Anal Bioanal Chem
DOI 10.1007/s00216-016-9471-6

REVIEW

Determination of elemental impurities in pharmaceutical products and related matrices by ICP-based methods: a review

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Received: 22 November 2015 / Revised: 27 February 2016 / Accepted: 7 March 2016

Abstract Interest in the determination of elemental impurities in pharmaceuticals has increased in recent years because of changes in regulatory requirements and the need for changing or updating the current limit tests recommended in pharmacopeias. Inductively coupled plasma (ICP) optical emission spectrometry and ICP mass spectrometry are suitable alternatives to perform multielemental analysis for this purpose. The main advantages and limitations of these techniques are described, covering the applications reported in the literature in the last 10 years mainly for active pharmaceutical ingredients, raw materials, and pharmaceutical dosage forms. Strategies used for sample preparation, including dissolution in aqueous or organic solvents, extraction, wet digestion and combustion methods are described, as well as direct solid analysis and ICP-based systems applied for speciation analysis. Interferences observed during the analysis of pharmaceutical products using ICP-based methods are discussed. Methods currently recommended by pharmacopeias for elemental impurities are also covered, showing that the use of ICP-based methods could be considered as a trend in the determination of these impurities in pharmaceuticals. However, the development of a general method that is accurate for all elemental impurities and the establishment of an official method are still challenges. In this regard, the main drawbacks and suitable alternatives are discussed.

Keywords Determination of elemental impurities · Pharmacopoeia · Atomic spectrometry · Sample preparation · Heavy metals · Pharmaceutical analysis

ABC Highlights: authored by *Rising Stars and Top Experts.*

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Introduction

Most of the analytical procedures routinely used to evaluate the quality of pharmaceuticals are described in official pharmacopeias that recommend tests to ensure the identity and purity of raw materials and commercial products. Nowadays, because of the requirements of maximum tolerable limits of impurities in pharmaceuticals, many of the analytical methods have been revised or updated. Accurate evaluation is one of the most important challenges to ensure the quality of drugs [1–4]. In this regard, several active pharmaceutical ingredients (APIs), excipients, and dosage forms have been evaluated. Analytical techniques used for this purpose can be classified as selective (e.g., chromatography and spectroscopy) or nonselective (e.g., titrimetry and spectrophotometry). Selective techniques, especially those based on atomic spectrometry, allow the quantitative determination of impurities in bulk drugs and pharmaceutical formulations. However, there is still a need for the development of analytical methods to overcome many drawbacks and also to be in agreement with the new trends in analytical chemistry such as higher throughput, lower consumption of reagents, and lower effluent generation [5–7]. Moreover, with recent advances in the sample preparation field (e.g., the increased use of microwave systems), further improvements can be expected in the next few years.

Published online: 28 March 2016

However, nonselective approaches, such as the heavy metals limit test, are still used widely, and they are described in most of the pharmacopeial monographs [8, 9]. This classic test is based on precipitation of toxic elements as sulfides. The color is compared visually against that of a lead reference/standard solution. In this case, the sample solution is approved if its color is not darker than that of the reference solution. As expected, this test has several limitations and is dependent on the nature of the test solution. The information obtained is semiquantitative, and a relatively low number of elements can be determined (about ten elements). Moreover, it is not possible to determine what the precipitated elements are, and consequently the extent of possible contamination of pharmaceutical products cannot be evaluated. This limit test has been recommended in pharmacopeias since at least the beginning of the last century. For example, the *United States Pharmacopeia* (11th edition) proposed in 1936 the use of precipitation of metallic sulfides using hydrogen sulfide for the determination of elemental impurities [10]. Nowadays, this method is essentially the same as described in several pharmacopeias and only a few changes have been proposed (e.g., the use of thioacetamide instead of hydrogen sulfide as a sulfide ion source).

In a similar way as for the heavy metals limit test, digestion procedures applied to elemental impurities described in pharmacopoeias presented a few improvements in recent years. Many of them are still performed in open vessels (e.g., digestion by dry ashing at high temperatures, up to 800 °C, in muffle furnaces). Although dry ashing can be performed in a simple way, this method is time-consuming and can be prone to losses or contamination for some elements. Because of these drawbacks, many classical methods have been replaced by the use of closed vessel digestion systems using oxidant acids [11–13].

In spite of the limitations observed for determination elemental impurities by classical methods, only a few reports have been described in the literature to evaluate the performance of these methods [11, 12, 14]. On other hand, several articles have proposed the use of atomic spectrometry techniques as an alternative for quantitative and selective determination of elemental impurities in pharmaceuticals [11, 15–20]. In this sense, inductively coupled plasma (ICP) optical emission spectrometry (OES) and ICP mass spectrometry (MS) have attracted widespread interest because their fast and multielemental analysis capability [12–14, 21–26].

In this review, the suitability of ICP-based methods (e.g., ICP-OES and ICP-MS) for the determination of metals and metalloids in pharmaceutical materials (drug products, APIs, raw materials, and intermediates) is presented, covering the period between 2005 and 2015. In addition, the sample preparation methods involving direct dissolution of APIs in aqueous or organic solvents and by use of wet digestion or combustion methods are discussed. Medicinal herbs and dietary supplements are not covered, and more information on them can be obtained from specific reviews or selected articles [27–30]. The coupling of ICP-OES and ICP-MS with separation techniques is also covered for speciation applications analysis in pharmaceuticals. Current methods recommended in pharmacopeias such as the *United States Pharmacopeia*, the *European Pharmacopoeia* and the *Brazilian Pharmacopeia* are also considered for discussion.

Elemental impurities in pharmaceutical products

The term “heavy metals” has been widely (but erroneously) used in the literature to refer to a group of metals, metalloids, and some nonmetals that have been associated with contamination and potential toxicity [31]. However, the term “heavy metal” has no basis in connection with chemical or toxicological data, and different meanings can be found. This usage implies that all the compounds of some element (organic and/or inorganic) have the same physical, chemical, biological, and toxicological properties, which is not true for most elements. Moreover, the term “heavy” implies high density, but the knowledge of density contributes little to the prediction of biological effects of metals [31]. Most pharmacopeias state that heavy metals are “metallic impurities that are colored by sulfide ion, under the specified test conditions” [8]. In addition, it is stated that the elements that typically respond to the limit test are silver, arsenic, bismuth, cadmium, copper, mercury, molybdenum, lead, antimony, and tin [8]. However, some elements with toxicological relevance are not covered, such as the platinum-group elements that are commonly used as catalysts for synthesis of pharmaceutical compounds.

Therefore, the term “heavy metals” will become obsolete and its use should be avoided. However, categorization of substances can be very useful to allow quicker and simpler assessment of those elements that have common properties. An excellent discussion about the use of the term “heavy metals” was provided about one decade ago [31], and some new classifications were proposed by Hawkes [32] and Appenroth [33]. In spite of these efforts, classification of the elements present as contaminants in pharmaceuticals remains difficult. “Metallic impurities” is not a suitable term because it could suggest impurities from metals or metal alloys and does not cover the impurities from nonmetals such as arsenic. The term “inorganic impurities” could be used, but it excludes the organic species of elements, which could be more toxic than the inorganic ones. A new term to designate the elements evaluated in tests is “elemental impurities,” in which elements are chosen in a risk-based approach to check these impurities in drug products. In this sense, different limits were proposed according to the way of administration (oral, parenteral, and inhalation) and permitted daily exposure [34, 35]. Therefore, this is a reasonable way to establish the maximum allowed

limits for each element, and this term will be used in this review.

The elemental impurities can be classified into three classes on the basis of their toxicity (based on the respective permitted daily exposure) and likelihood of occurrence in the drug product, as shown in Table 1. It is important to highlight that all elements which were used in the production of APIs are considered as intentionally added and should be evaluated independently from the route of administration and respective class [34]. There are many acceptable approaches for summarizing and documenting the risk assessment, and these are based on the identification of the elemental impurities, their sources, and the controls and acceptance criteria. These parameters have been carefully discussed, and more information regarding the establishment of maximum limits for each element can be found in literature [34, 35]. In this sense, some pharmacopeias such as the *United States Pharmacopeia* and the *Brazilian Pharmacopeia* follow this tendency and they are currently implementing this approach in their respective compendia [36, 37]. On the other hand, some elements that are not included as elemental impurities must be determined in specific pharmaceutical products. This is the case of aluminum determination in large- and small-volume solutions used in total parenteral nutrition, which remains as a relevant issue. Aluminum contamination could lead to toxic accumulation in the tissues of individuals receiving total parenteral nutrition therapy, especially neonates and patient populations with impaired kidney function. Thus, the risk of exposure to an unsafe amount of aluminum should also be evaluated for these products [38]. Despite the importance of aluminum determination in such products, this element is not covered in this review, which focuses on the elemental impurities described in Table 1.

