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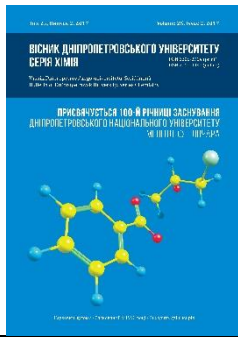

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PHARMACOPOEIA METHODS FOR ELEMENTAL ANALYSIS OF MEDICINES: A COMPARATIVE STUDY

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Abstract

The article is devoted to the problem of quality assurance of medicinal products, namely the determination of elemental impurity concentration compared to permitted daily exposures for and the correct choice analytical methods that are adequate to the formulated tasks. The paper goal is to compare characteristics of four analytical methods recommended by the Pharmacopoeia of various countries to control the content of elemental impurities in medicines, including medicinal plant raw materials and herbal medicines. Both advantages and disadvantages were described for atomic absorption spectroscopy with various atomising techniques, as well as atomic emission spectroscopy and mass spectrometry with inductively coupled plasma. The choice of the most rational analysis method depends on a research task and is reasoned from the viewpoint of analytical objectives, possible complications, performance attributes, and economic considerations. The methods of ICP-MS and GFAAS were shown to provide the greatest potential for determining the low and ultra-low concentrations of chemical elements in medicinal plants and herbal medicinal products. The other two methods, FAAS and ICP-AES, are limited to the analysis of the main essential elements and the largest impurities. The ICP-MS is the most efficient method for determining ultra-low concentrations. However, the interference of mass peaks is typical for ICP-MS. It is formed not only by impurities but also by polyatomic ions with the participation of argon, as well as atoms of gases from the air (C, N and O) or matrices (O, N, H, P, S and Cl). Therefore, a correct sample preparation, which guarantees minimisation of impurity contamination and loss of analytes becomes the most crucial stage of analytical applications of ICP-MS. The detections limits for some chemical elements, which content is regulated in modern Pharmacopoeia, were estimated for each method and analysis conditions of medicinal plant raw materials and herbal medicinal products.

Keywords: elemental impurities; atomic absorption and emission spectroscopy; mass-spectrometry; inductively-coupled plasma; detection limit; pharmacopoeia; medicinal herbs; herbal medicinal product

ФАРМАКОПЕЙНІ МЕТОДИ АНАЛІЗУ ЕЛЕМЕНТІВ У ЛІКАРСЬКИХ ЗАСОБАХ: ПОРІВНЯЛЬНЕ ДОСЛІДЖЕННЯ

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Анотація

Статтю присвячено вирішенню проблем забезпечення якості лікарських засобів, а саме визначення вмісту в них елементних домішок у порівнянні з гранично допустимими добовими дозами та вибору аналітичних методів, адекватних поставленим задачам. Метою роботи є проведення порівняльного аналізу характеристик чотирьох аналітичних методів, що рекомендуються Фармакопеями різних країн для контролю вмісту елементних домішок у лікарських засобах, у тому числі лікарській рослинній сировині та лікарських засобах рослинного походження. Визначено як переваги, так і недоліки атомно-абсорбційної спектроскопії з різними методами атомізації, а також атомно-емісійної спектроскопії та мас-спектрометрії з індуктивно-зв'язаною плазмою. Вибір найбільш доцільного методу аналізу залежить від завдання дослідження та обґрунтовується з точки зору поставлених аналітичних цілей, наявних ускладнень, експлуатаційних властивостей та економічних міркувань. Показано, що методи ІЗП-МС та ЕТААС надають найбільші можливості щодо визначення низьких та ультра низьких концентрацій хімічних елементів у лікарській рослинній сировині та засобах рослинного походження, в той час як два інших методи, ПААС та ІЗП-АЕС, обмежуються визначенням основних компонентів та найбільших домішок. Мас-спектрометрія з ІЗП є найбільш ефективним методом для визначення ультра низьких концентрацій. Але для цього методу

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типовою є інтерференція масових піків, що утворюються не тільки домішками, але також поліатомними іонами за участю аргону, а також атомів газів із повітря (C, N, O) або матриці (O, N, H, P, S, Cl). Тому для цього методу дуже важливою є коректна пробопідготовка, спрямована на мінімізацію забруднень або втрати аналітів. Межі визначення ряду хімічних елементів, вміст яких регламентовано в сучасних Фармакопеях, оцінено для кожного методу для умов аналізу лікарської рослинної сировині та лікарських засобів рослинного походження.

