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Review

An overview of recent applications of inductively coupled plasma-mass spectrometry (ICP-MS) in determination of inorganic impurities in drugs and pharmaceuticals☆

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Abstract

The recent applications of inductively coupled plasma-mass spectrometry (ICP-MS) in determination of trace level inorganic impurities in drugs and pharmaceuticals have been reviewed. ICP-MS coupled with LC, GC and CE was used for speciation of heavy metals in pharmaceutical products. The review covers the period from 1995 to 2005 during which the technique was applied not only for determination of metallic impurities but also the assay of various trace elements in pharmaceuticals.

Keywords: Trace elements; Heavy metals; Impurities; Speciation; Inductively coupled plasma-mass spectrometry (ICP-MS); LC-ICP-MS; Drugs and pharmaceuticals

Contents

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1. Introduction

Safety and efficacy of pharmaceuticals are two fundamental issues of importance in drug therapy. The safety of a drug is determined by its pharmacological–toxicological profile as well as the adverse effects caused by the impurities in bulk and dosage forms. The impurities in drugs often possess unwanted pharmacological–toxicological effects by which any benefit from their administration may be outweighed [1]. Therefore, it is quite obvious that the products intended for human consumption must be characterized as completely as possible. Monitoring and controlling of impurities generally gives assurance of the quality and safety of a drug. Thus the analytical activities concerning impurities in drugs are among the most important issues in modern pharmaceutical analysis [2–5].

1.1. Heavy metals in drugs

The inorganic impurities generally originate from various sources and phases, i.e., raw materials, reagents, solvents, electrodes, catalysts, reaction vessels, plumbing and other equipments used during the synthesis of pharmaceuticals. These are characteristic of the synthetic route of a manufacturing process. Palladium and its compounds are the potential impurities of several drugs and routinely monitored [6]. Determination of residual tungsten in process intermediates and drugs is common as tungsten containing catalysts are used in synthesis of several pharmaceuticals. Monitoring of heavy metals in process intermediates and final drug substances is an important activity in pharmaceutical industry. It is not only because of their ability to catalyze decomposition but also potential for toxicity. Heavy metals like lead and cadmium in pharmaceuticals pose the risk of serious health hazards even at very low doses [7,8]. Longer occupational exposures to lead cause adverse effects on psychological and behavioral activities in living beings. An intake of 0.06 mg of Pb/day for a period of one month is enough for chronic poisoning. It is chronic toxicity causes kidney dysfunction, osteomalacia and obstructive lung diseases. Cadmium is another human carcinogen [9] associated with the risks of serious health hazards. It accumulates in the human body and has a biological half-life of 30 years. The permissible levels of heavy metals in pharmaceuticals are usually defined by the regulatory agencies and controlled by limit tests. These tests ensure that no inorganic-based contaminants are introduced into the drugs at any of the steps during the manufacturing process. European Pharmacopoeia (EP) has proposed a limit of 20 $\mu g\, g^{-1}$ of Pt in calcium folinate [10]. The United States Pharmacopoeia (USP), British Pharmacopoeia (BP), European Pharmacopoeia (EP) and Japanese Pharmacopoeia (JP) propose collective monitoring of total metal content in pharmaceutical products. The methods involve the precipitation of metal sulfides from an aqueous solution and visual comparison of the color to that of a simultaneously and similarly treated standard solution of lead. These methods are non-specific, less sensitive, time-consuming and less accurate. Thus there is a great need for development of highly sensitive and selective techniques for determination trace metals in pharmaceutical substances not only to meet the stringent specifications but also ensure the safety and efficacy of drugs for human consumption. The detrimental effects of some of the heavy metals usually found in medicinal products and the guidelines on specification limits for residues have been described by European Medicines Agency (EMEA) [11].

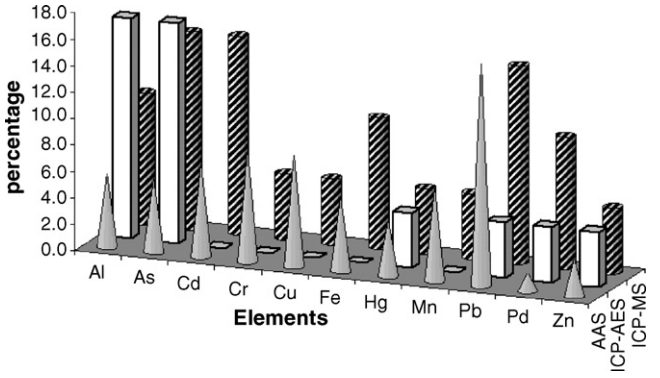

Fig. 1. Usage pattern of atomic spectrometric techniques in detection of trace elements in drugs during 1995–2005.

1.2. Atomic spectrometric techniques

Atomic spectrometric techniques, viz., AAS, ICP-AES and ICP-MS are widely used for analysis of trace elementals [12,13]. AAS is probably the most extensively used technique for determination of metals in different sample matrices [14]. Generally flame-AAS (FAAS) is used when concentration of the analyte is high enough or graphite furnace AAS (GF-AAS) when it is low. Its application to the analysis of impurities is limited due to relatively high detection limits. Highly specific hollow cathode lamps are used for determination of each metal. Inductively coupled plasma-atomic emission spectrometry (ICP-AES) plays a significant role in the analysis of pharmaceuticals [15,16]. It is a multi elemental technique but suffers from complex spectral interferences and accuracy at ultra trace levels. Mass spectrometer coupled with inductively coupled plasma ionization (ICP-MS) is one of the most sensitive analytical techniques for fast multi element determination of heavy metals in trace and ultra trace concentrations in different sample matrices. Recently, it has emerged as a powerful technique and at present, it is the most suitable technique for the analysis of trace elements in bulk drugs and pharmaceuticals. It provides a major service to the pharmaceutical industry in the analysis of heavy metals in drugs. However, the limitations of ICP-MS include high capital investment, non-availability of certified reference standards for most of the pharmaceutical products. Many research papers have dealt with the latest developments in its instrumentation and applications [17–19]. During the period of review, the pattern of elements analyzed by different atomic spectrometric techniques is shown in Fig. 1.

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

Fig. 2 shows a schematic diagram of a quadruple ICP-MS instrument with pneumatic sample introduction system.

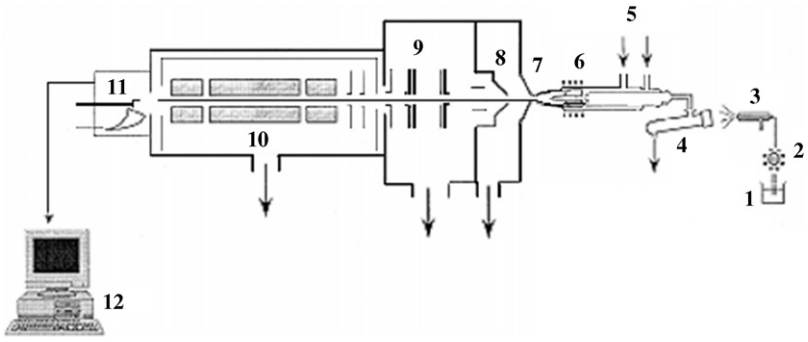

Fig. 2. Schematic diagram of inductively coupled plasma-mass spectrometer: (1) liquid sample, (2) pump, (3) nebulizer, (4) spray chamber, (5) argon gas torch inlets, (6) torch, (7) sampler cone, (8) skimmer cone, (9) ion lenses, (10) quadrupole mass analyzer, (11) electron multiplier detector, and (12) data collection. Reproduced from Ref. [19] with permission.

