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Review

The use of atomic spectroscopy in the pharmaceutical industry for the determination of trace elements in pharmaceuticals

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ABSTRACT

The subject of the analysis of various elements, including metals and metalloids, in the pharmaceutical industry has seen increasing importance in the last 10–15 years, as modern analytical instrumentation has afforded analysts with the opportunity to provide element-specific, accurate and meaningful information related to pharmaceutical products. Armed with toxicological data, compendial and regulatory agencies have revisited traditional approaches to the testing of pharmaceuticals for metals and metalloids, and analysts have begun to employ the techniques of atomic spectroscopy, such as flame- and graphite furnace atomic absorption spectroscopy (FAAS, Flame AA or FAA and GFAAS), inductively coupled plasma-atomic emission spectroscopy (ICP-AES) and inductively coupled plasma–mass spectrometry (ICP-MS), to meet their analytical needs. Newer techniques, such as laser-induced breakdown spectroscopy (LIBS) and Laser Ablation ICP-MS (LAICP–MS) are also beginning to see wider applications in the analysis of elements in the pharmaceutical industry.This article will provide a perspective regarding the various applications of atomic spectroscopy in the analysis of metals and metalloids in drug products, active pharmaceutical ingredients (API's), raw materials and intermediates. The application of atomic spectroscopy in the analysis of metals and metalloids in clinical samples, nutraceutical, metabolism and pharmacokinetic samples will not be addressed in this work.

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1. Introduction

1.1. Historical overview

The toxicities of various elements have been well-known and documented for many years. As early as the second century BCE, it was apparent that exposure to lead (Pb) could be detrimental [1], and the Chinese emperor, Ying Zhen is reported to have died as a result of mercury (Hg) poisoning, having taken pills containing Hg that were intended to make him immortal [2]. Toxicologists continue to study the effects of elements on humans and revised permitted limits based on safety data, thus leading to the need to test pharmaceuticals for various elements.

For more than 100 years, the standard for testing pharmaceuticals sold in the United States for elements has been the Heavy Elements Test, Chapter 231, as found in the United States Pharmacopeia (USP). The first USP chapter on heavy elements was intended as a screening tool for a limited number of elements [3], and this procedure has been revised over time, in an effort to improve its performance and provide more reliable information. In its present iteration, USP 231, *Heavy Elements* [4] is based on a sulfide precipitation of the analyte elements, and assumes that all potential analytes behave similarly to the lead standard with which samples are compared. When the USP heavy elements method was first published, most of the concern regarding elements in pharmaceuticals was associated with antimony (Sb), arsenic (As), cadmium (Cd), copper (Cu), iron (Fe), lead (Pb) and zinc (Zn) [5], there was no validation performed, and the method was intended only as a screening tool. Even in the current chapter, no element-specific information is provided by USP 231, nor is quantitative information provided, either. Results are reported as a limit test. Additionally, although USP 231 is listed as the "heavy elements" chapter, there is no clear delineation of which elements the method is expected to detect. Furthermore, there is no internationally agreed-upon definition of a "heavy metal," considerably complicating the understanding and use of USP 231.

In addition to USP 231, the general chapter on heavy metals, the USP also includes several other chapters related to the analysis of metals and/or metalloids. General Chapters 241 [6], 251 [7], 261 [8], 291 [9], 591 [10] and 206 [11] provide methods for the determination of Fe, Pb, Hg, Se, Zn and Al, respectively. General Chapter 191 [12], Identification Tests—General, provides procedures for identifying Al, Sb, Ba, Bi, Ca, Co, Cu, Fe, Pb, Li, Mg, Mn, Hg, K, Na and Zn. Some of these tests, however, are not instrumentally based and are limited in their ability to provide adequate analytical information, in some cases, yielding only qualitative information.

1.2. Aims and scope

As modern instrumental techniques have developed and matured, however, it has become possible to provide element-specific and quantitative information regarding the content of metals (including the transition metals, other metals or post transition metals, alkali metals, alkaline earth metals, inner transition elements) and metalloids (boron (B), silicon (Si), germanium (Ge), arsenic (As), antimony (Sb), tellurium (Te), polonium (Po)) in pharmaceuticals. As demands for more rapid and more specific information related to the elements content of pharmaceuticals increase, analytical chemists are more frequently turning to the use of the techniques of atomic spectroscopy to provide critical information regarding the metal and/or metalloid content at all phases of the drug development process [13–17].

This paper will focus on the analysis of pharmaceutical materials (drug products, active pharmaceutical ingredients (API's), raw materials and intermediates) for metals and metalloids using the techniques of atomic spectroscopy. Included are brief discussions of instrumental techniques, method development and method validation.

1.3. Analytes of interest and limits

While the analysis of elements has long been of interest to the pharmaceutical industry, there has never been agreement on which metals and/or metalloids should be monitored. Various compendial methods refer to "heavy elements," but this term is misleading. Because the term, heavy metal, does not have a universally accepted definition, it is difficult to establish a clear set of analytes for routine analysis. In his paper on the meaning of the term, heavy metal, Duffus [18] highlights the variety of ways used to categorize elements into a grouping of heavy elements: atomic weight, atomic number, density, chemical properties, toxicity. Duffus concluded that no authoritative body has established a clear definition of the term "heavy metal." While USP 231 was originally intended to screen for Cu, Fe, Sb, As, Cd, Pb and Zn, other elements, such as Hg, Ag, Pt, Pd have significance in the pharmaceutical industry for various reasons, as well. Additionally, in some cases, the compendial method has been demonstrated to be incapable of detecting a metal of interest, such as Hg [4].

The European Agency for the Evaluation of Medicinal Products (EMEA) attempted to provide some guidance to the industry regarding analytes of interest, as well as possible limits based on safety concerns for those elements, when it issued its Guideline on the Specification Limits for Residues of Metal Catalysts [19]. The EMEA Guideline, intended to cover elements that are part of the process (catalysts), is provided in Table 1.

More recently, in an attempt to address questions regarding which elements should be monitored, and what limits may be acceptable, the USP proposed two methods, 232 and 233 [20,21]. The elements and limits proposed by the USP were selected on the basis of toxicity [22]. As with the EMEA Guideline, many elements were not included in proposed Chapter 232, but the USP chapters address not only those elements added during the manufacture of pharmaceuticals, but also those that might inadvertently find their way into a product. Even so, proposed USP chapter 232 largely harmonizes with the EMEA Guideline on permitted daily exposures (PDE's), with the following deviations: the EMEA Guideline does not include information regarding As, Cd, Pb, Hg; USP proposed Chapter 232 does not include information regarding Fe or Zn. USP proposed Chapter 232 permits the use of any sample preparation procedure or analytical technique, provided that the validation requirements of the chapter are met. The proposed chapter provides guidance for sample preparation and the use of either inductively coupled plasma-atomic emission spectroscopy (ICP-AES) or inductively coupled plasma-mass spectrometry (ICP-MS), in the event that a valid method is not available. Acceptable limits for analytes of interest in a given sample are based on the PDE's provided in proposed Chapter 232, and are also based on daily dose. For this reason, the limits for a given pharmaceutical product must be determined by the analyst.