Ключові слова: елементні домішки; атомно-абсорбційна та емісійна спектроскопія; мас-спектрометрія; індуктивно-зв'язана плазма; межа визначення; фармакопея; лікарська рослинна сировина; лікарські засоби

ФАРМАКОПЕЙНЫЕ МЕТОДЫ АНАЛИЗА ЭЛЕМЕНТОВ В ЛЕКАРСТВЕННЫХ СРЕДСТВАХ: СРАВНИТЕЛЬНОЕ ИССЛЕДОВАНИЕ

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Аннотация
Статья посвящена решению проблем обеспечения качества лекарственных средств, а именно определения содержания в них элементных примесей в сравнении с предельно допустимыми суточными дозами и выбора аналитических методов, адекватных поставленным задачам. Целью работы является проведение сравнительного анализа характеристик четырех аналитических методов, рекомендуемых фармакопеями разных стран для контроля содержания элементных примесей в лекарственных средствах, в том числе лекарственном растительном сырье и лекарственных средствах растительного происхождения. Определены как преимущества, так и недостатки атомно-абсорбционной спектроскопии с разными способами, а также атомно-эмиссионной спектроскопии и масс-спектрометрии с индуктивно-связанной плазмой. Выбор наиболее целесообразного метода анализа зависит от задачи исследования и обосновывается с точки зрения поставленных аналитических целей, имеющихся осложнений, эксплуатационных свойств и экономических соображений. Показано, что методы ИСП-МС и ЭТААС предоставляют наибольшие возможности по определению низких и ультра низких концентраций химических элементов в лекарственном растительном сырье и средствах растительного происхождения, в то время как два других метода, ПААС и ИСП-АЭС, ограничиваются определением основных компонентов и наибольших примесей. Масс-спектрометрия с ИСП является наиболее эффективным методом для определения ультра низких концентраций. Но для этого метода типична интерференция массовых пиков, которые образуются не только примесями, но также полиатомными ионами с участием аргона, а также атомов газов из воздуха (C, N, O) или матрицы (O, N, H, P, S, Cl). Поэтому для данного метода очень важна корректная пробоподготовка, направленная на минимизацию загрязнений или потери аналитов. Пределы обнаружения ряда химических элементов, содержание которых регламентируется в современных Фармакопеях, оценены для каждого метода для условий анализа лекарственного растительного сырья и лекарственных средств растительного происхождения.

Ключевые слова: элементные примеси; атомно-абсорбционная и эмиссионная спектроскопия; масс-спектрометрия; индуктивно-связанная плазма; предел обнаружения; фармакопея; лекарственное растительное сырье; лекарственные препараты

Introduction

The control of the content of elemental impurities is an important component of the quality assurance system in the pharmaceutical industry. Some problems may appear in the course of the organisation of such control: from the establishment of a permitted daily exposure (PDE) for each element of toxicological concern to the optimal selection of analytical methods for controlling the impurity content.

Modern versions of the pharmacopoeia and documents of world organisations, which regulate elemental impurity contents, divide 28 chemical elements in medicinal products into four classes depending on their toxicity and likelihood of occurrence in the medicinal products [1–3]. Such a division forms the idea of the potential impact of elements on the human body and also sets the requirements for the sensitivity of analytical methods to be used for their detection. More difficulties arise in the production and control of herbal medicinal products (HMPs). In medicinal plants, as well as in plants used as nutritional supplements and spices, the concentrations of only five the most toxic elements are currently regulated. For other elemental impurities, there are no generally accepted limit values. However, plants can accumulate certain chemical elements in large quantities depending on the conditions of growth or the environment [4–7]. Therefore, producers of HMPs often have to formulate their own requirements for analytical methods and their instrumental implementation in the course of development of a pharmaceutical system of the quality assurance [8–12].

To date, pharmacopoeias offer using analytical methods based on three fundamentally different physical processes. These processes are as follows: atomic absorption, atomic emission and mass-spectrometry [13–15].

The atomic absorption spectroscopy uses the principle that free atoms in the gaseous state generated in an atomiser can absorb electromagnetic radiation at a particular frequency and studies absorption spectra of individual elements. Excitation of spectra is usually performed by flame atomization or electrothermal atomization in a graphite cuvette. Respectively, flame atomic absorption spectroscopy (FAAS) and graphite furnace atomic absorption spectroscopy (GFAAS) are of the highest practical importance. Typically, FAAS is applied when the element concentrations are high enough, whereas GFAAS is useful when the concentrations are low.

The characteristics of optical emission spectra form a basis for atomic emission spectroscopy (AES). Emission spectra can be excited by different sources, such as hollow cathode discharge, laser irradiation, arc discharge, etc. Last years, inductively coupled plasma (ICP) combined with AES is widely adopted in application to analytical practice.

In mass spectroscopy (MS) the studied substance is ionised, and the ions are separated in accord with their mass/charge ratios. Then the number of ions generated during the ionisation represents a mass/charge array which is recorded as a spectrum. If an ICP source ionises atoms and a mass-spectrometer records ions, such a method is called the mass spectrometry with inductively coupled plasma (ICP-MS). ICP-MS is one of the most sensitive tools for fast simultaneous determination of many elements in trace or ultra-trace concentrations. This method has recently become the mainstay for the analysis of trace elements in medicinal products.