Sources of contamination

Since the impurity profile of a drug material depends on its synthetic route, the sources of elemental impurities could be different as could the level of contamination. In spite of the importance of toxicological aspects, the presence of impurities can be used to indicate inadequate handling and storage or can be used as a fingerprint for the raw material used for drug production [4]. In this way, elemental profiling can be linked to the synthesis route, the salting-out method, and the solvent used in the extraction process [39].

Contamination by elemental impurities can arise from intentional addition of the element in the production process, such as catalysts. In some cases, elements cannot be completely removed from APIs after synthesis. Therefore, the contamination can be predicted and the maximum tolerable amount of these impurities should be considered [34]. In this way, several articles have proposed atomic spectrometry techniques to evaluate the content of residues of catalysts such as iridium, osmium, palladium, platinum, rhodium, ruthenium, and tungsten in pharmaceuticals [13, 20–23, 40–44].

Other sources of contamination are related to the materials used in equipment and all surfaces (generally metals) that are in direct contact with the API or commercial product. Corrosion, extraction/leaching, or delamination could result if inadequate materials were used, leading to incorporation of elemental impurities in the product [45–47]. This could be the case for contamination by aluminum from glass [48], zinc from plastic [49] and rubber [50, 51] materials, and aluminum, arsenic, and tungsten from glass syringe container-closure systems [52].

In general, the raw material is often the most important source of contamination, and some contaminants from starting materials or reagents could be present in the final products. If contamination was not detected in the quality control, some side effects of pharmaceutical dosage forms may be related not to the drug itself but to the effect of the contaminant. Nonselective methods such as the heavy metals limit tests are prone to this problem because of the lack of sensitivity and specificity. An alarming example occurred in Brazil in 1999 related to meglumine antimoniate [53]. This drug, used for the treatment of leishmaniasis, is composed of a pentavalent antimony injectable solution. As pentavalent antimony reacts with sulfide ion, when the limit test for heavy metals is used, an orange precipitate is formed, and visual comparison against a lead standard solution (black precipitate) is impossible. Thus, some batches of this drug were used in therapeutics with contamination levels of arsenic and lead as high as 84 and 52 mg L^{-1} respectively, leading to several side effects and even deaths [53, 54]. Nowadays, the method for determination of elemental impurities in meglumine antimoniate has been changed in the *Brazilian Pharmacopeia*, and it is done by atomic spectrometry techniques, such as ICP-MS, to overcome the reported limitations [55].

Another source of elemental impurities could be related to the use of unsuitable water purification systems. As water is used in many process, from synthesis to the production of pharmaceutical dosage forms, if problems related to water quality are not detected, the product could contain some degree of contamination that is sometimes difficult to detect. Because of this, the determination of elemental impurities in water is strongly recommended in all pharmacopeias.

Heavy metals limit test

The limit test for elemental determination is a very simple procedure that can be performed with materials commonly used in chemical laboratories. There is no need to be a highly skilled analyst to conduct this procedure, and almost all laboratories can perform it. Basically, the procedure consists of a

Table 1 Classification of elemental impurities and the need for risk assessment considering the route of administration

Class	Elements	Characteristics	Risk assessment			
			If intentionally added (all routes)	If not intentionally added		
				Oral	Parenteral	Inhalation
1	As, Cd, Hg, and Pb	Toxic elements that have limited or no use in the manufacture of pharmaceuticals; require risk assessment across all potential sources of elemental impurities and routes of administration	Yes	Yes	Yes	Yes
2A	Co, Ni, and V	High probability of occurrence in drug product; require risk assessment across all potential sources of elemental impurities and routes of administration	Yes	Yes	Yes	Yes
2B	Ag, Au, Ir, Os, Pd, Pt, Rh, Ru, Se, and Tl	Reduced probability of occurrence in drug product; excluded from the risk assessment unless they are intentionally added during the manufacture of drug substances and other components of the drug product	Yes	No	No	No
3	Ba, Cr, Cu, Li, Mo, Sb, and Sn	Low toxicities by the oral route of administration, but may require consideration in the risk assessment for inhalation and parenteral routes	Yes	No	Yes for Cu, Li, and Sb; no for Ba, Cr, Mo, and Sn	Yes

Adapted from [34]

previous sample preparation step (including solubilization), pH adjustment to 3.5, and reaction with sulfide ion (from thioacetamide, hydrogen sulfide, or sodium sulfide). A visual comparison is done against a 10 or 20 mg L^{-1} lead standard solution in Nessler tubes, according to Eq. 1 for monovalent, trivalent, and pentavalent ions and according to Eq. 2 for divalent and tetravalent ions:

$$m\,M^{n+} + n\,H_2S_{(aq)} \leftrightarrow M_mS_{n(s)} + 2n\,H^+, \quad (1)$$

$$m\,M^{n+} + 1/2n\,H_2S_{(aq)} \leftrightarrow M_mS_{n/2\,(s)} + n\,H^+. \quad (2)$$

To pass the test, the color produced by the sample must be equal in intensity or less intense than the color produced by the lead standard solution. As mentioned before, in spite of its simplicity, this test has many limitations. The information is semiquantitative and unspecific, because the final color is proportional to the color (or intensity) sum of each sulfide, making the test unable to distinguish which element is the main contaminant. The sulfides of elements evaluated in this test could have different solubilities, which is also a problem when the comparison with the lead standard solution is performed [56]. Moreover, a determination based on color comparison is subject to systematic errors due to the dependency on the visual acuity of the analyst and the ambient luminosity. In addition, thioacetamide is a toxic and unstable reagent and must be prepared daily. One aspect that must be considered is that, in general, the pharmacopeias have no recommendation regarding cleaning of glassware, and the next sample to be analyzed could show a false positive result if the same glassware is used without proper decontamination [56].

Other important elements of toxicological concern cannot be determined by the classical limit test (e.g., Cr, Ni, and V). In addition, the determination of these elements is dependent on the chemical form present in solution. Some elements (e.g., As, Hg, and Sn) could occur as organic species and others could be found in different oxidation states that have a different reaction profile with sulfide ion. The reaction of some elements with sulfide ion as recommended in pharmacopeias was evaluated and negative results were observed for silver, arsenic, cadmium, mercury, and tin [57]. This should be not a surprise in the case of arsenic and cadmium, because these elements form yellow or orange sulfides that are less intense than the black lead sulfide. Therefore, if these elements are present as contaminants, the limit test cannot detect them and a sample can be approved by the test even with high levels of impurities. In this way, biased results were found for arsenic, cadmium, and mercury (negative bias) and bismuth, copper, and lead (positive bias), and ambiguous values were found for molybdenum and antimony [56]. These results show the limitations of the heavy metals limit test and reinforce the need of its urgent substitution in official compendia by more reliable methods, such as ICP-based methods.

Analytical protocols described in pharmacopeias require a wide range of equipment and analytical chemistry expertise. In this sense, a complete monograph test often requires several analytical methods. To perform even some basic monograph tests, laboratories must have a wide range of instrumentation, such as infrared spectrometers, liquid chromatographs, and UV–vis spectrophotometers. However, the use of instrumentation for the determination of elemental impurities is recommended in pharmacopeias in only a few cases. Considering this aspect, in this review, we evaluate analytical procedures described in pharmacopeias and discuss in more detail the use of ICP-based methods for determination of elemental impurities in pharmaceuticals because this can be seen as a trend in this field.

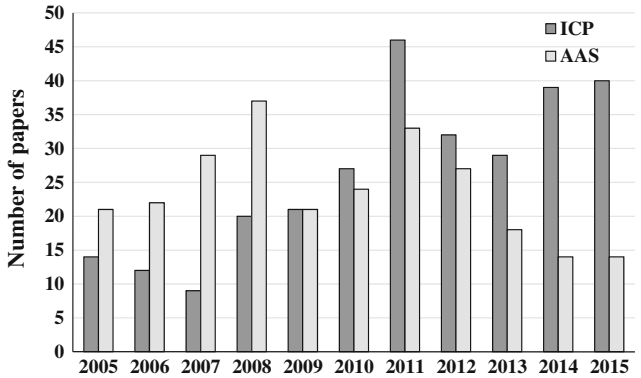

Fig. 1 Articles published from 2005 to 2015 (up to October 2015) regarding to the use of inductively coupled plasma (*ICP*)-based and atomic absorption spectrometry (*AAS*) methods for the determination of elements elemental impurities in pharmaceutical products. Data obtained from Web of Science with the keywords "pharmaceuticals" and "inductively coupled plasma" or "atomic absorption spectrometry"

Plasma-based spectrometric techniques

Plasma-based techniques are characterized by high temperatures (from 6000 to 10,000 K), allowing the atomization and ionization of most elements. The gas used for plasma generation for most ICP-based instruments is argon. Other gases such as He or N_2 can be used but they will be not covered in this review nor will other alternative ways for plasma generation [58–60].