The plasma is usually produced in argon at atmospheric pressure, sustained by a high frequency (30 MHz) energy field of 1000–2000 W. The temperature in the plasma ranges from 6 to 10×10^3 K, suitable for atom excitation and ionization of elemental species [20]. The quartz torch consists of three concentric tubes into which different argon flows are introduced. When samples are introduced into the plasma, they go through desolvation, vaporization, atomization and ionization before entering the mass analyzer. There are many methods for introducing solid, liquid or gaseous samples into the plasma. Conventional pneumatic nebulization is the most common way for liquids. The ions emerging from the ICP are extracted into the low-pressure mass spectrometer interface through the sampling and skimmer cones usually made of nickel. The ions are then focused on to the mass analyzer using a series of ion lenses. The positively charged ions are then separated according to their mass to charge ratio. The ions are typically detected by an electron multiplier and amplified. The quadrupole has been the most widely used mass analyzer in ICP-MS. To achieve higher resolutions and thereby reduce isobaric interferences, e.g., $^{40}Ar^{35}Cl^+$ interference with $^{75}As^+$, double focusing sector field mass analyzers are used. The time-of-flight (TOF) mass analyzer has a great potential for speciation analysis. The introduction of samples in to the source of ICP at atmospheric pressure makes it possible of coupling separation techniques to ICP-MS. High resolution mass analyzers reduce the appearance of the isobaric overlap, or to move the ion of interest to a different *m*/*z* via chemical reactions [21]. The percentage of different elements analyzed by ICP-MS during 1995–2005 is shown in Fig. 3.

2.1. Sample preparation

The samples are generally prepared by simple dissolution and digestion in dilute acids [22]. Microwave digestion has clear advantages over the traditional acid digestion in terms of better recovery of volatile elements, lower contamination, minimal volumes of reagents, more reproducible procedures and a better working environment. However in pharmaceutical analysis, the acid dissolution as well as microwave digestion methods are more appropriate due to volatility of some of the metals in digestion and need for ultra trace detection limits. Solid samples can also be analyzed using laser ablation technique [23]. A number of excellent reports cover these topics in more detail [24–26]. Some of the sample preparation methods are summarized in Table 1.

2.2. Detection limits

ICP-MS offers extremely low detection limits ranging from sub part per billion (ppb) to trillion (ppt) for most elements. It has a rapid multi-element scanning capability over a wide range of masses with lower detection limits compared to GF-AAS and ICP-AES. In most of the cases, the detection limits are 100–1000 times superior to those achieved by ICP-AES. These detection limits are broadly achieved for almost all the elements across the periodic table. Also, the simple nature of the mass spectra of the elements makes it a quick tool for automated qualitative and quantitative analysis. Detection limits generally depend on the element, sample matrix, preparation, and the instrumental conditions used for analysis. The detection limits in ICP-MS particularly for elements which occur abundantly in nature, are often determined by blank values.

Recently, Haung et al. have reviewed some of the applications of ICP-MS in pharmaceutical and biomedical analysis

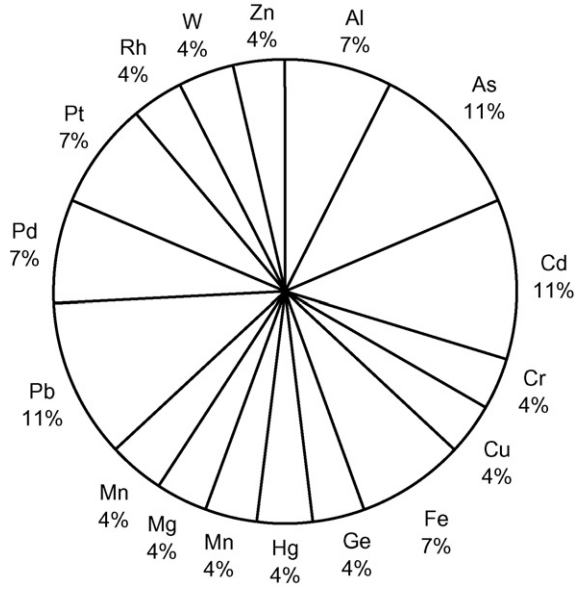

Fig. 3. Individual elements analyzed by ICP-MS during 1995–2005.

Table 1
Sample preparation procedures for analysis of trace elements by ICP-MS

Element	Bulk drug/formulation	Procedure	Medium	Calibration[a]	Reference
W	Bulk drugs	Dissolution	80:20 (v/v) HNO_3	EC with ^{209}Bi for IS	[34]
Fe	Methotrexate	Microwave-assisted, vapor-phase digestion	$H_2SO_4 + HNO_3$	EC with ^{56}Fe	[30]
Pd, Pt, Rh	Enalapril maleate, calcium folinate, levodopa	Dissolution, Dissolution, Dissolution	1:1 HNO_3, 0.3 M, 0.2 M HNO_3, 0.2 M HNO_3	EC with In for IS	[36]
Pd	Fosinopril sodium	Dissolution	25% (v/v) 2-butoxy ethanol and water	EC with In for IS	[35]
69 elements	Drug substances intermediates and raw materials	Dissolution, sonication	1 or 80% (v/v) HNO_3	EC	[38]
Cr, Ni, Sn, Pb	Vitamin E	Microwave digestion, emulsion preparation	$HNO_3 + H_2O_2$, Triton X + tetralin	EC, Y, In and Tl for IS	[39]
Na, Br, Pd, Ba, I	Methamphetamine HCl	Dissolution	H_2O	EC	[40]
As, Se, Mo, Ru, Pd, Cd, In, Sn, Sb, Pt, Hg, Bi, Ag	API with various functionalities	Dissolution	2-Butoxy ethanol/water (25:75 v/v)	EC with Co, Au and Rh for IS	[41]
Cr and Cu, Mg, Mn, Mo, P, Se, Zn	Multimineral, and multivitamin	Microwave digestion	HNO_3	EC with Co for IS	[42]
Li, B, V, Cr, Mn, Ni, Cu, Zn, Br, Sr, Sn, Ba, Pt and Pb	Ecstasy tablets	Dissolution	1% (v/v) HNO_3	EC with Rh for IS	[44]
Ti, Cr, Mn, Fe, Co, Ni, Cu, Zn, Cd, Hg, Pb	Dicyclomine HCL, ethambutol, pyrazinamide, furazolidone	Dissolution and digestion	5% (v/v) HNO_3 $HNO_3 + H_2O_2 + H_2O$	EC	[45]
As, Cd, Hg, Pb	Dietary supplements	Microwave digestion	HNO_3	EC with Rh, In, Lu, Bi for IS	[46]

[a] EC: external calibration; IS: internal standardization.

[27]. It was mainly focused on the introduction of ICP-MS in biomedical analysis including DNA, proteins, metabolites, biopharmaceuticals and traditional Chinese medicine. However, the determination of trace metals as impurities and their speciation in bulk drugs and formulations was not discussed. Considering the importance of evaluation of inorganic impurities in quality control and assurance of bulk drugs and their formulations for regulatory purposes, the present manuscript reviews in detail some the very recent and important applications of LC, GC, CE and IC coupled with ICP-MS for speciation of metals, as well as the individual metal content in drugs and pharmaceuticals published during the period 1995–2005.

3. Trace elements in drugs and pharmaceuticals

Several ICP-MS procedures have been reported for determination of single and multielements in drugs and pharmaceuticals. Table 2 records some of the details of ICP-MS procedures described in the literature during the period of review.

