Spectrochimica Acta Part B: Atomic Spectroscopy 205 (2023) 106689

Contents lists available at ScienceDirect

Spectrochimica Acta Part B: Atomic Spectroscopy

journal homepage: www.elsevier.com/locate/sab

Analytical approach of elemental impurities in pharmaceutical products: A worldwide review

Augusto Cezar Magalhães Aleluia [a,c,*], Morgana de Souza Nascimento [b], Ana Maria Pinto dos Santos [c], Walter Nei Lopes dos Santos [d], Aníbal de Freitas Santos Júnior [b,*], Sergio Luís Costa Ferreira [c]

[a] Universidade Estadual do Sudoeste da Bahia (UESB), Campus Vitória da Conquista, 45031-300 Vitória da Conquista, BA, Brazil
[b] Universidade do Estado da Bahia (UNEB), Departamento de Ciências da Vida, 41150-000 Salvador, BA, Brazil
[c] Universidade Federal da Bahia (UFBA), Instituto de Química, Campus Ondina, 40170-290 Salvador, BA, Brazil
[d] Universidade do Estado da Bahia (UNEB), Departamento de Ciências Exatas e da Terra, 41150-000 Salvador, BA, Brazil

ARTICLE INFO

Keywords:
Elemental impurities
Pharmaceutical products
Spectroscopy techniques

ABSTRACT

Elemental impurities may occur in pharmaceutical products under different conditions. Impurity composition includes many types of species: metals and non-metals, which can be essentially toxic, due to their direct health damage potential, and those essential elements or compounds, which play a physiological role in the human body in defined levels. The essential ones may develop an illness profile or a non-desirable situation, since their concentrations exceed permitted and tolerable limits. Inorganic contamination in pharmaceuticals has been observed in several countries. A high number of reports on metal contamination in natural products, traditional eastern medicines, herbal medicines and medicinal plants have been presented, especially with lead, cadmium, mercury and arsenic. A simple explanation to this fact is mainly related to metal deposition in the soil, water contamination, fertilizer and pesticide poisoning. Synthetic products are faced to catalyst deposition, water contamination, glassware impurities, contaminated raw materials and excipients, as well as uncontrolled manufacturing processes. Several analytical methods have been developed and improved for years, allowing the application of better strategies to evaluate metal contamination in pharmaceutical products. Spectroscopy techniques are used by industries in routine investigations, and can also be improved to attend different types of matrices and materials. In Brazil, the Brazilian Pharmacopeia and National Health Surveillance Agency are the available guide and institution, respectively, onto which the investigation of elemental impurities is based. In the international scenario, The United States Pharmacopeia (USP), The European Pharmacopeia (EU), The European Medicine Agency (EMA) Guideline and The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use(ICH) Guideline are the four most important and complete manuals for the evaluation of impurities in pharmaceutical products, active pharmaceutical ingredients (APIs), raw materials and intermediates in the present days. A great amount of scientific research about inorganic impurities in pharmaceuticals has been conducted in recent years, but it still remains below the strategies of analytical applications due to the many possibilities of contamination. The continuous work on this theme, regulated by international agencies, is the best way to improve the quality of pharmaceutical products and to ensure safety in their use. The objective of this paper is to summarize spectroscopy techniques applied to inorganic evaluation in pharmaceuticals, considering the limits of element exposure to human beings reported by national and international references.

1. Introduction

Chemical elements can occur at different concentrations in biological systems. These levels are directly related to the corresponding functions of each element or group of elements. Some major essential ones as Ca, Fe, Mg, P and S are found at concentrations above 10 mg L^{-1} in body

* Corresponding authors.
E-mail addresses: augusto.aleluia@uesb.edu.br (A.C.M. Aleluia), amps@ufba.br (A.M.P. dos Santos), wlopes@uneb.br (W.N.L. dos Santos), afjunior@uneb.br (A. de Freitas Santos Júnior), slcf@ufba.br (S.L.C. Ferreira).

https://doi.org/10.1016/j.sab.2023.106689
Received 7 February 2023; Received in revised form 9 April 2023; Accepted 20 April 2023
Available online 23 April 2023

fluids or above 100 μg g^{-1} in tissues. Essential trace elements are also required for a normal and healthy body functioning, and whose deficiency induces adverse health effects. These trace elements occur instead at concentrations of 10 μg L^{-1} up to 10^4 μg L^{-1} in body fluids or 0.01–100 μg g^{-1} in tissues and play important and rather specific biological roles as components of enzyme systems (Cu, Mn, Mo, Se and Zn), vitamins (Co) and hormones (I) [1,2]. Some chemical elements can be used as therapeutic agents acting, as many other possibilities, to control symptoms, to block an illness or to enhance a well state of health. Li, B, Mg, Ti, Fe, Co, Sb, Au, Ga, as well as other elements, are used either in atomic form or in compound structures in different kinds of pharmaceuticals [3]. Elements are toxic when they have the capacity to cause negative health effects. These species act in the metabolic human process to cause illness or to make a disorder with physiological functions and some of these disorders may be irreversible. The toxicity of an element depends on its solubility and bioavailability and, therefore, can bioaccumulate in human body, causing hazardous chronic health conditions, as illustrated in Fig. 1 [4,5].

Some metals traditionally toxic, in different samples, are serious and widely dangerous due to their high bioavailability, potential toxicity and ease of accumulation by various plant and animal organisms, and environmental [6]. Not only can these elements be harmful; some essential ones at very low concentrations generally need to be present in the human diet to guarantee normal physiological functions. For example, Cu and Zn are necessary at low levels as catalysts for enzyme activities, but high levels of these essential metals may be hazardous to human health. It was demonstrated that some potentially toxic and essential (macro and micro) elements can cause bad health conditions in people who have their intake significantly higher than the recommended amount, when they consume some certain pharmaceutical products [7]. Leitão et al. [8] studied the relationship between the bioaccumulation and toxicity from the mapping of the distribution of Hg (II) and other trace elements in zebrafish (*Danio rerio*). The results showed that the high levels of Hg measured in zebrafish tissues indicated bioaccumulation in some organs (visceral mass and gills) and that physiological accumulation is dose-dependent. In addition, other trace elements (Fe, Cu and Zn) did not show changes in concentration after the exposure of zebrafish to Hg (II), indicating that the latter is not able to reduce or increase accumulation of other metals.

Several analytical techniques can be applied for element evaluation in pharmaceuticals and cosmetics, from spectrophotometric and atomic absorption to mass spectrometry, which can be coupled to other instruments in order to enhance the quality of analysis or with other sample preparation techniques. Choosing the best technique for elemental determination in one product involves studying the matrix, the possible content and the chemical relationship among them. The Brazilian Pharmacopeia points UV-VIS spectrophotometry and atomic absorption spectrometry (flame, FAAS; graphite furnace, GF AAS; hydride generation, HG AAS; cold vapor, CV AAS) as analytical approaches for the analysis of pharmaceutical products. It also includes optical emission spectrometry and mass spectrometry, both with inductively coupled plasma (ICP OES and ICP-MS, respectively), besides fluorescence spectrometry [9].

Therefore, the Brazilian Pharmacopeia, the United States Pharmacopeia, the European Pharmacopeia, the European Medicine Agency Guideline and the International Conference on Harmonisation Guideline have to be constantly updated with the development of science and technology, as international reference textbooks for pharmaceutical-medical topics. Thus, the purpose of this review is to summarize spectroscopy techniques applied to inorganic evaluation in pharmaceutical products from different sources, considering the limits of element exposure to human beings reported by national and international references. The perspectives of future analytical strategies for element determination were also discussed.

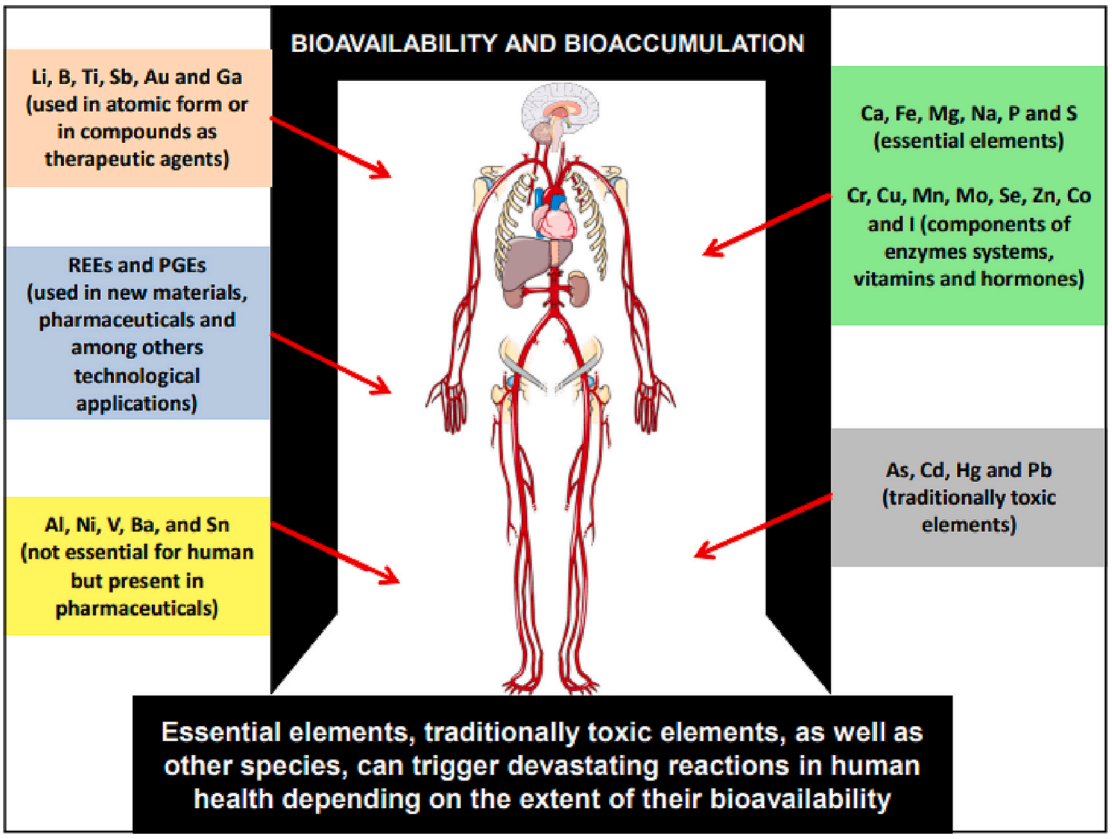

Fig. 1. Exposure profile of essential and non-essential chemical elements as a function of their bioavailability and bioaccumulation in the human body (The authors, 2023). Legend: REE - Rare earth elements; PGE - Platinum group of elements.

The strategic word combinations used for the research of these articles were: pharmaceutical AND AAS; pharmaceutical AND ICP; pharmaceutical AND inorganic contamination; pharmaceutical AND impurities; pharmaceutical AND metals; pharmaceutical AND ICP AND metals; metal AND contamination AND medicines; pharmaceutical formulations AND ICP OR pharmaceutical formulations AND AAS. These words were entered in Web of Science and in Science Direct to access the articles. Scientific papers and books published over the past thirty three years about pharmaceutical impurities and analytical methods were considered. The discussion was made considering data on impurity determination related to reference parameters established in national and international guidelines. The discussion also considered the novelty of the analytical approaches and their suitableness to the main objective of the research.

2. Elemental impurities: ocurrence and importance

The health effects of chemical contaminants in medicines are a major health concern today. A very vulnerable and sensitive time in human development is in the womb and during the first five years of childhood. Unfortunately, it is during this time that we take between 70 and 80% of the toxicants accumulated by the body during our lifetime [10].

Some metals may be just one of the several contaminants in pediatric syrups either produced or imported into Nigeria. In Nigeria, it is a common practice for doctors to recommend some drugs known to cure specific ailments (such as indigestion, headache, malaria, cough, measles, cold, catarrh, anaemia, stomach upset etc) to pregnant women and lactating mothers and children. A possible route of these metals into these drugs may be during processing such as lead solder, use of contaminated water, poor assaying of raw materials, packaging, poor hygiene and storage facilities. Another contamination route is focused on the excipients. These compounds are considered as inert ingredients and are generally safe. However, some adverse effects have been attributed to excipients used in the preparation of multivitamins, which are widely prescribed for infants and children [11]. Even if the first five years of childhood are a critical period for toxicants to accumulate in the body, it is also known that these impurities may cause health problems to humans in any period of life.

Studies have shown that the inert nature of excipients is questionable, and the impairment of drug transport functions may be attributed to them. Soodvilai et al. [12] investigated whether excipients frequently used in the production of dosage forms are capable of interfering with organic cation transporters (OCT). These transporters play a crucial role in the excretion of a wide variety of organic cations, including endogenous compounds and therapeutic agents, such as: quinidine, cisplatin, morphine, metformin, phenoxybenzamine, prasozine, procainamide and cimetidine. It was evidenced that solubilizing agents such as "Tweens" are capable of inhibiting the transport function of the mediators OCT1 and OCT2, and these have a crucial role in the hepatic and renal clearance of cationic drugs. The results showed that Tweens exhibited greater potency in inhibiting OCT1 and OCT2 transport compared to Cremophor RH40. Compromising the function of these mediators by excipients can result in alterations in pharmacokinetics, drug-drug interactions and deposition of these drugs in tissues, which may cause toxicity and compromise drug efficacy. Studies such as this show the need to develop methodologies that can elucidate the contribution of excipients in medicines both from the point of view of efficacy and the assessment of toxicity as a function of the presence of metallic impurities.

Still in Nigeria, Nduka et al. [13] developed a recent study to evaluate the risk assessment of heavy metals from adult consumption of locally manufactured painkillers, drugs with analgesic, antipyretic and anti-inflammatory effects. The contents of As, Cd, Cr, Ni, Pb and Hg were determined, using an atomic absorption spectrometer with acid digestion pretreatment. Due to the frequent medicine intake, especially in overdose cases or prolonged use, individuals could be continuously exposed to toxic metals, highlighting the need to monitor these products and impurities. In a similar study carried out by Li et al. [14], in the United States, the concentrations of impurities in various excipients present in pharmaceutical products were determined. The samples were subjected to acid digestion in microwaves and subsequently measured by ICP-MS. Of the total of 190 analyzed samples, with 31 different types of excipients, the results showed that, with the exception of Pb, the elements Cd, As and Hg, exhibited low concentrations in the analyzed samples. Cd and Hg levels were < 1 μg mL^{-1} for all excipients. Titanium dioxide showed relatively high concentrations for Pb (2.15 ± 1.81 μg mL^{-1}). Excipients of synthetic origin and cellulose-based drugs achieved levels below LOD or in the range of 1 to 10 μg L^{-1}. Four excipients exceeded the limits recommended by European Agencies for oral concentrations in 1 or more elemental impurities: titanium dioxide and zinc stearate exceeded the concentration for Pb, and granular magnesium hydroxide and calcium carbonate exceeded the concentration for Cd. In general, excipients showed low concentrations of impurities in relation to the safety limits established for finished drugs. However, in the case of drugs produced with one or more of the excipients that contain a high amount of impurities, final concentrations higher than the permitted daily intake (PDE) may be observed.

Increasing cases of As poisoning were reported, induced by *Niuhuang Jiedu* (NHJDT), a patented traditional chinese medicine used for the treatment of hyperactivity of stagnated fire, aphthae, swelling and gingiva, throat and eye ache [15]. As_2S_2 is the main constituent of realgar, a mineral used in the pharmaceutical preparation of this product. As species were determined, separated by High Performance Liquid Chromatography (HPLC), including inorganic As, which is the most toxic for humans. Therefore, the determination of As and other mineral elements in NHJDT is critical for clinical safety [16].

Traditional medicines (TM) have been in use since ages. People around the globe use TM due to their historical behavior and according to their cultural creeds. Since the beginning of the 90's, according to the World Health Organization (WHO), about 70% of the world population still depended on TM to fulfill their health needs [17]. As traditional medicines (TM) are from natural source, it is a misconception that TM are comparatively safer than synthetic drugs produced using chemical compounds [18]. TM are also contaminated with environmental pollutants, specially metals, which can lead to serious health issues in the long term [19]. These metals could be toxic and essential: toxic metals, mainly Pb, Cd, Hg and As can cause metal poisoning to the patients. Some metals such as Fe, Cu and Zn are essential and required by the human body in trace amounts. However, they become toxic when their levels in the blood increase. They may cause damage to vital organs, as heart, liver, kidneys and brain [18]. For example, Hg was found as a major pollutant and health concern in populations using Malaysian Drug Product (a marketed herbal drug available in markets of Malaysia, used as antidiabetic agents). The Hg content (1.33 μg mL^{-1}) was out of the permissible limit (0.1 μg mL^{-1}) [20] in this product [21].

Recently, Hg was determined in Traditional Chinese Medicines (TCMs), which have been widely consumed in many eastern countries [22]. Metals, such as Hg, Pb, As and Cd, have been previously reported to be present in TCMs [23,24]. Both total and bioaccessible fractions of Hg were measured in 16 products. One sample showed exceeded values compared to the acceptable Hg intake by the Food and Agriculture Organization/World Health Organization (FAO/WHO) [22]. TCMs had also been analyzed by Yao et al. [25] for Cd accumulation in plants. It was shown that Cd could be deposited in different parts of a plant and the distribution significantly varied from species, habitat and soil pollution among TCM materials. This is a point of concern regarding the use of these materials for medical purposes.

The risk of chemical contamination due to the use of natural products can be quite higher than that of using synthetic products. A study demonstrated that while pharmaceuticals appear to have low concentrations of toxic elements, a small percentage of Natural Health Products (NHPs) have noteworthy concentrations, potentially exposing

consumers to adverse health sequelae associated with metal and metalloid bioaccumulation. This is particularly evident in certain NHPs from Chinese herbal sources [26,27]. Even though the low risk is clear, it is not possible to deny the possibility of toxic metal exposure by non-natural products.

In the case of natural products, a batch of plant material can be used for the preparation of traditional medicines and herbal infusions only if the content of toxic metals is below a certain threshold. When the herbs are used in the treatment of certain illnesses, it should be known that, besides their pharmacological effect, medicinal plants could be toxic if the content of some metals is high [28–30]. Therefore, controlling these elemental concentrations in both medicinal plants and their products is necessary to ensure safety and effectiveness of herbal products [31,32]. Plants can be easily contaminated by metals in the course of cultivation or during processing [33]. Along with other pollutants, metals can be added into the environment through industrial activities, municipal waste, automobile exhaust, pesticides and fertilizers used in agriculture [34].

In an Asian study involving natural products, in Korea, the toxic metal content was investigated in 52 frequently prescribed ayurveda, identifying herbal medicines with the possibility of exceeding The Korean Food and Drug Administration (KFDA) maximum limit for toxic metals. The KFDA established maximum limits for lead (Pb), arsenic (As), cadmium (Cd) and mercury (Hg), which were reported to act as endocrine disruptors. Nineteen samples of five kinds of herbal medicines exceeded the KFDA's maximum limit for Pb (5 mg kg^{-1}), no sample exceeded the maximum limit of 3 mg kg^{-1} for As, thirty samples of 14 types of herbal products exceeded the KFDA's range of 0.3–1.0 mg kg^{-1} for Cd and no sample exceeded the maximum Hg limit of 0.2 mg kg^{-1} [35].