General features and overall comparison between ICP-OES and ICP-MS

The multielemental capability of plasma-based instruments is one of the main advantages of ICP-OES and ICP-MS, especially when compared with atomic absorption spectrometry (AAS). The use of ICP-based methods for the determination of elemental impurities in pharmaceuticals was less common in the past but is increasing and it is expected that both AAS methods and ICP-based methods will be the method of choice in this field. As shown in Fig. 1, since 2010 the number of articles reporting the use of ICP-based methods has surpassed the number of articles reporting the use of AAS methods, and it is expected that the difference between the frequency of the use of these techniques will increase even more in the coming years.

In addition to the distinctive features of ICP-based methods, two important documents from the European Medicines Agency [35] and the US Pharmacopoeial Convention [61], both published in 2008, that refer to the evaluation of elemental impurities certainly contributed to increasing interest in these techniques. These documents indicated the importance of the establishment of concentration limits for each element according to the way of administration and permitted daily exposure, showing the changes in official compendia. In this sense, ICP-based methods were considered as a suitable alternative, taking into account the high number of elements to be determined [61], and new general chapters for the determination of elemental impurities in APIs were added in 2010 to the *United States Pharmacopeia* [62] and the *Brazilian Pharmacopeia* [36] and in 2012 to the *European Pharmacopoeia* [63]. In these pharmacopeias, the use of atomic spectrometry techniques, including ICP-OES and ICP-MS, is recommended. Therefore, interest in the determination of elemental impurities by ICP-based methods should increase even more, taking into account the need for implementation of these methods by the pharmaceutical industry.

An important feature of ICP-based methods is the relatively low limit of detection (LOD), which typically reaches micrograms per liter for ICP-OES and nanograms per liter for ICP-MS in conventional systems and the wide linear calibration range extending up to about six to nine orders of magnitude [64, 65]. In particular, some ICP-OES instruments allow the possibility to perform the determination at wavelengths below 190 nm (vacuum UV region), because purged optical systems or optical systems under vacuum allow the removal of interferences from air, which is an advantage, mainly in the determination of elements such as arsenic, selenium, phosphorus, sulfur, and halogens. ICP-OES instruments are available with sequential or simultaneous optical systems.

Powerful detection capability can be definitively achieved by ICP-MS. The commonest ICP-MS instruments are those with a quadrupole as a mass filter, but some characteristics may change, depending on the manufacturer. The use of double focusing sector field high-resolution ICP-MS instruments [66] is also a possibility, but the high acquisition cost and the high expertise for operation can limit their use. The instrumental variables include, among others, the number of cones (generally two or three) in the interface between the plasma and the mass spectrometer, the system for ion focusing, the presence and type of reaction and/or collision cell (quadrupole, hexapole, or octapole), and the number of mass filters [64, 65, 67, 68].

Interferences in ICP-based techniques: analytical challenges

Although plasma-based techniques have a significant number of advantages as described earlier, the determination of elemental impurities by ICP-OES and ICP-MS is affected by spectral and nonspectral interferences. Because of this, they can be considered less robust methods in contrast to others (e.g., AAS with flame or graphite furnace atomizers). In general, ICP-MS is significantly more prone to interferences than ICP-OES. Spectral interferences are observed if other species are detected at the same (or very close) wavelength or at the same *m*/*z* ratio of the analyte(s) for ICP-OES and ICP-MS instruments respectively. Nonspectral interferences can cause suppression or enhancement of the signal and generally occur if the sample composition is very different from that of analytical solutions, resulting in biased results. Therefore, the major composition of pharmaceuticals, solvent type, dissolved salts, residual carbon, and acidity of digests should be considered. As a consequence, the composition of pharmaceutical products should be evaluated before analysis to identify potential interferences. Most APIs are organic substances, and several of them contain elements other than carbon and hydrogen, such as chlorine, nitrogen, oxygen, and sulfur, in their chemical structure. In addition, acidic and basic APIs are generally presented as salts, which account for about half of all commercialized drugs (Table 2). Almost 20 % of APIs are hydrochlorides, and spectral interferences of chlorine in ICP-MS determination of some elements can be expected [13]. In this way, interferences in $^{51}V^{+}$, $^{52}Cr^{+}$, $^{53}Cr^{+}$ and $^{75}As^{+}$ determination have been reported for aqueous solutions containing chlorine at 100 mg L^{-1} [13]. Parenteral and ophthalmic solutions are generally prepared with sodium chloride to adjust osmotic pressure and interferences from chlorine are also expected. Sulfur caused interferences in $^{65}Cu^{+}$ determination and phosphorus caused interferences in $^{63}Cu^{+}$ and $^{65}Cu^{+}$ determination by ICP-MS [13]. Interferences were observed also for no-salt-addition APIs that contain these elements in their chemical structures (e.g., sulfonamides and thiazides), or even for excipients used in pharmaceutical dosage forms (e.g., calcium phosphates) [13].

Table 2 Salt forms of acidic and basic drugs commercialized in Brazil

Salts of basic drugs	Percentage	Salts of acidic drugs	Percentage
Acetate	2.9	Calcium	1.0
Bromide	1.0	Lysine	0.3
Fumarate	1.2	Magnesium	0.4
Hydrochloride	19.4	Potassium	0.6
Maleate	2.0	Sodium	5.9
Mesylate	1.4	Other[b]	0.9
Phosphate	1.0	Total of acidic salts	9.1
Sulfate	2.6		
Tartrate	1.0		
Other[a]	9.3		
Total of basic salts	41.8		
Total of other substances (no salts)	49.1		

Adapted from [69]. Active pharmaceutical ingredients used in pharmaceutical dosage forms for external use were not considered

[a] Benzoate, besylate, carbonate, chloride, citrate, estolate, hydrobromide lactate, malate, mucate, nitrate, pamoate, propionate, stearate, succinate, tosylate, and valerate

[b] Aluminum, lysine, meglumine, strontium, and trometamine

The API salts of alkaline and alkaline earth elements (e.g., Na, K, Ca, and Mg) account for about 8 % of commercial drugs (Table 2). Interferences due to the matrix of these APIs could be troublesome in both ICP-OES and ICP-MS analysis because of the high amount of easily ionizable elements (EIEs) in these molecules. Some studies have shown the effect of elements with low ionization potential in ICP-MS [70] and ICP-OES [71]. Considerable signal suppression has been reported for ICP-MS, and the intensity increases with the increase of the mass of the concomitant element. This was related with the space–charge effect, and evidence for a shift in the ion–atom equilibrium was also reported [70]. The effects of concomitant elements from the matrix in ICP-OES have been also studied, and the effects of EIEs and non-EIEs were reported to affect all the steps, from introduction in the plasma to the ionization/excitation of analytes [71].

The amount of carbon in solution is also an important parameter, because interferences could arise from solutions containing a high content of dissolved carbon. In this case, the effects can be different depending on the nature of the carbon present in solution [72, 73]. The carbon source could be the API, excipients, or even the residual carbon that was not digested during sample preparation. Nonspectral and spectral interferences could be observed in ICP-MS for solutions having a high content of dissolved carbon, mainly from the formation of polyatomic ions in the plasma, carbon deposition on the interface of the instrument, and changes in the plasma characteristics and ion distribution. These last changes occur mainly due to charge transfer reactions between the analyte and carbon-containing charged species [74]. Nonspectral interferences due to carbon content in solution were reported for arsenic determination by ICP-MS in parenteral solutions. An increase of signal intensity when the carbon concentration was higher than 750 mg L^{-1}, as well as spectral interferences of carbon on $^{52}Cr^{+}$ (by $^{40}Ar^{12}C^{+}$) and $^{53}Cr^{+}$ (by $^{40}Ar^{13}C^{+}$) were reported [23]. In the same way, interferences were observed for $^{52}Cr^{+}$ and $^{53}Cr^{+}$ during analysis of API digests with a carbon concentration higher than 250 mg L^{-1}, whereas for $^{60}Ni^{+}$ problems were observed for solutions containing carbon at a concentration of 2000 mg L^{-1}, but. In this case, the use of a

reaction cell reduced the extent of interferences (e.g., polyatomic interferences of $^{40}Ar^{12}C^{+}$ on $^{52}Cr^{+}$, $^{40}Ar^{13}C^{+}$ on $^{53}Cr^{+}$, and $^{12}C^{16}O^{16}O^{16}O^{+}$ on $^{60}Ni^{+}$) [13]. According to the experience of the authors, the efficiency of the digestion method must be high enough to allow a carbon content in the digest lower than 250 mg L^{-1}. As will be discussed in the next section, only some systems and conditions can allow this, at least for a considerable amount of sample, necessary to reach the required LODs. Thus, this aspect and the possible interferences that can impair the results can be considered a warning when one is using ICP-based methods for the determination of elemental impurities in pharmaceuticals.