1.4. Atomic spectrometric techniques

Several of the various techniques that encompass the field of atomic spectroscopy, flame atomic absorption spectrometry (FAAS), graphite furnace atomic absorption spectrometry (GFAAS), inductively coupled plasma-atomic emission spectroscopy (ICP-AES) 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 [23]. Of these more common techniques of atomic spectroscopy, FAAS and GFAAS, based on the Beer–Lambert Law, have been in use longer for the analysis of metals and/or metal-

Table 1
Class exposure and concentration limits for individual metal catalysts and metal reagents [12].

Classification	Oral exposure		Parenteral exposure		Inhalation exposure[a]
	PDE (μg/day)	Concentration (ppm)	PDE (μg/day)	Concentration (ppm)	PDE (ng/day)
Class 1A: Pt, Pd	100	10	10	1	Pt: 70[a]
Class 1B: Ir, Rh, Ru, Os	100[b]	10[b]	10[b]	1[b]	Ni: 100
Class 1C: Mo, Ni, Cr, V	250	25	25	2.5	Cr (VI): 10
Metals of significant safety concern					
Class 2: Cu, Mn	2500	250	250	25	
Metals with low safety concern					
Class 3: Fe, Zn	13000	1300	1300	130	
Metals with minimal safety concern					

[a] See Section 4.4 of the EMEA Guideline and the respective monographs, Pt as hexachloroplatinic acid.
[b] Subclass limit: the total amount of listed metals should not exceed the indicated limit.

loids in pharmaceuticals than have either ICP-AES or ICP-MS. FAAS is considered to be a less sensitive technique than GFAAS, with FAAS generally expected to have sensitivities in the range of low parts per million (ppm, w/w), and GFAAS capable of low parts per billion (ppb, w/w); and with the former usually requiring milliliter quantities and the latter requiring microliter quantities of sample. FAAS is generally the less-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 (HCL) or electrodeless discharge lamp (EDL) for each analyte in question.

ICP-AES and ICP-MS, also used for a variety of sample types [24], have seen greater use within the pharmaceutical industry in more recent years [25,26]. Both techniques are capable of rapid, multi-element analyses, with ICP-MS offering much greater sensitivity – often down to parts per trillion (ppt) than ICP-AES – pm to ppb, which has more potential spectral interferences. Analyst skills for ICP-AES and ICP-MS are greater than for either FAAS or GFAAS, with ICP-MS requiring the greatest level of skill among the four techniques. ICP-MS is ideally suited to the use of gas chromatographic (GC) or liquid chromatographic (LC) separation techniques as part of the sample introduction system, as well. Additionally, ICP-MS is the most expensive of these instrumental techniques, and consumables for ICP-MS are also the most expensive.

In addition to these more commonly used techniques of atomic spectroscopy, laser ablation inductively coupled plasma-mass spectrometry (LA-ICP-MS) and laser induced breakdown spectroscopy (LIBS) have also begun to see more use in the analysis of pharmaceutical compounds for metals and/or metalloids [27,28], although they still are not widely used within the pharmaceutical industry. Both are solid-sampling techniques, requiring little or no sample preparation. Difficulties with these techniques include the lack of availability of appropriate solid standards and, in the case of LIBS, limited availability of off-the-shelf, ready-to-use LIBS instrumentation.

2. Atomic absorption spectrometry

2.1. Flame AAS (FAAS)

In flame AAS, a liquid sample is aspirated into a flame via a nebulizer. In the nebulizer, the sample is converted to a mist, and the droplets of the mist are easily burned in the flame, which serves as the sample cell. The flame provides a source of neutral atoms or molecules to absorb energy, and acts to desolvate and atomize the sample, as well. The most commonly used flame is an air/acetylene flame, which burns within a temperature range of 2120–2400 °C, while the nitrous oxide flame, which may help to destroy oxides that could form, burns within a temperature range of 260–2800 °C [29].

An external light source, in the form of continuum, electrodeless discharge lamps (EDL) or hollow cathode lamps (HCL), is used to emit spectral lines corresponding to the energy required to elicit the electronic transition from the ground state to an excited state in the sample. Absorption of radiation from the external light source is proportional to the population of the analyte species in the ground state, which is proportional to the concentration of the analyte that is sprayed into the flame.

2.2. Graphite furnace AAS (GFAAS)

In GFAAS, a sample (usually a liquid) is deposited through a small opening into a heated graphite tube, known as a mini-Massmann furnace. Inside the furnace, which serves as the sample cell, neutral atoms or molecules are excited from their ground state when the tube is heated, thereby heating the sample, as well. Samples may be deposited either directly onto the wall of the graphite furnace, or onto a small graphite platform, known as a L'vov platform, which sits inside of the graphite furnace. A series of heating steps are employed, with the main steps including drying, charring or ashing, atomizing and clean-out. Other heating steps may be used, depending on the nature of the sample. At the atomization step, the furnace is heated quickly to a high temperature (usually to incandescence), often in the range of 2500–2700 °C. The transient absorption signal emitted by the sample in the tube is produced by the atomized analyte and measured. As in flame AA, the Beer–Lambert Law is used to relate the concentration of the analyte with the absorption signal. Spectral interferences can occur in GFAAS, and different approaches to background correction have been available for many years to help overcome interferences [30,31].

2.3. Inductively coupled plasma-atomic emission spectrometry (ICP-AES)

ICP-AES utilizes an argon plasma to excite and ionize elemental species within a given sample. The temperature of the plasma generally ranges from 6000 to 10,000 K. Samples are aspirated into the plasma by means of a nebulizer, which generates small droplets that pass through a spray chamber and then through the center tube of a concentric torch. Desolvation, vaporization, atomization and ionization of the sample occur in the high temperatures of the plasma, and the collisions of the ions and electrons of the argon plasma ionize and excite the analyte atoms. The excited atoms emit different frequencies of light that is characteristic of the energy transition for a given analyte. The light intensity is proportional to the analyte concentration. Since there are thousands of potential emission lines, the selection of the analyte wavelength is critical to the analysis.

Table 2
Examples of metals in pharmaceuticals.