One positive point of natural products is related to their pharmaceutical form and to the preparation steps before consumption that can be applied. Some medicinal products come in globular, granular and liquid dosage forms, but decoction is the most common dosage form in Korea. It was shown that the use of herbal medicines in decoction form is useful for minimization of risks associated with toxic metals (As, Pb, Cd and Hg) in herbal medicines, since these metal contents were reduced after decoction. It can be explained by the reaction among the elements with tannins and other organic compounds resulting in water-insoluble substances, which were not released in final decoction [36]. In a study carried out in Iran by Habibollahi, Sharafi and Omer [37], an evaluation of the accumulation of toxic elements and risk were associated with human health. It was evidenced that many brands had detectable amounts of the investigated elements, but much lower than the maximum limits established by the World Health Organization (WHO). In addition, the lifetime cancer risk (RCLV) for each carcinogenic metal and the total carcinogenic risk (RCT) for all carcinogenic metals were also below the acceptable threshold (RCLV and RCT $= 10^{-4}$). 15 brands of health products of natural origin (PSON) purchased in pharmacies were selected, totaling 225 samples, 11 elements, 9 (Cd, Pb, Ni, Cr, Cu, Fe, Zn, Mn and Al) of which were evaluated using ICP OES and the others (As and Hg), using ICP-MS. This study showed that there are products available in the market capable of meeting official regulations, offering greater safety to the population.

Medicinal plants and other natural products are critical when it comes to inorganic impurities. There are many possibilities of metal deposition in these products. Effective strategies to minimize or eliminate metal and metalloid deposition risk in complementary medicines are challenging for policy makers, but critical for optimizing health benefits. The quality and safety of these medicines have now become a serious issue as a function of element contamination and, therefore, information about their elemental content should be provided for practitioners and consumers to make right decisions [7,29,30,38].

Cannabis, the plant source of cannabinoids (CB), has two molecules of great chemical and pharmacological interest: cannabidiol (CBD) and tetrahydrocannabidiol (THC). Besides the already known effects on pain reduction, recent studies highlight a reduction in mortality from opioid overdose in places where medical cannabis is already legalized, reducing opioid doses in chronic pain patients. However, there is a difference between CBD and THC: the latter is a psychogenic molecule responsible for promoting arousal in recreational use, while the former does not lead to intoxication and offers a better safety profile when compared to THC. In a study conducted by Capano et al. [39], the impact of cannabidiol extract (CBD) on both opioid use and life quality in patients with chronic pain was investigated. A total of 131 patients, aged 18 to 65 years, who had chronic pain for at least 1 year, were accompanied over 8 weeks. The results showed that cannabidiol-rich hemp can reduce opioid use and improve life quality, especially in pain and sleep management in patients with chronic pain, with significant improvements. More than half of the patients taking the substance experienced reduction or elimination of opioids over 8 weeks.

Poli et al. [40] conducted a study aimed at evaluating the effects of cannabis use and associated benefits in patients diagnosed with chronic pain, affected by fibromyalgia, radiculopathy, headache, arthritis, various forms of neuropathic pain and other chronic conditions. A total of 338 patients at different stages of chronic pain treated with a decoction of Cannabis Flos over a 12-month period, in combination with established pharmacological therapy, were accompanied. The research demonstrated that Cannabis therapy, as an adjunct to traditional analgesic treatments, reduces pain intensity, improves daily functionality and allows for a reduction in anxiety and depression symptoms. However, Cannabis is not the answer to everyone's pain. Negatively, difficulty in accessing Cannabis, regulatory barriers and miraculous popular beliefs about the results of Cannabis use were observed throughout the study, culminating in patients being temporarily or permanently discontinued from therapy. The study also points out that it is only a trial; therefore, randomized controlled trials and further analysis are needed to demonstrate whether cannabis therapy is more effective than traditional analgesic therapy and for what reasons.

Studies in industrialized hemp show that the Cannabis plant can bioaccumulate potentially toxic metals from the soil, being used as a "metal scavenger", as well as in phytoremediation of contaminated soils and adulteration, from the addition of potentially toxic metals to increase its weight and, consequently, its market value. Due to regulations imposed by the USP and ICH, the minimum acceptable limits have been reduced in order to protect human health from risks associated with consumption. In the study proposed by Viviers et al. [41], metal determinations were performed on 310 samples of cannabis products purchased on the South African market. The results showed that, when comparing individual metal residues (Cd, Pb, As and Ni) against the oral limit, with the exception of Cd, all others showed concentrations higher than the oral limits set by the USP/ICH. Regarding the inhalation use presentations, when considering USP/ICH inhalation limits, the three metals responsible for most failures were mercury (Hg), nickel (Ni) and lead (Pb). Of all the samples evaluated in this study, 15% (48 of 310) failed the specified USP/ICH oral ingestion limits. This analysis included a wide variety of product types: drops, capsules, drinks, edibles and suppositories. The high failure rate to meet USP/ICH limits is of most concern, particularly for class 1 and class 2A impurities. Despite the published standards and the existence of safety limits, the application and control of these limits need to be strictly monitored in cannabis products.

Cannabis products have been widely consumed all around the world, even in countries where they are prohibited, but the chemical element composition was still not completely investigated. The inorganic content of these products was evaluated by Menezes et al. [42], in a very recent study, using an ICP OES. Samples were obtained from different sources, as Romania, United Kingdom, Canada and Brazil, where the study was conducted. It is important to notice that concentrations of inorganic species were related to the manufacturing processes used for the different hemp products and the use of organic solvents for cannabinoid extraction resulted in extracts with low inorganic contents. The authors

also show the need for further studies and monitoring inorganic content due to the increasing use of cannabis-based materials in the pharmaceutical industry for therapeutical purposes, besides the possibility of soil contamination by metals, where cannabis species are cultivated.

In recent years, another plant has been used as a drug of abuse, especially due to its relaxing, analgesic and psychoactive properties. The plant Kratom (*Mitragyna speciosa*) is registered as a food ingredient with the FDA and the US Drug Enforcement Administration Policies. It remained legal in many states in the USA until 2020. However, many states, such as Alabama, Florida, Indiana, Arkansas, Wisconsin and Tennessee, have passed laws prohibiting the local sale and possession of kratom. It is a plant native to the Southeast Asian region, belongs to the Rubiaceae family and can reach over 25 m in height. It has stimulating, dose-dependent properties, which have aroused the interest of scientists and researchers due to its pharmacological profile of acting on opioid, adrenergic and serotoninergic receptors, as well as other neurotransmitter systems [43].

In a survey by Tobacyka et al. [44], from 106 independent FDA registrations, the following were established as the main popular uses for kratom: mental health, pain improvement, substance use disorder, focus improvement, insomnia and fatigue reduction. These data corroborate the findings of Grundmann et al. [43], who point out an increase in the number of cases involving Kratom in the United States, at the American poison center. Among them, the case of a 30-year-old man who, within one hour of using this plant, presented agitation, mental confusion and convulsion. Upon admission to the emergency room, signs of tachycardia, hypertension and absence of responsiveness were recorded. In another report, a 56-year-old man with the intention of bringing relief for chronic pain, associated Kratom with high doses of the drug *Oxycontin* and, when he abruptly discontinued the use of the plant, he manifested nausea, vomiting, anxiety, rhinorrhea and irritability. In another case, a 68-year-old man on chronic use of buproprion, fluoxetine, fentanyl and Kratom for pain control, attended the emergency room with signs of mental confusion and difficulty walking. Upon examination, signs of tachycardia, hypertension, diaphoresis and hyperreflexivity were recorded, and he was diagnosed with serotoninergic syndrome due to drug interaction with Kratom.

In a study by Fleming et al. [45], 27 Kratom products were obtained from tobacco stores in Richmond, Virginia, USA. These products included 9 powders, 5 teas, 12 extracts and 1 carbonated beverage. In an analysis performed using ICP OES, Al, As, Cu, Fe, Mg, Mn, Ni and Pb were found. Of all the elements analyzed, only Mn presented a risk to users. Three tea samples exceeded the tolerable upper intake level for Mn by 5 to 20 times, with samples ranging from 95.04 to 284.79 mg per day. Mn toxicity can lead to manganism, a neurodegenerative condition that manifests symptoms of dystonia, muscle spasms and difficulty walking. The findings of these researchers highlight the need for regulation of Kratom products, not only for consumers, but also reaching out to producers.

Prozialecket al. [46] conducted a research with the FDA and the US Centers for Disease Control, to increase surveillance of Kratom products for toxic metals (such as Pb and Ni) and microorganisms such as *Salmonella*. Eight Kratom products purchased from tobacco stores in the western suburbs of Chicago were evaluated and tested from both a microbiological and toxicological standpoint. Concentrations of the chemical elements Ni, Pb, Cr, As, Hg and Cd, as well as levels of mitragynine alkaloids, were determined. All analyzed samples contained significant amounts of mitragynine (3.9 to 62.1 mg g^{-1}), indicating that the analyzed products were from Kratom. In metal evaluation, seven products presented significant amounts of Ni (0.73 to 7.4 μg g^{-1}), Pb (0.16 to 1.6 μg g^{-1}) and Cr (0.21 to 5.7 μg g^{-1}), while the other analyzed elements were not detected.

Pb is one of the most common toxic elements found among the medicines studied. The actual exposure level of some metals, including Pb to individuals, is of extreme importance from a clinical and public health perspective [38]. The daily intake of any element can be calculated using the highest recommended daily intake of the medicine, which provides the "worst case" scenario. The element intake is then dependent on the dose of the medication taken, whose information is provided by the product manufacturer. There are maximum concentration limits to many chemical elements, which are the parameter for industries in manufacturing quality control. The Brazilian Pharmacopeia [9], the United States Pharmacopeia [47,48], and the ICH Q3D Guideline [49] permitted concentrations of elemental impurities, based on a maximum 10-g dose of product per day, are shown in Table 1. The Pharmacopeial Forum (PF) 48 (6) updates were also considered in USP values [50]. The European Medicines Agency (EMA) has already adopted the ICH Q3D Guideline about elemental impurities in pharmaceutical products since March 2019, when it was published on the EMA website.

In USP and ICH Q3D, the elements were classified according to their toxicity and the likelihood of occurrence in drug products: class 1 (Cd, Pb, As and Hg), class 2A (Co, V and Ni), class 2B (Tl, Au, Pd, Ir, Os, Rh, Ru, Se, Ag and Pt) and class 3 (Li, Sb, Ba, Mo, Cu, Sn and Cr). This classification reflects the increase in acceptable values for the elements from class 1 (lowest values, since Cd, Pb, As and Hg are the most toxic elements) up to class 3 (highest values, since these elements have relatively low toxicities by the oral route). It is important to notice that manganese is neither considered by USP nor by ICH Q3D, only by the Brazilian Pharmacopeia. Meanwhile, the Brazilian compendium does not consider inhalation and cutaneous concentrations for elemental impurities.

For most elements, the maximum concentrations established for the dermal route are derived from their respective permissible daily exposure limits (PDE); however, for some elements, such as Ni and Co, an additional concentration can cause skin reactions in already sensitized individuals. This additional value is called the cutaneous and transcutaneous concentration limit (CTCL). Thus, even if the maximum cutaneous concentration values in drug products are 5 μg g^{-1} for Co and 20 μg g^{-1} for Ni, the CTCL for both is considered to be 35 μg g^{-1}. It is important to note that this CTCL value is lower than PDE values for Co (50 μg/day) and Ni (200 μg/day), requiring the need for monitoring these elements, since product risk assessment must be confirmed by considering the total value of Co and Ni to be less than or equal to the PDE, without exceeding the CTCL value in the drug product concentration [47,49,50].

The United States Pharmacopeia also considers elemental impurity limits for dietary supplements, as presented in chapter 2232. The total concentration of each element (only As, Cd, Pb and Hg are presented) in finished products should not be higher than the PDE, and each component used to prepare the finished dietary supplement should meet the limits (Table 2), considering the maximum daily intake of 10 g of a dietary product [51].

USP and ICH guidelines are the major references of chemical impurities used worldwide. Almost all scientific research pointed in this review had these two textbooks as a principle reference. Furthermore, they also used national guidelines from their countries, as observed in Brazil with the Brazilian Pharmacopeia, whose metal and non-metal parameters in pharmaceuticals are very close to those mentioned in USP and ICH. Despite the fact that developing countries could have poor information from their technical manuals, the Brazilian Pharmacopeia can provide great subjects to support national and international chemical research involving medicines. It is important to notice that both the Brazilian and the United States Pharmacopeias are not complete regarding elemental impurity limits, once there are other chemical elements in the periodic table that can be a significant impurity in manufactured and natural products; thus, these compendiums must be continuously upgraded.

The evaluation of elemental impurities in pharmaceuticals also includes the concept of bioaccessibility and bioavailability. Bioaccessibility is defined as the total amount of an element or other chemical compound (a nutrient, for example) that is not linked to its

Table 1
Permitted limits of metal and non-metal impurities (drug product maximum dose of 10 g per day).

Element	Maximum oral dosage (μg g^{-1})			Maximum parenteral dosage (μg g^{-1})			Maximum inhalation dosage (μg g^{-1})		Maximum cutaneous dosage (μg g^{-1})	
	Braz. Pharma. 6ª ed. 2019	USP 43 2020 PF 48(6) 2023	ICH Q3D (R2) 2022	Braz. Pharma. 6ª ed. 2019	USP 43 2020 PF 48(6) 2023	ICH Q3D (R2) 2022	USP 43 2020 PF 48(6) 2023	ICH Q3D (R2) 2022	USP 43 2020 PF 48(6) 2023	ICH Q3D (R2) 2022
Cadmium (Cd)	0.5	0.5	0.5	0.05	0.2	0.2	0.3	0.3	2	2
Lead(Pb)	1.0	0.5	0.5	0.1	0.5	0.5	0.5	0.5	5	5
Arsenic(As)	1.5	1.5 *inorganic	1.5	0.15	1.5 *inorganic	1.5	0.2	0.2	3	3
Mercury(Hg)	1.5	3 *inorganic	3	0.15	0.3 *inorganic	0.3	0.1	0.1	3	3
Cobalt(Co)	–	5	5	–	0.5	0.5	0.3	0.3	5	5
Vanadium (V)	25	10	10	2.5	1	1	0.1	0.1	10	10
Nickel(Ni)	25	20	20	2.5	2	2	0.6	0.6	20	20
Thallium(Tl)	–	0.8	0.8	–	0.8	0.8	0.8	0.8	0.8	0.8
Gold(Au)	–	10	30	–	10	30	0.3	0.3	300	300
Palladium (Pd)	10	10	10	1	1	1	0.1	0.1	10	10
Iridium(Ir)	10	10	10	10	1	1	0.1	0.1	10	–
Osmium(Os)	10	10	10	10	1	1	0.1	0.1	10	–
Manganese (Mn)	250	–	–	25	–	–	–	–	–	–
Rhodium (Rh)	–	10	10	–	1	1	0.1	0.1	10	–
Ruthenium (Ru)	–	10	10	–	1	1	0.1	0.1	10	–
Selenium (Se)	–	15	15	–	8	8	13	13	80	80
Silver(Ag)	–	15	15	–	1	1.5	0.7	0.7	15	15
Platinum(Pt)	10	10	10	1	1	1	0.1	0.1	10	10
Lithium(Li)	–	55	55	–	25	25	2.5	2.5	250	250
Antimony (Sb)	–	120	120	–	9	9	2	2	90	90
Barium(Ba)	–	140	140	–	70	70	30	30	700	700
Molybdenum (Mo)	25	300	300	2.5	150	150	1	1	1500	1500
Copper(Cu)	250	300	300	25	30	30	3	3	300	300
Tin(Sn)	–	600	600	–	60	60	6	6	600	600
Chromium (Cr)	25	1100	1100	2.5	110	110	0.3	0.3	1100	1100

Table 2
Permitted individual limits of toxic metal impurities in components of dietary supplements (product maximum dose of 10 g per day) by United States Pharmacopeia.

Element	Individual component concentration (μg g^{-1})
Cadmium (Cd)	0.5
Lead(Pb)	1.0
Arsenic(As)^{Inorganic}	1.5
Mercury(Hg)^{Total}	1.5
Methylmercury (as Hg)	0.2

matrix and that is ready to be absorbed into the gastrointestinal system [52]. Bioavailability can be defined as the total amount of an element, drug, nutrient or other chemical compound that is available in blood fluids after any possibility of elimination by liver first-pass metabolism [53]. Therefore, research in pharmaceutical field has been incorporating bioaccessibility and bioavailability studies in order to provide information about the right concentration of chemical elements distributed in human organism.

A study was conducted [54] to evaluate the bioaccessibility of As, Cr, Cu, Hg, Mn and Pb in nine ayurvedic medicines purchased in India. The results showed that As, Cr, Cu and Hg from some products exceeded the tolerable intake levels, considering the bioaccessible fraction. It is important to notice how dangerous some natural products can be to human health and the importance of analytical chemistry application. In a study carried out in China by Yang et al. [55], significant associations were found between high concentrations of urinary As or low concentrations of dimethylarsinous acid (DMA) and increased risk of Alzheimer's Disease (AD). Levels of urinary As and DMA were associated with changes in Mini Mental Examination (MMSE) status scores. Individuals with low Se and high As levels were 2–3 times more likely to develop AD. Leko et al. [56] obtained similar results when evidencing, in a study conducted with 193 participants, that the levels of toxic metals (As, Cd, Hg, Ni, Pb and Ti), essential elements (Ca, Co, Cu, Fe, Mg, Mn, Mo, Na, K and Zn) and essential non-metals (P, S and Se) have a strong association with phosphorylated tau isoforms (VILIP-1, S100B, NFL and YKL-40) in the cerebrospinal fluid (CSF).

Devipriya et al. [57] published a review with *meta*-analysis about ayurvedic treatment protocols and its relation to analytical chemistry. Among others determinations, the elemental composition of herbs was evaluated using classical and important techniques in chemistry, as atomic absorption spectrometry (AAS), inductively coupled plasma mass spectrometry (ICP-MS), inductively coupled plasma atomic emission spectrometry (ICP AES) and laser induced-breakdown spectroscopy (LIBS). It was proved that the stability, therapeutic potency and standardization of an ayurvedic formulation can only be authenticated using analytical chemistry procedures.

Not only can medicines and natural products be contaminated by elemental impurities. Many types of pharmaceutical supplements can also be a threat to human health, as these items are made through different manufacturing processes. It is common to find Ca supplements in international health markets, but also other dietary elements, whose composition may diversify due to the main goal of the product [53]. Since many pharmaceutical supplements are over-the-counter (OTC) medicines, they are sold with no medical requirements, and this can be a public health problem if these supplements are contaminated by a dangerous chemical impurity.

Pharmaceuticals and dietary supplements can be a potential source of Hg ingested orally by consumers. In recent years, particularly in developed countries such as the United States, Canada and European countries, an increase in the consumption of drugs and dietary supplements has been observed [26,58–63]. Nonetheless, a positive result was found in Poland: a recent study demonstrated that pharmaceuticals available in the market, analyzed in this study, do not pose a threat to human health, once their amount of Hg is far lower than the value

recommended by the WHO as the provisional tolerable weekly intake of Hg. It should be emphasized that, despite the fact that manufacturers of drugs and dietary supplements pay attention to the purity of production, it is still necessary to control both the initial production stages and the final product which goes to the consumer [64].