The acidity of solutions used in both ICP-OES and ICP-MS should also be controlled to avoid interferences in sample introduction (e.g., aspiration rate, aerosol generation, and aerosol transport) and plasma characteristics [75]. Spectral interferences could be present when some acids are used, such as HCl (e.g., for As) and H_2SO_4 (e.g., for Cu) in ICP-MS measurements [76]. In some cases, inorganic acids could be used for the direct dissolution of APIs and for element extraction. However, the residual acidity might not be suitable for further analysis. On the other hand, similar problems can be caused by excessive acid remaining in solution after digestion (residual acidity). The use of organic solvents is also prone to spectral interferences, resulting in changes in sample introduction and plasma characteristics [72, 77, 78] as well as the previously mentioned interferences caused by dissolved carbon. In spite of the possibility of dilution to avoid these interferences, the low LOD commonly required in this kind of analysis can be a limiting factor for procedures using a high amount of acids or solvents.

Nowadays, one of the best option to reduce or eliminate spectral interferences in ICP-MS (mainly polyatomic ones) is the use of reaction and/or collision cells [79, 80]. Depending on the manufacturer, the name of this device may change, but the effect/result is the same as: (1) addition of a reactive gas, which could eliminate the interference by changing its *m*/*z* (e.g., NH_3); (2) by reaction with the analyte (e.g., O_2) [81]; or (3) by bond breaking of the polyatomic interference by collision with, for example, helium [82], changing its *m*/*z*. In this sense, a dynamic reaction cell with NH_3 was used for the determination of elemental impurities in APIs [13], drug tablets [42], and parenteral solutions [23], avoiding polyatomic interferences for chromium, copper, manganese, and vanadium. On the other hand, helium has been successfully used in collision cells for palladium determination in APIs dissolved in organic solvents [41]. In spite of the possibility of removing interferences with those technologies, we stress the necessity of careful optimization of the conditions to guarantee that the same effects are affecting standards and sample solutions.

Nonconventional uses of ICP-based methods

Depending on the sample preparation method, conventional pneumatic nebulization, ultrasonic nebulization, chemical vapor generation (CVG), and other methods can be used. An interesting approach is the use of a membrane desolvation unit that can be coupled to nebulization systems for introduction of organic solvents into the ICP instrument. This device was used in ICP-OES for a "dilute-and-shoot" procedure for the determination of elemental impurities in APIs, with *N*,*N*-dimethylformamide as a "universal" organic diluent [22].

Flow injection systems were combined with ICP-MS to achieve high sample throughput and low sample consumption for the determination of elemental impurities in APIs [66, 83]. CVG is other alternative for analyte introduction in ICP-based instruments, allowing efficient separation of the analyte from the matrix, which often leads to a reduction of interferences and better LODs [84]. As an example, the use of a CVG-ICP-MS system was successfully applied for the determination of mercury in pharmaceuticals [13, 23]. In this case, problems related to memory effects were minimized and an improvement of the LOD was achieved in comparison with the conventional nebulization system.

On the other hand, when no sample preparation method is performed, solid or semisolid samples can be introduced into the plasma by use of laser ablation (LA) [85] or electrothermal vaporization (ETV) [42, 86] systems. LA is a powerful tool for screening of elemental impurities in pharmaceuticals (e.g., coupled with ICP-MS [85]) because practically no sample preparation is required and analytical signals can be obtained fast [87]. However, in some cases, it presents difficulties in calibration and representativeness (only nanogram quantities of sample are introduced into the plasma), making quantitative analysis more difficult. However, some strategies have been proposed to overcome these limitations in LA-ICP-MS, and new improvements can be expected in the next few years [87–89].

For the determination of elemental impurities in solid pharmaceutical samples (by direct introduction of solid samples or slurries), ETV was coupled with both ICP-OES [86] and ICP-MS [42]. With use of this approach, relatively higher sample masses (e.g., up to 2.5 mg) can be used in comparison with LA-ICP-MS [86]. Another advantage is the possibility of matrix removal by a pyrolysis step before analyte vaporization, allowing calibration with aqueous reference solutions. However, in some cases an additional gas (e.g., Freon) [86] or chemical modifier solution [42] may be required to improve the vaporization of analytes. However, some elements cannot be determined because of losses in the pyrolysis step [86].

Other techniques

The selection of an instrumental technique requires the evaluation of many parameters, including sensitivity, precision, accuracy, time of analysis, and sample preparation requirements. Considering that there are several manufacturers, configurations, and accessories for each instrument, a full comparison is difficult because of the high number of possibilities. In spite of the increased use of ICP-based techniques, AAS is still used for the determination of elemental impurities in pharmaceuticals, as can be seen in Fig. 1. These techniques are well established, and many applications have been described in the literature for several pharmaceutical applications [11]. Suitable and quantitative determination of a number of elements can be achieved, even at trace levels. Therefore, we briefly compare AAS and ICP-based methods.

Concerning the LOD, the analytical technique should allow the determination of elemental impurities at a concentration equivalent to or lower than the maximum limits recommended in pharmacopeias. This could explain the limited use of a flame as an atomizer in AAS in comparison with graphite furnace AAS, which allows better LODs to be attained. The LODs for ICP-OES are similar to those obtained by graphite furnace AAS, whereas ICP-MS is by far the most sensitive technique.

In general, samples in solution can be analyzed in less than 10 min for several elements by ICP-OES or ICP-MS, whereas graphite furnace AAS allows the determination of one element per sample in only 2 or 3 min, which should be an obvious disadvantage if several elements must be determined. However, the sample preparation step is not included in this comparison, and in some cases the sample throughput could be similar for all techniques. Analysis by ICP-MS is more prone to interferences and requires an efficient sample preparation, which implies the use of specific and powerful equipment for sample digestion (e.g., microwave-assisted digestion in closed vessels). Consequently, the time spent for sample preparation must be considered, and the sample throughput is decreased. For ICP-OES, this problem is less severe and for graphite furnace AAS it is almost negligible, because a pyrolysis step is performed before atomization. Moreover, nowadays there are accessories for conventional graphite furnace AAS instruments that allow the direct analysis of elements in solid samples without sample preparation, with consequent increase in sample throughput, and lower risks of losses and contamination associated with the sample preparation step [19, 20, 90].

In spite of some limitations of graphite furnace AAS, almost all toxic elements can be determined with use of this technique. On the other hand, the applicability of CVG in AAS (mainly hydride generation and cold vapor AAS) is restricted to a few elements that form volatile hydrides (or Hg in cold vapor AAS), and its use for determination of elemental impurities in pharmaceuticals reported in the literature is relatively low [54, 91]. CVG of transition and noble metals with subsequent determination by AAS has also been proposed [92]. In this case, the analyte is volatilized, most often by reaction with borohydride, in a similar way as for hydride generation. In this way, new possibilities were created [93, 94] and could make CVG-AAS more attractive for the determination of some elemental impurities in pharmaceuticals.

Some alternative techniques for the determination of elemental impurities can be found in the literature, such as total reflectance X-ray fluorescence spectrometry. Solids and liquids in inorganic and organic matrices (powders and liquids), used in the manufacture of APIs and drug products, can be analyzed by this technique with minimum sample preparation and negligible matrix effects in most cases. However, most applications of these technique for the pharmaceutical industry have been reported as qualitative or semiquantitative methods, but quantitative analysis of palladium and copper [17, 18] and also zinc, iron, and nickel [16] in API samples was performed by X-ray fluorescence spectrometry. Precipitation with thioacetamide with subsequent filtration was used for the improvement of LODs in for manganese, iron, cobalt, copper, zinc, lead, mercury, and cadmium by X-ray fluorescence spectrometry [15].

Electrochemical techniques, such as anodic stripping voltammetry [95], have also been used for this purpose but are extremely dependent on the degree of digestion (low residual carbon content), limiting their applicability.

Sample preparation methods

As mentioned before, many sample preparation methods described in pharmacopeias involve several steps, low throughput, high risk of contamination or losses, and the use of several reagents [5, 6]. Therefore, the development of sample preparation strategies to overcome these drawbacks in the determination of elemental impurities in pharmaceuticals has been explored in the literature, focusing mainly on three approaches: (1) direct dissolution in aqueous or organic solvents or extraction; (2) wet digestion; and (3) combustion (Fig. 2). Both wet digestion and combustion have been performed in closed vessels under microwave irradiation, which avoid the loss of volatile elements and reduces the amount of reagents consumed [5]. When no sample preparation is required, some strategies have been developed by use of ETV and LA devices coupled to ICP-OES or ICP-MS instruments. Considering that each sample preparation method has advantages and limitations, we briefly discuss the strategies most used on the basis of the applications reported in the literature (Table 3).