3.1. Determination of single elements

Krone et al. [28] have used ICP-MS to detect Cd in several of the Zn supplements. Supplements in the form of gluconate contained lowest amount of Cd. Bourgoin et al. [29] have determined Cd and Pb in calcium supplements using ICP-MS, FAAS, ETAAS and anodic stripping voltammetry. Niemela et al. [30], have quantified iron and palladium in bulk drugs of methotrexate by GF-AAS, direct current plasma optical emission spectrometry and compared the results with those obtained by ICP-MS. Here the hexapole collision cell was used before the quadrupole mass analyzer to eliminate polyatomic interference of $^{40}Ar^{16}O$ with ^{56}Fe. Microwave-assisted vapor-phase digestion was used to reduce contamination and improve efficiency of digestion and NIST 8433 (corn bran) as a reference standard. The use of ICP-MS for determination of lead and its isotope ratios in calcium supplements was reported [31]. Samples were digested in nitric acid at 230 °C and 1770 psi pressure. Matrices matching with the standard solutions of lead were prepared using high purity calcium carbonate. Calibration was carried out in the range of 10–200 ng ml^{-1} of Pb with 40 mg ml^{-1} Re as an internal standard. NIST (981) lead isotope standard wire was used and the results were compared with ICP-AES. Different methods based on ICP-MS were proposed for determination of lead in antacids and calcium drug supplements for compliance of California proposition 65 [32,33]. Wang et al. [34] have determined tungsten in bulk drug substances and their intermediates. The matrix effects were minimized by studying the recovery of spiked samples. The spectral interferences were monitored with the help of different isotopes. The method was linear from

Table 2
Determination of single and multi elements in drugs and pharmaceuticals

Drug/formulation	Elements	MDL	Detector	Reference
Dicyclomine HCl, ethambutol, pyrazinamide, furazolidone	Ti, Cr, Mn, Fe, Co, Ni, Cu, Zn, Cd, Hg, Pb	Not reported	Varian Ultra Mass 700	[45]
Neusilin	Al, Mg	40 and 6 $\mu g\,g^{-1}$	Laser ablation system: CETAC LSX-100, Perkin-Elmer SCIEX, ELAN 6000 ICP-MS	[37]
Drug substances, intermediates and raw materials	69 elements	0.004–19 ppm	Elan 600 ICP-MS 1300 W rf, Cross, flow nebulizer, Scott spray chamber	[38]
Vitamin E	Cr, Ni, Sn and Pb	3.02, 0.22, 2.91, 0.07 ppb (emulsion), 0.13, 0.05, 0.70, 0.08 ppb (15% HNO_3)	Agilent7500 ICP-MS, 1100 W rf, Meinhard nebulizer	[39]
Methamphetamine hydrochloride	Na, Br, Pd, Ba, I	Not reported	Seiko ICP-MS SPQ-6100, 1.35 kW quadrupole	[40]
Fosinopril sodium (Monopril)	Pd	0.1 $\mu g\,g^{-1}$	Plasma Quad PQ 11 Turbo plus ICP-MS Jacketed Scott type spray chamber, cooled to 5 °C, platinum sample cone	[35]
Enalapril maleate, calcium folinate, levodopa	Pd, Pt, Rh	15, 2.8, 2.5 ng g^{-1}	Plasma Quad II STE Peristaltic pump:spay chamber: double-pass, water cooled (10 °C)	[36]
API	As, Se, Mo, Ru, Pd, Cd, In, Sn, Sb, Pt, Hg, Bi, Ag	0.37, 0.42, 0.08, 0.2, 0.18.0.03, 0.17, 0.35, 0.16, 0.03, 1.82, 1.51, 0.15 $\mu g\,g^{-1}$	VG Plasma Quad PQ II Turbo Plus, ICP-MS and Micro mass platform ICP-MS	[41]
Multivitamin	Cr and Cu, Mg, Mn, Mo, P, Se, Zn	48.3 and 47.1, 24.3, 9.0, 43.2, 750, 24, 109 ng l^{-1}	VG Plasma Quad 3 ICP-MS, 1380 W	[42]
Methotrexate	Fe	0.2 $\mu g\,g^{-1}$	Thermo elemental ICP-MS with collision, cell technology	[30]
Bulk drug substances	W	0.04 ppm	Perkin-Elmer Elan 6000 ICP-MS, AS-91 auto sampler 1300 rf	[34]
Ecstasy tablets	Li, B, V, Cr, Mn, Ni, Cu, Zn, Br, Sr, Sn, Ba, Pt, Pb	Not reported	Perkin-Elmer SCIEX Elan 6000 ICP-MS, Gibson peristaltic pump, rf 1000 W, Nebulizer: Ruton cross flow with gem tips	[43]
Dietary supplements	As, Cd, Hg, Pb	8.2, 18, 140, 25 ng l^{-1}	Micromass Plasma Trace-2 HR ICP-MS, rf 1350 W	[46]
Chinese medicinal, material	As, Hg	0.19, 0.32 $\mu g\,l^{-1}$	ELAN 6000 ICP-MS rf 1000 W, HP 4500 ICP-MS rf 1200 W, Babington type cross-flow nebulizer, peristaltic pump, double pass spray chamber	[47]
Dietary supplements	Pb, Hg, Cd, As, U, Cr, V, Cu, Zn, Mo, Pd, Sn, Sb, Tl, W.	Not reported	Micromass Platform ICP-MS Meinhard concentric nebulizer	[48]

0.1- to 5 $\mu g\,ml^{-1}$, which was equivalent to 300 ppm in bulk drug substances. Limit of detection was 0.000246 $\mu g\,ml^{-1}$. The accuracy was checked by the spike recoveries at 5, 10, 50 ppm levels and the precision by repeated analysis of the 1 ppm spiked sample by evaluating the degree of the reproducibility in terms of S.D. and R.S.D., which were less than 1.3% and 3.5%, respectively. Bismuth was used as an internal standard. The method covered the range up to 2500 ppm tungsten in the samples. The ICP-MS results were in agreement with those obtained by ICP-AES and Microwave Induced Plasma-Mass Spectrometry (MIP-MS). Lewen et al. [35] demonstrated a method for determination of palladium in fosinopril sodium by ICP-MS. 2-Butoxy ethanol–water (25:75, v/v) was used as a medium due to good solubility of palladium species. Indium was used as an internal standard for quantitative work. Linearity of the method was 2.5–50 ng ml^{-1}. The LOQ of the method was 0.1 $\mu g\,g^{-1}$ of palladium in fosinopril sodium. Bulk drugs of enalapril maleate, calcium folinate and levodopa were analyzed to determine palladium, platinum, and rhodium by ICP-MS [36]. The usefulness of ICP-MS for rapid screening of inorganic impurities was demonstrated. Screening was carried out for Rh, Pd, Pt, Be, V, Mn, Co, Ni, Cu, Zn, Mo, Cd, Sn, Th and Pb metals, by selecting Rh^{103}, Pd^{105} and Pd^{106}, Pt^{195} isotopes. Indium 10 ng ml^{-1} was used as an internal standard. The platinum content of calcium folinate was found to be in good agreement with direct dissolution measurements. The Rh content in L-dopa was comparable to that determined by GF-AAS. Lam and Salin [37] have studied the use of laser ablation with ICP-MS and ICP-AES for analysis of neusilin tablets consisting of magnesium aluminosilicate in a microcrystalline cellulose matrix. Two methods (i) single spot and (ii) continuous ablation were tested. Laser ablation of Cu indicated the precision of the laser power. The R.S.D. between nine sites using one laser shot per site was found to be 9% for Cu. The R.S.D.'s for Al and Mg were 47% and 61%, respectively.

3.2. Multielements in synthetic drugs

ICP-MS has clear advantages in terms of speed and detection limits for analysis of multielements. As an alternative to

USP/BP/EP pharmacopoeial limit test for heavy metals, Wang et al. [38] have described a multi elemental survey method using ICP-MS. Samples prepared in dilute HNO_3 were analyzed by the instrument calibrated with 69 elements of a working standard and verified by NIST 1643d (trace metals in water). Calibration standards were prepared in the same sample matrix to minimize the interferences. Specific cases of spectral interferences monitored with more than one isotope, were discussed. The catalysts used in the synthesis were considered to be the source of contamination of relatively high concentration of Rh, Pd, Os and Sn in some of the bulk drugs.