Ca supplements are consumed worldwide for bone-related problems. Osteoporosis is a multi-factorial process; therefore, a good quality supplement with not only adequate elemental Ca is required. It is also imperative that the supplement has other supporting minerals as part of a multivitamin/multi-mineral preparation, since Ca alone is not a very effective medicine to mitigate the damage assigned to bone-related diseases. These trace minerals are required in small quantities, but are essential for the health of bones and joints [65]. Pharmaceutical research has created diverse formulae of Ca supplements, where Ca is complexed with other minerals for their effective use as a supplement. Unfortunately, such products are sold in the markets unchecked for impurities by any national regulatory agency. As, Br, Ce, Co, Cr, Fe, K, Na, Sb, Sn, Sr and Zn were measured in eleven different national and multinational Ca supplements (chelated) by Instrumental Neutron Activation Analysis (INAA) and Cd, Cu and Ni by Atomic Absorption Spectrometry (AAS). Most of the elements in all supplements were detected at minor or trace levels, while Na was quantified as a major element. Thus, hypertensive people and those who are advised to take limited Na diets should be careful in using these supplements for long periods. The presence of these elements in supplements could be due to the impurities in basic Ca constituents (chelates), artificial or natural colors and sweeteners. According to this study, different trace metals in supplements can play a positive or adverse role in human health [66].

Sulfur is another element of great importance for human health, besides being an ingredient for chemicals and pharmaceutical products. However, the content of sulfur in different matrices should be evaluated, in order to establish values under acceptable limits. Ozbek and Baysal [67] reviewed scientific studies over the past 10 years, on the determination of sulfur using high-resolution continuum source atomic absorption spectrometry (HR-CS AAS). They concluded that sulfur has been used in many industries, as a pharmaceutical, petrochemical, food and geochemical agent, with a wide variety of applications, showing the importance of sulfur use and highlighting the concern about sulfur determination.

The manufacturing process of a medicine, supplement, herbal medicine and other types of pharmaceuticals include the addition of many chemical elements or compounds. This process can also include synthesis, depending on the protocols and manufacturing scope of the industry. Active Pharmaceutical Ingredients (APIs), excipients, catalysts and other substances are mainly used in manufacturing processes.

It is already known that some organic compounds from plants, can be used as APIs in manufactured drugs or can also be used as excipients in these products. Two compounds, dihydroquercetin (DHQ) and arabinogalactan (AG), were synthesized, coupled to Mn and Se, respectively, and were analyzed by wavelength-dispersive (WDXRF) and total-reflection (TXRF) x-ray fluorescence methods to quantify Mn and Se elements by Chuparina et al. [68]. It was demonstrated that Mn-DHQ and Se-AG complexes exhibit higher healing properties compared to the original organic molecules. The authors determined the content of Mn and Se in the synthesized products and also the strange content of each element (possible contamination) in the same samples. It is important to show the use of metal-organic compounds in the pharmaceutical manufacturing chain and the quality control in these samples. The chemical elements used in the synthesis can be above tolerable limits and cause harmful effects to final consumers.

A recent market surveillance study conducted in Germany, with 113 samples analyzed, shows consistently negative results according to current regulatory documents: EMA; USP; The European Pharmacopeia and ICH Q3D Guideline. It proves that randomly sampled medicinal products from the official German health market, together with their corresponding Active Pharmaceutical Ingredients (APIs), have a good quality with respect to potential contamination with metals [69]. This study is another example of the other side of the scenario, in which pharmaceutical products and APIs were free of inorganic impurities.

Manufacturers of APIs, raw materials and intermediates used in the pharmaceutical industry can, in theory, use any element possible on the periodic table as part of a synthetic process and, once pharmaceutical products and the raw materials used to prepare them can come into contact with a variety of materials during manufacture, both extraneous elements and those added as part of the synthesis are of interest. A wide variety of metals and metalloids are used in the manufacture of pharmaceuticals, and some are also used as API in medicines. Due to the potential routes of entry for metals and metalloids into pharmaceutical products, the pharmaceutical industry is interested in monitoring elements at all stages of the development process [70].

As part of continuing efforts to improve the safety and efficacy of drugs, both pharmaceutical companies and regulatory agencies have focused on impurity control. Metal impurities can be introduced in API from various sources (i.e. raw materials, reagents, solvents, catalysts, reaction vessels, plumbing and other equipment used during the synthesis of pharmaceuticals) [71]. Due to the potential toxicity of some metals, the Food and Drug Administration (FDA) Guidance indicates that the control of residual metal contents is critical in pharmaceutical manufacturing [58]. This can be partially explained as a function of the complexity of a medicinal product. It contains a variety of compounds, materials and substances that are not only produced by their manufacturer, but also imported from other companies all around the globe. Quality control seems to be very critical as the medicinal product can be formulated with different items from different sources.

The determination of inorganic contents in different pharmaceutical products can be affected by an unusual but not less important contamination from the presence of metals in the laboratory glassware. These materials may contain part per billion levels of copper and/or iron which can impact susceptible compounds by producing new impurities as artifacts of sample test solution instability, leading to falsely high impurity results. Falsely low results can also be produced by the degradation of susceptible impurities in test solutions due to the presence of metals. Thus, robust purity methods can be developed to provide an accurate assessment of the quality of pharmaceutical compounds [72].

Falsified and counterfeit peptide drugs such as anti-obesity peptides, neurohormones, insulin, human chorionic gonadotropin, human growth hormone (hGH), growth factors and monoclonal anti-cancer antibodies constitute another group of pharmaceutical products that can be affected by metal contamination. The uncontrolled use and the wide commercialization of these items highlight the high risk to human health and raise the question about the quality of chemicals used in manufacturing and purification steps, since Janvier et al. [73] determined Pb and As in these drugs and the results demonstrated high levels of both toxic elements.

Some metals, such as Al, As, Cu, Cd, Cr, Hg, Ni, Pb, Se and U get into the human body through the ingestion of food, medicines and drinking water, as already known. These metals, responsible for many health problems, can also be introduced into human organs by the air. Environmental scientists worked on the ill-effects of toxic trace elements suchas Cr, Cu, Ni, Cd, As, Hg, Pb and U in the past [74–76]. However, many other elements, which were not commonly used in the past, e.g., the rare earth elements (REEs) and the platinum group of elements (PGEs), have been increasingly used in modern industries for the production of numerous new materials, finished products including drugs and pharmaceuticals, and for several technological applications. Consequently, a new group of elements (REEs and PGEs) has been added to those already existing, depending on their function in the environment and their toxicity in terms of human health [77]. Technological innovations in medical and pharmaceutical sciences and healthcare, in addition to modern living conditions, have enhanced the intake of significant quantities of these toxic elements into the human body, leading

to health problems [78].

Rare earth elements could also be presented in compounds used as contrast agents during diagnosis with magnetic resonance images (MRI), for example. Gadolinium-based contrast agents (GBCAs) are a type of medicine injected into millions of patients before MRI exams. Salem and Barrat [79] determined REEs, Y, Ba and Pb in five GBCAs samples currently used in France by ICP-MS. They concluded that GBCAs solutions contain significant and important amounts of non-Gd REEs and Y, which can be considered as impurities. The mode of action of such elements in the human body, especially in the skin, bone and brain tissues, should be deeply considered and continuously studied.

In their research, Reddy et al. [75] determined several elements in some commercial pharmaceutical preparations by ICP-MS, after the samples were digested by open acid digestion. Sc, V, Cr, Co, Ni, Cu, Zn, Ga, Rb, Sr, Y, Zr, Nb, Cs, Ba, La, Ce, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, Lu, Hf, Ta, Pb, Th and U were determined and the concentration values were compared with permitted daily exposure (PDE) limits from the United States Pharmacopeia [47]. There were only established limits for V, Cr, Co, Ni, Cu, Ba and Pb. Since there were not existing limits in this chapter for the rest of the elements, it was not possible to evaluate the metal content of these commercial products, whose quality is totally questionable.

Impurities such as As, Cd, Cu, Sn, Sb, Pb, Bi, Ag, Hg, Mo, In, Os, Pd, Pt, Rh, Ru, Cr, Ni and V in pharmaceutical products or drug substances may originate from various sources, as metal catalysts and metal reagents used during the synthesis of an active pharmaceutical substance (e.g., from naturally derived plant or mineral sources) and excipients (e.g., stabilizers, fillers, binders, release agents, flavors, colors and coatings), impurities from manufacturing equipment (e.g., leaching from pipes), water and the container closure system. In spite of exercising maximum care, pharmaceutical raw materials may be contaminated by factors such as environmental conditions, selective use, or as a consequence of natural processes. Moreover, any product or raw material can come into contact with a wide range of materials during manufacture and processing. Sometimes, storage conditions can impact leaching (heat, UV radiation and storage time) [78]. In addition, metal ions can also affect the stability and expiration date of the formulation, catalyze the degradation of APIs, leading to the formation of unqualified degradates, or pose a toxicity threat on their own [80].

Table 3 summarizes the concentration of the main impurities found in pharmaceutical samples, highlighting the highest concentration values, the type of sample analyzed in each scientific research, as well as the analytical technique used in the determinations.

Inorganic impurities should be monitored in pharmaceutical preparations due to the possibility of toxic effects to human health. Control has to occur during the entire manufacturing process, starting from the raw material up to the finished products, including items that are imported from other places. Thus, metals and metalloid impurities are gaining an increasing focus for pharmaceutical regulators, anticipating high standards of quality control/quality assurance (QC/QA) for pharmaceuticals with regard to efficacy and patient safety. The recent changes in the Brazilian Pharmacopeia, the European Medicines Agency (EMA), the United States Pharmacopeia (USP) and in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) regarding regulations for inorganic impurities, require companies to adopt new strategies for metal analysis [81].

3. Analytical strategies for the determination of inorganic species

Inorganic impurities can be evaluated by different kinds of analytical techniques according to the matrix and the characteristics of the sample. The methods proposed to determine elemental concentration have to show high sensitivity and satisfactory limits of detection and quantification. Furthermore, some direct methods have been developed in order to attend the current requirements of Green Chemistry about the lowest

Table 3
Highest concentration values of the main impurities in pharmaceutical samples, found in literature.

Impurities	Highest concentration values	Sample	Technique	Ref.
Cr, Mn and Ni	Cr: 0.58 mg L^{-1}; Mn: 28,23 mg L^{-1}; Ni: 4.13 mg L^{-1}	Pediatric syrups	AAS	11
As, Cd, Cr, Hg, Ni and Pb	As: 0.350 mg kg^{-1}; Cd: 0.144 mg kg^{-1}; Cr: 6.637 mg kg^{-1}; Hg: 0.470 mg kg^{-1}; Ni: 0.448 mg kg^{-1}; Pb: 2.47 mg kg^{-1}	NSAIDs	AAS	13
As,Ag, Au, Cd, Co, Hg, Ir, Ni, Pb, Pd, Pt,Rh, Se, Tl andV	As: 0.80 mg kg^{-1}; Ag: 0.08 mg kg^{-1}; Au: 0.04 mg kg^{-1}; Cd: 0.77 mg kg^{-1}; Co: 123.5 mg kg^{-1}; Hg: 0.04 mg kg^{-1}; Ni: 154.4 mg kg^{-1}Os: 0.01 mg kg^{-1}; Pb: 2.15 mg kg^{-1}; Pd: 0.13 mg kg^{-1}; Pt: 6.39 mg kg^{-1}; Rh: 0.01 mg kg^{-1}; Se: 0.14 mg kg^{-1}; Tl: 0.04 mg kg^{-1}; V: 436 mg kg^{-1};	Excipients	ICP-MS	14
As, Ba, Ca, Cd,Co, Cr, Cu, Fe, Hg, K, Mg, Mn, Mo, Na, Ni, Pb, Se,Sr, V, and Zn	As: 86.45 μg g^{-1}; Ba: 64.78 μg g^{-1}; Ca: 18.95 μg g^{-1}; Cd: 0.092 μg g^{-1}; Co: 0.363 μg g^{-1}; Cr: 5.656 μg g^{-1}; Cu: 3.385 μg g^{-1}; Fe: 1.439 μg g^{-1}; Hg: 1.168 μg g^{-1}; K: 12.97 μg g^{-1}; Mg: 3.526 μg g^{-1}; Mn: 22.52 μg g^{-1}; Mo: 1.400 μg g^{-1}; Na: 1.182 μg g^{-1}; Ni: 4.524 μg g^{-1}; Pb: 1.795 μg g^{-1}; Se: 23.61 μg g^{-1}; Sr: 104.3 μg g^{-1}; V: 1.321 μg g^{-1}; Zn: 43.34 μg g^{-1}	*Niuhuang Jiedu* tablets (TCM)	ICP-MS and HPLC-ICP-MS	16
Cd, Co, Cr, Cu, Fe, Ni Pb, and Zn	Cd: 4.91 μg g^{-1}; Co: 77.97 μg g^{-1}; Cr: 186.75 μg g^{-1}; Cu: 120.21 μg g^{-1}; Fe: 1652.89 μg g^{-1}; Ni: 76.97 μg g^{-1};Pb: 30.46 μg g^{-1}; Zn: 433.76 μg g^{-1}	Herbal drugs	AAS	19

(*continued on next page*)

Table 3 (*continued*)

Impurities	Highest concentration values	Sample	Technique	Ref.
Cd, Cr, Cu, Fe, Mn, Ni, Pb and Zn	Cd: 1.55 mg kg^{-1}; Cr: 6.58 mg kg^{-1}; Cu: 15.55 mg kg^{-1}; Fe: 48.76 mg kg^{-1}; Mn: 21.03 mg kg^{-1}; Ni: 9.15 mg kg^{-1}; Pb: 8.79 mg kg^{-1}; Zn: 31.38 mg kg^{-1}	Medicinal plants	AAS	20
Ca, Cd, Cu, Fe, Hg, Mg, Mn, Na, Ni and Zn	Ca: 15.63 mg kg^{-1}; Cd: 0.04 mg kg^{-1}; Cu: 0.10 mg kg^{-1}; Fe: 3.16 mg kg^{-1};Hg: 1.33 mg kg^{-1}; Mg: 2.03 mg kg^{-1}; Mn: 0.54 mg kg^{-1}; Na: 9.17 mg kg^{-1}; Ni: 0.02 mg kg^{-1}; Zn: 0.29 mg kg^{-1}	Medicinal plants	AAS	21
Hg	Hg: 11.89 mg g^{-1}	Chinese patent medicines	ICP-MS	22
Cd, Mn	Cd: 0.314 mg L^{-1};Mn: 18.545 mg L^{-1}	Chinese herbal medicines	AAS	23
As, Cd, Hg and Pb	As: 33.7 μg kg^{-1}; Cd: 2.32 μg kg^{-1};Hg: 97.7 μg kg^{-1}; Pb: 73.8 μg kg^{-1}	Chinese herbal medicines	ICP-MS	24
As, Cd, Cu, Hg and Pb	As: 9.9 mg kg^{-1}; Cd: 5.2 mg kg^{-1}; Cu: 23.8 mg kg^{-1}; Hg: 406.3 μg kg^{-1}; Pb: 40.3 mg kg^{-1}	Roots and rhizomes of Chinese herbal medicines	ICP-MS	27
As, Cd, Co, Cr, Cu, Fe, Mn, Mo, Ni, Pb and Zn	As: 0.118 mg kg^{-1}; Cd: 0.071 mg kg^{-1}; Co: 0.090 mg kg^{-1}; Cr: 0.007 mg kg^{-1}; Cu: 1.685 mg kg^{-1}; Fe: 34.103 mg kg^{-1};Mn: 26.250 mg kg^{-1}; Mo: 0.002 mg kg^{-1}; Ni: 2.764 mg kg^{-1}; Pb: 1.520 mg kg^{-1}; Zn: 1.014 mg kg^{-1}	Medicinal plants	ICP OES	28
Al, Ba, Ca, Cr, Cu, Fe, K, Mg, Mn, Na, Ni, P, Se, Sn, Sr, V and Zn	Al: 1261.64 μg g^{-1}; Ba: 63.18 μg g^{-1};Ca: 19,957.40 μg g^{-1}; Cr: 1.38 μg g^{-1}; Cu: 21.99 μg g^{-1}; Fe: 627.49 μg g^{-1}; K: 32,297.19 μg g^{-1}; Mg: 6174.52 μg g^{-1}; Mn: 205.64 μg g^{-1}; Na: 18,596.45 μg g^{-1}; Ni: 0.99 μg g^{-1}; P: 2899.91 μg g^{-1}; Se: 3.71 μg g^{-1}; Sn: 12.43 μg g^{-1}; Sr: 84.31 μg g^{-1};V: 0.24 μg g^{-1}; Zn: 30.56 μg g^{-1}	Medicinal plants and herbal medicines	ICP OES	30
Al, As, Ba, Ca, Cd, Co,Cr, Cu, Fe, Hg,Mg, Mn, Ni, Pb, Sb, Se, Sr, V and Zn	Al: 6130 mg kg^{-1}; As: 0.750 mg kg^{-1}; Ba: 180.6 mg kg^{-1}; Ca: 34070 mg kg^{-1}; Cd: 4.772 mg kg^{-1}; Co: 1.061 mg kg^{-1}; Cr: 12.42 mg kg^{-1}; Cu: 22.42 mg kg^{-1}; Fe: 2321 mg kg^{-1}; Hg: 0.041 mg kg^{-1};Mg: 7739 mg kg^{-1}; Mn: 352.7 mg kg^{-1}; Ni: 9.194 mg kg^{-1}; Pb: 64.40 mg kg^{-1}; Sb: 0.102 mg kg^{-1}; Se: 0.508 mg kg^{-1}; Sr: 212.1 mg kg^{-1}; V: 7.721 mg kg^{-1}; Zn: 61.95 mg kg^{-1}	Herbal tea products	ICP-MS	31
As, Cd, Co, Cu, Fe, Mn, Ni, P, Pb, V and Zn	As: 0.23 μg g^{-1}; Cd: 0.03 μg g^{-1}; Co: 0.05 μg g^{-1}; Cu: 0.05 μg g^{-1}; Fe: 15 μg g^{-1}; Mn: 46.8 μg g^{-1};Ni: 0.52 μg g^{-1}; P: 314 μg g^{-1}; Pb: 0.2 μg g^{-1}; V: 0.12 μg g^{-1}; Zn: 24.6 μg g^{-1}	Herbal preparations derived by the lichen *Cetrariaislandica*	ICP OES	32
Ca, Cd, Co, Cr, Cu, Fe, K, Mg,Mn, Na, Ni, Pb and Zn	Ca: 41,210.94 mg kg^{-1}; Cd: 1.66 mg kg^{-1}; Co: 11.26 mg kg^{-1}; Cr: 29.49 mg kg^{-1}; Cu: 19.19 mg kg^{-1}; Fe: 6796.88 mg kg^{-1}; K: 17,786.25 mg kg^{-1}; Mg: 6350.63 mg kg^{-1}; Mn: 105.56 mg kg^{-1}; Na: 2174.38 mg kg^{-1}; Ni: 15.80 mg kg^{-1}; Pb: 10.63 mg kg^{-1}; Zn: 65.85 mg kg^{-1};	Medicinal plants	AAS	33
As, Cd, Hg, and Pb	As: 0.81 mg kg^{-1}; Cd: 0.31 mg kg^{-1}; Hg: 0.04 mg kg^{-1}; Pb: 3.18 mg kg^{-1}	Herbal medicines	ICP-MS	35
Al, As, Cd, Cr, Cu,	Al: 2640 μg kg^{-1}; As: 1.65	Herbal medicines	ICP OES and AAS	37