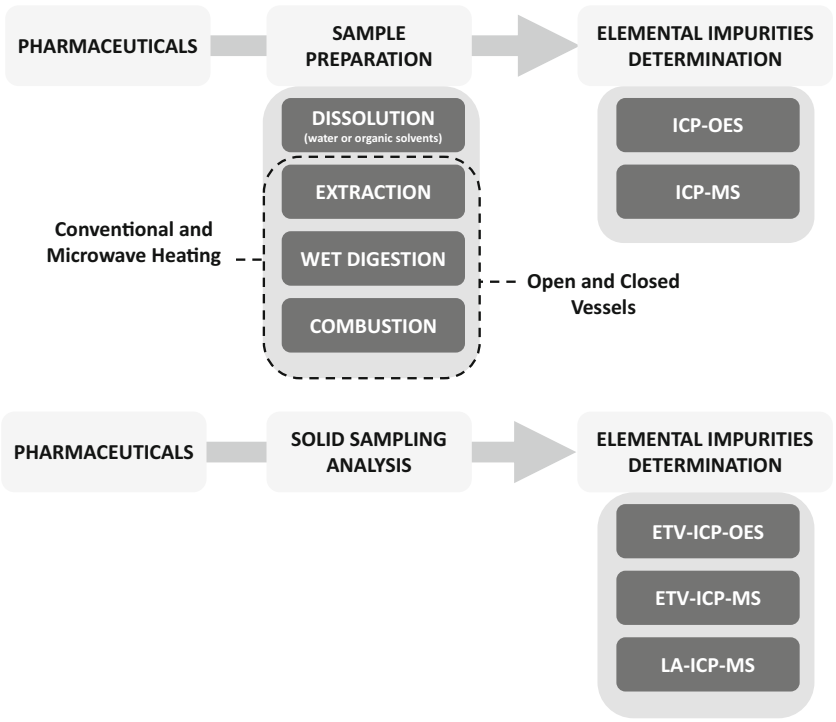

Fig. 2 Summary of strategies used for determination of the total amount of elemental impurities in pharmaceuticals by inductively coupled plasma (*ICP*)-based methods published in the literature. *ETV* electrothermal vaporization, *LA* laser ablation, *MS* mass spectrometry, *OES* optical emission spectrometry

Dissolution in aqueous or organic solvents and extraction

In spite of the possibility of analysis of solid samples by use of LA or ETV systems, most ICP-based methods are (and at least in the next few years will continue to be) based on the analysis of solutions.

The conventional and most efficient approach for sample preparation before element determination is matrix digestion (discussed in detail in "Wet digestion" and "Combustion"), aiming at the degradation of organic compounds and minimizing spectral interferences. Although dissolution in aqueous or organic solvents can be performed as a simple, fast, and practical way of sample preparation, careful optimization and evaluation of potential interferences needs to be performed before the analysis.

Dissolution in aqueous medium is generally performed with dilute acidic solutions (e.g., dilute HCl or HNO_3 solutions), but the sample mass is limited to a few milligrams (from 10 to 100 mg) mainly to minimize interferences caused by its carbon content. This limitation of sample mass impairs better LODs, but reduces the organic content introduced into the plasma. Another alternative to introduce small sample amounts and consequently lower the carbon content is the use of flow injection systems for acquisition of transient instead of continuous signals [66, 83]. When compared with digestion methods, dissolution in aqueous solution has the advantage of avoiding drawbacks for some elements such as osmium, which can be lost even when closed vessels are used in digestion systems [66]. However, the main limitation of methods using dissolution in aqueous solution is the low solubility of many APIs [12].

In spite of some work showing the feasibility of the use of solvent introduction in plasmas, this approach is still controversial [106]. In the literature, some alternatives for introduction of organic solvents have been described, such as membrane desolvation systems, additional oxygen flow mixed with nebulization gas, and mathematical correction. As previously mentioned for aqueous solution, dissolution using organic solvents can also prevent losses by volatilization when compared with sample digestion [41]. Diethylene glycol monoethyl ether, *N*,*N*-dimethylformamide, and ethanol are among the organic solvents reported for dissolution of APIs [22, 41, 83]. In general, for those APIs that are not soluble in aqueous solution (e.g., with dilute HCl and/or HNO_3), the dissolution in organic solvents can be considered a complementary approach. In spite of some disadvantages of dissolution in aqueous or organic solvents, some interesting advantages, taking into account their application for routine analysis, can be highlighted, such as the reduction of the analysis time, the possibility of automation, and reduced sample handling and blank values [22, 41, 66, 83].

Extraction methods can be considered as an alternative because generally elemental impurities are not present in the molecular structure of APIs. They can be incorporated during the synthesis and are probably not chemically bonded to APIs. However, there are a few articles reporting the use of extraction methods such as cloud point extraction (CPE) [43] and ultrasound-assisted extraction [98]. Conventional CPE

Table 3 Selected references from the literature (2005–2015) regarding the determination of elemental impurities in pharmaceuticals by inductively coupled plasma (*ICP*)-based methods

Samples	Elements	Sample preparation details	Quantification techniques	Reference
Acetylsalicylic acid and L-serine	As, Cd, Cr, Cu, Fe, Hg, Ir, Mn, Mo, Ni, Os, Pb, Pd, Pt, Rh, Ru, V, and Zn	Dissolution in aqueous solution, 100 mg + 10 g of 1 % HNO_3/0.15 % HCl (v/v) solution Microwave-assisted digestion in closed vessel, 100 mg + 3 mL HNO_3, 25 min (maximum 600 W), temperature up to 160 °C, maximum pressure 25 bar. Hg and Os were stabilized after digestion with HCl and thiourea solution respectively	FI-ICP-MS, FI-ICP-SFMS	[66]
Acetylsalicylic acid tablets	As, Cd, Cr, Cu, Hg, Ir, Mn, Mo, Ni, Os, Pb, Pd, Pt, Rh, Ru, and V	Microwave-induced combustion, 400–700 mg + 5 mL of 20 % (v/v) HNO_3 + 20 bar O_2; 5 min	ICP-MS	[96]
Antibiotic tablets	Ag, Al, As, Ba, Be, Bi, Ca, Cd, Co, Cr, Cu, Fe, Ga, In, Mg, Mn, Ni, Pd, Pb, Se, and Zn	Digestion in closed vessel using conventional heating, 100–300 mg + 5 mL HNO_3 + 1 mL H_2O_2, 130 °C for 2 h Solid sampling (slurries), 2.5 % (m/v) slurries prepared with 0.5 mol L^{-1} $HNO_3$and 0.5 % Triton X-100	ICP-OES	[97]
Antihypertensive tablets	Cd, Cr, Mo, Pb, Pd, and Pt	1. Solid sampling (slurries), 0.1 g in 10 mL water + APDC (1 %, m/v) and 8-HQ (0.025 %, m/v) + 5 min of sonication 2. Microwave-assisted digestion in closed vessel, 200 mg + 3 mL HNO_3 + 1 mL HCl. Microwave heating program: (a) 80 % power, 20-min ramp, 100 psi, hold 15 min; (b) 80 % power, 10-min ramp, 175 psi, hold 15 min; (c) 80 % power, 10-min ramp, 175 psi, hold 15 min. After cooling, 2 mL H_2SO_4 + 1 mL HNO_3 + 1 mL HCl and heating again	1. ETV-DRC-ICP-MS 2. DRC-ICP-MS	[42]
Several APIs	Ag, As, Bi, Cd, Cu, Hg, Mo, Pb, Sb, and Sn	Ultrasound-assisted automated extraction, 100 mg + 9 mL of acidified DMSO (2:98 HCl–DMSO)	ICP-OES	[98]
Arbidol	Cd, Co, Cu, Mn, Ni, and Pb,	1. Solid sampling, 100 mg of pelletized sample 2. Microwave-assisted digestion in closed vessel, 100 mg + 6 mL HNO_3 + 2 mL H_2O_2, 125 °C for 30 min	1. LA-ICP-MS 2. ICP-MS	[85]
Capsules (empty)	Cr	400 mg + 1 mL HNO_3 + 3 mL H_2O_2 + 5 min vortex	ICP-OES	[99]
Carbamazepine, amitriptyline hydrochloride, and imipramine hydrochloride	As, Cd, Hg, and Pb	Microwave-induced combustion, 500 mg + 6 mL of 7 mol $L^{-1}HNO_3$ + 20-bar O_2, 5 min	ICP-MS	[12]
Enalapril and ramipril tablets	Pd, Pt, and Rh	Microwave-assisted cloud point extraction, 40 mL Triton X-100 0.5 % with 2-mercaptobenzothiazole, heating at 600 W until cloud point temperature (around 72 °C, 5 min), 1 min 0 W, 5-min cycles of continuous irradiation followed by 1 min of cooling at 360 W. The surfactant-rich phase was dissolved in 1 mol L^{-1} HCl	ICP-MS	[43]
Fingolimod	Cu, Fe, Ni, Pb, Pd, and Zn	Wet digestion using a ultra-high-pressure chamber assisted by microwave irradiation, 200 mg + 4 mLHNO_3 + 0.2 mL $HClO_4$, 250–260 °C for at least 45 min	ICP-OES	[100]
Isosulfan blue	Cd, Cu, Cr, Pb, and Sn	UV photolysis assisted digestion, 75 mg + 3 mL $HNO_3$for 10 min + 200 μL H_2O_2+ 2 mL water + UV irradiation at 85 ± 5 °C for 1 h (with addition of 0.1 mL H_2O_2 + 1 mL HNO_3during digestion)	ICP-MS	[101]
Levetiracetam	Ag, Au, As, Bi, Cd, Cr, Cu, Fe, Hg, Ir, Mn, Mo, Ni, Os, Pb, Pd, Pt, Rh, Ru, Sb, Sn, V, and Zn	Microwave-assisted digestion in closed vessel, 1000 mg + 15 mL HNO_3 + 2 mL H_2O_2 predigestion, reduction of volume to 5 mL, ramp of about 10 °C and hold at 250 °C for 10 min	ICP-OES	[56]
Levodopa, primaquine diphosphate, propranolol	1. Cd, Ir, Mn, Mo, Ni, Os, Pb, Pd, Pt, Rh, Ru		1. ICP-MS 2. DRC-ICP-MS	[13]