Each of the methods above has its advantages and disadvantages compared to others which depend on the research tasks ahead. Therefore, the purpose of this paper is to substantiate the criteria for choosing the most appropriate method for controlling the content of elemental impurities in medicinal products, including herbal medicines. The following aspects of the optimal choice are considered:

1) The analytical goals. The key analytical characteristics of the method, such as a list of traceable elements, operative concentration ranges and detection limits, etc., determine the feasibility of its application and thus are the primary criterion of the optimal choice;

2) Available interferences (complications) inherent in the method when it is applied. The interferences characterise the complexity of using the method, and sometimes set the boundary of method's suitability for a particular application;

3) Performance characteristics that are relatively less important in conducting research but become more important in the practice of analytical laboratories incorporated in production processes;

4) Economic aspects that are of primary importance in the course of origination of a research centre, since they determine, together with other factors, the choice of laboratory equipment and techniques.

Results and discussion

Comparison of instrumental methods' characteristics

The key analytical parameters of the instrumental methods are compared in Table 1. The main drawback of atomic absorption methods is their essentially mono-elemental nature. They allow one to determine the concentration of only one element during one measurement. The use of emission spectra or mass spectra allows registration of all available elements in one operation.

A burner-nebuliser system in FAAS is a rather inefficient sampling tool because only a small fraction of atomised atoms reaches the flame and holding time of the atomised particles along the optical axis is rather limited. GFAAS provides both better atomization and increased time along the optical axis that improves the detection limit compared to FAAS. Also, this method makes it possible to analyse samples of small sizes.

Upgrade of the FAAS spectrometer with the necessary equipment for the implementation of the GFAAS method is relatively simple since the equipment for atomic absorption analysis usually implies the use of different atomiser types. Such an upgrade of the instrumentation is accessible, and it significantly expands the capabilities of atomic absorption in general.

Flaming and electrothermal atomization are the most popular but not the only methods of atomization in AAS. Other atomisers, such as hydride generation and cold vapour techniques, can significantly expand a list of traceable elements.

The method of hydride generation implies the reduction of an element to its hydride, the distillation of steam to a flame-heated analytical cuvette and in which the thermal decomposition of hydrides to the atomic vapour occurs. This method is suitable for the elements forming

volatile hydrides in reactions with a reducing agent (As, Sn, Bi, Sb, Te, Se, and Ge).

Table 1

Pharmacopeia methods of elemental analysis: Comparison of key analytical parameters

Parameters	FAAS	GFAAS	ICP-AES	ICP-MS
Number of elements	≥ 67	~ 50	≥ 73	≥ 80
Analytical performance	One element per analysis	One element per analysis	Many elements	Many elements
Screening ability	Not available	Not available	Available	Available (semi-quantitative)
Detection limit, ppm	0.1–1 ppm	0.1–1 ppb = 10^{-4}–10^{-3} ppm	1–10 ppb = 10^{-3}–10^{-2} ppm	1–10 ppt = 10^{-6}–10^{-5} ppm
Linear dynamic range	10^3	10^2	10^6	10^9
Short term precision, %	0.1–1%	0.5–5%	0.1–2%	1–2%
Long term precision, %	1–10%	1–10%	1–5%	2–4%
Spectral interferences	Very few; optical resolution at 0.2–0.5 nm is sufficient	Very few; resolution at 0.2–0.5 nm is sufficient	Many; resolution at ≤0.01 nm is necessary	Few; resolution at 0.8 Da is sufficient with some exceptions (see Table 2)
Chemical interferences	Many	Very many	Very few	Some
Physical interferences	Some	Very few	Very few	Some
Dissolved solids (max tolerable conc.), %	≤ 5%	≤ 10%	≤ 20–30%	≤ 0.1–0.4%
Sample volume, ml	> 5	0.5–5	> 5	> 5
Additional advantages	Easy upgrade to GFAAS	Analysis of micro samples (< 1–2 mL); upgrade from FAAS	Determination of S and P	Standardless analysis; isotope analysis; upgrade to hyphenated (*) methods

(*) For example, ICP-MS with laser ablation to study solid samples; ICP-MS with liquid chromatography to analyse the chemical state of impurities, etc.

The main advantages of the hydride generation method are as follows:

- Good sensitivity due to a 100% sampling efficiency;
- Faster than GFAAS;
- Good precision;
- No matrix interferences due to the separation of analysed elements as hydrides.

Nevertheless, the method has some limitations because it applies to a few specific elements, has some chemical interferences and needs complicated sample preparation.