(*continued on next page*)

Table 3 (*continued*)

Impurities	Highest concentration values	Sample	Technique	Ref.
Fe, Hg, Mn, Ni, Pb and Zn	μg kg^{-1}; Cd: 0.78 μg kg^{-1}; Cr: 188.3 μg kg^{-1}; Cu: 354.5 μg kg^{-1}; Fe: 3423 μg kg^{-1}; Hg: 0.35 μg kg^{-1};Mn: 230.2 μg kg^{-1}; Ni: 44.14 μg kg^{-1}; Pb: 7.65 μg kg^{-1};Zn: 1253 μg kg^{-1}			
As, Cd, Cu, Fe,Hg, Pb and Zn	As: 36.71 mg kg^{-1}; Cd: 363.25 mg kg^{-1}; Cu: 560 mg kg^{-1}; Hg: 58.95 mg kg^{-1}; Fe: 5570 mg kg^{-1}; Pb: 11,750 mg kg^{-1}; Zn: 1134 mg kg^{-1}	Complementary medicines	ICP-MS	38
Ba, Ca, Cr, Cu, Fe, K, Mg, Mn, Mo, Na, Ni, P, Sr and Zn	Ba: 11.0 mg kg^{-1}; Ca: 1780 mg kg^{-1}; Cr: 1.9 mg kg^{-1}; Cu: 24.0 mg kg^{-1}; Fe: 168 mg kg^{-1}; K: 14,000 mg kg^{-1}; Mg: 8000 mg kg^{-1}; Mn: 152 mg kg^{-1}; Mo: 1.3 mg kg^{-1}; Na: 87.0 mg kg^{-1}; Ni: 3.7 mg kg^{-1};P: 17,500 mg kg^{-1}; Sr: 22.0 mg kg^{-1}; Zn: 96 mg kg^{-1}	Cannabis products	ICP OES	42
Al, As, Cu, Fe, Mg, Mn, Ni and Pb	Al: 66.0 mg kg^{-1}; As: 0.28 mg kg^{-1}; Cu: 5.6 mg kg^{-1};Fe: 897.7 mg kg^{-1}; Mg: 32,271 mg kg^{-1}; Mn: 863 mg kg^{-1};Ni: 28 mg kg^{-1}; Pb: 3 mg kg^{-1}	Kratom products	ICP OES	45
As, Cd, Cr, Fe, Hg, Ni and Pb	As: 0.36 μg g^{-1}; Cd: 0.063 μg g^{-1}; Cr: 5.7 μg g^{-1};Fe: 850 μg g^{-1}; Hg: 0.025 μg g^{-1}; Ni: 7.4 μg g^{-1};Pb: 1.6 μg g^{-1}	Kratom products	ICP-MS	46
As, Cr, Cu, Hg, Mn and Pb	As: 479,000 mg kg^{-1}; Cr: 643 mg kg^{-1}; Cu: 675,000 mg kg^{-1}; Hg: 15,600 mg kg^{-1}; Mn: 243 mg kg^{-1}; Pb: 248 mg kg^{-1};	Ayurvedic formulations	ICP OES and GFAAS	54
As, Cd, Hg and Pb	As: 3770 μg kg^{-1}; Cd: 368 μg kg^{-1}; Hg: 16,800 μg kg^{-1}; Pb: 48,600 μg kg^{-1}	Dietary supplements	ICP-MS	60
Hg	Hg: 2.35 mg kg^{-1}	Herbal preparation	AAS	61
As	As: 531 ng g^{-1}	Prenatal and children's dietary supplements	IC-ICP-MS	63
Hg	Hg: 476.1 ng g^{-1}	Prescription, non-prescription medicines and dietary supplements	CV-AFS	64
As, Br, Cd, Ce, Co, Cr, Cu, Fe, K, Na, Ni, Sb, Sn, Sr and Zn	As: 2.27 μg g^{-1}; Br: 6.63 μg g^{-1}; Cd: 0.520 μg g^{-1};Ce: 0.610 μg g^{-1}; Co: 0.835 μg g^{-1}; Cr: 0.890 μg g^{-1};Cu: 2.56 μg g^{-1}; Fe: 55.3 μg g^{-1}; K: 1573 μg g^{-1};Na: 3.73%; Ni: 6.78 μg g^{-1}; Sb: 2.15 μg g^{-1}; Sn: 2.26 μg g^{-1}; Sr: 57.7 μg g^{-1}; Zn: 0.230 μg g^{-1};	Calcium supplements	INAA and AAS	66
Mn and Se	Mn: 18.2%; Se: 13.6%;	Synthesized compounds	WDXRF and TXRF	68
Ba, Ce, Dy, Er, Eu, Gd, Ho, La, Nd, Pb, Pr, Sm, Tb and Y	Ba: 102 ng g^{-1}; Ce: 36 ng g^{-1}; Dy: 205 ng g^{-1}; Er: 55 ng g^{-1}; Eu: 444 ng g^{-1}; Gd: 1.21x10^{8}ng g^{-1};Ho: 49 ng g^{-1}; La: 161 ng g^{-1};Nd: 220 ng g^{-1}; Pb: 26 ng g^{-1};Pr: 98 ng g^{-1}; Sm: 355 ng g^{-1}; Tb: 618 ng g^{-1}; Y: 264 ng g^{-1}	Gadolinium-based contrast agents	ICP-MS	79
Fe and Pt	Fe: 182.8 μg g^{-1}; Pt: 2.8 μg g^{-1}	Tablets	ICP OES	81
Hg	Hg: 0.65 μg mL^{-1}	Commercial cosmetics and Thailand traditional medicines	Flow injection spectrophotometry	93
Cd and Pb	Cd: 1.57 mg kg^{-1}; Pb: 5.45 mg kg^{-1}	Thailand herbal medicines	FAAS	100
Pb	Pb: 943 μg g^{-1}	Antacids	GF AAS	101
Cd and Pb	Cd: 9.9 ng g^{-1}; Pb: 43.9 ng g^{-1}	Anaesthetics for teething (gels) based on herbs	ET AAS	102
Pb	Pb: 7.068 μg g^{-1}	Iron supplements	ET AAS	103
Cd and Pb	Cd: 51 ng g^{-1}; Pb: 318 ng g^{-1}	Pharmaceutical formulations	HR CS GF AAS	106
Cr	Cr: 1.92 mg kg^{-1}	Pharmaceutical products	HR CS GF AAS	107
Cr, Cu and Ni	Cr: 0.09 μg/tablet; Cu: 0.04 μg/tablet; Ni: 0.15 μg/tablet	Pharmaceutical products	HR CS GF AAS	108
Cd, Cr and Pb	Cd: 121 μg kg^{-1}; Cr: 320 μg kg^{-1}; Pb: 563 μg kg^{-1}	Herbal medicines	USAEME-GF AAS	109

(*continued on next page*)

Table 3 (*continued*)

Impurities	Highest concentration values	Sample	Technique	Ref.
Cd	Cd: 54.5 ng g^{-1}	Omega-3 dietary supplements	TS-FF-AAS	110
Cr, Cu, Fe, Ni and Zn	Cr: 1.09 mg L^{-1}; Cu: 2.22 mg L^{-1}; Fe: 4.68 mg L^{-1}; Ni: 5.3 mg L^{-1}; Zn: 2.15 mg L^{-1}	Pharmaceutical products	TXRF	113
Cr, Mn, Mo, Os and Ru	Cr: 63.12 μg g^{-1}; Mn: 896.08 μg g^{-1}; Mo: 10.44 μg g^{-1}; Os: 3.39 μg g^{-1}; Ru: 23.27 μg g^{-1}	Pharmaceutical products and dietary supplements	WDXRF	114
Ca, Cl, Fe, K, Mg, Na, P, S, Si and Ti	Ca: 9.33%; Cl: 6.25%; Fe: 0.77%; K: 0.68%; Mg: 1.09%; Na: 4.85%; P: 7,21%; S: 0.47%; Si: 1.78%;Ti: 1.09%;	Pharmaceutical products	EDXRF	115
Al, Ba, Cd, Cr, Cu, Mn, Ni, Pb, Sb, Sr, Ti, V and Zn	Al: 21,900 μg g^{-1}; Ba: 104 μg g^{-1}; Cd: 6.93 μg g^{-1};Cr: 66.6 μg g^{-1}; Cu: 14.5 μg g^{-1}; Mn: 1190 μg g^{-1};Ni: 40.7 μg g^{-1}; Pb: 5.06 μg g^{-1}; Sb: 10.5 μg g^{-1};Sr: 46.0 μg g^{-1}; Ti: 440 μg g^{-1}; V: 1.7 μg g^{-1}; Zn: 2600 μg g^{-1}	Eye shadows	ICP OES	124
As, Cd, Co, Ge and Ni	As: 0.80 mg kg^{-1}; Cd: 0.34 mg kg^{-1}; Co: 0.97 mg kg^{-1}; Ge: 11.3 μg kg^{-1}; Ni: 0.72 mg kg^{-1}	Traditional chinese medicine	HG and PVG coupled with ICP OES	131
As, Cd and Pb	As: 0.198 μg g^{-1}; Cd: 0.096 μg g^{-1}; Pb: 1.06 μg g^{-1}	Medicinal plants	ICP-MS	132
As, Ba, Cd, Co, Cr, Cu, Li, Mo, Ni, Pb, Sb and V	As: 0.107 μg g^{-1}; Ba: 1.9 μg g^{-1}; Cd: 0.012 μg g^{-1}; Co: 0.031 μg g^{-1}; Cr: 0.16 μg g^{-1}; Cu: 0.12 μg g^{-1}; Li: 0.050 μg g^{-1}; Mo: 7.5 μg g^{-1}; Ni: 3.43 μg g^{-1}; Pb: 0.014 μg g^{-1}; Sb: 0.008 μg g^{-1};V: 0.202 μg g^{-1}	Omeprazole drug samples	ICP-MS	133
Cl	Cl: 576 μg g^{-1}	Pharmaceutical excipient	ICP OES	135
Ag, As, Cd, Co, Cr, Cu, Hg, Ni, Pb and Sn	Ag: 0.996 μg g^{-1}; As: 0.997 μg g^{-1};Cd: 1.000 μg g^{-1}; Co: 1.000 μg g^{-1}; Cr: 0.999 μg g^{-1}; Cu: 1.000 μg g^{-1};	Metronidazole API	ICP OES	136

Table 3 (*continued*)

Impurities	Highest concentration values	Sample	Technique	Ref.
As, Cr, Cu, Ni and Pb	Hg: 0.993 μg g^{-1}; Ni: 3.500 μg g^{-1}; Pb: 0.999 μg g^{-1}; Sn: 0.999 μg g^{-1} As: 0.44 μg g^{-1}; Cr: 5.40 μg g^{-1}; Cu: 66.13 μg g^{-1};Ni: 2.95 μg g^{-1}; Pb: 0.27 μg g^{-1}	Herbal medicines	ICP OES	137
Ca, Cu, Fe, Mg, Mn, P and Zn	Ca: 170 mg g^{-1}; Cu: 1.30 mg g^{-1}; Fe: 9 mg g^{-1}; Mg: 72 mg g^{-1}; Mn: 3.6 mg g^{-1};P: 95 mg g^{-1};Zn: 16 mg g^{-1}	Pharmaceutical tablets	LIBS	145

chemical waste possible.

In the pharmaceutical scenario, there is a demand for analytical methods to possibly identify and quantify all known and unknown impurities during the manufacturing process of a chemical compound with pharmaceutical properties. Analytical methods are necessary for clinical assays, therapeutic drug monitoring, individual dosage scheme adjustment, and also for monitoring of pharmaceutical residues in the environment. These methods are based on well defined techniques and should considerer different approaches during manufacture [82]. One statistical consideration has to be pointed: the measurement uncertainty evaluation from data obtained in the methods should occur independently of the validation strategy used. This allows reliable results and more accurate information from the developed analytical methods [83].

Several techniques that encompass the field of atomic spectroscopy such as flame atomic absorption spectrometry (FAAS), graphite furnace atomic absorption spectrometry (GFAAS), inductively coupled plasma optical emission spectroscopy (ICP OES) and inductively coupled plasma mass spectrometry (ICP-MS) have been used, for many years, for the analysis of metals and metalloids in a variety of sample types, including pharmaceutical compounds [84,85]. Other techniques and the association of the existing ones have been recently described. Therefore, methods should provide chemical information about the medicine, but they also should support a good quality control of these products when it comes to health problems related to elemental impurities.

Another topic of concern regarding analytical techniques is the validation step of a method. At this time, scientists should first guarantee accuracy and reproducibility for the developing strategy. Data generated from validation steps reveals the quality of the study, which justify the reason for performing an efficient scientific method validation. The principal goal of an analytical method is to ensure future determinations chemically and statistically supported in order to obtain reliable results [86].

The Brazilian Pharmacopeia (volume I) [9] and the United States Pharmacopeia (chapters 232 and 233) [47,48] show an important discussion about analytical techniques and parameters when it comes to elemental impurity determination. Although these references have already great information, they remain incomplete to cover all analytical possibilities and strategies applying to pharmaceutical matrix analysis. Besides, elemental impurity limits are not yet completely established.

Chapter 233 describes suitable analytical procedures for evaluating

the elemental impurity limits established in chapters 232 and 2232. Chapter 233 presents procedure 1 (ICP OES-based) and procedure 2 (ICP-MS-based), but it also considers alternative procedures, since they meet the validation requirements. These alternative procedures must be validated and equivalent to the compendial procedures in order to meet the purpose of the analytical test. Chapter 1225 - Validation of Compendial Procedures [87] covers the principles of validation, but where the information differs from that presented in Chapter 1225, the analytical parameters and acceptance criteria of Chapter 233 take precedence. Validation of limit procedures must be demonstrated experimentally, using an appropriate protocol with reference materials, for detection limit, repeatability (for instrumental methods), and specificity assays. Validation of quantitative procedures should also include tests for accuracy, precision and limit of quantification, range and linearity. When these analytical parameters are in accordance with their respective acceptance criteria, a given alternative procedure can be considered equivalent to the pharmacopeial procedures 1 and 2 described in Chapter 233. It is important to highlight that this chapter also mentions and describes sample preparation strategies, such as neat, direct aqueous solution, direct organic solution and indirect solution, which includes closed vessel digestion. The choice of the appropriate sample preparation method reflects on the success of the proposed analytical method for evaluating elemental impurities [48].

Sample preparation is a prior step and has to be cautiously developed. In the pharmaceutical scenario, there are a lot of sample preparation options that fit analytical techniques in order to guarantee very low limits of detection and quantification. It is already known that, the more the matrix is separated, digested, isolated or inactivated, the more the analytes will be available for the determination step. Therefore, Pinheiro and Nóbrega [88] discussed about sample preparation procedures for elemental impurity determination in medicines. They pointed, among other comments, according to the United States Pharmacopeia, that direct aqueous or organic dilution/dissolution can be adopted when the sample is soluble in aqueous or organic solvents, respectively. Digestion procedures with heating programs must be applied when the matrix is not possible to be dissolved with simple dissolution, up to the very well-known microwave-assisted digestion in closed vessels, widely used for pharmaceutical sample preparations. Other challenges and particularities in this subject, such as acid solutions, organic toxic solvents and chemical modifiers, for example, must be continuously evaluated in the development of sample preparation methods.

3.1. Spectrophotometric techniques

A spectrophotometer is an instrument in which radiant energy of a very narrow wavelength range is selected from a source and passed through the sample solution, which is in a glass or quartz cell. The quantitative basis of spectrophotometry is that the amount of radiation absorbed at an appropriate wavelength is proportional to the concentration of the light-absorbing elements or compounds in the sample. Absorbance requires the measurement of the ratio of the radiant powers of two beams. Thus, spectrophotometry is a very fast and convenient technique of quantitative analysis [89]. This technique is very powerful in the pharmaceutical field due to the possibility that many chemical elements and compounds present in the products are able to absorb specific radiation, allowing to set a concentration and evaluation of the risk the element or compound poses on the medicine. UV-based spectrometry is an important strategy for impurity analysis, considering maximum absorption, which allows great analytical methods for chemical screening with good selectivity [90].

UV/Visible spectrophotometry has become popular, since it is relatively low cost, rapid and simple. Spectrophotometry uses light in the visible, ultraviolet and near infrared ranges. According to the Beer-Lambert law, the absorbance of a solution is directly proportional to the concentration of the absorbing species in solution and the path length. Thus, for a fixed path length, UV/VIS spectrophotometry can be used to determine the concentration of several metals. Although some desired constituents are self-colored, UV/Visible spectrophotometry also involves the use of ligands which selectively bind to metals such as iron (II) and copper (II) to produce colored complexes with a higher molar absorptivity to enable a sensitive determination of these metals in different pharmaceutical samples [78,91].

A recent spectrophotometric method was established by Tarighat et al. [92]. It was a new micelle-mediated extraction method for the preconcentration of trace amounts of Cu^{2+} and Zn^{2+} as a prior step to their simultaneous spectrophotometric determination: The continuous wavelet transformation (CWT) of visible spectra for the simultaneous analysis of both elements in medicinal plant samples. This method is a selective, very sensitive, simple, eco-friendly and low-cost spectrophotometric procedure. The surfactant Triton X-100 was used for the preconcentration of Cu^{2+} and Zn^{2+} and, therefore, toxic solvent extraction was avoided. There is a good agreement between the results obtained by this method and those obtained by standard graphite furnace atomic absorption spectrometry (GFAAS).

Prasertboonyai et al. [93] reported a spectrophotometric method for Hg (II) determination using dithizone, by adding sodium dodecyl sulphate (SDS) in the presence of ascorbic acid in sulphuric acid medium. An extraction system was not required in this method. It was satisfactorily applied for Hg (II) determination in commercial cosmetics and local Thailand traditional medicines. The results obtained by the proposed method are favorably compared with those analyzed by inductively coupled plasma mass spectrometry (ICP-MS).

Recently, Fashi et al. [94] developed a method for a fast and sensitive determination of bismuth in bismuth subcitrate tablets and human plasma samples. It was an electromembrane-microextraction (EME) followed by microcell UV/Vis spectrophotometeric detection. The developed method was successfully applied for the determination of bismuth in real samples. Another recent study, conducted by Al-Saidi and Alharthi [95], discussed the enhancement of a spectrophotometric method using microcell of long optical paths and an effective pretreatment technique using dispersive liquid-liquid microextraction for the determination of Co in waters and pharmaceutical preparations. This study proposed the reduction in toxic organic solvents used in extraction steps and established great limits of detection (0.08 μg L^{-1}) for Co in these matrices.

3.2. Atomic absorption spectrometry

It was already demonstrated that mass has the capacity to interact with electromagnetic radiation, whose total intensity can be reduced proportionally to the mass absorption ability. Therefore, some techniques have been developed to allow the quantification of absorption in different kinds of materials [96]. In spectroscopy, absorption is a process in which a chemical species selectively attenuates (decreases the intensity of) certain frequencies of electromagnetic radiation. A very common technique with atomic absorption is the electrothermal atomizer, in which a few microliters of sample are introduced in a graphite tube in order to achieve the atomization step of the analyte according to its corresponding temperature. The absorption of the atomized analyte is then monitored to obtain absorbance values, with which concentration data can be calculated [96]. Other possibilities for AAS include flame, cold vapor and hydride generation, as illustrated in Fig. 2.