Table 3 (continued)

Samples	Elements	Sample preparation details	Quantification techniques	Reference
hydrochloride, and sulfamethoxazole	2. Cr and Cu 3. As and Hg	Microwave-assisted digestion in a single reaction chamber, 10-min ramp and hold at 270 °C for 20 min, pressure up to 199 bar (a) 500 mg + 6 mL HNO_3 for As, Cd, Cr, Cu, Hg, Mo, Ni, Pb, and V determination (b) 250 mg + 4.5 mL HNO_3 + 1.5 mL HCl for Ir, Os, Pd, Pt, Rh, and Ru determination	3. FI-CVG-ICP-MS	
Lu tablets	As, Cd, Cu, Cr, Fe, Hg, It, Mn, Mo, Ni, Os, Pb, Pd, Pt, Rh, Ru, V, and Zn	Microwave-assisted digestion in closed vessel, 450 mg + 12 mL of freshly prepared acid mixture (HNO_3 + HCl, 3:1), 30-min ramp to 220 °C, 40 min at 220 °C	ICP-OES	[102]
Microcrystalline cellulose	Os	Wet digestion using an ultra-high-pressure chamber assisted by microwave irradiation or a high-pressure asher, 100 mg + 3 mL HNO_3, 280 °C for 30 min. A solution of acetic acid (0.5 %) containing thiourea (0.01 mol L^{-1}) and ascorbic acid (0.1 g L^{-1}) was used after digestion for the analyte stabilization	ICP-MS	[103]
Parenteral solutions	1. As, Cd, Mo, and Pb 2. Cr, Mn, Ni, and V 3. Hg	Dilution in aqueous solution, 5 % HNO_3	1. ICP-MS 2. DRC-ICP-MS 3. FI-CVG-ICP-MS	[23]
Several APIs	As, Cd, Cr, Cu, Mn, Mo, Ni, Pb, Pd, Pt, Rh, Ru, and V	1. Direct solid sampling, 2.5 mg + Freon (modifier) 2. Microwave-induced combustion, 125 mg + 6 mL HNO_3 + 20-bar O_2; 5 min	1. ETV-ICP OES 2. ICP-MS	[86]
Several APIs	Pd	Dissolution in organic solvents, 20–500 mg + 20 g diethylene glycol monoethyl ether + 200 mg thioacetamide	ICP-MS	[41]
Several APIs	Al, Co, Cr, Cu, Fe, Mn, Mo, Ni, Pd, Pt, Rh, Ru, W, Zn, and Zr	Dissolution in organic solvents,10 mg + 5 mL of 2 % EDTA solution prepared in *N*,*N*-dimethylformamide	ICP-OES	[22]
Several APIs	Cr, Pd, and Rh	Dissolution in ethanol and the use of solid adsorbents for screening test	FI-ICP-MS	[83]
Several APIs	Ru	Dissolution in aqueous solution ,10 mg (solid API) or 100 μL (liquid API or solution) dissolved in up to 10 mL with 80 % HNO_3	ICP-MS	[44]
Several APIs and finished products (tablets)	1. Cd, Co, Ir, Mn, Mo, Ni, Os, Pb, Pd, Pt, Ru, Rh, Sn, Sb, and V 2. Cu, Fe, and Zn	Microwave-assisted digestion in closed vessel, 400 mg + 2 mL water + 4 mL of HNO_3 plus HCl (1:1); temperature program of 85 °C (8 min), ramp to 130 °C (5 min), ramp to 200 °C (5 min), and hold at 200 °C for 30 min	1. ICP-MS 2. ICP-OES	[104]
Several API tablets	Al, B, Cr, Cu, Fe, Mg, Mn, Pb, Ti, and Zn	Digestion in closed vessel using conventional heating, 100–300 mg + 5 mL HNO_3 + 1 mL H_2O_2, 130 °C for 2 h	ICP OES	[105]

APDC ammonium pyrrolidine dithiocarbamate, *API* active pharmaceutical ingredient, *CVG* chemical vapor generation, *DMSO* dimethyl sulfoxide *DRC* dynamic reaction cell, *ETV* electrothermal vaporization, *FI* flow injection, *8-HQ* 8-hydroxyquinoline, *LA* laser ablation, *MS* mass spectrometry, *OES* optical emission spectrometry, *SFMS* sector field mass spectrometry

consists in the use of a mixture containing surfactant and ligand, where the analytes are moved to the surfactant-rich phase. CPE is generally applied for extraction and preconcentration of elements from liquid samples, but for solid matrices a microwave-assisted approach can be useful to accelerate extraction and/or increase the extraction efficiency. The simplicity and suitable throughput are among the advantages of microwave-assisted extraction combined with CPE compared with conventional solid–liquid extraction. Although the combination of microwave-assisted extraction and CPE is useful, it is necessary to use a selective ligand to ensure quantitative recoveries [43].

On the other hand, ultrasound-assisted extraction can be used for liquid or solid samples. Especially for solids, the high turbulence and cavitation result in the erosion of solid material (by the action of microjets formed during cavitation) and consequently this increases the transfer of analytes to the liquid phase. In spite of the suitable efficiency of ultrasound-assisted extraction methods, careful optimization of the operational parameters of the

ultrasound instrument (e.g., power, frequency, amplitude, temperature, and solvent) and evaluation of the way to apply the ultrasound energy (using bath or probe systems) are required [98, 107].

Wet digestion

The treatment of a material with oxidant reagents conventionally heated or by means of microwave radiation is the commonest approach for matrix digestion to obtain a solution containing analytes and components from the matrix partially or completely oxidized. This approach is known as "wet digestion" and has been applied for almost all matrices [5, 6]. Wet digestion of organic matrices is done mainly with oxidizing acids, nitric acid being the most commonly used because of its suitable oxidizing power, the possibility of obtaining it at high purity or of purifying it by subboiling distillation, and also because several elements will be in solution as soluble nitrates. Mixtures of HNO_3 with HCl, HF, $HClO_4$, H_3PO_4, and H_2SO_4 are also used, depending on the matrix, analytes, and/or digestion system [108, 109].

Although wet digestion can be performed in open or closed systems, closed vessels are preferred for pharmaceutical products and related matrices. Many APIs or related products are very hard to digest even under extreme temperature and pressure conditions [14, 102, 110]. The use of closed vessels is considered advantageous because it is possible to use a higher digestion temperature without dryness of acid or analyte losses. Therefore, the degradation of organic compounds is possible, contributing to better digestion efficiency [110]. In addition, the use of closed vessels minimizes the risk of losses and contamination. It is important to consider that in closed vessels sample masses are generally limited to approximately 500 mg in contrast to open vessels, which allow sample masses higher than 1 g [108, 109]. This is probably explained by the chemical resistance of some related substances that usually require temperatures higher than 200 °C, which are easily reached in closed systems. In this sense, wet digestion in closed polytetrafluoroethylene vessels was used for antibiotics [97] and several APIs [105] with use of HNO_3 and H_2O_2 for digestion and further determination of elemental impurities by ICP-MS and ICP-OES respectively. The sample mass in both cases ranged from 100 to 300 mg, which can sometimes be not enough to reach suitable LODs depending on the material and the determination technique. High efficiency of digestion using conventional heating and closed vessels can be performed with a high-pressure asher system, which allows temperature above 300 °C [103, 108]. The suitability of this system was demonstrated for microcrystalline cellulose for trace determination of osmium by ICP-MS [103].