Product	Therapeutic area	Manufacturer	Metal/metalloid
ProHance®	Imaging agent	Bracco Diagnostics, Inc.	Gd
Multi-Hance®	Imaging agent	Bracco Diagnostics, Inc.	Gd
Ferinject®	Imaging agent	Syner-Med Ltd.	Fe
Venofer®	Imaging agent	Syner-Med Ltd.	Fe
Dexferrum®		Vifor Pharma	Fe
LumenHance®	Imaging agent	ImaRx Pharm. Corp.	Mn
Tagitol®	Imaging agent	Bracco Diagnostics, Inc.	Ba
Lithobid®	Treatment of Schizophrenia	Noven Therapeutics, LLC	Li
Gastrografin®	Imaging Agent	Bracco Diagnostics	Na
Platinol®	Chemotherapy	Bristol-Myers Squibb Co.	Pt
Paraplatin®	Chemotherapy	Bristol-Myers Squibb Co.	Pt
Silvadene®	Antimicrobial	Monarch Pharmaceutical	Ag
Ferroquine	Antimalarial		Fe

2.4. Inductively coupled plasma-mass spectrometry (ICP-MS)

Like ICP-AES, ICP-MS uses an argon plasma to excite and ionize elemental species within a given sample, and the sample introduction system is the same as in ICP-AES. ICP-MS, however, uses a mass spectral detection, rather than wavelength-based detection. ICP-MS has seen use in a variety of applications over the years [32]. Quadrupole mass spectrometers are more commonly used, however, time-of flight instruments are available, as are high resolution instruments. As the ions generated within the plasma pass into the mass spectrometer, the ions are separated in the magnetic field according to their mass-to-charge ratio (m/z). Because the sample is, theoretically, reduced to its ionic components, due to the heat of the plasma, the mass range for ICP-MS typically covers from 6 to 240 atomic mass units (amu). This, therefore, offers an advantage over ICP-AES, as ICP-MS has significantly fewer potential interferences. The nature of interferences in ICP-MS is typically due to the formation of multiply charged ions, oxides and polyatomic isobaric interferences formed in the plasma. Instrument technology, as well as optimization of instrumental parameters may greatly help to reduce or eliminate such interferences, depending on the sample.

2.5. Solid analysis techniques: laser induced breakdown spectroscopy (LIBS) and laser ablation ICP-MS (LA-ICP-MS)

LIBS and LA-ICP-MS can be useful in the analysis of solid samples, with little or not sample preparation, and have been used for many years on a limited basis [33]. For both techniques, a variety of lasers are available, and lasers are selected based on analytical need. In the case of LIBS, a laser is focused on the surface of a solid sample, and when sufficient laser power is used, the sample vaporizes and produces both neutral and ionic species in their excited states. As with ICP-AES, LIBS is an emission-based technique, and because it is a solid-sampling technique, LIBS can be used for depth-profiling of samples and elemental mapping.

LA-ICP-MS is very similar to LIBS, except it can also be used with ICP-AES, if desired. A laser beam is focused onto the surface of a solid sample, which causes material from the sample to be sputtered and vaporized. An argon carrier gas is used to transport that material into the plasma, where it is atomized and ionized. Like LIBS, LA-ICP-MS can also be used for depth-profiling and elemental mapping of samples.

Both LIBS and LA-ICP-MS provide good sensitivity (ppm to ppb), but for true quantitation, appropriate solid standards are required. Where standards may not be purchased, it is possible to prepare them, however, thorough mixing is absolutely essential.

2.6. Cold vapor and hydride generation techniques

Cold vapor and hydride generation techniques are used most often for the determination of mercury, or for some hydride-forming elements, such as tin, arsenic, selenium, antimony, bismuth. Both techniques may be coupled with the solution-based techniques of atomic spectroscopy.

In the case of mercury analysis by cold vapor generation, a chemical reduction is used to generate atoms, and the cold vapor is swept into either the flame or plasma by an inert gas. In the case of hydride-forming elements, a reaction with sodium borohydride and hydrochloric acid generates the hydride of the analyte of interest. Both techniques are extremely sensitive, with detection limits ranging from ppb to ppt, depending upon the sample and laboratory environment.

3. Applications

Because manufacturers of active pharmaceutical ingredients (API's), raw materials and intermediates used in the pharmaceutical industry can, in theory, use any element possible on the periodic table as part a synthetic process, and because 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, regardless of whether they are included in either the EMEA Guideline or proposed USP 232 and 233. A wide variety of metals and metalloids are used in the manufacture of pharmaceuticals, and some are also used as the active pharmaceutical ingredient (API) in drug products. Table 2 provides examples of pharmaceuticals with a significant metallic component.

Numerous other metals and metalloids, though they may not represent a significant component in a pharmaceutical product, may be used in the synthesis of a pharmaceutical product as reagents or catalysts. Palladium (Pd) and platinum (Pt) are commonly used catalysts in the pharmaceutical industry [34,35]. In addition to the metals or metalloids which are have the potential to be present in a pharmaceutical product by virtue of the synthesis, other metals or metalloids may be of concern, due to their toxicity. Such is the case with Pb, Hg, As and Cd, which are, as was previously mentioned, addressed by both the EMEA Guideline on Residues of Metal Catalysts and proposed USP Chapter 232 [19–21].

Because of 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. Due to the high attrition rate for potential API's evaluated, valuable resources are allocated depending on the stage of development for a given compound. As a result, analytical needs, and therefore the need for the analysis of metals and/or metalloids, varies greatly depending upon the stage of development. Very early discovery and pre-clinical compounds are usually prepared in very limited quantities, so analytical testing is limited only to essential tests. As a compound moves through the development process into the clinical phases, analytical testing requirements

become more involved, and metals testing is often performed not only on the API, but on intermediates, raw materials and equipment. Elements analyses using atomic spectroscopy cover not only the API, but also cleaning validations [13,36] and fingerprinting of drugs [37]. Additionally, techniques of atomic spectroscopy are being used in combination with other analytical techniques to provide pharmaceutical chemists with valuable information regarding the metal content of compounds, using high throughput screening to evaluate pharmaceutical samples [38], and process intermediates [39]. As the pharmaceutical industry expands the inclusion of biologically derived compounds in their portfolios, the use of atomic spectroscopy for the evaluation of elements in these types of samples has seen more attention [40].

Additionally interest in the industry focuses on potential metals contamination in large volume parenterals (LVP's) [41] and identification or fingerprinting of counterfeits and drugs [28,37,42]. Elemental content of packaging and containers is also important to the industry [42,43].

For these reasons, the application of the various techniques of atomic spectroscopy is no longer limited to those instances where a compendial method is available or applicable. The number of analytes that may be monitored in the pharmaceutical applications of atomic spectroscopy is now limited only by the technique selected and sensitivity requirements of a given analysis. In any event, with the publication of the EMEA Guideline and the USP's proposed chapter 232, it is clear that the traditional limit test approach to elements analysis in pharmaceuticals is no longer adequate to meet the needs of either the industry or patients. Table 3 provides a more comprehensive listing of papers associated with the analysis of metals and/or metalloids in pharmaceuticals.