Atomic absorption spectrometry (AAS) is widely used in the pharmaceutical industry for elemental analysis, and it can be used to determine over 70 different elements [70,97,98]. However, most AAS instruments use line radiation sources, such as hollow cathode lamps, which only allows for the analysis of a particular element (the analyte) that is specific for the lamp used [71,99]. Flame atomic absorption spectrometry (FAAS) is a very well known technique, in which it is possible to determine classical toxic metals by developing simple, low-cost and even direct methods. Siriangkhawut et al. [100] proposed an

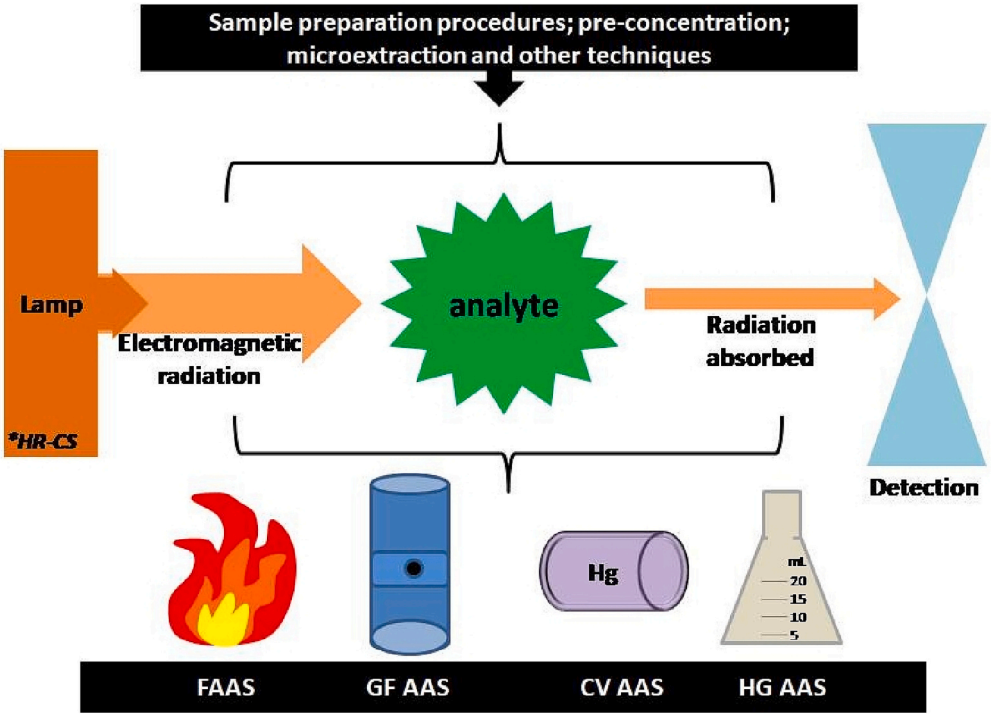

Fig. 2. Illustrative scheme on the main AAS techniques.HR-CS: High-resolution continuum source. (The authors, 2023).

ultrasound-assisted digestion (UAD) procedure for sample pretreatment followed by FAAS determination of trace Cd and Pb in various types of medicinal plants and traditional medicines consumed in Thailand. Limits of quantification were obtained as 1.87 μg L^{-1} and 40.3 μg L^{-1} for Cd and Pb, respectively, which recommend this method for routine analysis as an alternative strategy for toxic metal evaluation in pharmaceuticals, faster and with low chemical consumption, compared to conventional wet acid digestion procedures.

Portugal et al. [101] proposed a method for the determination of Pb, in aluminum and magnesium antacids, using electrothermal atomic absorption spectrometry (ET AAS). The samples were also analyzed after complete dissolution by inductively coupled plasma mass spectrometry (ICP-MS). No statistical difference was observed between the results obtained by the procedures, indicating high accuracy, precision and sensibility of the ET AAS method. In this study, it was found that some samples showed high levels of Pb and they are cause of concern, given lead toxicity for humans. Another study using ET AAS was conducted by Jurowski et al. [102], to determine Pb and Cd in anaesthetics for teething (teething gels) based on herbs available in Polish pharmacies, especially for infant use. All samples had metal contents above the limit of quantification, but under the acceptable limits, in accordance with ICH Q3D guideline.

Barbosa et al. [103], using atomic absorption spectrometry, determined lead in twelve Brazilian samples of iron supplements using high-resolution continuum source graphite furnace atomic absorption spectrometry (HR-CS GF AAS). The principal advance of this technique is the quality of the lamp, which allows the determination of different elements, sequential and simultaneous determinations, great background signal correction and better electromagnetic source radiation. In this study, samples were also determined by ICP-MS as one of the steps for accuracy evaluation. This is the first report for the determination of lead in iron supplements. Based on the maximum values for lead established by the Brazilian and the United States Pharmacopeias, the concentrations in some samples exceed these limits. Since these supplements may be administered for long intervals, these results are of high significance. Analytical techniques based on atomic absorption spectrometry with graphite furnace have been providing widespread applications for elemental impurity analysis [104,105].

Another method using high-resolution continuum source graphite furnace atomic absorption spectrometry (HR-CS GF AAS) was proposed by Aleluia et al. [106]. Cd and Pb were sequentially determined after optimization steps of experimental conditions, which were conducted using a two-level full factorial design. The measures were performed using the primary atomic absorption lines of Cd and Pb at 228.8018 and 217.0001 nm, respectively. This was important to obtain great values of absorbance with very low background signal interference, which allowed the development of a method with limits of detection and quantification of 4 and 13 ng g^{-1} for cadmium and 49 and 165 ng g^{-1} for lead, respectively. Ten samples were analyzed in this method and the concentrations of Cd and Pb were under the maximum values established by the Brazilian and the United States Pharmacopeias, which are 5 μg per day for each element. The principal advantage of this method was the heating program, established using one pyrolysis temperature and two atomization temperatures (first Cd temperature and then Pb atomization temperature) with a single sample injection, allowing sequential determination, minimizing the consumption of graphite tubes and the time for analysis.

A direct analysis of solid samples was conducted by Barrera et al. [107] for chromium determination in eighteen pharmaceutical drugs and three excipients, using HR-CS GF AAS. Encapsulated samples were opened and only its powder content was evaluated, and the other solid drugs were completely grinded before determination. The results obtained from this method were in accordance with those obtained from acid digestion of samples using closed-vessel microwave oven device, being a fast, direct, reliable and simple method for routine pharmaceutical analysis. In all the samples analyzed, Cr levels were under the maximum limit established by the Brazilian, the United States and the European Pharmacopeias. HR-CS GF AAS has proven to be a very potent technique for analytical impurity screening methods, considering the recently updated requirements of international guidelines, as confirmed by Mattiazzi et al. [108].

In a recent study from Iran, Aghamohammadi et al. [109] developed a method to determine Pb, Cr and Cd in herbal medicines. The ultrasound-assisted emulsification microextraction (USAEME),

combined with graphite furnace atomic absorption spectrometry (GF AAS), showed to be an efficient, rapid, inexpensive and eco-friendly method for the determination of Pb, Cr and Cd in these products. The results indicated that the values obtained were not excessive for the analyzed samples.

Carazza et al. [110] proposed a new method for the determination of Cd^{2+} in omega-3 dietary supplement using extraction induced by emulsion breaking (EIEB) and thermospray flame furnace atomic absorption spectrometry (TS-FF-AAS). The method was based on the formation of a water-in-oil emulsion by the addition of an extracting solution consisting of Triton X-114 and HNO_3 in the oil sample and further breaking of this emulsion by heating. Two well-defined phases were formed and the acid aqueous one containing the extracted cadmium ions was analyzed by TS-FF-AAS using a flow injection system. The accuracy of the proposed method was guaranteed by a good accordance with the results achieved by microwave-assisted acid digestion without any statistical differences (95% confidence) and by spiking the samples with known concentrations of 50 ng g^{-1} Cd^{2+}. Samples analyzed in this study were safe for Cd content, according to the United States Pharmacopeia maximum limits for elemental impurities.

3.3. X-ray fluorescence techniques

X-ray fluorescence is widely used. Basically, in this technique, a ground-state atom population is irradiated by x-rays and then the emitted fluorescent radiation is measured. This measurement results from the return of the excited electron to its ground state [111,112].

Solids and liquids in inorganic and organic matrices (powders and liquids), used in the manufacture of active pharmaceutical ingredients (API) and medicines, can be analyzed by total reflectance X-ray fluorescence (TXRF) with minimal sample preparation and negligible matrix effects, in most cases. The cost per analysis can be dramatically reduced as no other chemicals or complicated sample manipulations are required. TXRF is a fast analytical method for elemental screening and the simultaneous, quantitative analysis of multiple elements [99,113]. This method has been investigated for quantitative metal analysis in pharmaceuticals. The results demonstrate acceptable quantitation criteria in terms of detection/quantification limit, accuracy, and precision. When applied to 14 real API samples, TXRF shows comparable results with ICP-MS for Pd and Cu determination [71].

Figueiredo et al. [114] investigated the availability of Wavelength Dispersive X-ray Fluorescence (WDXRF) spectrometry for the measurement of As, Cd, Cr, Cu, Hg, Ir, Mn, Mo, Ni, Os, Pb, Pd, Pt, Rh, Ru and V impurities in 30 different pharmaceuticals and 25 dietary supplements, according to EMA, USP and ICH guidelines. It was observed that this method is an alternative to the compendial analytical procedures recommended for such elements. The novelty of this study is the application of WDXRF to medicines and not only to active pharmaceutical ingredients and/or excipients. It also shows how the analysis of finished products, not only the analysis of isolate substances, are important to achieve good quality in medicines.

X-ray fluorescence spectrometry can be applied to elemental screening in pharmaceutical products according to the ICH Q3D guideline, as proposed by Sauer et al. [115]. Energy-dispersive x-ray fluorescence spectrometry (EDXRF) is a suitable analytical technique, whose method allowed the determination of Cd, Pb, As, Hg, Co, V and Ni in oral solid dosage products with great limits of quantification, according to the European Pharmacopeia. EDXRF was also explored by Chowdhury et al. [116], by developing a non-destructive, quick and reliable quantitative analytical method for the estimation of class I (Pb, Cd, Hg and As) and class II (Co, V and Ni) metal elements present in pharmaceuticals, according to ICH Q3D and USP.

Recently, XRF analysis has become increasingly attractive when compared to other techniques, especially due to the ease in sample preparation. XRF spectrometry involves irradiation of the sample with high energy excitation X-rays and measurement of element-specific fluorescence X-rays at a particular wavelength or energy from the sample. As it is a non-destructive technique, it is possible to reuse the sample after measurements. Recently, total-reflection XRF (TXRF) has been found to be useful for the determination of trace elements in several drugs [78].

3.4. ICP-based techniques

Plasma is a kind of energy source very powerful and useful that has been for a long time coupled to spectrometric techniques. Mass spectrometry and optical emission spectrometry are the two principal strategies in analytical chemistry. Both provide elemental determination from all kinds of materials with great limits of detection and quantification. It can be partially explained due to the capacity of the plasma to afford the correct atomization and ionization of the elements during the analysis. In the pharmaceutical industry and institutions of medical research, inductively coupled plasma mass spectrometry (ICP-MS) and inductively coupled plasma optical emission spectrometry (ICP OES) have been constantly used as routine techniques or technical support for developing instrument-based methods [117–119]. Both techniques comprise the major procedures established by the United States Pharmacopeia in chapter 233 for elemental impurity analysis [48]. ICP-MS traditionally has the ability to provide extremely low levels of elemental impurities when compared to ICP OES. However, Menoutis et al. [120] recently proved significant improvement in detection limits by coupling an ultrasonic nebulizer to an axial ICP OES for the determination of elemental impurities in oral drugs, according to USP, chapters 232 and 233.

ICP-based methods have gained widespread use due to their unique characteristics, making them suitable for routine analysis. Several options for sample preparation are available, including dissolution in water or organic solvents, wet digestion, combustion in closed vessels and extraction under microwave heating, leading to suitable limits of detection (LODs) for all elements of pharmaceutical interest. Spectral interferences in ICP-MS can be overcome by the use of reaction or collision cells. ICP-MS can also be coupled to separation techniques, allowing the speciation of impurities, which remains a difficult analysis and requires more development [121,122].

The four main toxic elements (As, Cd, Hg and Pb) used to be widely investigated in pharmaceutical samples. Silva et al. [123] determined these analytes in eight drug samples and two excipients (completely digested using microwave-assisted digestion with inverse aqua regia in closed vessels) by ICP OES and ICP-MS methods, according to the United States Pharmacopeia (USP), chapters 232 and 233. The Spike test was performed for the four metals and the recoveries obtained by ICP OES ranged from 75 to 148% and, for ICP-MS, it ranged from 74 to 120%. Moreover, limits of detection for ICP OES ranged from 0.4 to 17 mg kg^{-1} and, for ICP-MS, from 7.4 to 41.6 μg kg^{-1}, showing great parameters of accuracy and sensitivity, which is already expected from ICP methods. It is important to notice that all samples contained As, Cd, Hg and Pb below the maximum values established by USP.

Santana et al. [124] proposed a very important ICP OES method for multielement determination (essential and potentially toxic elements) in eye shadows exposed to consumption in Brazil. In this study, Al, Cd, Cr, Cu, Mn, Ni, Pb, Sb, Ti, V and Zn were above the recommended maximum tolerable limits, according to the Brazilian and international legislations, highlighting a public health concern about the risks involved in eye shadow consumption. ICP OES was also explored by Pinheiro et al. [125], who developed a pretreatment method for the determination of Cd, Co, Hg, Ni, Pb and V in oral and parenteral drug samples. They performed a dispersive liquid-liquid microextraction based on deep eutectic solvent prior to determination using ICP OES. This extraction step was responsible for reducing the limits of quantification 10 times in relation to the target limits recommended for drugs, according to USP, chapter 232. In this study, all analytes were below the respective LOQ values, thus lower than the limits proposed by USP, Chapter 232.

Tu et al. [126] developed a method for fast screening of metals in various pharmaceutical samples using flow injection coupled to ICP-MS (FI-ICP-MS). A modified high performance liquid chromatography (HPLC) configuration was applied for easy automation and standardization. This method has provided a means for high-throughput metal screening of a large amount of samples, such as raw materials, process intermediates and final drug substances, and it also has been successfully applied to metal analysis (palladium, rhodium and chromium) in adsorbent screening tests and in contamination investigations.

Fischer et al. [127] also developed a method based on the coupling of FI to ICP-MS. A high throughput FI-ICP-MS system was used for the analysis of impurities according to USP in several pharmaceutical products. The method revealed quantification limits lower than those required by the guideline by a factor of 5–10. Another ICP-MS method, also in accordance with USP, chapters 232 and 233, was developed and validated by Chahrour et al. [128] for the determination of elemental impurities in an API candidate (TP-6076), which has been used in phase I and II clinical trials. The authors revealed great analytical figures of merit for all 15 USP elements.

Rudovica et al. [129] proposed a method using laser ablation (LA) coupled to ICP-MS for fast direct elemental analysis of active pharmaceutical substances using laboratory-made standards. LA-ICP-MS is a powerful and fast analytical method for multi-elemental analysis. A disadvantage in using this method is the lack of matrix reference materials for validation and calibration purposes. Six elements (Mn, Co, Ni, Cu, Pb, Cd) were determined in arbidol. The results meet the Pharmacopeia requirements for analysis of elemental impurities in pharmaceutical products. Another method was developed by Pluhácek et al. [130], using LA-ICP-MS for screening elemental impurities in different pharmaceutical matrices. It is important to notice the great advantage of laser ablation application to avoid acid solution preparation steps and the consolidation of this technique in routine quality control analysis at different stages of pharmaceutical production.

Shen et al. [131] proposed a different method in which a simultaneous hydride generation of As, Cd and Ge and photochemical vapor generation of Co and Ni were conducted in dual mode, and the volatile species were introduced into the ICP OES for simultaneous multi-element analysis. This is the first attempt of combination of two different chemical vapor generation (CVG) technologies for sample introduction to ICPOES, and higher sample introduction efficiency, less matrix and spectral interferences, higher selectivity and multielement determination were achieved for real samples. After an acid-evaporation/catching procedure involving formic acid addition and/or proper dilution, satisfactory analytical results were obtained for vegetal-matrix celery certified reference material (CRM) and *Curcuma wenyujin* traditional chinese medicine (TCM) samples for trace elements.

Muller et al. [132] proposed a microwave-assisted digestion procedure using diluted HNO_3 solution (4 mol L^{-1}) for medicinal plants to determine As, Cd and Pb by ICP-MS and also Hg by flow injection cold vapor generation (FI-CVG) coupled to ICP-MS. The digests obtained were compatible with ICP-MS analysis and the proposed procedure was in agreement with the recommendations of Green Chemistry. Microwave-assisted digestion in closed vessels fulfills the US pharmacopeial requirements for digestion of medicinal plants, since it allows the use of diluted solutions, reducing blank values and, consequently, the limits of detection and quantification. This digestion procedure was also used by Pinheiro et al. [133], but now applied to a different type of matrix, when an ICP-MS method was proposed for the determination of elemental impurities in different commercial samples of omeprazole. In this study, 23 elements were determined, whose concentration values were under the limits proposed by USP, chapter 232. Besides the large application of microwave-assisted digestion, ICP OES methods for the determination of elemental impurities may be coupled to a dilute-and-shoot procedure, a fast and simple strategy for sample preparation, developed by diluting the sample and performing the direct introduction to the equipment, avoiding the use of time-consuming digestion steps before analyte determination, as shown by Pinheiro et al. [134] in another study.

A combustion step followed by pyrohydrolysis reaction method coupled to ICP OES is another alternative strategy for elemental determination in pharmaceuticals. In a study conducted by Druzian et al. [135], total chlorine was evaluated in the excipient hydroxypropyl cellulose (HPC), with great results of accuracy and sensitivity. It is important to notice that combustion followed by a pyrohydrolysis system was easily built and feasible for routine analysis, corroborating the European Pharmacopeia requirements.

ICP-based methods are undoubtedly more sensitive and specific than AAS-based methods. However, this is not the reason for industries and research centers to replace a simple and feasible AAS-method by an expensive and laborious ICP-method. The analytical strategy of choice has to comply with the objectives of the research and with the chemical characteristics of the analyte(s) and the matrix. On the other hand, ICP OES methods are truly recommended [136] for elemental impurity determinations in API samples, for example, as a function of the high accuracy and sensitivity, in comparison with trace elements limit tests, which used to be described in previous versions of different pharmacopeias. Traditional colorimetric limit tests for toxic metal evaluation, which is still performed by many industries, must be discouraged, since their results are neither specific nor exact for many toxic impurities.

A different type of application using ICP OES could be explored by Gonçalves et al. [137], with the promising method called Multi-Wavelength Calibration (MWC), in which calibration and quantification steps were performed with only two solutions: the first containing the sample and standard solution of known concentrations of each element, and the second containing the sample and a blank sample solution. The results demonstrated excellent accuracy, in accordance with international guidelines, being an alternative method for elemental impurity determination in medicinal and phytotherapeutic plants.