The cold vapour technique is used for the determination of mercury only as Hg has a large enough vapour pressure at ambient temperature. It includes the reduction of Hg to the atomic state by a strong reducing agent ($NaHB_4$ or $SnCl_2$), the dissociation of a pair of metal atoms into the quartz cuvette stream and the measurement of absorption of Hg at a resonant wavelength. The method is characterised by a good sensitivity and precision, is faster than GFAAS and eliminates many matrix interferences.

Among the methods under consideration, the ICP-MS exhibits the highest detection limit at 1-10 ppt, which is ~10^5 times better than that in the FAAS method and ~100 times better than for GFAAS. Also, mass spectrometry allows one to record peaks of a much larger number of elements than GFAAS. An important advantage of mass spectrometry is the ability to build on its basis more sophisticated analytical methods, so-called hyphenated instruments [14]. For example, ICP-MS is increasingly applied as a detector for a range of chromatographic separation methods. The front-end technique separates the different compounds with time, and the ICP-MS instrument functions as a mass selective detector to measure the elements associated with the compound(s) of interest as they elute from the chromatograph.

Concentration sensitivity of the ICP-AES method occupies an intermediate position between FAAS and GFAAS: It is ~100 times more sensitive than FAAS, but on average ten times less than GFAAS. Compared with AAS, emission spectroscopy techniques typically have the advantage of identifying heavy elements, whereas AAS is very sensitive to alkaline metals. Also, the determination of some elements (for example, S, Ca, Fe, K, and Se) has serious impediments to ICP-MS while modern ICP-AES spectrometers are most suitable for the determination of some metalloids (S, P, Cl, Br, and I).

The ICP-AES method uses two variants of the geometry of the signal registration, radial and axial [16]. In the case of radial registration, when the plasma torch is located in a vertical plane, the detection limit is lower. However, the limited plasma thickness minimises the adverse effects of spectral and background interferences. In the axial registration of the signal, the plasma rotates in a horizontal plane. The axial mode provides a 5 to 10 fold increase in the detection limit, but at the same time, it enhances the influence of interference, which makes it necessary to apply special measures to eliminate this effect.

An important indicator is the dynamic range of the method: A range of concentrations in which quantitative results can be obtained without recalibrating the system. It directly affects the number of dissolution operations necessary for the preparation of solutions: The wider linear range, the fewer standards require.

FAAS and GfAAS have a limited dynamic range of 10^2–10^3. Therefore, the range of concentrations suitable for the analysis of solutions is narrow. The ICP-AES has a much wider dynamic range (up to 10^6), which makes it a more appropriate method for highly concentrated samples or samples with various concentrations of analyte elements. In ICP-MS, a linear dynamic range of 10^8-10^9 can be achieved. Fig. 1 schematically shows the concentration areas in which the efficient use of one or another method is possible, illustrating the influence of the dynamic range. Evidently, a larger area in the scheme corresponds to wider performances of analysis.

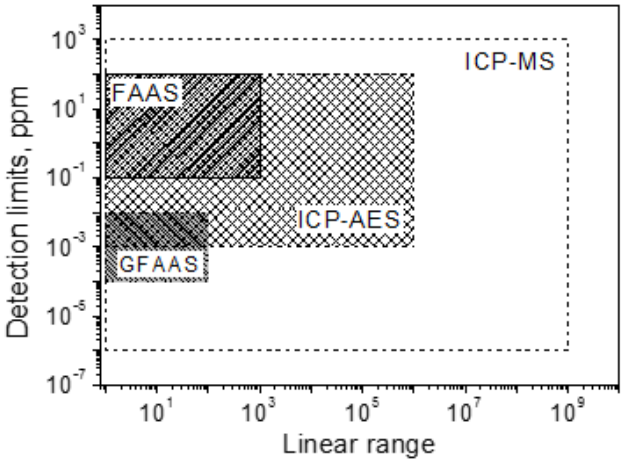

Fig. 1. Comparison of detection limits and linear dynamic ranges for FAAS, GFAAS, ICP-AES and ICP-MS methods

The comparison of FAAS and ICP-AES shows that the latter method completely closes all performance capabilities, regarding the working concentration range, inherent in FAAS. At the same time, GFAAS has an absolute advantage of better sensitivity. The ICP-MS method has an evident advantage over all other methods from the viewpoint of the working concentration range.

The maximal tolerable concentration of the dissolved solid phase in the solution (Table 1) is one more practically important analytical parameter. In this respect, the method of ICP-MS is significantly (up to 100 times) inferior to other methods because the application of saturated solutions in the ICP-MS provokes the emergence of strong matrix effects. Accordingly, the real advantage of ICP-MS regarding its detection limit in the solid phase even if remains uncontested but, however, becomes less pronounced in magnitude. In some cases, the ICP-MS detection limit may be commensurate with that provided by the GFAAS method.