4. Sample preparation techniques and validation

4.1. Digestion and direct dilution of solid samples

Because of the wide number of potential analytes and the wide variety of sample types, there is no one sample preparation technique that could satisfy the requirements of all analysts. Sample preparation may take the form of a direct dilution [24], acid digestion [44], the use of slurries [45], or solid sample analysis, requiring no sample preparation [46], for a wider variety of sample types. Of greater importance than identifying a single sample preparation technique that works for all samples, is the need for a sample preparation technique that works for a given sample and the analytes of interest in that sample, at the needed levels.

In general, unless the analytical method involves direct analysis of solid samples, pharmaceutical samples need to be in solution in order to be analyzed. Historically, analysts in the field of atomic spectroscopy have found it important to perform some form of acid digestion in order to properly prepare samples for elements analyses. When performing acid digestions, it is critical that the acid used to digest the sample not contaminate the sample with metals and/or metalloids. Ultra-high purity acids, with elemental concentrations in the ppb to sub-ppt range, are readily available, and although they are more expensive than poorer quality acids, they are critical to the success of an analysis.

Digestions can be performed in a number of ways: open vessel, closed vessel, microwave assisted (mostly high temperature and high pressure), hot plate. Digestions typically involve the use of an acid, with nitric acid being the most commonly used for atomic spectroscopy applications; however, hydrochloric acid, sulfuric acid, and hydrofluoric acid are also used. Hydrogen peroxide, also available in ultra-high purity, is also often used to aid in digestion of organic-based samples. The selection of the digestion technique and the acid or combination of acids and peroxide is dependent on the nature of the sample matrix, as well as on the analyte(s) in question. Some elements, such as Hg, are volatile under digestion conditions, and open vessel digestions may not be appropriate. Some samples cannot be completely digested without very high temperatures or pressures, so microwave assisted digestion may be required. When hydrogen peroxide is necessary to effect a complete digestion, it should only be added after the sample has been pre-digested with nitric acid, since peroxide may react explosively with organics.

Though acid digestion may sometimes be needed for accurate analysis of samples for elements, it is not always necessary. The easiest sample preparation technique is the direct dilution approach, where samples are dissolved in some solvent and analyzed. In the case of many pharmaceuticals, direct dilution provides a viable alternative to digestion as a means of sample preparation [47]. Regardless of the solvent selected for direct dilution of a sample, all analytical solutions – samples, standards and blank – should be matrix matched whenever possible. This will help to minimize matrix effects.

When using direct dilution for the preparation of samples for analysis, analysts must be careful not to introduce potential contaminants via the solvent being used. As water plays prominently in the preparation of sample, standard and blank solutions, the quality of the water is extremely important. Deionized water should have a resistivity of at least 18 MΩ cm (conductivity = 0.056 μS cm^{-1}). In with acids used in acid digestions, the use of the case of acids, ultra-high quality acids containing ppt and sub-ppt concentrations of various elements, are readily available, and efforts should be made to use those, wherever possible. Organic solvents, however, are not generally available with certified low concentrations of metals and metalloids, so care must be taken when selecting an organic solvent for direct dilution of a sample.

4.2. Analytical approaches to elemental analysis

The predominant means to perform metal analyses in pharmaceuticals still involve FAAS, GFAAS, ICP-AES, or ICP-MS. USP Chapter 851, Spectrophotometry and Light Scattering [48], provides analysts with guidance on using atomic absorption in pharmaceutical applications, and some USP methods use flame AA [11].

A variety of pharmaceuticals have been examined for many elements, with analyses including Pb and Cd in commercial pediatric syrups [49] to Mg distribution in tablets [50]. AA based techniques have also been used to provide indirect determinations of pharmaceuticals such as ciprofloxacin, amoxicillin and diclofenac sodium [51]. Despite the availability of more sensitive or more versatile techniques for elements analysis, atomic absorption based methods are still often used in the pharmaceutical industry.

While the industry had already been using these techniques for the analysis of pharmaceuticals for elements [15], with the publication of the General Chapter on Plasma Spectrochemistry, 730, in 2004, the USP further facilitated use of ICP-AES and ICP-MS for elements analyses in the pharmaceutical industry [52].

The publication of proposed USP chapters 232 and 233 in 2010 further spotlighted the applicability of ICP-AES and ICP-MS for the analysis of pharmaceuticals [20,21]. As a result of the publication of 232 and 233, analysts in the pharmaceutical industry are also looking at other techniques that might be used for the analysis of elements. Techniques such as laser-induced breakdown spectroscopy (LIBS) have begun to see greater use in the analysis of pharmaceuticals for elements. Much of the work being done with LIBS in the arena of pharmaceutical analysis centers on the analysis of intact solid samples, with much emphasis on tablet coatings and blend uniformity [53–56], although some preliminary work has been done on liquid samples [57].

Table 3
Sample preparation procedures and techniques for analysis of pharmaceuticals using atomic spectroscopy techniques.