Of the most common atomic spectroscopy techniques, FAAS and GFAAS, based on the Beer–Lambert Law, have been in use longer for the analysis of metals and/or metalloids in pharmaceuticals than have either ICP OES or ICP-MS. According to Table 4, FAAS is considered a less sensitive technique than GFAAS; it is generally expected to have sensitivities in the range of low parts per million (ppm, μg mL^{-1}, w v^{-1}) using FAAS, while GFAAS shows low parts per billion (ppb, μg L^{-1}, w v^{-1}), with the former usually requiring milliliter quantities and the latter requiring microliter quantities of sample. FAAS is generally the least-expensive of the two techniques, and also requires less of a skill level for an analyst than GFAAS. Analyses performed using FAAS can be much quicker than those performed using the more time-consuming GFAAS. Regardless of the technique, both FAAS and GFAAS require the use of a hollow cathode lamp (HCL) or an electrodeless discharge lamp (EDL) for each analyte in question [70].

As shown in Table 4, both ICP OES and ICP-MS are capable of rapid, multi-element analyses, with ICP-MS offering much greater sensitivity – frequently down to parts per trillion (ppt, ng L^{-1}, w v^{-1}) than ICP OES – μg mL^{-1} to μg L^{-1}, which has more potential spectral interferences. Analyst skills for ICP OES and ICP-MS are greater than for either FAAS or GFAAS, with ICP-MS requiring the greatest level of skill among the four techniques. Additionally, ICP-MS is the most expensive of these instrumental techniques [70]

Table 4
Comparative board of different spectroscopy techniques.

FAAS	GFAAS	ICP OES	ICP-MS
μg mL^{-1}	μg L^{-1}	μg mL^{-1} - μg L^{-1}	ng L^{-1}
mL quantities	μL quantities	μL quantities	μL quantities
less-expensive	more-expensive	more-expensive	most expensive
low skill level	high skill level	high skill level	highest skill level
quicker	time-consuming	time-consuming	time-consuming

3.5. Speciation techniques

The need to distinguish between chemical forms of an element has become critical for pharmaceutical analysis. The process of separation and quantification of different chemical forms of an element is more specifically named speciation analysis. This can be further associated with oxidation state and organo-metallic nature or complex form [93]. Speciation analysis is becoming important especially for studying the biological activity, metabolism and side-effects of metal-based pharmaceuticals. It is used for the elucidation of chemical form(s), as well as the quantitative determination of a specific element when conducting toxicological and biochemical investigations, which will provide additional information, helpful in guiding future drug design [78].

It is also known that individual metal species have different chemical activity and ability to transform. As a result, it has become necessary to measure trace metals as "total", as well as quantitatively determine the different chemical forms of these trace metals, especially in pharmaceutical samples [58]. Some metals (e.g., Pd, Rh, Ru) are currently used as catalysts in pharmaceutical industries in the synthesis of raw materials, intermediates and final active pharmaceutical ingredients [138,139]. The ability of a metal ion to react and, in particular, its catalytic activity is to a great extent dependent on the forms in which the metal exists in solution. Therefore, the ability of distinguishing and identifying the presence of various species of a catalyst metal at various stages of a reaction may provide a better insight into the mechanism of catalytic reaction. Thus, speciation analysis can increase the informative capacity of the collected results, characterizing in detail some of the most important chemical forms of an element in order to understand transformations among forms that are likely to occur, and to infer the probable environmental- and health-related consequences [140]. Jo et al. [141] proposed HPLC-ICP-MS and HPLC-ESI-TOF-MS for the speciation of Pd impurities in some API samples, considering the use of Pd as a metal catalyst for mediating C-C, C-N and C-O cross-coupling reactions. The combination of chromatography techniques with mass spectrometer represented powerful tools for the separation, identification and quantification of various Pd species, in order to meet regulatory requirements.

By coupling chromatographic techniques with element specific detectors, very powerful and sensitive systems for the separation and detection of elemental species are made available. Although the various combinations of instruments are capable of quantifying the amount of free and bound metal, it has been observed that only the most sensitive techniques are suitable for speciation analysis. Speciation techniques using ICP-MS, ICP OES, and GF AAS could be considered as the most sensitive and selective techniques [142–144]. As, Hg and Cr exhibit different toxicities among their inorganic and organic forms [78]; therefore, speciation analysis is totally applicable and desirable to investigate which form is responsible for contamination. As well as was observed for Cr, other elements may play different roles in toxicological response in the human body, depending on the chemical form in occurrence.

3.6. Other techniques

In general, sample preparation procedures yet represent the most critical and time-consuming step in spectrochemical analysis of pharmaceutical products. In this sense, the development of direct methods for the determination of elements in these matrices is relevant for improving quality programs in the pharmaceutical industry [145]. Direct solid analysis of agricultural, environmental, industrial and pharmaceutical samples by laser induced breakdown spectroscopy (LIBS) is an alternative way for the simultaneous multielemental determination of macro and micro elements in solid materials [146]. Carvalho et al. [145] indicates that LIBS rightly fits for the simultaneous determination of Ca, Cu, Fe, Mg, Mn, P and Zn in multielement pharmaceutical tablets. Thus, LIBS contributes with the Green Chemistry concept as the analysis by ICP OES generally requires concentrated acids to achieve total digestion prior to elemental determination. Therefore, LIBS can be recommended as an alternative method, as the current wet chemistry analysis may incur significant costs and long test times for the pharmaceutical industry.

Laser ablation/laser ionization coupled to time-of-flight mass spectrometry (LALI-TOF-MS) is another technique for the direct analysis of solids, with the ability to simultaneously determine several chemical elements. This technique has historically been called surface analysis laser ionization, laser desorption and ionization, two-step laser mass spectrometry and laser desorption laser post-ionization time-of-flight mass spectrometry. The essence of this technique consists of a laser ablation of the solid material as an initial step, followed by an ionization of the ablated material. Finally, the ions are directed to the mass spectrometer where separation, identification and quantification take place (Fig. 3). LALI technique has a considerable increase in ion transmission efficiency, since the LALI source is already under vacuum, avoiding the loss in the transmission of particles generated at atmospheric pressure to vacuum, as occurs in traditional ICP-MS instruments, for example. Removing this interface between vacuum and atmospheric pressure also results in increased sensitivity and decreased matrix effects by removing plasma-ion spatial interaction effects. Consequently, LALI-TOF-MS can be considered a technique that provides quantitative analyses with high specificity and sensitivity, without the need for complex quantification schemes or matrix-matched standard materials [147].

Instrumental neutron activation analysis (INAA) is a relatively direct analytical technique for determining elemental abundance in a wide range of materials. This technique relies on the measurement of characteristic radiation from radionuclides formed directly or indirectly by neutron irradiation of the material of interest. The energy of the emitted gamma rays is used to identify the modified atom and the intensity of the radiation can be used to determine its abundance. In the last fifty years, this analytical technique has been extremely useful in the determination of trace and minor elements in several types of environmental, geological, plant, food and pharmaceutical materials [78].Smichowsky et al. [148] recently published a review about analytical techniques in the determination of metals and metalloids in pharmaceutical products. The application of neutron activation analysis, isotope dilution mass spectrometry and hyphenated methodologies for speciation studies based on the use of separative techniques in combination with specific detectors are also discussed. There is a lack of research about inorganic impurities in pharmaceutical products, and there are still several possibilities of analytical applications.

In 2011, a new commercial instrument representing yet another analytical technique called microwave plasma atomic emission spectrometry (MP-AES) was introduced, appearing to provide an attractive alternative to flame AAS and ICP OES for the analysis of pharmaceutical samples. The MP-AES system uses a relatively new design of plasma torch, with nitrogen gas, as reported by Hammer [149]. In contrast to previously reported systems [150], the newly commercialized MP-AES system couples energy from the microwave magnetic field rather than the microwave electric field, using a hollow rectangular metal section called waveguide. MP-AES is a potential analytical technique for the analysis of drugs and pharmaceutical samples for their inorganic contents, once it has a number of obvious advantages over techniques such as FAAS and ICP OES [78]. Balaram [151] recently reviewed important topics about MP-AES, exploring hyphenation possibilities to enhance analytical strategies for elemental impurity evaluation. Cold vapor (CV), hydride generation (HG), photochemical vapor generation (PVG), gas chromatography (GC) and high pressure liquid chromatography (HPLC) have been hyphenated to MP-AES over the recent years, obtaining sensitive and accurate determinations of elements such as Hg, As and Se.

A scanning electron microscopy with energy dispersive X-ray spectroscopy (SEM-EDXS) was developed by Bezrodnykh et al. [152] to evaluate residual metals in chitosan samples. The SEM-EDXS analysis showed the presence of Fe, Si, Al, N and S in the particles of chitosan,

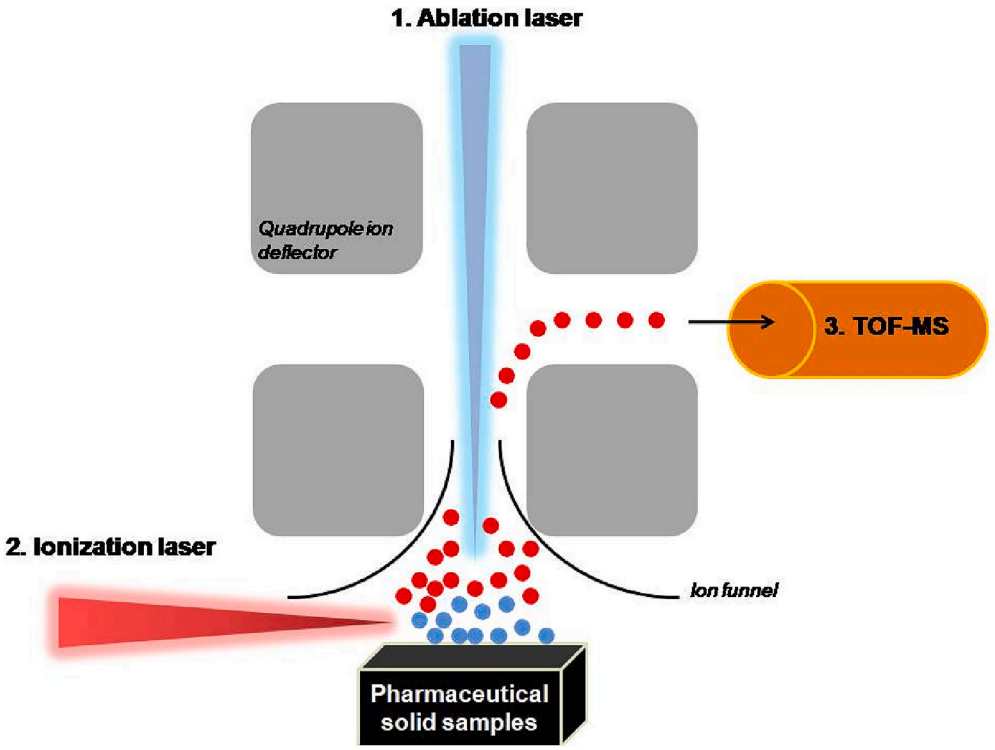

Fig. 3. The LALI-TOF-MS main analytical steps: 1. Laser ablation of pharmaceutical solid samples, followed by 2. Laser ionization of the ablated material and 3. Determination of analytes by time-of-flight mass spectrometry. TOF-MS: Time-of-flight mass spectrometry. (The authors, 2023).

after filtration steps. It is important to notice that both scanning electron microscopy experiments and energy dispersive x-ray analysis were performed using the same equipment. The study highlighted the evaluation of some metals using a series of sample filtration for SEM-EDXS analysis, allowing the determination of Fe, Cr, Ni, for example, and also highlighted the importance of chitosan quality control in the pharmaceutical industry scenario. Dispas et al. [153] discuss the importance of improving analytical technologies, methods and instrumentation. They emphasize that innovation is a permanent process to provide faster, more efficient and more sensitive analytical tools. Furthermore, the importance of developing eco-friendly and less expensive methods is highlighted.

4. Discussion

The interest about inorganic impurities in different pharmaceutical products is well established and widespread. It is already considered as a global health problem, which can be explained by the increase in medicine consumption and the high occurrence in contamination cases from several situations.

Different chemical elements can cause toxic reactions in humans depending on the amount ingested and the exposure frequency [53]. Non-toxic elements that could be essential to human health may have a toxicological profile, since the levels exceed the tolerable intake. Toxic metals are also tolerable in very low quantities, though their high potential may cause severe and irreversible damage to human organs. All elements can intensify illness and exacerbate some disorders.

As shown in different studies throughout this text, the occurrence of inorganic impurities in pharmaceuticals, especially in herbal medicines and natural products, is possible in several ways. This is in part explained by the high exposure of these formulations and preparations to impurity contaminations, due to their manufacturing process. Several plants and other materials that are used in the obtention of the final herbal medicine may be contaminated by metals before processing, in agricultural steps, collection of materials, bad storage, use of contaminated water, among others. Synthetic drugs may not be exposed to this kind of contamination, although many impurities may be present in the final product. The quality control of pharmaceuticals should include analysis for the whole line of manufacturing, determining if elemental contents in API, excipients, intermediates and other substances, produced or imported, are truly safe for medicinal use by humans.

There are a high number of studies on herbal medicines, medicinal plants and natural pharmaceuticals that come from eastern countries. It could be explained as a function of the high consumption of these products by the population and the high production of this kind of formulation by local industries. Fig. 4 shows a distribution global map of scientific papers and books according to the origin country of the researchers and the local where the studies were conducted. The United States of America are so far the most responsible for publications on elemental impurities. In Latin America, there is lack of studies about this theme, regardless of the presence of a huge biodiversity from which many people and companies extract medicinal products and natural material to produce active pharmaceutical ingredients (APIs), intermediates, cosmetics, medicines and any other medicinal compounds. Although Latin America has few publications, Brazil is the second country in the world in number of publications. It is also possible to notice that African countries have a thin contribution about inorganic impurities in pharmaceutical matrices, despite the great culture and biodiversity when it comes to natural sources for health purposes with precarious manufacturing conditions; the same was observed for Central and Southern American countries.

In Brazil, there are studies about inorganic contamination in pharmaceutical products, but not still in a representative number, considering the potential of work. Not only here, but in many other developing countries, there is a lack of concern on this theme and there is not sufficient financial support. The Brazilian Pharmacopeia is not as complete as other international manuals about inorganic impurities and metal contamination, such as the US Pharmacopeia and ICH Q3D (R2) Guideline. It allows the occurrence of uncontrolled manufacturing

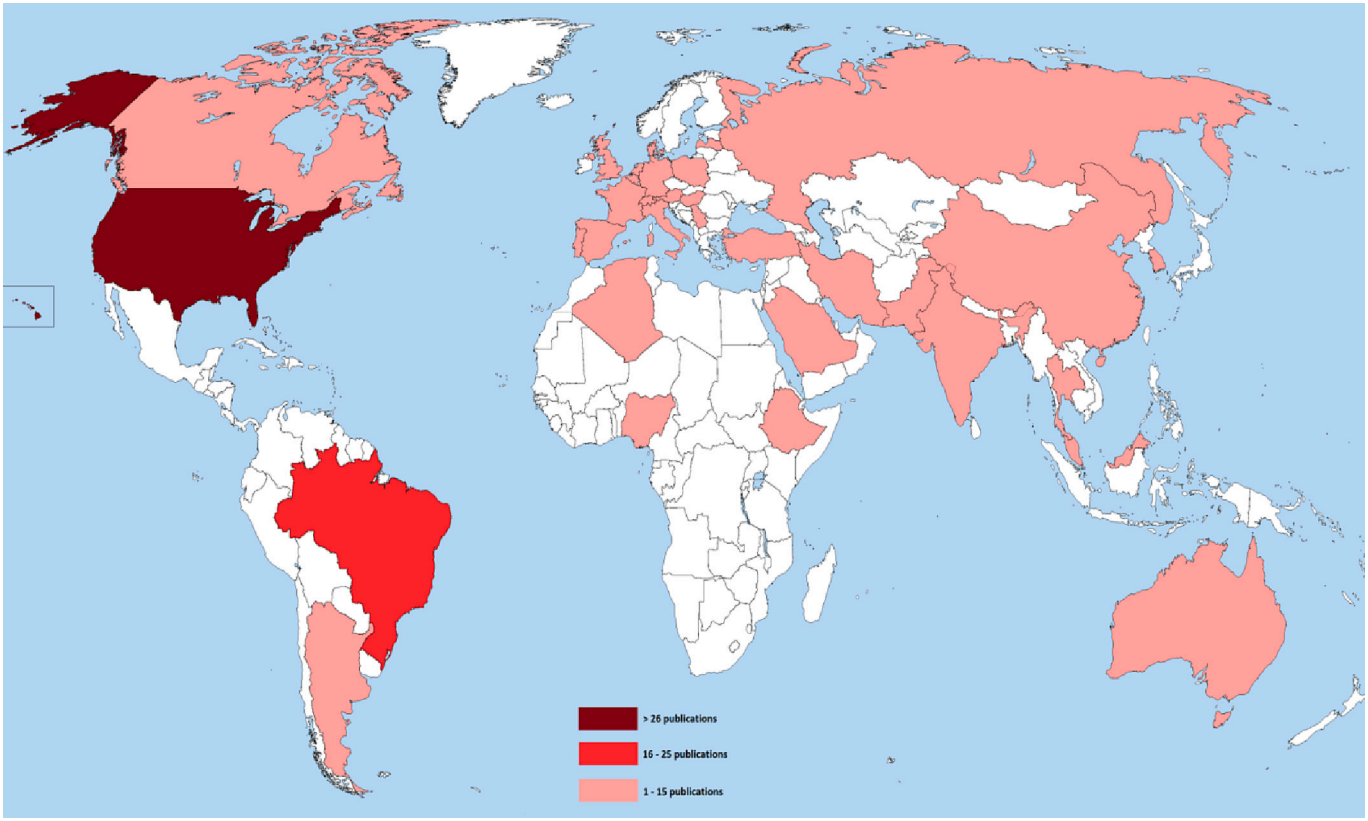

Fig. 4. Distribution global map of scientific papers and books analyzed in this review according to the origin country of the researches since 1990. The United States of America is the most responsible for publications in the world, followed by Brazil with a great number of scientific articles. The other colored countries in the map show less than fifteen publications about elemental impurities in pharmaceutical products during these 33 years. (The authors, 2023).

processes, poor analytical strategies for impurity evaluation, less quality of the final product and the increase in health problems, especially for the elements Pb, Cd, Hg and As.

Otherwise, The United States Pharmacopeia, The European Pharmacopeia, The European Medicines Agency guideline (EMA) and The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) are the mostly used international compendiums for elemental impurity reference. The most recent studies used inorganic parameters from these documents to compare the element levels established with those encountered experimentally. Authors from all over the world consider at least the limits of 24 elements established in the compendiums, which can be used for the evaluation of metal contamination in several pharmaceutical formulations. Although the textbooks do not address contamination limits for excipients, studies point to their important contribution to contamination by metallic impurities. The concentration parameters from the guidelines mentioned above were estimated by analytical methods with high accuracy, precision and sensitivity, as ICP OES and ICP-MS. However, ICP-based methods are not the only ones that have to be developed; as it was previously mentioned, the use of other techniques, especially those eco-friendly and direct, should also be encouraged, since expressive results can be comparatively achieved by these strategies.