When working for a short time (during one analysis), the FAAS method demonstrates the best accuracy, which characterises the magnitude of the oscillation around the mean and is expressed through the coefficient of variation. The worst indicator is inherent in the ICP-MS (Table 1). In long-term work (work throughout a working day), the situation changes to the opposite, and the mass spectrometric technique has somewhat better results than others. The FAAS method has the worst accuracy in time, first of all, because of the instability in the long work of a flame burner.

The analytical characteristics of the methods often depend on the matrix to be analysed, since various interferences or matrix effects influence the results of the analysis. Among the different types of interferences we note:

- spectral, which is related to the effect of the thin structure of atomic or molecular spectra and consists in a partial or complete overlapping of various spectral lines or mass peaks;
- backgrounds that are related to the effect of the background on analysis results, which often reveals a complex dependence on wavelength or other experimental factors.

Among the various matrix effects, the greatest influence has:

- ionisation, which can reduce the concentration of neutral atoms in the analyte;
- chemical, when the chemical reactions in the sample affect the composition of the analyte;
- physical, in which the physical and chemical properties of elements and compounds in the matrix (viscosity of the solution, surface tension, etc.) affect the results of the analysis.

Each of the methods under comparison has its particular tolerance for matrix effects of different types. For example, the ICP-AES method is known to be more suitable for the analysis of complex matrices than the ICP-MS. The most common matrix effects, as well as methods of combating them, based on the use of optimal tools and adjusting the conventional analysis programs, are given in Table 2.

Table 2

Pharmacopeia methods of elemental analysis: Comparison of interference types and methods for their suppression by either instrumental correction (I.C.) or routine program optimisation (R.P.O.)

Methods	FAAS	GFAAS	ICP-AES	ICP-MS
		Spectral interference		
	Very few. Most elements require 0.5 nm resolution except for Fe, Ni, Co requiring ≤0.2 nm	Few spectral interferences with some exceptions (e.g. Fe on Se at 196.0 nm)	Available due to a high number (>50000) of spectral lines	Rather moderate because of a limited peak number (~300). Some exceptions are: ^{58}Ni & ^{58}Fe, ^{40}Ar & ^{40}Ca, ^{40}Ar^{16}O & ^{56}Fe, ^{40}Ar$_2$ & ^{80}Se. Interference with doubly charged ions: (^{138}Ba^{2+}&^{69}Ga^{+}, ^{208}Pb^{2+}&^{104}Ru^{+})
I.C.		Use of Zeeman correction	Use of spectrometers with better resolution	Use of: magnetic sector spectrometers with resolution <0.1 Da; collision cells; & small additives of N_2 or NH_3 to Ar
R.P.O.			Use of other lines, introduction of correcting parameters	Use of alternative isotopes; isotope ratio study; introduction of correcting parameters
		Background effects		
	Available and should be corrected	Available and should be corrected	Available including molecular bands formed by OH-groups from water solvents	Virtually absent due to a very low background (<10 counts/s) except for ultra-trace analysis
I.C.	D_2 correction	D_2 or Zeeman corrections		
R.P.O.		Careful programming of ash stage; use of chemical modifiers	Optimisation of plasma regimes; use of other lines; either dynamic or off-line background correction	
		Chemical matrix effects		
	Available	Possible due to atomization of the analyte into a cooler gas environment	Minimal	Ions of some acids (HCl, $HClO_4$, H_3PO_4 & H_2SO_4) form with Ar^{+}, O^{+}, H^{+} ions interfering with some elements, e.g.: ^{35}Cl^{40}Ar on ^{75}As, ^{35}Cl^{16}O on ^{51}V.
I.C.	Use of hotter flame (N_2O / C_2H_2) minimises chemical effects	Tubes with platforms to delay atomization and inject samples into a hot gas environment	Optimisation of plasma height	Use of electro-thermal vaporisation of sample
R.P.O.	Use of «releasing agents»	Use of chemical modifiers		Avoidance of HCl, $HClO_4$, H_3PO_4 & H_2SO_4 and use of HNO_3
		Ionization effects		
	Higher for hotter flame (N_2O / C_2H_2) and group II elements		Possible for samples with high contents of groups I and II elements	Possible for samples with high contents of groups I and II elements
I.C.				Chromatographic separation
R.P.O.	Use of ionisation buffers (Cs, Li & K salts) for samples and standards			
		Physical matrix effects		
	Spray chamber effects. Differences in viscosity between sample solutions and standards affect the aerosol formation and analyte transportation	Effect of viscosity and surface tension of injected sample	Differences in viscosity between sample & standard solutions. The effect is stronger than in AAS because of finer aerosol droplets	Differences in viscosity between sample & standard solutions. Also, positive space charge interacts with ion beam (stronger for light and weaker for heavy ions)
I.C.				Reduction of ion current
R.P.O.	Use of appropriate standards	Use of appropriate standards	Use of appropriate standards	Use of appropriate or internal standards

Correspondence of the analytical characteristics of the method to the parameters of the sample is a necessary, but insufficient condition. The compliance of the analytical task with the operational requirements that characterise this technique is also of importance. For example, using some methods for certain applications may be too slow and do not provide the required amount of information for a limited time. Therefore, considering the analytical characteristics and assessing the complications caused by matrix effects are insufficient to

answer the question of the feasibility of using an analytical method. The parameters that characterise the advantages and disadvantages arising from the operation of the methods should be added to complete the method evaluation.