Leon et al. [39] have reported traces of Cr, Ni, Sn, and Pb in synthetic Vitamin E by ICP-MS. Acid mineralization and microwave emulsion were compared. Acid mineralization was carried out with nitric acid and hydrogen peroxide in a microwave vessel. In emulsion preparation, Triton X was used as an emulsifier and tetralin was added to decrease its viscosity. Y, In and Tl were used as internal standards. Matrix effects were studied by comparing the slopes obtained by standard addition and external calibration.

Na, Br, Pd, Ba, and I were determined in Methamphetamine hydrochloride prepared by two different methods involving different catalysts and reagents [40]. Ba, Pd, Br and Na were detected in the drug prepared by Emed's method while I, Br and Na were detected in the drug, prepared by Nagai's method. The determined levels of Na, Br, Pd, Ba and I in methamphetamine hydrochloride by ICP-MS were compared with those obtained by neutron activation analysis (NAA). Lewen et al. [41] have determined As, Se, Cd, In, Sn, Sb, Pb, Bi, Ag, Pd, Pt, Hg, Mo and Ru by ICP-MS. Out of seven solvents, four were considered to be best in the following order 0.5% HCl, 2-butoxy ethanol/water, 5% HNO_3 and water. Due to insolubility of many API's in 0.5% HCl, 2-butoxy ethanol/water (25:75, v/v) was used. All the samples and standard solutions were added with internal standards of Co, Au, Rh in 25 ng ml^{-1} and the instrument was tuned to 25 ng ml^{-1} of indium solution. The USP procedure was compared with ICP-MS analysis. The average recovery of a particular element in different matrices with respective to the functional groups was studied by ICP-MS.

Soltyk et al. [42] have determined Cr, Cu, Mg, Mn, Mo, P, Se and Zn in multimineral and multivitamin preparations by ICP-MS. Samples dissolved in concentrated nitric acid were mineralized by a high-pressure microwave system. Cobalt was used as an internal standard. The accuracy was checked by the analysis of CRM green algae (P-ACHK Number12-2-02) and oriental tobacco leaves (CTA-OTL-1). The contents of Cr, Ca and Fe determined by electrothermal atomic absorption spectrometry (ET-AAS) were also reported.

Waddell et al. [43] investigated the usefulness of ICP-MS data of ecstasy tablets to provide linkage information from seizure to seizure. The generated data was analysed using principal component analysis, hierarchical clustering and artificial neural networks. The relative merits of each technique were discussed. Caffeine and sugars such as glucose, fructose and lactose were present as adulterants and diluents in illicit samples of amphetamine and 3,4-methylenedioxymethylamphetamine. Samples of caffeine and four diluents were analysed in triplicate for comparison with the spectra of the illicit tablets. Chemometric procedures and artificial neural network algorithms were applied to group tablets according to their original seizure and to identify links among similar seizures. A solution containing Mg, Ba, Pb, Ce and Rh, at a concentration 10 ng mL^{-1} in distilled water was used as a standard to calibrate the instrument while the solution of seronorm^{TM} trace elements in urine as a certified standard. Rh and Y were used as internal standards. The sample was prepared and heated in a microwave digester. Seven ecstasy seizures confiscated in the Strathclyde region and five obtained from the national laboratory of forensic science in Sweden were analyzed.

A number of inorganic impurities were identified in methamphetamine [44] by anion-exchange ICP-MS. A SAM-125 anion-exchange column with a 4.4 mM sodium carbonate and 1.2 mM sodium bicarbonate mobile phase was used. The metals and non-metals were separated and identified. The discrimination of various methamphetamines by inorganic elements was carried out. Ion chromatography was used to screen F, Cl, Br, I, NO_2, NO_3, SO_4 and PO_4 in the methamphetamine crystals and detection limits were from 4 to 60 ppb. Chlorine and bromine were detected in all samples while the bromine content in three different samples was 11.2, 114.0 and 44.1 ppm. The calibration graphs for Na and Br were prepared with in the range of 0–100 ppb and Pd, Ba, and I from 0 to 4 ppb. Besides Na, Pd, Ba, Br, and I another 15 elements were detected in trace levels.

Murthy and co-workers [45] have demonstrated the usefulness of ICP-MS for monitoring of inorganic impurities during the synthesis of dicylcomine HCl, ethambutol, pyrazinamide and furazolidone. The drugs were analyzed for Ti, Cr, Mn, Fe, Co, Ni, Cu, Zn, Cd, Hg, Pb metals by selecting suitable isotopes. Cr, Fe, Ti and Cu were found above the threshold limits. Ni and Hg were absent in all the four drugs, while traces of Cd was found in ethambutol and pyrazinamide. Accuracy of the method was determined by the analysis of NIST 1643b (trace elements in water) with R.S.D. < 5%. Two methods of sample preparation, i.e. direct dissolution in 5% (v/v) HNO_3 and digestion with HNO_3 and H_2O_2 were compared.

3.3. Multielements in herbal drugs

Presence of undesired metals in some of the dietary supplements was reported [46]. Arsenic, cadmium, mercury, and lead were primary concern due to their toxicity and potential contaminants in dietary supplements. High-resolution (HR) ICP-MS was used to analyze the products for As, Cd, Hg, and Pb. It provided separation of analyte signals from known spectral interferences. The samples were digested in a microwave digester and the method was validated using the reference materials obtained from NIST. Limits of quantification were 5, 10, 80, and 20 μg kg^{-1} for As, Cd, Hg, and Pb, respectively. The concentration ranges were arsenic, 5–3770 μg kg^{-1}; cadmium, 10–368 μg kg^{-1}; mercury, 80–16,800 μg kg^{-1}; lead, 20–48,600 μg kg^{-1}. The estimated exposures or intakes were assessed.

Wu et al. [47] have described the analysis and leaching characteristics of Hg and As in Chinese medicine material (CMM)

realgar and cinnabar using ICP-MS. The results were compared with those obtained by hydride generation atomic fluorescence spectrometry. Microwave assisted and soxhlet extractions were carried out to compare with the conventional sequential extraction. The leachable amounts of the target elements into artificial stomach and intestinal fluids in 0.5% trypsin were compared. The later gave the greatest amounts of leach able arsenic (0.41%) from realgar and mercury (1× 104%) from cinnabar, otherwise no significant effect on the leach able amounts was observed upon changing the temperature (37–60 °C), HCl concentration (0.5–6 M), and CMM sample particle size (74 and 250 μm). The low leaching efficiencies confirmed the presence of arsenic and mercury as insoluble sulfides in mineral drugs. Sequential extraction was used to determine the species of mercury and arsenic in formulated drugs containing the minerals. Trace amounts of arsenic and mercury were found which could be the transformation products derived from the origin of cinnabar or realgar minerals in drug formulation. Indium was used as an internal standard. Accuracy was demonstrated by analyzing two reference materials, GBW-08505 (tea leaves) and GBW-08508 (rice). Raman et al. [48] have studied, a variety of plant species and dietary supplements from different manufactures for lead, mercury, cadmium, arsenic, uranium, chromium, vanadium, copper, zinc, molybdenum, palladium, tin, antimony, thallium, and tungsten by ICP-MS. The samples were prepared by digestion with HNO_3. Indium and bismuth were used as internal standards. All the samples were devoid of mercury contamination. The botanical supplements did not contain unacceptable concentrations of any of heavy metals. The supplements were also evaluated for microbial contamination, and most of the samples showed the presence of bacteria or fungi or both.