Drug and/or application	Analyte(s)	Technique	Sample Preparation	References
Cleaning validation	Li	ICP-AES	Nitric acid digestion	[13]
ICP-MS screen for heavy metals in pharmaceuticals	14 elements: As, Sb, Sn, Cd, Pt, Pd, Pb, Hg, Ru, Mo, Se, Bi, In, Ag	ICP-MS	Direct dilution in 25% 2-butoxyethanol/water solution	[14]
ICP-MS survey for heavy metals in pharmaceuticals	69 elements: Li, Be, B, Na, Mg, Al, Si, P, K, Ca, Sc, Ti, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, Ga, Ge, As, Se, Rb, Sr, Y, Zn, Nb, Mo, Ru, Rh, Pd, Ag, Cd, In, Sn, Sb, Te, Cs, Ba, La, Ce, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, Lu, Hf, Ta, W, Re, Os, Ir, Pt, Au, Hg, Tl, Pb, Bi, Th, U	ICP-MS	Direct dilution in either 1% or 80% nitric acid/water solution	[15]
Fosinopril sodium	Pd	ICP-MS	Direct dilution in 25% 2-butoxyethanol/water solution	[17]
Two API's and two intermediates	W	ICP-MS, ICP-AES	80% nitric acid, direct dilution	[24]
P-containing and F and Cl-containing tablets	P, F, Cl	LA-ICP-MS	None – solid sample	[27]
Cannabis fingerprinting	Various	LA-ICP-MS	None – solid sample	[28]
Cleaning validations (rinse water)	Pt	GFAAS	Extracted sample with methylene chloride and acetonitrile	[36]
Heroin fingerprinting	Li, Be, B, Na, Mg, Al, Si, P, S, Cl, K, Ca, Sc, Ti, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, Ga, Ge, As, Se, Br, Rb, Sr, Y, Zr, Nb, Mo, Ru, Rh, Pd, Ag, Cd, In, Sn, Sb, Te, I, Cs, Ba, La, Ce, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, Lu, Hf, Ta, W, Fe, Os, Ir, Pt, Au, Hg, Tl, Pb, Bi, Th, U	ICP-MS	Direct dilution in 3% nitric acid	[37]
High throughput: adsorbent screening kit for metals removal; possible Cr contamination in filled pharmaceutical product; comparison of autosamplers	Pd, Cr, Rh	Flow injection ICP-MS	Ethanol and also digestion verification – 80% nitric acid; 1% nitric acid; acetonitrile	[38]
Intermediates	Rh	HPLC with ICP-MS and ESI	Trifluoroacetic acid, methanol, acetonitrile	[39]
Large volume parenterals (LVP) and injection bag	Al	ICP-MS	Method of standard addition in 1% nitric acid for LVP; microwave digestion with nitric acid for the injection bags	[41]
Five counterfeit and four genuine packaging samples	Ca, Pb	LA-MC-ICP-MS	None – solid samples	[42]
Extractables, leachables in packaging materials, containers, formulated products: Type 1 glass vials; high-density polyethylene (HDPE) bottles, polyester bottles, polycarbonate bottles, rubber lyophilization stoppers	Ag, Al, As, Au, B, Ba, Be, Bi, Ca, Cd, Ce, Co, Cr, Cu, Fy, Er, Eu, Fe, Ga, Gd, Ge, Hf, Ho, In, Ir, K, La, Li, Lu, Mg, Mn, Mo, Na, Nb, Nd, Ni, P, Pb, Pd, Pr, Pt, Re, Rh, Ru, Sb, Sc, Se, Si, Sm, Sn, Sr, Ta, Tb, Th, Ti, Tl, Tm, U, V, W, Y, Yb, Zn, Zr	ICP-MS and ICP-AES	Acid digestion for ICP-AES: 10% nitric acid Acid digestion for ICP-MS: 2% nitric acid Open and closed vessel digestions: Single acid digestion: nitric acid 2-acid digestion: nitric acid and sulfuric acid 2-acid digestion: nitric acid and hydrofluoric acid 3-acid digestion: nitric acid, sulfuric acid and perchloric acid	[43]
Antibiotics: Klarithromycin, Cefadroxil, Cefaclor and Amoxicillin drug products	Ag, Al, As, Ba, Be, Bi, Ca, Cd, Co, Cr, Cu, Fe, Ga, In, Mg, Mn, Ni, Pb, Pd, Se, Zn	ICP-AES	Slurries: 0.5 M nitric acid, 0.5% (v/v) Triton	[44]
Tablets	Ca, Ti, Si, Mg	LIBS	None – solid samples	[45]
API's and Intermediates	Pd	GFAAS	70% nitric acid – direct dilution	[46]
Pediatric syrups (50 different syrups)	Pb, Cd	FAAS	Ashed, followed by acid digestion with aqua regia	[48]
Tablets (4 drug products) and magnesium stearate	Mg	FAAS	Extracted with 0.1 M nitric acid	[49]
Ciprofloxacin, Amoxicillin, Diclofenac Sodium –indirect analyses	Fe	FAAS	Added ferric sulfate, heated, cooled, added 12 M hydrochloric acid, extracted with diethyl ether	[50]
Tablets: macro and micronutrients	Ca, Cu, Fe, Mg, Mn, P, Zn	LIBS	Tablets ground and pelletized	[52]
Tablet film coating	Fe, Ti	LIBS	Tablets pressed and coated	[53]
Tablets and magnesium stearate	Mg	LIBS	None – solid samples	[54]

Table 3 (*Continued*)

Drug and/or application	Analyte(s)	Technique	Sample Preparation	References
Tablets, magnesium stearate in API's and solid dosage forms; Blend uniformity	Mg	LIBS	None – solid samples	[55]
Sodium chloride solutions, isotonic solution	Na	LIBS	Analysis of bulk material; analysis of flowing surface; analysis of non-flowing surface – no sample preparation	[56]
Four API's	Pd	GFAAS	2% nitric acid, DMSO, acetonitrile:phosphoric acid (0.1%) (1:1); Verified results using microwave digestion	[57]
Sugars; sorbitol, mannitol, paracetamol, amidopyrine, chloral hydrate	Co, Cd, Ni, Pb, Cr (III), Cr (VI)	FI-IDAEC/ GFAAS (and TXRF)	Dissolved in 20% (v/v) methanol/water, preconcentration with IDEAC in NH_4-form	[62]
Infusion solutions, heparins, plasma replacement solutions, Transylol 50000, Dobutrex, Dopamin, Arterenol, Zinadef, Disoprivan 1%, Sostril, Lasix 20, Albumins	V	GFAAS	Aliquots lyophilized, acid digested at high pressure, complexed V with cupferron at pH 2, extracted 3×, evaporated the organic layer, dissolved residues in formic acid	[63]
Organic pharmaceutical compounds: iodine-containing compounds, Gadolinium metal complex, Iohexal, Iodixanol	I, Gd	LC–ICP-MS	For Gd metal complexes: glacial acetic acid, tiethylamine (adjusted to pH 6.5–7.0 with 1 M acetic acid); for I-containing compounds: solvent A: acetonitrile, solvent B: 100% water with 1% formic acid; initial conditions of 98%A/2%B for 10 min then 50%A/50%B after 15 min	[64]
Dry yeast used in pharmaceutical formulations	Fe, Zn, Ca, Mg, Na, K	FAAS for Fe, Zn, Ca, Mg; ICP-AES for Na, K	Seven different digestion procedures	[65]
Enalapril Maleate	Pd	GFAAS	Solid sampling	[66]
Levothyroxine (and degradation products)	I	HPLC–UV–ICP-MS	Tablets powdered and dissolved in water, filtered through 0.45 μm membrane filters	[67]
Methamphetamine (impurities)	Na, Pd, Ba, I, Br, Mg, Al, Si, Cl, Ca, Sc, Ti, V, Cr, Zn, Sr, Pb, Cu, Ag, Sn	ICP-MS (and IC)	Direct dilution in water (0.1% solution)	[68]
Cimetidine	S	ST-ICP-MS	Dissolved in 0.05 M ammonium acetate (adjusted to pH 5 with acetic acid and methanol 70:30) and sonicated	[69]
Neusilin (10% and 20%) tablets	Al, Mg	LA-ICP-MS and LA-ICP-AES	None – solid sample	[70]
Meglumine sulfate	Sb	FAAS	Hydride generation; Samples diluted 1:2,500,000 with 1 M HCl and treated with 5% (m/v) KI for Sb (V) reduction	[71]
Atropine, diphenhydramine, tolazoline, levamisole	Indirect determination using Hg	FAAS	Added tetraiodomercurate	[72]
Enalapril maleate, calcium folinate, levodopa	Pd, Pt, Rh (others cited: Be, V, Mn, Co, Ni, Cu, Zn, Mo, Cd, Sn, Tl, Pb)	ICP-MS and GFAAS	Calcium folinate and levodopa: dissolved in 0.2 M nitric acid; enalapril maleate dissolved in 1:1 nitric acid and diluted to 0.3 M.	[73]
Metals leached from pharmaceutical packaging materials: type 1 glass, amber glass, SiO_2-coated glass, PET, LDPE and HDPE; liquid formulation components: USP water, polysorbate 80, EDTA and 10 mM buffer (pH 6.8)	Mg, Ca, Mn, Al, Cr, Cu, Fe, Cd, Pb, V, Co, Ni, Zn	ICP-OES	Glass vials (all types) and PET bottles: 40 °C or 60 °C with 10 ml extracting solution; LDPE and HDPE: 1.0 cm × 2.5 cm strip cut and placed into clear type I glass vial, sealed and heated to 40 °C or 60 °C with 10 ml extracting solution	[74]