Table 3 illustrates the main performance characteristics of the compared methods.

Table 3

Pharmacopeia methods of elemental analysis: Comparison of performance parameters

Parameters	FAAS	GFAAS	ICP-AES	ICP-MS
Analytical performance	One element	One element	Many elements	Many elements
Sample throughput	15 s/element/sample	2–5 min/element/sample	5–40 elements/ min/sample	3–min/sample All elements
Number of samples	Low or medium	Low or medium	Medium or high	Medium or high
Ease of use	Easy	Easy	Easy	Moderately easy
Operator skills	Minimal	Moderate	Moderate	A higher level of expertise
Method development	Easy	Skill required. Frequent calibrations are necessary	Skill required	More complicated compared to other methods
Instrument compactness	Very compact	Very compact	Relatively small	Relatively compact
Unattended operation	No due to combustible gases	Yes	Yes	Yes
Availability of programs/applications	A large number of well-developed programs	Well-developed programs	Well-developed programs	A limited but rapidly growing number of applications
Additional requirements to rooms		Clean room for ppt impurity analysis	Supply of Ar in large amount	Clean room for ppt impurity analysis. Supply of Ar in large amount
Ideal application	Limited number of elements with rather high concentrations in a large number of samples	Limited number of elements with low concentrations in a limited number of samples	High number of elements in a moderate or large number of samples	High number of elements of both trace and ultra-trace concentrations in a large number of samples

The performance of a method, which depends on the number of samples or elements that can be analysed per unit time, is among the most critical parameters. Typically, time for analysis is a function of the complexity of the task. If it is necessary to analyse the content of the elements near the detection limit or with the highest possible accuracy, then it will take longer time compared with routine analyses. If the task includes conventional analyses, the study time obviously depends on the number of elements that can be determined in one operation.

FAAS provides a relatively high processing speed when analysing a large number of samples with a limited number of elements. The typical analysis of one component requires approximately 10 seconds. However, the determination of each element requires the use of a particular light source, and different elements may need different gases. Therefore, this method is a one-element technique in its essence.

The GFAAS method has a relatively low performance. Using a graphite cuvette, the analysis of one element in one sample usually takes 2-3 minutes.

ICP-AES is a multi-element analysis method with exceptionally high performance. This method can simultaneously detect more than 70 elements in a few minutes in one sample. However, a 15–30 s delay before entering each new sample is necessary to establish equilibrium and obtain sustainable metrological characteristics.

ICP-MS is also a multi-element analysis with the same benefits and limitations as the ICP-AES. The ICP-MS method can usually detect more than 80 elements in a few minutes in a single sample. The performance depends on a few factors, such as the required precision and concentration range. Based on the comparison of performance characteristics, the most suitable application area can be outlined for each method (Table 3).

Comparison of the parameters of the operation of analytical equipment is of particular importance at the stage of analytical laboratory origination. The optimal choice of equipment according to the tasks ahead allows one to reduce daily expenses, as well as initial investments in the organisation of the laboratory. The capital and running costs for all four methods are compared in Table 4. As seen, the ICP-MS method is the most valuable in everyday use. Therefore, it is economically expedient to use it only when analysing a large number of samples. Due to high productivity, running costs in this application of the ICP-MS are superior to the AAS methods.

Table 4

Pharmacopeia methods of elemental analysis: Comparison of economic parameters

Parameters	FAAS	GFAAS	ICP-AES	ICP-MS
Capital investments	Low	Medium	High	Very high
Investment ratio	1	2	4–9	10–20
Running costs	Low	High	Medium	High
Cost per sample (many samples – few elements)	Low	High	Medium	Medium
Cost per sample (many samples – many elements)	Medium	High	Low-medium	Low-medium
Spare parts	Hollow cathode lamps; combustible gases; standards; reagents	Hollow cathode lamps; argon gas; standards; graphite tubes and cones; water	Argon gas; quartz torches; nebulisers; cones; reagents and standards; water	Argon gas; sampling and skimmer cones; nebulisers; quartz torches; reagents and standards; water; vacuum system spare parts

Detection limits for elemental impurities in herbal medicinal products by different methods

The detection limits of each analytical method depend not only on the possibilities of the method itself but the objects and elements under investigation. As already mentioned, the elemental composition of medicinal plants is variable in nature [17]. Therefore, it is advisable to compare the analytical capabilities of different instrumental methods in the determination of individual elements in the medicinal plants and HMPs.