5. Conclusion and future perspectives

Pharmaceutical products are complex matrices and impurities, presenting toxicological, chemical and environmental risks, depending on each inorganic species. In the literature, numerous possibilities of inorganic contamination presented in the manufacture, handling and consumption scenario of pharmaceutical products are discussed. Although regulatory agencies have worked to ensure the quality control and safety of medicines and related products, contamination by various chemical elements is still the subject of constant investigation. The improvement in analytical techniques and methodologies and the increase in inorganic pharmaceutical studies can contribute to a better control of APIs, intermediates, catalysts, natural medicines, synthetic products and other chemical compounds, in order to guarantee their safe therapeutic use.

Consolidated techniques based on ICP (ICP OES and ICP-MS) remain the first choice in the analysis of potentially toxic elements in pharmaceutical products due to their high sensitivity, robustness, precision and accuracy. Spectroanalytical techniques (flame, FAAS; graphite furnace, GF AAS; hydride generation, HG AAS; cold vapor, CV AAS), continue to be promising for studies on this topic, for the coming decades. Methodologies for analysis and quality control of drugs using Vibrational spectroscopy, Near-infrared (NIR) and Raman spectroscopy, Supercritical fluid and Multidimensional chromatography are trends for the improvement of tests and guidelines regulated by production control agencies, in the next two decades. In parallel, analytical strategies focused on the investigation of impurities in other pharmaceutical ingredients, such as excipients and packaging, are also alternatives for the quality assurance of medicines.

The central issue as a future perspective in the quality control of these matrices is to question the development of new analytical methodologies, with the optimization of variables for sample preparation, using reduced amounts of acids and oxidizing agents, opting for reagents that cause less impact on the environment and the analyst. Furthermore, systems can be adapted for in-line or on-line analysis, reducing the possibility of sample contamination, making the analysis faster and safer. In addition, the variables under study can be optimized in a multivariate way and the methodologies can be rigorously validated before entering the routine. Therefore, continuous innovations and

trends in analytical chemistry can support the improvement in more sustainable and environmentally friendly methods and support regulatory agencies to establish and review tolerable limits of exposure to these chemical species.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

As a review article, all data are available in manuscript

Acknowledgements

The authors gratefully acknowledge to Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), PRONEX/Fundação de Amparo à Pesquisa do Estado da Bahia (FAPESB), and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) for the financial support and fellowships.

References

[1] C. Frazzoli, B. Bocca, A. Mantovani, The one health perspective in trace elements biomonitoring, J. Toxicol. Environ. Health Part B 18 (2015) 344–370.
[2] P.J. Agget, Toxicity due to excess and dificiency, J. Toxicol. Environm. Health Part A 73 (2010) 175–180.
[3] M. Gielen, E.R.T. Tiekink, Metallotherapeutic Drugs and Metal-Based Diagnostic Agents: The Use of Metals in Medicine, John Wiley & Sons, England, 2005.
[4] M. Vázquez, M. Calatayud, C.J. Piedra, G.M. Chiocchetti, D. Vélez, V. Devesa, Toxic trace elements at gastrointestinal level, Food Chem. Toxicol. 86 (2015).
[5] P.K. Gupta, Fundamentals of Toxicology, Essential Concepts and Applications, 1st ed., Academic Press, USA, 2016.
[6] I. García, C. Dorronsoro, Contaminación por Metales Pesados. En Tecnología de Suelos. edafologia.ugr.es, 2005. Spain.
[7] A.F. De Santos Junior, R.A. Matos, E.M.J. Andrade, W.N.L. Dos Santos, H.I. F. Magalhães, F.N. Costa, M.G.A. Korn, Multielement determination of macro and micro contents in medicinal plants and phytomedicines from Brazil by ICP OES, J. Braz. Chem. Soc. 28 (2017) 376–384.
[8] R.G. Leitão, M.P. Silva, M.S. Diniz, M. Guerra, Mapping the distribution of mercury (II) chloride in zebrafish organs by benchtop micro-energy dispersive X-ray fluorescence: a proof of concept, J. Trace Elem. Med. Biol. 69 (2022).
[9] Brazil, Brazilian Pharmacopeia 6th ed, vol. 1, 2019.
[10] L.R. Goldman, Children-unique and vulnerable: environmental risks facing children and recommendations for response, Environ. Health Perspect. 103 (1995) 13–18.
[11] J.K. Nduka, O.E. Orisakwe, Heavy metal hazards of pediatric syrup administration in Nigeria: a look at chromium, nickel and manganese, Int. J. Environ. Res. Public Health 7 (2009) 1972–1979.
[12] S. Soodvilai, V. Chatsudthipong, T. Ngawhirunpat, T. Rojanarata, P. Opanasopit, Interaction of pharmaceutical excipients with organic cation transporters, Int. J. Pharm. 520 (2017).
[13] J.K. Nduka, H.I. Kelle, E.C. Ogoko, Hazards and risk assessment of heavy metals from consumption of locally manufactured painkiller drugs in Nigeria, Toxicol. Rep. 7 (2020) 1066–1074.
[14] G. Li, D. Schoneker, K.L. Ulman, J.J. Sturm, L.M. Thackery, J.F. Kauffman, Elemental impurities in pharmaceutical excipients, J. Pharm. Sci. 104 (2015).
[15] Pharmacopoeia of the People's Republic of China, China Medical Science and Technology Press, Beijing, 2010.
[16] P. Jin, X. Liang, L. Xia, F. Jahouh, R. Wang, Y. Kuang, X. Hu, Determination of 20 trace elements and arsenic species for a realgar-containing traditional Chinese medicine Niuhuang Jiedu tablets by direct inductively coupled plasma-mass spectrometry and high performance liquid chromatography-inductively coupled plasma-mass spectrometry, J. Trace Elem. Med. Biol. 33 (2016) 73–80.
[17] Guidelines for the Assessment of Herbal Medicines, Document No. WHO/TRM/91.4, World Health Organization, Geneva, 1991.
[18] A.H. Uddin, R.S. Khalid, S.A. Abbas, Determination of heavy metal concentration of different traditional medicine formulations available at the east coast region of Malaysia, Afr. J. Pharm. Pharmacol 6 (2012) 1487–1491.
[19] B. Hina, G.H. Rizwani, S. Naseem, Determination of toxic metals in some herbal drugs through atomic absorption spectroscopy, Pak. J. Pharm. Sci. 24 (2011) 353–358.
[20] A. Niaz, N. Ullah, A. Rehman, I. Ahmad, M. Ikhlaq, H.U. Rehman, Pollution based study of heavy metals in some selected medicinal plants by dry digestion method, Int. J. Pharm. Sci. Res. 4 (2013) 17–24.
[21] S. Akram, R. Najam, G.H. Rizwani, S.A. Abbas, Determination of heavy metal contents by atomic absorption spectroscopy (AAS) in some medicinal plants from Pakistani and Malaysian origin, Pak. J. Pharm. Sci. 28 (2015) 1781–1787.
[22] L. Liu, Y. Zhang, Z. Yun, B. He, G. Jiang, Estimation of bioaccessibility and potential human health risk of mercury in Chinese patent medicines, J. Environ. Sci. 39 (2016) 37–44.
[23] A. Ting, Y. Chow, W. Tan, Microbial and heavy metal contamination in commonly consumed traditional Chinese herbal medicines, J. Tradit. Chin. Med. 33 (2013) 119–124.
[24] C.-M. Yang, M.-Y. Chien, P.-C. Chao, C.-M. Huang, C.-H. Chen, Investigation of toxic heavy metals content and estimation of potential health risks in Chinese herbal medicine, J. Hazard. Mater. 41 (2021) 125–142.
[25] T. Yao, S. Jiang, K. Hou, H. Sun, H. Wang, Cadmium (cd) accumulation in traditional chinese medicine materials (TCMMs): a critical review, Ecotoxicol. Environ. Saf. 242 (2022).
[26] S.J. Genuis, G. Schwalfenberg, A.K.J. Siy, I. Rodushkin, Toxic element contamination of natural health products and pharmaceutical preparations, PLoS One 7 (2012).
[27] X. Wu, P. Wu, M. Gu, J. Xue, Trace heavy metals and harmful elements in roots and rhizomes of herbs: screening level analysis and health risk assessment, Chin. Herb. Med. 14 (2022) 622–629.
[28] A. Stanojkovic-Sebic, R. Pivic, D. Josic, Z. Dinic, A. Stanojkovic, Heavy metals content in selected medicinal plants used as components of herbal formulations, J. Agric. Sci. 21 (2015) 317–325.
[29] E. Charen, N. Harbord, Toxicity of herbs, vitamins, and supplements, Adv. Chronic Kidney Dis. 27 (2020) 67–71.
[30] C.A. De Tannus, F.S. De Dias, F.B. Santana, D.C.M.B. Dos Santos, H.I. F. Magalhães, F.S. De Dias, A.F. De Santos Júnior, Multielement Determination in Medicinal Plants and Herbal Medicines Containing *Cynara scolymus* L., Harpagophytum procumbens D.C., and Maytenus ilifolia (Mart.) ex Reiss from Brazil Using ICP OES v. 199, Biol Trace Elem Res, 2021.
[31] S. Nookabkaew, N. Rangkadilok, J. Satayavivad, Determination of trace elements in herbal tea products and their infusions consumed in Thailand, J. Agric. Food Chem. 54 (2006) 6939–6944.
[32] P. Giordani, V. Minganti, D. Brignole, P. Malaspina, L. Cornara, G. Drava, Is there a risk of trace element contamination in herbal preparations? A test study on the lichen *Cetraria islandica*, Chemosphere 181 (2017) 778–785.
[33] S. Jabeen, S.M. Tahir, S. Khan, H.M. Qasim, Determination of major and trace elements in ten important folk therapeutic plants of Haripur Basin, Pakistan, J. Med. Plants Res. 4 (2010) 559–566.
[34] L. Järup, Hazards of heavy metal contamination, Br. Med. Bull. 68 (2003) 167–182.
[35] D. Kim, K.H. Hwang, M. Lee, J.H. Kim, K. Jung, S.K. Park, Toxic metal content in 52 frequently prescribed herbal medicines on the Korean market, Food Additiv. Contamin. Part B Surveil. 8 (2015) 199–206.
[36] D. Kim, S. Lee, I. Yu, K. Jung, S. Park, Transfer rates of toxic metals during decoction preparation from herbal medicines and safety evaluation of the final decoction products, Food Sci. Biotechnol. 24 (2015) 757–763.
[37] M.H. Habibollahi, K. Sharafi, A.K. Omer, Analysis of minerals and toxic elements in commonly consumed herbal medicines in Zahedan, Iran, and associated human health risk assessment, J. Food Prot. 85 (2022).
[38] S. Bolan, R. Naidu, A. Kunhikrishnan, B. Seshadri, Y.S. Ok, T. Palanisami, M. Dong, I. Clark, Speciation and bioavailability of lead in complementary medicines, Sci. Total Environ. 539 (2016) 304–312.
[39] A. Capano, R. Weaver, E. Burkman, Evaluation of the effects of CBD hemp extract on opioid use and quality of life indicators in chronic pain patients: a prospective cohort study, Postgrad. Med. 132 (2020).
[40] P. Poli, F. Crestani, C. Salvadori, I. Valenti, C. Sannino, Medical cannabis in patients with chronic pain: effect on pain relief, pain disability, and psychological aspects. A prospective non randomized single arm clinical trial, Clin. Ter. 169 (2018).
[41] H.J. Vivers, A. Petzer, R. Gordon, An assessment of heavy metal contaminants related to cannabis-based products in the south African market, Forens. Sci. Intern. Rep. 4 (2021).
[42] I.M.N.R. Menezes, P.A. De Nascimento, C.I. Yamamoto, A. Oliveira, Evaluation of trace elements in cannabis products, J. Food Compos. Anal. 113 (2022).
[43] O. Grundmann, R.G. Hendrickson, M.I. Greenberg, Kratom: history, pharmacology, current user trends, adverse health effects and potential benefits, Disease-a-Month 68 (2022).
[44] J. Tobacyk, B.J. Parks, N. Lovelady, L.K. Brents, Qualitative content analysis of public responses to an FDA inquiry on the impact of scheduling changes to kratom, Int. J. Drug Pol. 108 (2022).
[45] J.H. Fleming, C.M. Babyak, E.A. Alves, Analysis of heavy metals content in commercially available kratom products in Richmond, Virginia, Forens. Chem. 33 (2023).
[46] W.C. Prozialeck, J.R. Edwards, P.C. Lamar, B.J. Plotkin, I.M. Sigar, O. Grundmann, C.A. Veltri, Evaluation of the mitragynine content, levels of toxic metals and the presence of microbes in kratom products purchased in the western suburbs of Chicago, Int. J. Environ. Res. Public Health 17 (2020).
[47] USA, Elemental Impurities <232> United States Pharmacopeia, 2020.
[48] USA, Elemental Impurities – Procedures <233> United States Pharmacopeia, 2018.
[49] ICH, The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Guideline for elemental impurities Q3D (R2), 2022.