Determination of arsenic, cadmium and lead in herbal raw materials is of considerable importance for drug quality and safety. Soltyk et al. [49] have mineralized herbal materials like black-wrack, mint leaves, and nettle leaves by high pressure microwave mineralizer and analyzed by ICP-MS. Quantitative analysis was carried out in the range of 0.2–200 ppb for As, 0.1–20 ppb for Cd and 0.1 ppb–10 ppm for Pb. Recoveries were found in between 91.8 and 106.3% with R.S.D. 0.22–13.26%. Flow injection-ICP-MS with microwave digestion was used [50] for determination of arsenic in traditional Chinese medicine (TCM) in the form of uncoated tablets, sugar coated tablets, black pills, capsules, powders, and syrups. The precision and accuracy was checked with a certified reference material for external calibration and by spiking studies. Recoveries of 89–92% were reported for CRM and 95% for spiked TCM.

4. Speciation of elements by ICP-MS

A number of elements including iron, copper and zinc, at trace levels, as well as selenium; cobalt and manganese, in ultra-trace amounts are essential to human nutrition and survival. Likewise, many elements, such as arsenic, mercury and lead, are known to be quite toxic to human beings. However, the potential of these elements to be harmful or beneficial is highly dependent upon their speciation [51,52]. For example, arsenic is present in wide variety compounds of widely differing toxicity. Inorganic compounds such as arsenite and arsenate are known to be highly toxic, while organics are generally considered to be non-toxic. Acids such as dimethylarsinic acid and monomethylarsonic acid have intermediate toxicities [53]. Thus it is of great interest to know the species of essential and toxic elements present in foods, vitamins, food supplements, drugs and pharmaceuticals. Current standards of USFDA [54], world health organization (WHO) [55], rely only on total element concentration to determine if a particular food, beverage or drug is safe to consume. Identification of elemental species which are harmful to humans, as well as techniques to detect them accurately and effectively will foster the development of more appropriate regulations, and enable critical evaluation of drugs and pharmaceuticals for safety of human beings. Identification of species within the body containing toxic elements may provide information about the ways in which organisms have adapted to sequester, accumulate, or detoxify the harmful elements. It can be extended to include therapeutic drugs as well [56]. Thus, elemental speciation is employed in a wide range of disciplines including clinical, medicinal chemistry [57,58] and bioinorganic chemistries [59]. It represents a broad, multidisciplinary field of study, and a number of recent reviews and books provide an excellent reference on to the role of various elements in these chemistries [60–62]. The fields of health and nutrition benefit tremendously from the information that speciation analysis provides [51]. Table 3 gives some of the recent applications of ICP-MS in analysis of metal species of drugs and pharmaceuticals found in the literature.

ICP-MS combined with chromatographic techniques is of great importance in characterization and identification of impurities, degradation products and speciation studies in pharmaceuticals. It provides valuable information on impurity profiling of drugs and pharmaceuticals. It is becoming the method of choice for quality control and assurance with in the pharmaceutical industry. A number of chromatographic techniques, viz., HPLC, CE, GPC, IC, SFC and GC have been coupled with ICP-MS for the purpose of speciation. A number of reviews cover these topics in detail [63–65]. In particular, HPLC-ICP-MS has been widely used as a routine tool for speciation studies in recent years [66]. The use of ICP-MS as a complementary technique to electro spray MS and MALDI MS was reviewed by Lobinski et al. [67]. It focused on the recent advances in ICP-MS in biological speciation analysis, including sensitive detection of non-metals, especially of sulfur and phosphorus, coupling to capillary and nanoflow HPLC and capillary electrophoresis. It can detect trace-element-containing species, even when a particular element is distributed amongst a large number of species. In particular, improvements in its sensitivity have allowed the detection of more and more arsenic and selenium compounds in biological matrices and food supplements [68,69]. In addition to its low detection limits, the dynamic range of ICP-MS allows detection of both major constituents and trace components simultaneously. Furthermore, the multielemental capability of ICP-MS enables the detection of individual isotopes, which permit the use of isotopic-dilution techniques for internal standardization and also to monitor species transforma-

Table 3
Speciation of trace elements by ICP-MS

Drug/formulation	Element	Column	Mobile phase	Detector	MDL	Reference
Chromium, picolinate	Cr	RPHPLC Baxter ODS, C18: Dionex + IC Anion exchange	Methanol + water AS_7ammonium sulfate ammonium hydroxide and deionised water	Fison PQ II + TurboICP-MS	Not reported	[87]
Cobalamins Vitamin B_{12}	Co	MEKC, CZE	pH 2.7, 20 mM phosphate + 20 mM formate Buffer	Perkin-Elmer Sciex Elan 6000 ICP-MS, 1.0 kW, Jacketed spray chamber, 5 °C	50 ng/ml	[88]
Cobalamins and cobinamides	Co	Microbore reversed-phase Brownlee Aqua pore (C8) (100 mm × 1 mm × 7 μm) vydac C8 (150 mm × 1 mm × 5 μm)	25 mM ammonium acetate in water, pH 4, CH_3COOH	Elan 600, Perkin-Elmer Sciex, 1.2 kW rf micro concentric nebulizer with no spray chamber (DIN)	0.01–0.05 μg ml^{-1}	[89]
Selenium enriched yeast	^{82}Se	Reversed-phase Zorbax SB-C8 (4.1 mm × 15 cm)	98 + 2 water methanol, 0.1% (v/v) TFA	Elan 500 ICP-MS Perkin-Elmer ScI, Cross flow nebulizer double-pass spay chamber	Not reported	[79]
Selenized yeast samples	Se	CE: 363 μm o.d. fused silica capillaries coated externally with poly (imide), inside poly (vinyl sulfonate)	100 mmol L^{-1} formic acid, 0.01% poly(vinyl sulfonate), pH 3.0, run voltage + 30 kV, injection: 82 mbar for 100 s	PE-SCIEX ELAN 6000 instrument (Perkin-Elmer, USA), 1150 W rf, direct injection nebulizer	15 μg l^{-1}	[80]
Organo-germanium containing medicine	Ge	Dionex AS10 4 mm (10–32), total flow 1 ml/min, pressure 1375 PSI	Isocratic elution: 0.37 mmol/1 H_2SO_4	Q-ICP-MS HP-4500 peristaltic pump, rf 1300 W, nebulizer: V-grove, spray chamber: Scott type and HR-ICP -MS ELEMENT 2	Not reported	[91]
Levothyroxine, degradation, products in tablets	I	Cyno-Spherisorb narrow bore, 250 mm × 2.0 mm × 5 μm	22% (v/v) acetonitrile 0.08% (v/v) TFA pH 2.3 adjusted with trifloroacetic acid	Perkin-Elmer SCIEX Elan 6000 ICP-MS, Gem Tip cross flow, nebulizer, Ryton spray, Chamber, rf 1250 W	<0.2 μg l^{-1}	[92]
Methamphetamine	Na, Ba, Pd, I, Br and IC detected F, Cl, Br, I, NO_2, NO_3, SO_4, PO_4	IC500 with conductivity SAM 3-125 anion, exchange pre column, PAM 3-035	4.4 mM sodium carbonate + 1.2 mm sodium bicarbonate	Model PMS 100 ICP-MS system, 1.5 kW rf	0.005–0.08 ppb, 4–60 ppb (anions)	[44]
Cimetidine	S	Novapak C18 (3.9 mm × 150 mm × 4 μm)	CH_3COOH and MeOH (70:30), 0.05 mol L^{-1} ammonium acetate, pH 5	Thermo SF-ICP-MS, nebulizer: mein hard jacketed quartz cyclonic, single pass spray, 5 °C	4–20 ng g^{-1}	[94]
Diclofenac, chlorpromazine	Cl^{35}/Cl^{37}	Apex C_2 4.6 mm × 250 mm	Gradient elution-isocratic 65:35, 0.05% formic acid in H_2O/methanol	Micro mass plot form ICP-MS	Not reported	[93]
Cobalamin analogues	Co	three types of columns: C8, 150 × 4.6, 5 μm NPS ODS-II, 33 × 4.6, 1.5 μm, TSKgel Super ODS, 50 × 4.6, 2 μm	ACN used with 1.5 mm, methanol in other. Buffer: 25 mM ammonium acetate in water/organic solvent pH 4 adjusted with acetic acid	ELAN 6000 ICP-MS, 0.9 kW, Meinhard nebulizer, 4 °C spray chamber, Minipuls 3 peristaltic pump	4–8 ng ml^{-1}	[90]
Selenium-enriched yeast	SeMet	HPLC: anion exchange Hamilton PRPx-100 (250 mm × 4.6 mm × 5 μm), RP: Prevail C18 (150 mm × 2.1 mm × 5 μm)	Acetic acid + ammonium acetate + water. Formic acid in water and in acetonitrile	ELAN 6000 ICP-MS Ryton spray chamber cross-flow nebulizer, rf 1100 W	Not reported	[84]
Selenium MC Tab.	Se	HPLC: anion-exchange Hamilton PRP-X100 (250 mm × 4.1 mm × 10 μm), RP-IP Zorbax Rx-C_8 (250 mm × 4.6 mm × 5 μm), Size-exclusion TSK gel G 3000 PWxL (30 mm0 × 7.8 mm × 6 μm)	5 mM NH_4 hydrogen citrate (pH 5.9), 2% (v/v) MeOH, 0.1% TFA, 2% (v/v) MeOH, 10 mM NH_4Ac	Agilent 7500i ICP-MS rf 1300 W	Seleno-cystine (2) Selenite (6.1), Seleno-methionine (3.7) Selenate (1.12) ng l^{-1}	[81]