4.3. Method validation considerations

Selection of the analytical technique depends heavily on the nature of the sample matrix, the analytical instrumentation available in a laboratory, the amount of sample material available, the desired analyte(s) and the desired method sensitivity. The availability of a variety of analytical techniques and instrumentation, as well as the variety of possible sample preparation techniques and sample types makes choosing the right analytical approach critical for method development and validation. Improper sample preparation cannot be offset by a versatile analytical technique, and analytical instrumentation may be limited within a given laboratory. In some cases, only an acid digestion will provide adequate results, and if direct dilution is used instead, it is important to verify that accurate results have been obtained [58].

Determining what constitutes acceptable levels of elements in a pharmaceutical sample depends not only on the toxicity of the metal, but also on product quality – both esthetic and practical. Even trace amounts of iron, for example, may alter the color of an API. With the increased interest in large molecule pharmaceuticals, the importance of elements to protein and enzyme [59] activity and stability will result in increased elements analysis in biologics products.

During method validation for trace levels of elements, it is important to follow the requirements of the International Conference on Harmonisation (ICH) [60,61] and the USP [62]. Among the key points to include in method validation is method sensitivity, which must be satisfactorily demonstrated. Where the analyte(s) in question may be present at higher concentrations, the sensitivity of the method is not normally an issue, however the accuracy, precision and robustness are still of great importance.

Of special importance, whether working at trace levels or higher concentrations, is the demonstration of the lack of spectral interferences, which could lead to erroneous results. In addition, it is also important to demonstrate adequate recovery of analytes. The method of standard additions may be employed to demonstrate the accuracy of a method, as well as the adequacy of spike recoveries [41]. Additionally, the precision of the method must also be demonstrated, with the determination of the relative standard deviation (RSD). Robustness should be demonstrated as well, with multi-

ple day, multiple analyst and/or multiple instrument verification of results.

5. Conclusion

The need for the analysis of elements in pharmaceuticals is becoming increasingly more important, both from product quality and patient safety perspectives. The analytical challenges associated with sample matrix make the selection of sample preparation key to the success of an analysis. The variety of instrumental techniques available, ranging from the more mature techniques of flame and graphite furnace AA to newer technologies, such as ICP-MS, makes it possible to monitor all elements at concentrations ranging from sub-ppb's to percents. In the future, it seems more likely that acceptable limits for elements in pharmaceuticals will be reduced, rather than increased, thereby leading to the conclusion that more sensitive techniques, such as ICP-MS, will begin to play a greater role in the analysis of elements in pharmaceuticals. In addition, solid sampling techniques will play an important role in the future of elements analysis in pharmaceuticals. The versatility of the various techniques available to the analyst makes it possible to meet the challenges of difficult sample matrices and low limits of detection to address both product safety and product quality issues.