The use of microwave irradiation instead of conventional heating contributed to widespread use of wet digestion by many laboratories. Many attempts using microwave-assisted wet digestion for pharmaceutical products and related matrices have been made to improve the methods for detection of elemental impurities and to obtain digests suitable for analysis by ICP-based methods. Microwave-assisted wet digestion can also be performed in open and closed vessels but the use of a focused-microwave radiation system has not been reported for pharmaceuticals (probably because usually temperatures close to the boiling temperature of HNO_3 are reached, even when cold-finger or similar devices are used, thus limiting the digestion efficiency). Microwave-assisted wet digestion in closed vessels has been considered the "state of the art" in sample preparation of organic matrices because it combines high digestion efficiency and faster heating in contrast with the methods using conventional heating. Many applications for pharmaceutical products and related matrices have been developed in recent years aimed for the development of sample preparation methods capable of producing digests almost free from interferences for analysis by both ICP-OES and ICP-MS [11, 56, 66, 102, 104]. In addition, this method has been used to obtain reference values by some authors [42, 85] when developing alternative methods. Commercial systems are available from many manufacturers, with several types of vessels (quartz, polytetrafluoroethylene, and other inert materials) allowing digestion at temperatures ranging from 200 to 280 °C and pressure up to 80 bar [108, 109]. In recent years, ultra-high-pressure systems were developed, allowing digestion at elevated pressures (higher than 100 bar) and some of them are suitable for digestion of APIs and for the determination of elemental impurities by ICP-MS [13] and for the drug fingolimod for further determination of elemental impurities by ICP OES [100].

The choice of the composition of the digestion solution has been the focus of much work devoted to optimization of the conditions for wet digestion. The digestion mixture plays an important role in the destruction of the compounds in the matrix but it must ensure the analytes are soluble and are retained in solution in a stable form for analysis. This aspect has been critical in the optimization of methods for elemental impurities, mainly for mercury, iridium, osmium, palladium, platinum, rhodium, and ruthenium [13, 21] and some reports have demonstrated the use of aqua regia for digestion as an alternative for those analytes [13, 21]. It was shown that osmium was unstable after 6 h in nitric acid digests [103]. In particular for osmium, solutions stabilized in 0.009 mmol L^{-1} $KBrO_3$ plus 1 % HCl [21] and thiourea (0.01 mol L^{-1} in 0.1 g L^{-1} ascorbic acid) as a complexing agent [66, 103] have been used. In the case of mercury, the use of HCl in the composition of the acidic mixture (about 5 % v/v) was suitable for complete recoveries and stabilization [66] as well as to avoid memory effects in a nebulization system in plasma-based techniques. The use of a solution containing gold was demonstrated to be feasible for this purpose [102]. In our experience, the determination of these elements (Hg, Os, and Pt-group

elements) in digests is not easy and careful optimization must be performed to evaluate the accuracy of the method. Attention must be paid to these elements even in some already published protocols because unsuitable results are not always reported (this fact was not investigated in some reports) and common mixtures are based just on HNO_3 or HNO_3 with H_2O_2. A summary of protocols using wet digestion (with conventional heating or microwave radiation) is given in Table 3, with details regarding sample mass, digestion mixtures, and the heating/irradiation program.

Combustion

As most APIs are organic substances, combustion methods can be very convenient for sample digestion, taking into account that they practically allows complete destruction of the matrix, reducing the carbon effects in ICP-based analyses [62]. The conversion of organic compounds by combustion results in the formation mainly of CO_2 and H_2O as reaction products, as well as inorganic residue (ash), which is generally solubilized by diluted reagents before analysis [5]. Moreover, as oxygen is usually the only necessary oxidant reagent, the interferences related to the use of concentrated acids can be significantly reduced [76].

In a general way, combustion methods can be considered as relatively simple and fast depending on the instrumentation used. In this sense, dry ashing can be highlighted as a simple method used for preparation of high sample masses (up to 10 g) of organic samples, because it does not require vessels specially designed for working under high-pressure conditions. However, although this procedure is still in use, many problems have been reported, especially because of the risks of analyte loss and contamination [5, 111].

Combustion methods performed in open vessels have some advantages related to sample mass and safety. However, closed vessels have been preferentially used for sample preparation and further ICP-based analysis. The most used combustion methods performed in closed vessels involve digestion using a Schöniger flask [111–113], combustion bombs [111], and microwave-induced combustion (MIC) systems [96, 114–118].

Despite the wide use of a Schöniger flask and combustion bombs for sample preparation of organic samples, these systems were not applied for digestion of APIs and further ICP-MS and ICP-OES analyses [111]. On the other hand, MIC was recently successfully used for digestion of APIs [13], tricyclic APIs [12, 86], and aspirin [96] for subsequent determination of elemental impurities by ICP-MS (Table 3). Especially for tricyclic APIs, MIC has been highlighted as suitable, because conventional wet digestion using concentrated HNO_3 decreases the reactivity of aromatic rings, making the sample digestion difficult [12].

MIC has some advantages over previous combustion systems such as the possibility of applying a reflux step immediately after the sample combustion, without any intervention by the analyst or instrument modification. Moreover, with this system it is possible to use an oxygen pressure as high as 25 bar to digest relatively high sample masses (125–700 mg) of pharmaceutical products. The use of MIC allows relatively high sample throughput (in general up to eight simultaneous combustions can be performed) and operational safety when compared with classic closed combustion systems [111].

Another important advantage is the possibility of using dilute solutions to retain efficiently the elements released from the sample during combustion. This approach prevents possible incompatibility of digests with ICP-based techniques as previously discussed in this review. Moreover, this system also allows the retention of halogens in a suitable solution, avoiding losses by volatilization, which is a drawback commonly reported for conventional digestion methods with concentrated acids or even a combustion method in open vessels [119]. In this sense, bromine and iodine were determined in APIs by ICP-MS after sample digestion by MIC and a suitable alkaline solution was used for analyte absorption. It was highlighted that this solution was very convenient for further ICP-MS determination, taking into account that problems related to memory effects were avoided, especially for iodine [120].

Despite the advantages related to the use of the MIC method, there are relatively few reports of work using MIC for digestion of pharmaceutical products and related matrices for further elemental determination by ICP-based techniques [13]. However, in our experience, MIC seems to be an alternative method that can be expected to be applied for digestion of APIs with advantages over other methods. In this regard, it is important to highlight that this method was recently proposed in the *Brazilian Pharmacopeia* as an alternative for sample preparation of APIs and related compounds [36].

Speciation analysis

Considering that many chemical species have different toxicities, information about the species of an element could be critical to evaluate the degree of contamination of a pharmaceutical product and mainly the consequences of contamination. Nevertheless, there are a few reports dealing with speciation analysis of elements in pharmaceutical products. Atomic spectrometry has brought an important contribution to the determination of elemental impurities in pharmaceuticals and related matrices, but the determination of the total concentration of elements has been the focus in most cases [14]. In particular, ICP-based methods have been used for the analysis of pharmaceuticals, partially due to the limitations of classical methods and also to improve the accuracy and

selectivity. Many ICP-based methods have been used for this purpose, but almost all the methods are devoted to total element concentration [14]. As ICP is a "hard" ionization source, no information regarding the chemical form of analytes can be obtained if conventional nebulization or direct sample introduction systems are used. Nevertheless, these techniques have a sensitivity independent of the chemical form and when coupled with use of a separation system—for example, liquid chromatography (LC), gas chromatography, or capillary electrophoresis—can provide information about the species [121]. These are known as "hyphenated" techniques and have been used in many fields for speciation purposes because analytes are separated according to their chemical forms before ICP-based analysis [122–127]. Selective sample introduction using CVG is another approach that has been used for speciation analysis, and many methods using CVG-AAS can be found in the literature for the speciation of arsenic [91, 128] and antimony [128–130] in drugs as well as methods using hydride generation coupled with infrared spectroscopy [131] and spectrophotometry [132, 133]. Speciation analysis of selenium has also been reported in the literature for supplements and dietary products [134–136].

Many drawbacks make speciation analysis a complex task. Most protocols require several analytical steps, which may include extraction, derivatization, preconcentration, cleanup, separation, and final detection. All these steps can be prone to drawbacks depending on the analyte species (and its concentration) and the sample matrix. Obviously, sample preparation methods for speciation analysis must consider that stability of species through the entire analytical process [123, 124, 137, 138]. However, the concentration of elemental impurities can be low, resulting in an additional difficulty for speciation analysis. In this regard, soft sample preparation methods, such as extraction using water or very dilute solutions, under mild temperature conditions and short times are recommended to minimize species conversion. Concerning the sample matrix, pharmaceuticals are commonly organic matrices and sometimes hard to digest, requiring extreme conditions (which are not recommended for speciation) to obtain analytes into a suitable solution. Thus, careful optimization of the method conditions to avoid conversion, losses, or precipitation is required.