MDL: method detection limit.

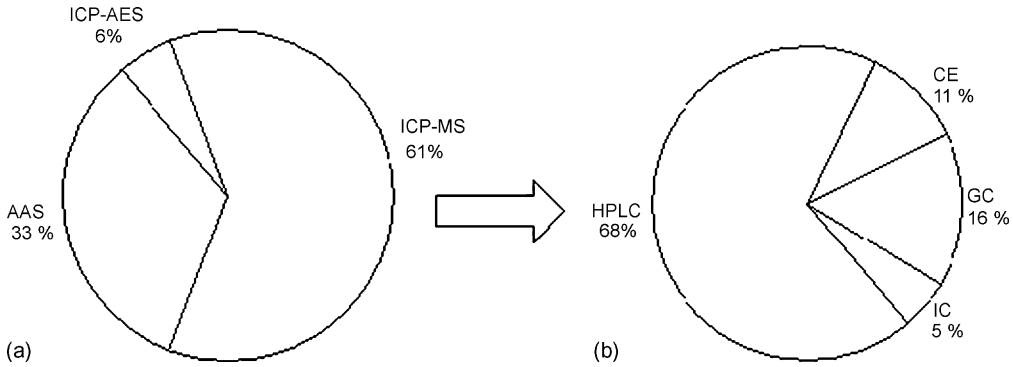

Fig. 4. (a) Pattern of use of atomic spectrometric techniques in speciation analysis in drugs. (b) Chromatographic techniques coupled with ICP-MS for speciation of metals in drugs.

tions occur during sample pre-treatment or separation [70,71]. Fig. 4 shows the comparison of AAS, ICP-AES and ICP-MS in speciation analysis of drugs and pharmaceuticals.

In addition to the advantages, a number of difficulties are also associated with ICP-MS in speciation analysis. The organic solvents used in HPLC or CE could destabilize the plasma as well as a build-up of carbon residue on the sampling cone [72]. These problems could be alleviated to some extent by addition of oxygen to the nebulizer-gas, increasing the rf power of the plasma, using a platinum sampling cone and using a nebulizer either with a low-flow direct-injection or an efficient desolvation unit. If analyte concentrations are high enough, post-column dilution with water or dilute HNO_3 may be carried out. The use of solvent gradients poses problems to the plasma temperature and electron density resulting in different ionization efficiencies and energies. Another difficulty in coupling of ICP-MS with separation techniques arises from the sample matrices. HPLC and CE require the use of a buffer or a solution of high ionic strength. High salt concentrations could result in signal suppression due to increased space-charge effects, which defocus the ion beam [73,74]. Thus, tradeoffs may be required with respect to separation efficiency and detection sensitivity. The matrix effects in the ICP can be alleviated to some extent by sample pretreatment, altering argon flow rates, modifying interface configurations and voltages, or post-column dilution [74,75].

4.1. Selenium

Selenium as a cancer preventive agent is of great interest as a food supplement in recent years. Its biological and toxicological effects strongly depend on its chemical form [76–78]. Therefore, there is an increasing interest in differentiation of its inorganic and organic species in food supplements, drugs and biological fluids. Selenomethionine is the principal form of selenium found in most of the foods absorbed and stored within the human body. Inorganic selenium is excreted more rapidly and is more toxic than selenomethionine. Selenium, both as toxic and an essential element, plays an important role in pharmaceutical analysis. Bird et al. [79] have analyzed selenium enriched yeast by HPLC-ICP-MS. Trifloroacetic acid was used as an ion-pairing agent in water–methanol as a mobile phase on an octyl silane stationary phase. Hot water and enzymatic hydrolysis extraction with a non-specific protease XIV were studied. Selenomethionine appeared as a major peak in the enzymatic hydrolysis. Selenoethionine was used as a chromatographic internal standard and the presence of selenocystine, selenomethionine and methyl selenocysteine was confirmed by comparing with the retention of standards. Total selenium in the yeast and extracts was determined by ICP-MS after microwave digestion and direct nebulization, respectively.

Bendahl et al. [80] have investigated the different species of selenium in nutritional supplements, using CE-ICP-MS. Fused silica capillaries, 363 μm OD coated externally with poly (imide) and internally with poly (vinyl sulfonate) were employed. Sample pre-treatment consisted of cold-water extraction by sonication and subsequent incubation of the cold-water extract with 6 M hydrochloric acid at 110 °C. The buffer with 10% methanol was used as a sheath liquid. More than 20 selenium compounds were separated from the aqueous extracts of yeast within 13 min. The total selenium content in the extracts was determined by standard addition using selenite as an internal standard. CE-ICP-MS detection is a promising technique to give a fingerprint of selenized yeast preparations.

Size-exclusion, ion exchange and reversed-phase ion-pair (RP-IP) HPLC were used in combination with ultrasonic nebulisation ICP-MS for specific detection and quantitation of Se-compounds in the extracts of yeast and methylselenocysteine (SeMC) based supplements [81]. On-line electro spray ionization (ESI)-MS/MS combined with RP-IP-HPLC allowed their characterization. The current status on elemental speciation by ICP-MS as a method of detection was reviewed by Waddell et al. [82]. It covered the on-line hyphenation of LC, GC, CE and FFF with ICP-MS published during the year 2002–2003. Hymer et al. have extensively reviewed the use of chromatographic and electrophoretic methodologies with emphasis on selenium speciation analysis using ICP-MS as a detector [83].

Two analytical techniques, LC–MS and LC-ICP-MS, were developed based on species-specific isotope dilution for determination of methionine (Met) and selenomethionine (SeMet) in selenized yeast [84]. The results were found to be in good agreement with GC–MS. Heumann et al. [85] discussed the conditions

under which the ICP-MS isotope dilution is suitable as a routine method for trace element and speciation analysis.