References

[1] J.M.S. Pearce, Burton's line in lead poisoning, Eur. Neurol. 57 (2007) 118–119.
[2] H.L. Zhao, X. Zhu, Y. Sui, Letters to the Editor: The short-lived Chinese emperors, J. Am. Geriatric. Soc. 54 (2006) 1295–1296.
[3] Pharmacopoeia of the United States of America, Procedure 121, Time-limit test for heavy elements, 8th revision, Lippincott, Philadelphia, PA, 1905.
[4] The United States Pharmacopeia/The National Formulary, USP 32/NF 27, The United States Pharmacopeial Convention, Rockville, MD, 2009. Chapter 231, Heavy Elements, pp. 134–136.
[5] D. Abernethy, A. DeStefano, T. Cecil, K. Zaidi, R. Williams, the USP Metal Impurities Advisory Panel. Metal Impurities in Food and Drugs, Pharm. Res. 27 (2010) 750–755.
[6] The United States Pharmacopeia/The National Formulary, USP 32/NF 27, The United States Pharmacopeial Convention, Rockville, MD, 2009. Chapter 241, Iron, pp. 2557–2558.
[7] The United States Pharmacopeia/The National Formulary, USP 32/NF 27, The United States Pharmacopeial Convention, Rockville, MD, 2009, Chapter 251, Lead, pp. 2558–2559.
[8] The United States Pharmacopeia/The National Formulary, USP 32/NF 27, The United States Pharmacopeial Convention, Rockville, MD, Chapter 261, Mercury, 2009, pp. 2558–2560.
[9] The United States Pharmacopeia/The National Formulary, USP 32/NF 27, The United States Pharmacopeial Convention, Rockville, MD, Chapter 291, Selenium, 2009, pp. 2560–2561.
[10] The United States Pharmacopeia/The National Formulary, USP 32/NF 27, The United States Pharmacopeial Convention, Rockville, MD, Chapter 591, Zinc, 2009, p. 2616.
[11] The United States Pharmacopeia/The National Formulary, USP 32/NF 27. The United States Pharmacopeial Convention, Rockville, MD, 2009. Chapter 206, Aluminum, pp. 2554–2555.
[12] The United States Pharmacopeia/The National Formulary, USP 32/NF 27. The United States Pharmacopeial Convention, Rockville, MD, 2009, Chapter 191, Identification Tests–General, pp. 2550–2551.
[13] N. Lewen, D. Nugent, The use of inductively coupled plasma-atomic emission spectroscopy (ICP-AES) in the determination of lithium in cleaning validation swabs, J. Pharm. Biomed. Anal. 52 (2010) 652–655.
[14] N. Lewen, S. Mathew, M. Schenkenberger, T. Raglione, A rapid ICP-MS screen for heavy elements in pharmaceutical compounds, J. Pharm. Biomed. Anal. 35 (2004) 739–752.
[15] T. Wang, J. Wu, R. Hartman, X. Jia, R. Eagan, A multi-element ICP-MS survey method as an alternative to the heavy elements limit test for pharmaceutical materials, J. Pharm. Biomed. Anal. 23 (2000) 867–890.
[16] N. Lewen, The application of several atomic spectroscopy techniques in a pharmaceutical analytical research and development laboratory, Spectroscopy 12 (1997) 14–23.
[17] N. Lewen, M. Schenkenberger, T. Larkin, S. Conder, H. Brittain, The determination of palladium in fosinopril sodium (monopril) by ICP-MS, J. Pharm. Biomed. Anal. 13 (1995) 879–883.
[18] J. Duffus, Heavy metals—a meaningless term? Pure Appl. Chem. 74 (2002) 793–807.
[19] European Medicines Agency, Doc. Ref. EMEA/CHMP/SWP/4446/2000, London, 21 February 2008.
[20] USP, Elemental impurities—limits 232, Pharm. Forum 36 (2010) 197–200.
[21] USP, Elemental impurities—procedures, Pharm. Forum 36 (2010) 201–207.
[22] USP, Elemental impurities—information, Pharm. Forum 36 (2010) 298–305.
[23] D. Beauchemin, Inductively Coupled Plasma Mass Spectrometry, Anal. Chem. 78 (2006) 4111–413524.
[24] T. Wang, Z. Ge, J. Wu, B. Li, A. Liang, Determination of tungsten in bulk drug substance and intermediates by ICP-AES and ICP-MS, J. Pharm. Biomed. Anal. 19 (1999) 937–943.
[25] J. Huang, X. Hu, J. Zhang, K. Li, Y. Yan, X. Xu, The application of inductively coupled plasma mass spectrometry in pharmaceutical and biomedical analysis, J. Pharm. Biomed. Anal. 40 (2006) 227–234.
[26] R. Rao, M.V.N. Kumar Talluri, An overview of recent applications of inductively coupled plasma-mass spectrometry (ICP-MS) in determination of inorganic impurities in drugs and pharmaceuticals, J. Pharm. Biomed. Anal. 45 (2007) 1–13.
[27] L. St-Onge, E. Kwong, M. Sabsabi, E.B. Vadas, Quantitative analysis of pharmaceutical products by laser-induced breakdown spectroscopy, Spectrochim. Acta B 57 (2002) 1131–1140.
[28] R.J. Watling, Sourcing the provenance of cannabis crops using inter-element association patterns "fingerprinting" and laser ablation inductively coupled plasma mass spectrometry, J. Anal. At. Spectrom. 13 (1998) 917–926.
[29] H.H. Willard, L.L. Merritt Jr., J.A. Dean, Instrumental Methods of Analysis, 5th edition, D. Van Nostrand Company, New York, 1974, p. 354.
[30] W. Slavin, Graphite Furnace AAS A Source Book, The Perkin-Elmer Corporation, Norwalk, CT, 1984, pp. 1–6.
[31] M. Wassall, Improving background correction capabilities in GFAAS, American Laboratory, February, 1994, 48JJJ–48MMM.
[32] A.R. Date, A.L. Gray, Applications of Inductively Coupled Plasma Mass Spectrometry, Chapman and Hall, New York, 1989.
[33] T.L. Thiem, Comparison of Optical Emission/Mass Spectroscopy Utilizing Laser Vaporization of Solid Samples for Inorganic Analysis, American Laboratory, February 1994, pp. 48CCC–48HHH.
[34] C. Torborg, M. Beller, Recent Applications of Palladium-Catalyzed Coupling Reactions in the Pharmaceutical, Agrochemical, and Fine Chemicals Industries, Adv. Synth. Catal. 351 (2009) 3027–3043.
[35] W.H. Jones, Platinum, Palladium in the pharmaceutical industry, Platinum Metals Rev. 2 (1958) 86–89.
[36] R. Raghavan, J.A. Mulligan, Low-level (ppb) determination of cisplatin in cleaning validations (rinse water) samples. I. An atomic absorption spectrophotometric method, Drug Dev. Ind. Pharm. 26 (2000) 423–428.
[37] R. Myors, R.J. Wells, S.V. Skopec, P. Crisp, R. Iavetz, Z. Skopec, A. Ekangaki, J. Robertson, Preliminary investigation of heroin fingerprinting using trace elemental concentrations, Anal. Commun. 35 (1998) 403–410.
[38] Q. Tu, T. Wang, C. 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.
[39] C. Welch, Q. Tu, T. Wang, C. Raab, P. Wang, X. Jia, X. Bu, D. Bykowski, B. Hohenstaufen, M. Doyle, Observations of rhodium-containing reaction intermediates using HPLC with ICP-MS and ESI–MS detection, Adv. Synth. Catal. 248 (2006) 821–825.
[40] V. Vergote, C. Burvenich, C. Van de Wiele, B. De Spiegeleer, Quality specifications for peptide drugs: a regulatory-pharmaceutical approach, J. Pept. Sci. 15 (2009) 697–710.
[41] K. Harigaya, Y. Kuwahara, H. Nishi, Determination of aluminum in large volume parenteral drug products used in total parenteral nutrition therapy by ICP-MS with a dynamic reaction cell, Chem. Pharm. Bull. 56 (2008) 475–479.
[42] R. Santamaria-Fernandez, J.-C. Wolff, Application of laser ablation multicollector inductively coupled plasma mass spectrometry for the measurement of calcium and lead isotope ratios in packaging for discriminatory purposes, Rapid Commun. Mass Spectrom 24 (2010) 1993–1999.
[43] D.J. Zuccarello, M.P. Murphy, R.F. Meyer, P.A. Winslow, A comprehensive approach for the determination of extractable and leachable elements in pharmaceutical products by inductively coupled plasma, PDA J. Pharm. Sci. Tech. 63 (2009) 339–352.
[44] G.A. Zachariadis, C.E. Michos, Development of a slurry introduction method for multi-element analysis of antibiotics by inductively coupled plasma atomic emission spectrometry using various types of spray chamber and nebulizer configurations, J. Pharm. Biomed. Anal. 43 (2007) 951–958.
[45] M.D. Mowery, R. Sing, J. Kirsch, A. Razaghi, S. Béchard, R.A. Reed, Rapid at-line analysis of coating thickness and uniformity on tablets using laser induced breakdown spectroscopy, J. Pharm. Biomed. Anal. 28 (2002) 935–943.
[46] T. Wang, S. Walden, R. Egan, Development and validation of a general nondigestive 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.
[47] The United States Pharmacopeia/The National Formulary, USP 32/NF 27. Chapter 851, Spectrophotometry and Light Scattering. The United States Pharmacopeial Convention, Rockville, MD, 2010, pp. 373–378.
[48] O.E. Orisakwe, J.K. Nduka, Lead and cadmium levels of commonly administered pediatric syrups in Nigera: a public health concern? Sci. Total Environ. 47 (2009) 5993–5996.
[49] K. Sugisawa, T. Kaneko, T. Sago, T. Sato, Rapid quantitative analysis of magnesium stearate in pharmaceutical powders and solid dosage forms by atomic absorption: method development and application in product manufacturing, J. Pharm. Biomed. Anal. 49 (2009) 858–861.
[50] M.M. Issa, R.M. Nejem, M. Al-Kholy, N.S. El-Abadla, R.S. Helles, A.A. Saleh, An indirect atomic absorption spectrometric determination of ciprofloxacin,