In pharmacopeias, no official methods are available for speciation purposes, but some recent efforts have been made in this field. Recently, a procedure for arsenic and mercury speciation in medicinal plants was introduced in the *United States Pharmacopeia*, and limits were established on the basis of the chemical species of the analyte [139]. Following this trend, it is possible to observe an increasing number of publications dedicated to the development of methods for speciation analysis in medicinal plants [140–145]. However, medicinal plants will be not covered in this review.

The speciation of antimony in meglumine antimoniate has been of concern in many reports, and some alternative approaches using ICP-based methods can be found in the literature [146–148]. In this sense, the determination of Sb(III) and Sb(V) was performed in injectable drugs by ICP-OES after separation of antimony ions in a Dowex resin [146]. The sample was solubilized (1:1000) in dilute HCl solution (1.5 mol L^{-1}), which was used to obtain Sb(III) and Sb(V) from organoantimonial compounds, without causing species conversion [146]. In other work, Sb(III) was determined by CVG-ICP-OES, with citric acid and $NaBH_4$ for selective generation of SbH_3. With this approach, the LOD was about 0.02 μg L^{-1} [147]. The use of hydride generation allows a low LOD to be obtained when compared with that obtained by use of ICP-OES and Dowex resin for separation of antimony species (LOD of 32 μg L^{-1}) [147]. Another report proposed the use of HCl solutions (5 mol L^{-1}) for sample dilution in deaerated conditions to minimize species conversion for antimony speciation by LC–ICP-MS [148]. In this case, the LOD for LC–ICP-MS was 0.1 μg L^{-1} [148].

Hyphenated ICP-based methods have also been used for the determination of metal-based drugs. In these cases, the particular suitability of ICP-MS and ICP-OES to detect metals combined with the hard plasma conditions to destroy the organic structure of pharmaceuticals is being explored with a separation technique before ICP-based determination. As a species-unspecific response is expected, the quantitative determination of a metal can be performed and it can be correlated with the metal-based drug. The same approach can be applied for the determination of metabolites or for potential metal-based impurities. It can be performed without use of standards for each molecule, as required for LC with UV detection and LC–MS, the methods most commonly used for pharmaceuticals [2, 26]. It has been demonstrated that this strategy resulted in better LODs and the best performance for gadolinium complexes (Gadodiamide®) as well as for iodine- or phosphorus-based drugs in comparison with the use of LC with UV detection and LC–MS [149]. A more detailed discussion about the use of ICP-based methods for speciation analysis of metal-based drugs can be found in a recent article [121].

Trends and challenges for the determination of elemental impurities

The determination of elemental impurities in pharmaceuticals is a challenging task, and the development of a universal method is difficult because of the particularities to be considered. APIs have a wide range of physical and chemical properties, as well as human and environmental toxicological impacts, which lead to the development of different approaches to fulfill these particularities. In this regard, the analytical

performance (e.g., accuracy, precision) of methods is not the only parameter to be considered. Routine applications often consider the sample throughput, the ease of use (related to the number and complexity of analytical operations), and costs. Automation could be also an important feature in such cases. Occupational safety and health is another important feature of analytical methods, and the use of toxic substances and dangerous operations has been discouraged. In the same way, the environmental impact is also an important feature, and the use of methods that follow green analytical chemistry is mandatory. Therefore, a brief discussion of specific points related to sample preparation and determination of elemental impurities by ICP-based methods was provided to show, at least partially, the complexity of such a task.

Because half of APIs are salts and have reasonable solubility in aqueous solvents, direct dissolution is an easy sample preparation alternative. However, the amount of API dissolved and its composition should be carefully considered to avoid interferences in ICP-based analysis. Despite ICP-OES instruments apparently being more robust and less prone to interferences, their use is restricted by their relatively low sensitivity when compared with ICP-MS instruments. The same logic for salts is valid for nonsalts and aqueous-insoluble substances, which despite the possibility of being dissolved in organic solvents, are prone to the similar limitations. In those cases, additional problems of handling with high vapor pressure and sometimes toxic organic solvents should be considered. In this sense, if a method that uses organic solvents is established as a routine method, the human and environmental health consequences as well as the energy demands associated with the reuse or disposal of such chemicals should be highlighted. Another important aspect to be considered in direct dissolution of APIs is the effect of these solutions on both human and environmental health, and some substances are active even at low concentration. Thus, the handling of such solutions during ICP-based analysis could be critical to ensure the safety of analysts. Therefore, occupational health and safety should be included when one is designing and implementing analytical methods for the determination of elemental impurities in pharmaceuticals.

With regard to the protocols using a previous digestion method, those safety concerns related to occupational health are minimized because the APIs are oxidized mainly to CO_2 and water. The concentrated acids used for digestion should be handled with care because of their high vapor pressure and/or corrosive properties. On the other hand, these problems are minimized when digests are diluted in water. Moreover, the use of dilute acids for digestion is an option and could be considered as an alternative to improve occupational health and safety. However, some APIs (e.g., tricyclic drugs) are extremely difficult to digest even with the use of high-pressure systems and concentrated acids, and in most cases digestion is still considered a challenge. In addition to wet digestion with oxidizing reagents, combustion methods (e.g., MIC) are a suitable alternative in such cases. Dilute solutions are often used in MIC as absorbing solutions because the destruction of the organic matrix is performed by the action of oxygen during the combustion process. Therefore, considering the advantages recently presented by MIC, it can be considered a trend in sample preparation for pharmaceutical products. However, even when closed systems are used, some elements can be lost during or after digestion (e.g., Os) and careful evaluation of the digestion procedure is recommended.

Extraction could be used as a mild sample preparation alternatively to digestion, with use of dilute reagents and relatively lower temperatures. However, in spite of the green appeal of such methods, their use is limited by the incomplete leaching of analytes and nondestruction of the matrix, which can result in interferences. As mentioned before, there are several sources of contamination by elemental impurities, and depending on the processing conditions used for synthesis of APIs, many chemical forms of contaminant species can remain in the matrix. In this way, the physical and chemical properties of elemental impurities can be different, and depending on the extraction conditions, incomplete analyte extraction could be achieved. This is not a problem for APIs always synthesized in the same way, but it should be considered for quality control of APIs provided by different manufacturers.

Solid sampling (e.g., using ETV or LA) is an alternative to avoid sample preparation and to perform direct analysis by both ICP-OES and ICP-MS. This is a suitable solution for hard-to-digest APIs, and it could avoid the excessive handling of a high amount of toxic substances in the laboratory. Moreover, for high-cost raw material or drugs that are in development, this could be an alternative to evaluate elemental impurities without the use of huge amounts of materials. However, the homogeneity of materials is critical, and problems in calibration should be considered.

Speciation analysis has been used mainly for determination of impurities of APIs containing a metal or other element (e.g., Gd, Pt, and Sb) as a way to find species generated during synthesis, degradation products, or even metabolites generated in vivo. However, considering the risk-based approach for establishment of impurities limits, the use of speciation analysis can be increased to ensure the safety of drugs. This is especially important if contamination is identified by means of the total content of an element, because depending on the species detected, no risks could be stated even if the total concentration of contaminant is above the maximum limit recommended in pharmacopeias. However, there are only a few analytical protocols for this purpose, and there is a need to develop methods in this regard.

Conclusion

The determination of elemental impurities in pharmaceuticals is a challenging task. ICP-based methods have gained widespread use because of their unique features that make 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 LODs for all elements of pharmaceutical concern. Spectral interferences in ICP-MS can be overcome by use of reaction or collision cells. The determination of elements such as osmium requires stabilization of analyte before their introduction in ICP-based methods to achieve reliable results depending on the selected sample preparation method. Both ICP-OES and ICP-MS can be used for solid sampling using ETV or LA devices with good performance for almost all elemental impurities. ICP-MS can also be coupled with separation techniques allowing the speciation of impurities, which remains a difficult analysis and requires more development. Considering that thousands of drugs are available on the market in different pharmaceutical dosage forms and excipients, the development of analytical methods for determination of elemental impurities will be an important research activity in the next few years. The advantages of these methods over conventional limit tests described in pharmacopeias are changing the official methods, leading to the introduction of these methods by manufacturers. In this regard, several strategies for sample preparation and direct determination of elements should be developed, because the composition of pharmaceuticals is diverse, leading to different solutions in each case. However, in the attempt to develop new methods, the lack of reference materials, the difficulty to develop a general method that is accurate for all elemental impurities, and the establishment of an official method are aspects contributing to the analytical challenge.

Acknowledgments The authors are grateful to Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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