calibration are used in clinical practice, *e.g.*, matrix matched calibration, standard addition calibration and the internal standard method, the latter being typically combined with the two above approaches.

Undoubtedly, the application of these approaches is associated with additional difficulties as compared with simpler approach, which consists in construction of the calibration plot using HNO_3 solutions (1 vol.%). For instance, the use of matrix-matched calibration requires preliminary evaluation of the composition of the sample solution, and, therefore, development of a dedicated procedure for determination of the target analyte in different samples is necessary. Substantial time consumption and excessive expenditure of samples form the bottleneck of the standard addition method. The necessity of selecting suitable elements to be used as internal standards and the absence of reliable criteria for this selection complicate the application of the internal standard approach. At the same time, little attention if any is paid to instrumental options for eliminating or minimizing the effects of matrix components, although these options could appreciably simplify the analysis due to the use of a simple (without selection of a matrix) calibration.

Non-spectral matrix interferences are of a rather complex nature. Not only the appearance of even one type of interferences can be diverse, but also their possible mechanisms are diverse. The situation is aggravated by the fact that it is difficult to compare the data available in the literature since non-spectral effects also depend on the instrument design and operating parameters, which are often not described in sufficient detail by the authors of a publication. All of these factors lead to the situation that, despite the more than forty-year experimental and theoretical study of this problem, it is still difficult to estimate the effect of a particular matrix component on the results of analysis and, what is more important, to eliminate this effect completely by the instrumental methods alone.[125] It is always necessary to use additionally some other method. An obvious approach which can supplement the calibration without matrix matching is the internal standard method. The above discussion of the available published data shows that the criteria for the choice of an internal standard and the opinions concerning the possibility of using a single element for this purpose without additional application of some mathematical techniques are contradictory. In this connection, worth noting are the studies[77, 78] suggesting a

procedure for determination of a wide range of analytes in biological fluids and pharmaceuticals on the basis of calibration using HNO_3 (1 vol.%)-based reference solutions and only one (moreover, anyone) internal standard.

It is necessary to touch upon an additional aspect of the application of ICP-MS in clinical laboratories. Despite all commonly recognized analytical advantages mentioned in the introduction, the method has one substantial disadvantage, which consists in the high cost of spectrometers (the cheapest instrument with a quadrupole mass filter costs ca. 150 – 200 thousand US dollars) and rather high cost of the analysis including the costs of high-purity argon, pure chemicals and consumable materials. Therefore, if determination of quite a small number of analytes is required, and their expected contents are >100 μg litre^{-1}, it is more reasonable to use atomic absorption spectroscopy with electrothermal atomizers. If it is necessary to determine a dozen or several dozens of elements with low content in the samples or if there is some limitation on the mass or volume of the sample, ICP-MS is the method of choice.

In analytical laboratories of large clinics and pharmaceutical companies in the USA, Japan and EU countries, ICP-MS instruments of different types have been widely used for more than ten years. Unfortunately, the difficult economic situation of the Russian medicine hampers the implementation of these instruments and analysis techniques in the practice of Russian clinical laboratories.

The review was prepared with a financial support of Russian Foundation for Basic Research (Project Nos 12-03-00804-a and 16-03-00428 A) and the Presidium of the Russian Academy of Sciences in the framework of the Program 'Development and improvement of methods for chemical analysis and structure investigation of compounds and materials' (the Project 'Development of a set of methods that improve figures-of-merit of inductively coupled plasma mass spectrometry analysis of complex samples').

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