Fig. 2 illustrates the detection limits for elemental impurities achieved in FAAS and GFAAS by [18–24]. The results of various authors have been used to minimise the influence of equipment and other factors on the results of the comparative analysis. The OX axis arranges the chemical elements in order of decreasing the detection limits for the FAAS.

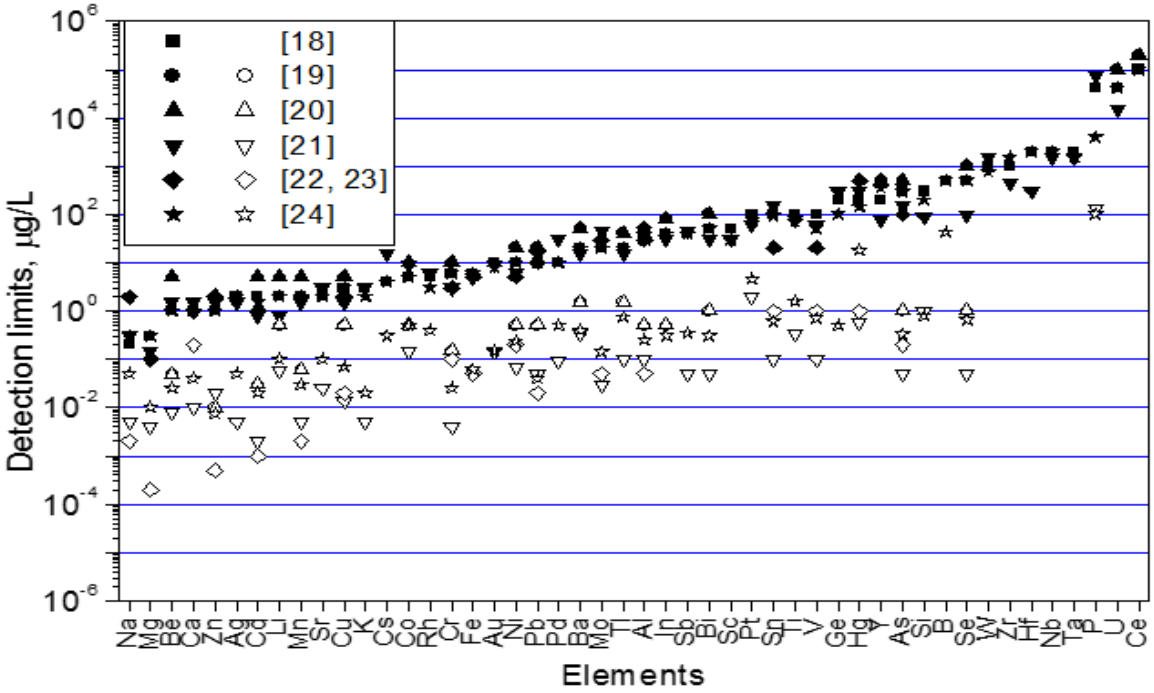

Fig. 2. Detection limits for elemental impurities by FAAS (shaded dots) and GFAAS (open dots)

For both methods, the detection limits are seen to depend on the nature of elements. So, for FAAS, the detection limit reaches approximately 1 µg/L in the most favourable cases, while this figure increases to 10^3 and even to 10^5 µg/L in the most unfavourable cases. The highest sensitivity for FAAS is observed for alkaline and alkaline earth metals, which usually present in sufficiently large quantities in the HMPs. Among the major impurities, which are typically characterised by a low content, we can name only cadmium. For other heavy metals, the detection limits of FAAS are already at 10 µg/L or even higher. The FAAS method demonstrates the worst sensitivity for refractory metals (Hf, Ta,

Nb), as well as some metalloids, e.g. phosphorus which is a typical essential element in plants.

The use of GFAAS, as a rule, leads to an improvement of the detection limit - in most cases, approximately by 100 times. The detection limits of GFAAS also depend on the nature of elements. This indicator deteriorates from left to right along the OX axis in Fig. 2 at approximately the same speed as the FAAS method. At the same time, Fig. 2 shows a smaller number of elements that can be determined by the GFAAS method compared to the FAAS. The use of GFAAS allows one to determine the presence of fewer than 1 μg/L of virtually all heavy metals (As, Hg, Pb and Cd), the content of which is regulated for HMPs.

Similarly, Fig. 3 illustrates the comparison results for ICP-AES and ICP-MS detection limits. The elements are arranged from left to right in order of decreasing the detection limits for the ICP-AES method.