4.2. Chromium

Chromium supplements have been used widely in the treatment of diabetes and high cholesterol levels. The trivalent chromium is essential while the hexavalent is highly toxic to human and has the ability to traverse biological membranes. Therefore, it is of inertest to evaluate chromium species to ascertain the quality of pharmaceutical formulations [86]. Ding et al. [87] have examined Cr(III) and Cr(VI) in chromium picolinates by IC/HPLC and ICP-MS. The chromium species present in the sample did not match with the retention times of the standards and chromium recovery was poor by ion chromatography (IC). So reversed-phase chromatography was used. Compared with ion exchange, reverse-phase chromatography showed excellent recovery based on the amount stated on the product label. Recovery of synthesized chromium picolinate by direct nebulization ICP-MS and RPLC-ICP-MS were in good agreement. Fig. 5 shows separation of chromium picolinate (commercial and synthesized product) samples using RPLC.

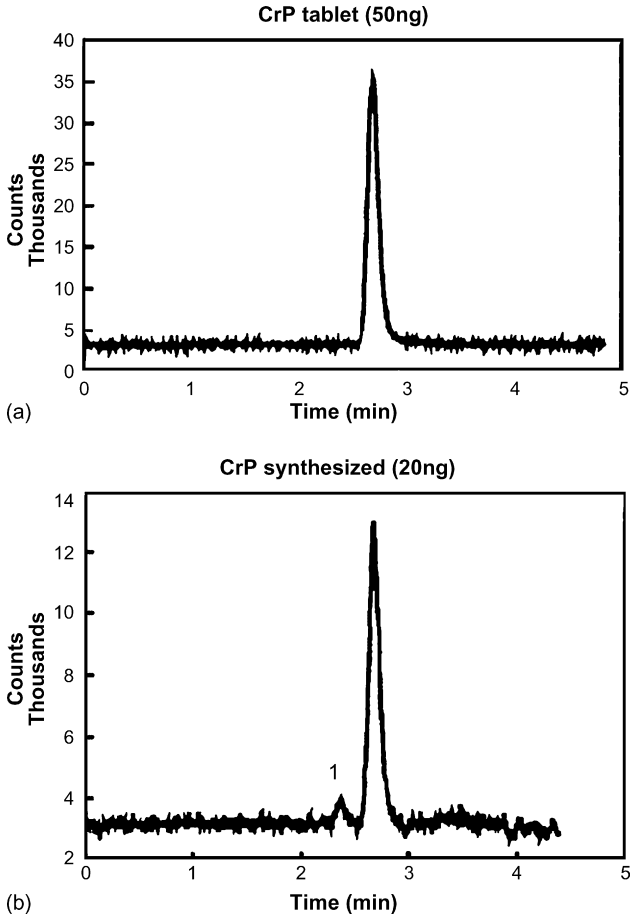

Fig. 5. Separation of chromium picolinate samples using RPLC. C-18 column 60% MeOH, flow rate 1 ml min^{-1} Injection volume 20 μl: (a) filtrate of commercial product, 2.5 ppm (as Cr); (b) filtrate of synthesized product, 1 ppm (as Cr). Reproduced from Ref. [87] with permission.

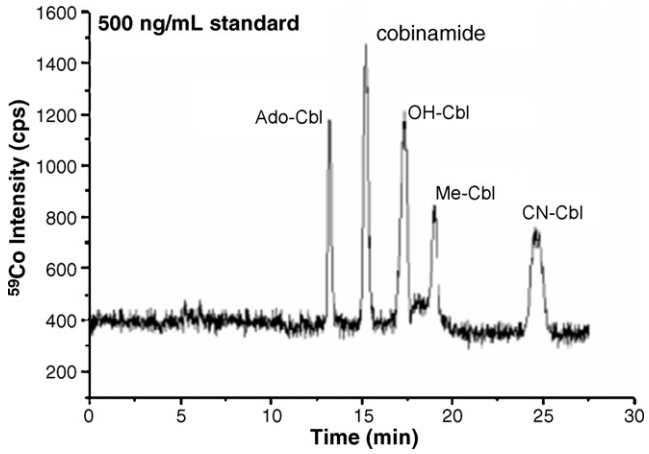

Fig. 6. Electropherogram of a 500-ng/ml mixture of cobalamins and cobinamide dicyanide (20 mM formate buffer, pH 2.5; run potential of 30 kV). Reproduced from Ref. [88] with permission.

4.3. Cobalt

CE-ICP-MS [88] in CZE and MEKC modes was used to determine cobalamins. The optimal separation of cynocobalamin, hydroxocobalamin, methylcobalamin, 5′-deoxyadenosylcobalamin and a potentially harmful cobinamide dicyanide was obtained using CZE at a pH of 2.5. Both 20 mM phosphate and formate buffers were used, but the formate buffer provided improved resolution. CZE-ICP-MS was used to quantify cynocobalamin in a vitamin supplement and the analytical results were in good agreement (±5%) with the values obtained by ICP-MS for total Co levels. The separation of cobalamin species by CZE-ICP-MS is shown in Fig. 6. The detection limits were approximately 50 ng ml^{-1}. Micellar electrokinetic chromatography (MEKC) was found to be useful for screening of vitamin preparations as it provided a rapid means of distinguishing cynocobalamin from free cobalt. The separation of free cobalt and cynocobalamin by MEKC was achieved in less than 10 min (Fig. 7).

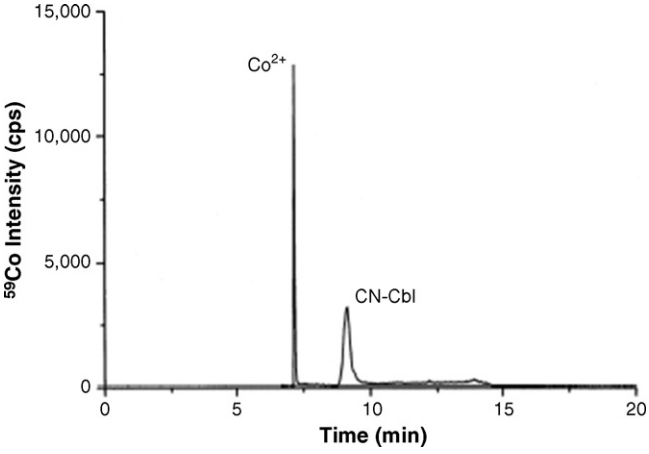

Fig. 7. Electropherogram of an injectable vitamin supplement containing cyanocobalamin and free Co^{2+} using MEKC (50 mM Tris + 12 mM SDS, pH 8.0; run potential of 30 kV). Reproduced from Ref. [88] with permission.

Chassaigne and Lobinski [89] have developed a method for determination of cobalamins present in the pharmaceutical formulations. Micro bore reversed-phase HPLC was optimized for separation of cyanocobalamin (CN), 5′-desoxyadenosylcobalamin (coenzyme B_{12}), methylcobalamin (CH_3), hydroxocobalamin (OH), aquocobalamin (H_2O), and cobinamide dicyanide isoforms. Various detection modes: UV at 278 nm, ion-spray (IS)-MS and direct-injection nebulization ICP-MS were compared.

Makarov and Szpunar [90] have studied the coupling of reversed-phase HPLC with ICP-MS for species-selective determination of cobalt complexes with macro cyclic ligands, e.g. Vitamin B_{12} and its analogues. The use of high efficiency micro columns of 33–50 mm with porous and non-porous small diameter 1.5–2 μm stationary phases was evaluated and compared with conventional (5 μm packing) HPLC. High concentrations of organic solvent (up to 50% of acetonitrile or methanol) could be introduced into the ICP using a meinhard-type nebulizer and a cooled spray chamber. A calibration curve was established by injection of freshly prepared mixture of hydroxocobalamin, cyanocobalamin, adenosylcobalamin and methylcobalamin in amounts of 0.05, 0.2, 1.0, 2.0 and 5.0 mg ml^{-1} (each). Compounds were identified by comparison of the retention times with that of standards. Gradient elution was used in all separations specific for each column. The choice of the column was dictated by the compromise among the analysis time, sensitivity and separation efficiency. The best results in terms of resolution and sensitivity were obtained using a C_8 (15 cm × 4.6 mm i.d.) column. Absolute detection limits of 80–160 pg (4–8 ng ml^{-1}) were achieved. The method developed was applied to determine the active components of cobalamin in pharmaceutical preparations and monitoring of its degradation.