[50] USA, PF 48(6) - Elemental Impurities Uptades, Pharmacopeial Forum, Nov 1st 2022 to Jan 31th 2023, 2023. <unofficial when accessed on March 13, 2023>.
[51] USA, Elemental Contaminants in Dietary Supplements <2232> United States Pharmacopeia, 2012.
[52] E. Fernández-García, I. Carvajal-Lérida, A. Pérez-Gálvez, In vitro bioaccessibility assessment as a prediction tool of nutritional efficiency, Nutr. Res. 29 (2009) 751–760.
[53] L.L. Brunton, R. Hilal-Dandan, B.C. Knollmann, As bases farmacológicas da terapêutica, AMGH, Porto Alegre, 2018.
[54] O. Abollino, A. Giacomino, G. Paparella, E. Magi, E. Conca, M. Malandrino, Potentially toxic elements in ayurvedic formulations: total and bioaccessible content, Microchem. J. 136 (2018) 236–243.
[55] Y.W. Yang, S.H. Liou, Y.M. Hsueh, W.S. Lyu, C.S. Liu, H.J. Liu, M.C. Chung, P. H. Hung, Risk of Alzheimer's disease with metal concentrations in whole blood and urine: A case-control study using propensity score matching, Toxicol. Appl. Pharmacol. 356 (2018).
[56] M.B. Leko, M. Mihelcic, J. Jurasovic, M.N. Perkovic, E. Španic, A. Sekovanic, T. Orct, K. Zubcic, L.L. Horvat, N. Pleic, S. Kidemet-Piskac, Ž. Vogrinc, N. Pivac, A. Diana, F. Borovecki, P.R. Hof, G. Šimic, Heavy metals and essential metals are associated with cerebrospinal fluid biomarkers of Alzheimer's disease, Int. J. Mol. Sci. 24 (2023).
[57] S. Devipriya, N.V. Ramesh, P.K. Vineeth, M. Arun, A review on the inextricable relation of ayurveda and analytical chemistry, Mater. Today: Proc. 46 (2021) 3089–3095.
[58] D.R. Abernethy, A.J. Destefano, T.L. Cecil, K. Zaidi, R.L. Williams, Metal impurities in food and drugs, Pharm. Res. 27 (2010) 750–755.
[59] K.L. Smith, J.L. Guentzel, Mercury concentrations and omega-3 fatty acids in fish and shrimp: preferential consumption for maximum health benefits, Mar. Pollut. Bull. 60 (2010) 1615–1618.
[60] S.P. Dolan, D.A. Nortrup, P.M. Bolger, S.G. Capar, Analysis of dietary supplements for arsenic, cadmium, mercury, and lead using inductively coupled plasma mass spectrometry, J. Agric. Food Chem. 51 (2003) 1307–1312.
[61] H.H. Ang, K.L. Lee, Contamination of mercury in tongkat Ali hitam herbal preparations, Food Chem. Toxicol. 44 (2006) 1245–1250.
[62] E.S. Harris, S. Cao, B.A. Littlefield, J.A. Craycroft, R. Scholten, T. Kaptchuk, Y. Fu, W. Wang, Y. Liu, H. Chen, Z. Zhao, J. Clardy, A.D. Woolf, D.M. Eisenberg, Heavy metal and pesticide content in commonly prescribed individual raw Chinese herbal medicines, Sci. Total Environ. 409 (2011) 4297–4305.
[63] M.M. Wolle, M.G.M. Rahman, H.M. Kingston, M. Pamuku, Speciation analysis of arsenic in prenatal and children's dietary supplements using microwave-enhanced extraction and ion chromatography-inductively coupled plasma mass spectrometry, Anal. Chim. Acta 818 (2014) 23–31.
[64] A. Kowalski, M. Frankowski, Levels and potential health risks of mercury in prescription, non-prescription medicines and dietary supplements in Poland, Regul. Toxicol. Pharmacol. 73 (2015) 396–400.
[65] M.E. Shils, M. Shike, A.C. Ross, B. Caballero, R.J. Cousins, Modern Nutrition in Health and Disease, 10th ed., Lippincott Williams & Wilkins, New York, 2006.
[66] S. Waheed, S. Rahman, N. Siddique, Y. Faiz, Calcium supplements as additional source of trace elements in health and disease part 1: adequacy and safety of chelated calcium supplements, J. Radioanal. Nucl. Chem. 298 (2013) 1453–1461.
[67] N. Ozbek, A. Baysal, Determination of sulfur by high-resolution continuum source atomic absorption spectrometry: review of studies over the last 10 years, Trends Anal. Chem. 88 (2017) 62–76.
[68] E.V. Chuparina, A.S. Maltsev, E.V. Stolpovskaya, N.A. Neverova, Analytical control of Mn and se in synthesized compounds, promising plant-derived medicines, by WDXRF and TXRF methods, Spectrochim. Acta B At. Spectrosc. 197 (2022).
[69] U. Wollein, B. Bauer, R. Habernegg, N. Schramek, Potential metal impurities in active pharmaceutical substances and finished medicinal products - A market surveillance study, Eur. J. Pharm. Sci. 77 (2015) 100–105.
[70] N. Lewen, The use of atomic spectroscopy in the pharmaceutical industry for the determination of trace elements in pharmaceuticals, J. Pharm. Biomed. Anal. 55 (2011) 653–661.
[71] F.J. Antosz, Y. Xiang, A.R. Diaz, A.J. Jensen, The use of total reflectance X-ray fluorescence (TXRF) for the determination of metals in the pharmaceutical industry, J. Pharm. Biomed. Anal. 62 (2012) 17–22.
[72] S.K. Dotterer, R.A. Forbes, C.L. Hammill, Impact of metal-induced degradation on the determination of pharmaceutical compound purity and a strategy for mitigation, J. Pharm. Biomed. Anal. 54 (2011) 987–994.
[73] S. Janvier, K. Cheyns, M. Canfyn, S. Goscinny, B.D. Spiegeleer, C. Vanhee, E. Deconink, Impurity profiling of the most frequently encountered falsified polypeptide drugs on the Belgian market, Talanta 188 (2018) 795–807.
[74] D.L. Sparks, Toxic metals in the environment: the role of surfaces, Elements 1 (2005) 193–197.
[75] V.M. Reddy, K.S. Babu, V. Balaram, M. Satyanarayanan, Assessment of the effects of municipal sewage, immersed idols and boating on the heavy metal and other elemental pollution of surface water of the eutrophic Hussainsagar Lake (Hyderabad, India), Environ. Monit. Assess. 184 (2012) 1991–2000.
[76] A. Rani, M. Rohit, D. Vikas, V. Balaram, Analysis of uranium concentration in drinking water samples using ICP-MS, Health Phys. 104 (2013) 251–255.
[77] V. Balaram, M. Satyanarananan, D.V. Avdeev, N. Berdnikov, P. Roy, S.S. Sawant, K.S.V. Subramanyam, K.V. Anjaiah, C.T. Kamala, R. Mathur, B. Dasaram, Use of xenon as internal standard for the accurate determination of trace elements in water samples by ICP-MS, At. Spectrosc. 33 (2012) 41–47.
[78] V. Balaram, Recent advances in the determination of elemental impurities in pharmaceuticals – status, challenges and moving frontiers, Trends Anal. Chem. 80 (2016) 83–95.
[79] D.B. Salem, J.-A. Barrat, Determination of rare earth elements in gadolinium-based contrast agents by ICP-MS, Talanta 221 (2021).
[80] K.A. Fliszar, D. Walker, L. Allain, Profiling of metal ions leached from pharmaceutical packaging materials, J. Pharm. Sci. Technol. 60 (2006) 337–342.
[81] C. Stoving, H. Jensen, B. Gammelgaard, S. Sturup, Development and validation of an ICP-OES method for quantitation of elemental impurities in tablets according to coming US pharmacopeia chapters, J. Pharm. Biomed. Anal. 84 (2013) 209–214.
[82] M. Katny, M. Frankowski, Impurities in drug products and active pharmaceutical ingredients, Crit. Rev. Anal. Chem. 47 (2017) 187–193.
[83] D. Milde, T. Pluháček, M. Kuba, J. Soucková, R.J.N.B. Da Silva, Measurement uncertainty evaluation from correlated validation data: determination of elemental impurities in pharmaceutical products by ICP-MS, Talanta 220 (2020).
[84] D. Beauchemin, Inductively coupled plasma mass spectrometry, Anal. Chem. 78 (2006) 4111–4136.
[85] J. Hu, P. Yang, X. Hou, Atomic spectrometry and atomic mass spectrometry in bioanalytical chemistry, Appl. Spectrosc. Rev. 54 (2019) 180–203.
[86] S. Zaza, S.M. Lucini, F. Sciascia, V. Ferrone, R. Cifelli, G. Carlucci, M. Locatelli, Recent advances in the separation and determination of impurities in pharmaceutical products, Instrum. Sci. Technol. 43 (2015) 182–196.
[87] USA, Validation of Compendial Procedures <1225>, United States Pharmacopeia, 2017.
[88] F.C. Pinheiro, J.A. Nobrega, An overview of sample preparation procedures for determination of elemental impurities in medicines, Microchem. J. 175 (2022).
[89] D.A. Skoog, D.M. West, F.J. Holler, S.R. Crouch, Analytical Chemistry, an Introduction, 7th ed., Saunders College, USA, 2000.
[90] O.A. Matveeva, E.L. Kovaleva, Modern approaches to estimating the content of genotoxic impurities in drugs (a review), Pharm. Chem. J. 49 (2015) 41–48.
[91] T.A. Melisew, M.I.M. Abdel, A.B. Adnan, Simultaneous spectrophotometric determination of iron (II) and copper (II) in tablets by chemometric methods. **Thai**, J. Pharm. Sci. 34 (2010) 93–106.
[92] M.A. Tarighat, A. Hasaninejad, G. Abdi, Chemometrics-enhanced micelle-mediated extraction spectrophotometric method for simultaneous determination of Cu^{2+} and Zn^{2+} in medicinal plant, rice and water samples using continuous wavelet transform, Food Anal. Methods 9 (2016) 1928–1938.
[93] K. Prasertboonyai, B. Liawraungrath, T. Pojanakaroon, S. Liawraungrath, Mercury(II) determination in commercial cosmetics and local Thai traditional medicines by flow injection spectrophotometry, Int. J. Cosmet. Sci. 38 (2016) 68–76.
[94] A. Fashi, M.R. Yaftian, A. Zamani, Electromembrane-microextraction of bismuth in pharmaceutical and human plasma samples: optimization using response surface methodology, Microchem. J. 130 (2017) 71–78.
[95] H.M. Al-Saidi, S.S. Alharthi, Efficiency enhancement of the spectrophotometric estimation of cobalt in waters and pharmaceutical preparations using dispersive liquid–liquid microextraction and microcells with long optical paths, Spectrochim. Acta A Mol. Biomol. Spectrosc. 253 (2021).
[96] D.A. Skoog, D.M. West, F.J. Holler, Fundamentals of Analytical Chemistry, 9th ed., Cengage Learning, USA, 2013.
[97] T. Wang, S. Walden, R. Egan, Development and validation of a general non digestive method for the determination of palladium in bulk pharmaceuticals and their synthetic intermediates by graphite furnace atomic absorption spectroscopy, J. Pharm. Biomed. Anal. 15 (1997) 593–599.
[98] A. Kelkó-Lévai, I. Varga, K. Zih-Perényi, A. Lásztity, Determination of trace elements in pharmaceutical substances by graphite furnace atomic absorption spectrometry and total reflection X-ray fluorescence after flow injection ion-exchange preconcentration, Spectrochim. Acta B At. Spectrosc. 54 (1999) 827–833.
[99] A. Lásztity, Á. Kélko-Lévai, I. Varga, K. Zih-Perényi, É. Bertalan, Development of atomic spectrometric methods for trace metal analysis of pharmaceuticals, Microchem. J. 73 (2002) 59–63.
[100] W. Siriangkhawut, P. Sittichan, K. Ponhong, P. Chantiratikul, Quality assessment of trace Cd and Pb contaminants in Thai herbal medicines using ultrasound-assisted digestion prior to flame atomic absorption spectrometry, J. Food Drug Anal. 25 (2017) 960–967.
[101] L.A. Portugal, G.D. Matos, D.C. Lima, G.B. Brito, A.P. Fernandes, S.L.C. Ferreira, Determination of lead in aluminum and magnesium antacids using electrothermal atomic absorption spectrometry, Microchem. J. 98 (2011) 29–31.
[102] K. Jurowski, M. Krosniak, M. Folta, M. Cole, W. Piekoszewski, Toxicological analysis of Pb and cd by ET AAS in local anaesthetics for teething (teething gels) based on herbs available in polish pharmacies, J. Trace Elem. Med. Biol. 52 (2019) 18–21.
[103] U.A. Barbosa, I.F. Dos Santos, A.M.P. Dos Santos, S.L.C. Ferreira, Determination of lead in iron supplements by electrothermal atomization atomic absorption spectrometry, Anal. Lett. 49 (2015) 799–807.
[104] D.J. Butcher, Recent highlights in graphite furnace atomic absorption spectrometry, Appl. Spectrosc. Rev. 52 (2017) 755–773.
[105] D.J. Butcher, Recent advances in optical analytical atomic spectrometry, Appl. Spectrosc. Rev. 48 (2013) 261–328.
[106] A.C.M. Aleluia, F.A. De Santana, G.C. Brandão, S.L.C. Ferreira, Sequential determination of cadmium and lead in organic pharmaceutical formulations using high-resolution continuum source graphite furnace atomic absorption spectrometry, Microchem. J. 130 (2017) 157–161.

[107] E.G. Barrera, D. Bazanella, P.W. Castro, W. Boschetti, M.G.R. Vale, M.B. Dessuy, Alternative method for chromium determination in pharmaceutical drugs by HR-CS GF AAS and direct analysis of solid samples, Microchem. J. 132 (2017) 365–370.
[108] P. Mattiazzi, D. Bohrer, E. Becker, C. Viana, P.C. Nascimento, L.M. Carvalho, High-resolution continuum source graphite furnace atomic absorption spectrometry for screening elemental impurities in drugs to adhere to the new international guidelines, Talanta 197 (2019) 20–27.
[109] M. Aghamohammadi, M. Faraji, P. Shahdousti, H. Kalhor, A. Saleh, Trace determination of lead, chromium and cadmium in herbal medicines using ultrasound-assisted emulsification microextraction combined with graphite furnace atomic absorption spectrometry, Phytochem. Anal. 26 (2015) 209–214.
[110] M.Z. Corazza, C.R.T. Tarley, Development and feasibility of emulsion breaking method for the extraction of cadmium from omega-3 dietary supplements and determination by flow injection TS-FF-AAS, Microchem. J. 127 (2016) 145–151.
[111] R.A. Day Jr., A.L. Underwood, Quantitative Analysis, 6th ed., Prentice-Hall International Inc, USA, 1991.
[112] G.D. Christian, P.K. Dasgupta, K.A. Schug, Analytical Chemistry, 7th ed., Wiley, USA, 2013.
[113] M. Wagner, P. Rostam-Khani, A. Wittershagen, C. Rittmeyer, B.O. Kolbesen, H. Hoffmann, Trace element determination in drugs by total reflection X-ray fluorescence spectrometry, Spectrochim. Acta B At. Spectrosc. 52 (1997) 961–965.
[114] A. Figueiredo, T. Fernandes, I.M. Costa, L. Goncalves, J. Brito, Feasibility of wavelength dispersive X-ray fluorescence spectrometry for the determination of metal impurities in pharmaceutical products and dietary supplements in view of regulatory guidelines, J. Pharm. Biomed. Anal. 122 (2016) 52–58.
[115] B. Sauer, Y. Xiao, M. Zoontjes, C. Kroll, Application of x-ray fluorescence spectrometry for screening pharmaceutical products for elemental impurities according to ICH guideline Q3D, J. Pharm. Biomed. Anal. 179 (2020).
[116] A.R. Chowdhury, N. Maheshwari, J. Soni, M. Kapil, T. Mehta, A. Mukharya, Quantitative X-ray fluorescence analysis: trace level detection of toxic elemental impurities in drug product by ED-XRF spectrometer, J. Pharm. Biomed. Anal. 189 (2020).
[117] J.A.C. Broekaert, Analytical Atomic Spectrometry with Flames and Plasmas, 2nd ed., Wiley-VCH, Germany, 2005.
[118] A. Montaser, Inductively Coupled Plasma Mass Spectrometry, Wiley-VCH, Germany, 1998.
[119] H.E. Taylor, Inductively Coupled Plasma-Mass Spectrometry: Practices and Techniques, 1st ed., Elsevier Science Publishing Co Inc, USA, 2000.
[120] J. Menoutis, A. Parisi, N. Verma, Study of the use of axial viewed inductively coupled plasma atomic emission spectrometry with ultrasonic nebulization for the determination of select elemental impurities in oral drug products, J. Pharm. Biomed. Anal. 152 (2018) 12–16.
[121] J.S. Barin, P.A. Mello, M.F. Mesko, F.A. Duarte, E.M. Flores, Determination of elemental impurities in pharmaceutical products and related matrices by ICP-based methods: a review, Anal. Bioanal. Chem. 408 (2016) 4547–4566.
[122] P. Pohl, A. Bielawska-Pohl, A. Dzimitrowicz, P. Jamroz, M. Welna, Impact and practicability of recently introduced requirements on elemental impurities, Trends Anal. Chem. 101 (2018) 43–55.
[123] C.S. Da Silva, F.C. Pinheiro, C.D.B. Do Amaral, J.A. Nóbrega, Determination of As, Cd, Hg and Pb in continuous use drugs and excipients by plasma-based techniques in compliance with the United States Pharmacopeia requirements, Spectrochim. Acta B 138 (2017) 14–17.
[124] C.M. Santana, T.L. De Sousa, A.L.O. Latif, L.S. Lobo, G.R. Da Silva, H.I. F. Magalhães, M.V. Lopes, C.M.J. De Benevides, R.G.O. Araujo, D.C.M.B. Dos Santos, A.F. De Santos Júnior, Multielement determination (essential and potentially toxic elements) in eye shadows exposed to consumption in Brazil using ICP OES, Biometals 35 (2022).
[125] F.C. Pinheiro, M.A. Aguirre, J.A. Nóbrega, N. González-Gallardo, D.J. Ramón, A. Canals, Dispersive liquid-liquid microextraction based on deep eutectic solvent for elemental impurities determination in oral and parenteral drugs by inductively coupled plasma optical emission spectrometry, Anal. Chim. Acta v (2021) 1185.
[126] Q. Tu, T. Wang, C.J. Welch, High-throughput metal screening in pharmaceutical samples by ICP-MS with automated flow injection using a modified HPLC configuration, J. Pharm. Biomed. Anal. 51 (2010) 90–95.
[127] L. Fischer, B. Zipfel, G. Koellensperger, J. Kovac, S. Bilz, A. Kunkel, C. Venzago, S. Hann, Flow injection combined with ICP-MS for accurate high throughput analysis of elemental impurities in pharmaceutical products according to USP <232>/<233>, J. Pharm. Biomed. Anal. 95 (2014) 121–129.
[128] O. Chahrour, J. Malone, M. Collins, V. Salmon, C. Greenan, A. Bombardier, Z. Ma, N. Dunwoody, Development and validation of an ICP-MS method for the determination of elemental impurities in TP-6076 active pharmaceutical ingredient (API) according to USP <232>/<233>, J. Pharm. Biomed. Anal. 145 (2017) 84–90.
[129] V. Rudovica, A. Viksna, A. Actins, Application of LA-ICP-MS as a rapid tool for analysis of elemental impurities in active pharmaceutical ingredients, J. Pharm. Biomed. Anal. 91 (2014) 119–122.
[130] T. Pluhácek, M. Rucka, V. Maier, A direct LA-ICP-MS screening of elemental impurities in pharmaceutical products in compliance with USP and ICH-Q3D, Anal. Chim. Acta 1078 (2019) 1–7.
[131] Y. Shen, C. Zheng, X. Jiang, X. Wu, X. Hou, Integration of hydride generation and photochemical vapor generation for multi-element analysis of traditional Chinese medicine by ICP-OES, Microchem. J. 123 (2015) 164–169.
[132] A.L.H. Muller, E.I. Muller, J.S. Barin, E.M.M. Flores, Microwave-assisted digestion using diluted acids for toxic element determination in medicinal plants by ICP-MS in compliance with United States pharmacopeia requirements, Anal. Methods 7 (2015) 5218–5225.
[133] F.C. Pinheiro, A.I. Barros, J.A. Nóbrega, Elemental impurities analysis in name-brand and generic omeprazole drug samples, Heliyon 6 (2020).
[134] F.C. Pinheiro, A.I. Barros, J.A. Nóbrega, Evaluation of dilute-and-shoot procedure for determination of inorganic impurities in liquid pharmaceutical samples by ICP OES, Microchem. J. 146 (2019) 948–956.
[135] G.T. Druzian, M.S. Nascimento, R.F. Santos, M.F. Pedrotti, R.C. Bolzan, F. A. Duarte, E.M.M. Flores, New possibilities for pharmaceutical excipients analysis: combustion combined with pyrohydrolysis system for further total chlorine determination by ICP-OES, Talanta 199 (2019) 124–130.
[136] D. Matmour, A. Bouaffad, Y. Merad, N.H. Ziani, From the limit test for trace elements control to the elemental impurities analysis by inductively coupled plasma optical emission spectrometry: application on six samples of metronidazole API, J. Trace Elem. Miner. 2 (2022).
[137] D.A. Gonçalves, I.D. De Souza, A.C.G. Rosa, E.S.P. Melo, A.-M.B. Gonçalves, L.C. S. De Oliveira, V.A. Do Nascimento, Multi-wavelength calibration: determination of trace toxic elements in medicine plants by ICP OES, Microchem. J. 146 (2019) 381–386.
[138] C.A. Busacca, D.R. Fandrick, J.J. Song, C.H. Senanayake, Transition metal catalysis in the pharmaceutical industry, in: M.L. Crawley, B.M. Trost (Eds.), Applications of Transition Metal Catalysis in Drug Discovery and Development, John Wiley & Sons, New Jersey, 2012, pp. 1–42.
[139] A. Elmekawy, Simultaneous determination of residual palladium and thiol homogeneous scavenger N-acetylcysteine in active pharmaceutical ingredients using inductive coupled plasma-mass spectrometry, Org. Process. Res. Dev. 25 (2021) 1352–1359.
[140] N. Benson, W.U. Anake, I. Olanrewaju, Analytical relevance of trace metal speciation in environmental and biophysicochemical systems, Am. J. Anal. Chem. 4 (2013) 633–641.
[141] J. Jo, Q. Tu, R. Xiang, G. Li, L. Zou, K.M. Maloney, H. Ren, J.A. Newman, X. Gong, X. Bu, Metal speciation in pharmaceutical process development: case studies and process/analytical challenges for a palladium-catalyzed cross-coupling reaction, Organometallics 38 (2019) 185–193.
[142] J.K. Nag, V. Balaram, R. Rubio, J. Albertyf, A.K. Das, Inorganic arsenic species in groundwater: a case study from Purbasthali (Burdwan), J. Trace Elem. Med. Biol. 10 (1996) 20–24.
[143] C. Casiot, J. Szpunar, R. Łobinski, M.P. Gautier, Sample preparation and HPLC separation approaches to speciation analysis of selenium in yeast by ICP-MS, J. Anal. At. Spectrom. 14 (1999) 645–650.
[144] A. Sahayam, Speciation of Cr (III) and Cr (VI) in potable waters by using activated neutral alumina as collector and ET-AAS for determination, Anal. Bioanal. Chem. 372 (2002) 840–842.
[145] G.G.A. De Carvalho, L.C. Nunes, P.F. De Souza, F.J. Krug, T.C. Alegre, D. Santos Jr., Evaluation of laser induced breakdown spectrometry for the determination of macro and micronutrients in pharmaceutical tablets, J. Anal. At. Spectrom. 25 (2010).
[146] C. Pasquini, J. Cortez, L.M.C. Silva, F.B. Gonzaga, Laser induced breakdown spectroscopy, J. Braz. Chem. Soc. 18 (2007) 463–512.
[147] J. Williams, J. Putman, Advances in trace element solid sample analysis: laser ablation laser ionization TOF mass spectrometry (LALI-TOF-MS), Spectroscopy 35 (2020).
[148] P. Smichowski, A. Londonio, The role of analytical techniques in the determination of metals and metalloids in dietary supplements: a review, Microchem. J. 136 (2018) 113–120.
[149] M.R. Hammer, A magnetically excited microwave plasma source for atomic emission spectroscopy with performance approaching that of the inductively coupled plasma, Spectrochim. Acta B At. Spectrosc. 63 (2008) 456–464.
[150] K. Jankowski, E. Reszke, Recent developments in instrumentation of microwave plasma sources for optical emission and mass spectrometry: tutorial review, J. Anal. At. Spectrom. 28 (2013) 1196–1212.
[151] V. Balaram, Microwave plasma atomic emission spectrometry (MP-AES) and its applications – a critical review, Microchem. J. 159 (2020).
[152] E.A. Bezrodnykh, O.V. Vyshivannaya, A.V. Polezhaev, S.S. Abramchuk, I. V. Blagodatskikh, V.E. Tikhonov, Residual heavy metals in industrial chitosan: state of distribution, Int. J. Biol. Macromol. 155 (2020) 979–986.
[153] A. Dispas, P.Y. Sacré, E. Ziemons, P. Hubert, Emerging analytical techniques for pharmaceutical quality control: where are we in 2022? J. Pharm. Biomed. Anal. 221 (2022), 115071.