amoxicillin and diclofenac sodium in pharmaceutical formulations, J. Serbe. Chem. Soc. 75 (2008) 569–576.
[51] The United States Pharmacopeia/The National Formulary, USP 32/NF 27. The United States Pharmacopeial Convention, Rockville, MD, 2010. Chapter 730, General Chapter on Plasma Spectrochemistry, pp. 285–290.
[52] G.G. Arantes De Carvalho, L.C. Nunes, P. Florencio De Souza, F.J. Krug, T. Correia Alegre, D. Santos Jr., Evaluation of laser induced breakdown spectroscopy for the determination of macro and micronutrients in pharmaceutical tablets, J. Anal. Atom. Spectrom. 25 (2010) 803–809.
[53] M.C. Madamba, W.M. Mullett, S. Debnath, E. Kwong, Characterization of tablet film coatings using a laser-induced breakdown spectroscopic technique, AAPS Pharm. Sci. Tech. 8 (2007), Article No. 103.
[54] L. St.-Onge, J.-F. Archambault, E. Kwong, M. Sabsabi, E.B. Vadas, Rapid quantitative analysis of magnesium stearate in tablets using laser-induced breakdown spectroscopy, J. Pharm. Pharm. Sci. 8 (2005) 272–288.
[55] R.L. Green, M.D. Mowery, J.A. Good, J.P. Higgins, S.M. Arrivo, K. McColough, A. Mateos, R.A. Reed, Comparison of near-infrared and laser-induced breakdown spectroscopy for determination of magnesium stearate in pharmaceutical powders and solid dosage forms, Appl. Spectrosc. 59 (2005) 340–357.
[56] L. St.-Onge, E. Kwong, M. Sabsabi, E.B. Vadas, Rapid analysis of liquid formulations containing sodium chloride using laser-induced breakdown spectroscopy, J. Pharm. Biomed. Anal. 36 (2004) 277–284.
[57] X. Jia, T. Wang, J. Wu, Determination of palladium by graphite furnace atomic absorption spectroscopy without matrix matching, Talanta 54 (2001) 741–751.
[58] P. Wilton, Proteins prove their metal, Physorg.com, July 7, 2010, http://www.physorg.com/news197728929.html.
[59] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline: Validation of Analytical Procedures: Text and Methodology Q2(R1), November 2005, Geneva, Switzerland.
[60] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline: Impurities in New Drug Substances Q3A(R2), October, 2006, Geneva, Switzerland.
[61] The United States Pharmacopeia/The National Formulary, USP 32/NF 27, The United States Pharmacopeial Convention, Rockville, MD, 2009. Chapter 1225, Validation of Compendial Procedures, pp. 733–736.
[62] A. Kelkó-Lévai, I. Varga, K. Zih-Perényi, A. Lászity, 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 Part B 54 (1999) 827–833.
[63] G. Heinemann, W. Vogt, Vanadium-Contaminated Perioperatively Administered Infusion Solutions and Drugs, Biol. Trace Element Res. 75 (2000) 227–234.
[64] B-O. Axelsson, M. Jörnten-Karlsson, P. Michelsen, F. Abou-Shakra, The potential of inductively coupled plasma mass spectrometry detection for high-performance liquid chromatography combined with accurate mass measurement of organic pharmaceutical compounds, Rapid Commun. Mass Spectrom. 15 (2001) 375–385.
[65] G. Zachariadis, E.S. Raidou, D.G. Themelis, J.A. Stratis, Determination of mineral content of active dry yeast used in pharmaceutical formulations, J. Pharm. Biomed. Anal. 28 (2002) 463–473.
[66] M. Resano, E. Garcia-Ruiz, C. Crespo, F. Vanhaecke, M.A. Belarra, Solid sampling-graphite furnace atomic absorption spectrometry for palladium determination at trace and ultratrace levels, J. Anal. Atom. Spectrom. 18 (2003) 1477–1484.
[67] S.S. Kannamkumarath, R.G. Wuilloud, A. Stalcup, J.A. Caruso, H. Patel, A. Sakr, Determination of levothyroxine and its degradation products in pharmaceutical tablets by HPLC–UV–ICP-MS, J. Anal. Atom. Spectrom. 19 (2004) 107–113.
[68] S. Suzuki, H. Tsuchihashi, K. Nkajima, A. Matshushita, T. Nagao, Analysis of impurities in methamphetamine by inductively coupled plasma mass spectrometry and ion chromatography, J. Chromatogr. Sci. 437 (1988) 322–327.
[69] E.H. Evans, J-C. Wolff, C. Eckers, Sulfur-specific detection of impurities in cimetidine drug substance using liquid chromatography coupled to high resolution inductively coupled plasma mass spectrometry and electrospray mass spectrometry, Anal. Chem. 73 (2001) 4722–4728.
[70] R. Lam, E.D. Salin, Analysis of pharmaceutical tablets by laser ablation inductively coupled plasma atomic emission spectrometry and mass spectrometry (LA-ICP-AES and LA-ICP-MS), J. Anal. Atom. Spectrom. 19 (2004) 938–940.
[71] E.C. Figueredo, J. Dědina, M.A.Z. Arruda, Metal furnace heated by flame as hydride atomizer for atomic absorption spectrometry: Sb determination in environmental and pharmaceutical samples, Talanta 73 (2007) 621–628.
[72] M.A. El Ries, S. Khalil, Indirect atomic absorption determination of atropine, diphenhydramine, tolazoline, levamisole based on formation of ion-associates with potassium tetraiodomercurate, J. Pharm. Biomed. Anal. 25 (2001) 3–7.
[73] A. Lásztity, Á. Kelkó-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.
[74] K. Fliszar, D. Walker, L. Allain, Profiling of metal ions leached from pharmaceutical packaging materials, PDA J. Pharm. Sci. Technol. 60 (2006) 337–342.