4.4. Germanium

Speciation of germanium [91] by HPLC coupled with ICP-MS was carried out. Two germanium isotopes ^{72}Ge and ^{74}Ge were measured. ^{72}Ge was chosen, to avoid the isobaric interference and overlap of ^{74}Se signal. Matrix-based interferences and semi quantitative analysis of 56 elements were investigated by high resolution ICP-MS in low ($R = 300$), medium ($R = 400$), high ($R = 100{,}000$) resolution mode with 27, 18, and 11 isotopes respectively. It allowed semi-quantitative screening of all 56 selected isotopes. Quantitative identification of beta-carboxyethyl germanium sesquioxide was carried out by reference substances. Separation of organic and inorganic germanium was carried out by anion exchange in an isocratic elution mode. The reported threshold value for determination of inorganic germanium in the sample matrix of beta-carboxy ethyl germanium sesquioxide was less than 0.0008%. Major elements Na (22), K (568), Ca (3), and Zn (2) in μg g^{-1} were determined. Medium abundant elements determined in semi quantitative medium were B, Mg, Al, Si, P, Mn, Fe, Co, Ni, Cu, Rb, Sr, Sn, Te, and Pb up to ∼0.8 μg g^{-1}. Spectral interferences based on the germanium matrix were observed. Isotopes like Rb^{85}, Sr^{88}, Y^{89}, Zn^{90} and Nb^{93} were determined in a high-resolution mode.

4.5. Iodine

Kumarath et al. [92] have developed an analytical methodology for determination of levothyroxine and its degradation products in pharmaceutical tablets by HPLC-UV-ICP-MS. It was useful for simultaneous separation and detection of iodine species. Inorganic iodine, 3,3′,5,5′-tetra iodothyronine (T_4); 3,3′,5-triiodothyronine (T_3); 3,5-diiodothyronine (T_2); 3,3′,5,5′-tetraiodothyroaceticacid ($TTAA_4$), 3,3′,5-triiodothyro acetic acid ($TTAA_3$) and 3,5-diiodothyroacetic acid ($TTAA_2$) were determined in commercial tablets exposed to accelerated degradation. The detection limits obtained with UV detection ranged from 28.9 to 34.5 μg l^{-1}, where as those obtained with plasma detector were about 175–375 times better. ICP-MS as an element specific detector could simplify the determination of iodine species originated by de iodination reaction of levothyroxine.

5. Other applications

Duckett et al. [93] have investigated HPLC-ICP-MS to detect and quantify diclofenac and chlorpromazine. 3,5-Dichlorobenzoicacid was used as an internal standard. The absolute concentration of chlorine was calculated from the integrated peak areas, against the concentration of known chlorine used as an internal standard. The reproducibility was checked by multiple injections. The standard deviation for the peak area of diclofenac was 0.43%, and for the internal standard, 2.5%. The chromatographic separation was carried out using an Apex C_2 250 mm × 4.6 mm column. Gradient elution using H_2O and MeOH as mobile solvent was used. Application of gradient chromatography and variation in the bulk mobile phase physicochemical properties was found to show little effect on the ICP-MS detection. It demonstrated that hyphenation of HPLC with ICP-MS is a valuable tool for quantitative analysis of metabolites for a range of chlorinated xenobiotics.

Cimetidine [94] a sulfur-containing drug was analyzed by RP-HPLC-ICP-MS with gradient elution of 0.05 M-ammonium acetate to 40% methanol. More than one peak in the chromatogram indicated an impurity when sulfur was monitored. The problem associated was polyatomic interference of ^{16}O $^{16}O^+$ with major sulfur isotope of $^{32}S^+$. High-resolution magnetic sector field ICP-MS was utilized to characterize impurities as low as 0.1% of the main component. The limit of detection by ICP-MS for cimetidine in solution was 4–20 ng g^{-1}. The sulfur-specific chromatogram obtained by ICP-MS matched with both UV and total ion current chromatograms. More than 20 sulfur-containing compounds were identified by SF-ICP-MS of which, the structures of a few were confirmed by electro spray mass spectrometry (ESI-MS).

Axelsson et al. [95] have reported the potential of ICP-MS detection for HPLC with accurate measurement of pharmaceutical products. LC-ICP-MS has shown to provide a generic detection for structurally non-correlated compounds with common elements like phosphorous and iodine. Detection of selected elements gave a better quantification of unknowns than UV and mass spectrometric detection. The ultrasonic neb-

uliser did not introduce any measurable dead volume and preserves the separation efficiency of the system. ICP-MS was used in combination with many different mobile phases ranging from 0 to 100% organic modifiers. The dynamic range was found to exceed 2.5 orders of magnitude. The application of LC-ICP-MS to pharmaceutical drugs and formulations has shown that impurities could be quantified below 0.1 mol% level. To test iodine containing samples, standards of iohexol containing three iodine atoms and iodixanol containing six iodine atoms were used. To test phosphorus containing samples 1,2-dipalmotoyl-*sn*-glycero-3-phosphatidylcholine (PC), 1,2-dipalmotoyl-*sn*-glycero-3-phosphatidyl ethanolamine (PE), 1,2-dipalmotoyl-*sn*-glycero-3-phosphatidyl glycerol (PG) were used. To determine the sensitivity of LC-ICP-MS gadolinium metal complex (gadiodiamide) was analyzed. The sensitivity was found to be 3 pg with a signal to noise ratio of 5.

6. Conclusions

The current state-of–the-art of ICP-MS for determination of various trace elements present in drug and pharmaceuticals has been reviewed. Our analysis of the published data has revealed that the ICP-MS is as an effective tool in impurity profiling of single, multi and speciation analysis of different elements present in bulk drugs and formulations. During the period of review, although atomic spectrometric techniques, viz., AAS and ICP-AES were widely used, ICP-MS was the technique of choice for determination toxic heavy metals, viz., cadmium, mercury, arsenic and lead. It was used for determination of residual amounts of Fe, Pd, W, Pt, Rh catalysts present in drugs and pharmaceuticals. The simple acid dissolution and microwave digestion were the methods of choice for sample preparation. Microwave digestion had clear advantages over the traditional acid digestion in terms of better recovery of volatile elements and reproducible procedures. Most of the methods conform to ICH validation guidelines. The particular advantage of ICP-MS when compared to other techniques is speciation studies for many elements and separation ability of chromatography coupled to ICP-MS offers a versatile tool for speciation. During the period of review in atomic spectrometric techniques, ICP-MS contributed a major share for speciation analysis. It was increasingly hyphenated with LC, GC and CE for better detection limits compared to other spectrometric methods. HPLC was the most widely used chromatographic technique, which occupied nearly 70% of speciation analysis. Speciation analysis of selenium was studied more by coupling different chromatographic techniques including HPLC, GC and CE. ICP-MS also played a major role in the analysis of heavy metals in food supplements and in herbal drugs. The use of ICP-MS for elemental specific assays for accurate determination of pharmaceuticals and impurities with out the need for standards was also reported. It became evident that matrix-matching standards, certified reference materials for total metal and speciation studies of various elements must be developed and made available for element specific assays and speciation methods for evaluation of pharmaceuticals and metabolites.

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