Attention is drawn to a much smaller difference in the sensitivity between the elements located on the left and right parts of Fig. 3 in comparison with Fig. 2. Thus, for the methods of FAAS and GFAAS, the detection limits for the most favourable elements approximately 1000 times better than those for hard-to-detect elements. For the ICP-AES method, this difference does not exceed 100 times, and for ICP-MS amounts to a factor of 10. Thus, the use of high-temperature plasma source (ICP) is much more efficient in suppressing the difference in the excitation of different atoms compared to the processes in relatively cold flames or heated graphite cuvettes.

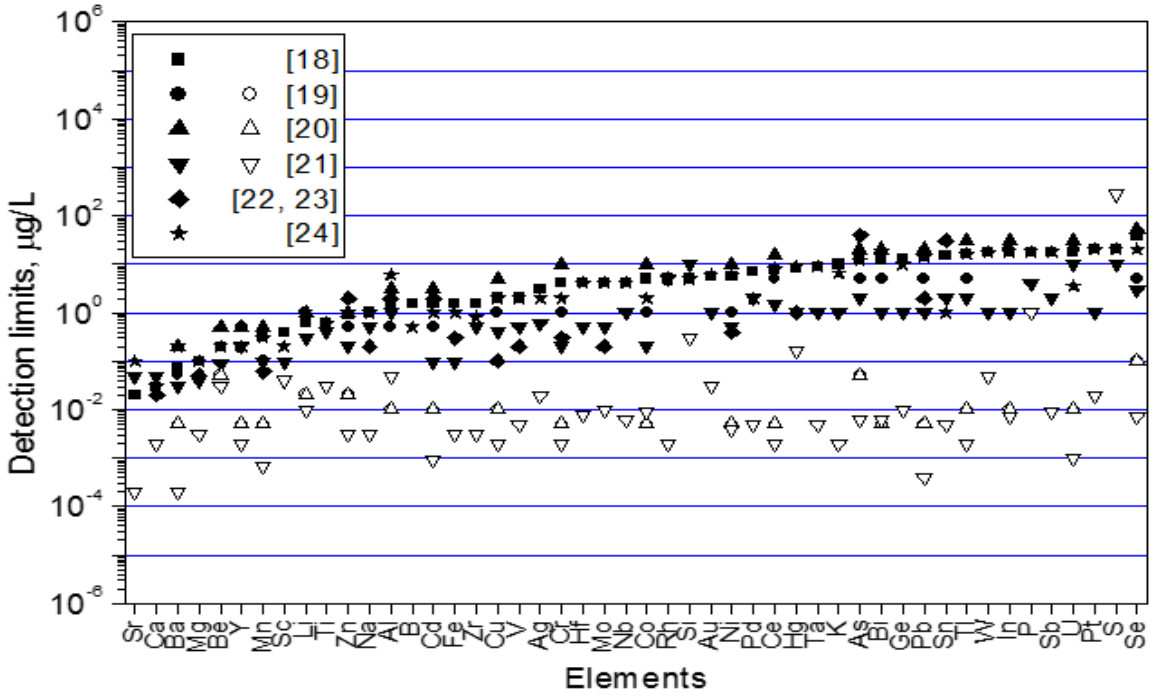

Fig. 3. Detection limits for elemental impurities by ICP-AES (shaded dots) and ICP-MS (open dots)

The application of the ICP-AES provides a detection limit at a level not less than 1 μg/L for about half of all elements, but at a level of 10μg/L for the rest analytes. For the most favourable cases, the sensitivity improves to 0.1 μg/L or even better. The use of ICP-MS provides a detection limit, usually not worse than 0.01 μg/L. As is shown in Fig. 3, the application of both methods provides an opportunity to determine more elements in comparison with atomic absorption techniques.

Conclusions

The results obtained allow us to conclude that the methods of ICP-MS and GFAAS provide the greatest potential for determining the low and ultra-low concentrations of chemical elements in medicinal plants and HMPs. The other two methods, FAAS and ICP-AES, are limited to the analysis of the main essential elements of plants and the largest impurities.

The main drawback of GFAAS is, in essence, its mono-element nature, which makes it very slow in the routine analysis. ICP-AES is an efficient method for multi-elemental rapid-analysis, but its sensitivity is limited.

The mass-spectrometry has high sensitivity, a wide linear dynamic range of concentrations, a low detection limit, ease and speed of measurement, and the possibility of multi-element analysis. Thus, ICP-MS is the most

efficient method for determining ultra-low concentrations.

However, the interference of mass peaks is typical for ICP-MS. It is formed not only by impurities but also by polyatomic ions with the participation of argon, as well as atoms of gases from the air (C, N and O) or matrices (O, N, H, P, S and Cl). Therefore, a correct sample preparation, which guarantees minimisation of impurity contamination and loss of analytes becomes the most crucial stage of analytical applications of ICP-MS.

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