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ATOMIC SPECTROSCOPY

Elemental Analysis of Phytotherapeutic Products by Inductively Coupled Plasma–Tandem Mass Spectrometry

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ABSTRACT

A procedure for the determination of As, Cd, Cr, Ni, Pb, and V in phytotherapy medicines by inductively coupled plasma–tandem mass spectrometry is reported. The use of tandem mass spectrometry with oxygen into an octopole reaction system at various gas flow rates and the combination of on-mass and mass-shift modes was evaluated. Cadmium, Cr, Ni, and Pb were determined as free atomic ions while As and V were determined as the oxides AsO^+ and VO^+ in the same run. Samples were prepared by microwave-assisted digestion with dilute nitric acid and hydrogen peroxide. Two plant-certified reference materials (apple leaves and tomato leaves) were used to check the accuracy. For tandem mass spectrometry with 0.5 mL min^{-1} O_2, recoveries in the 85–113% were typically obtained and no statistical differences were observed at the 95% confidence level (*t*-test) in comparison with the certified values. Using these conditions, the limits of detection for the method were 0.01, 0.0002, 0.008, 0.008, 0.003, and 0.002 µg g^{-1} for As, Cd, Cr, Ni, Pb, and V, respectively. The procedure was used for the analysis of four phytotherapic drugs and the determined concentrations were up to 0.168 µg g^{-1} As, 0.03 µg g^{-1} Cd, 0.82 µg g^{-1} Cr, 1.18 µg g^{-1} Ni, 0.52 µg g^{-1} Pb, and 2.4 µg g^{-1} V with average precision values of 8% as the relative standard deviation. The found concentrations were compared with limits proposed in official guidelines and, in most cases, the values were below the maximum limits allowed.

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Introduction

Medicinal plants are widely used as an alternative for treatment of diseases due to their therapeutic, prophylactic, and palliative properties. Besides the traditional forms of administration, these plants and their extracts may also be used as active ingredients in pharmaceutical preparations (Duke 1993). In addition to the therapeutic substances, phytomedicines may contain elemental impurities which are often present in trace levels and may be toxic or lead to product deterioration (Wang et al. 2000).

The main sources of elemental impurities in these drug formulations may be related to metal accumulation in plants (Barthwal, Nair, and Poonam 2008) and contamination of the

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raw materials or final product during manufacturing, packaging, and storage (Støving et al. 2013; Rudovica, Viksna, and Actins 2014). Similarly to all medicines, phytotherapy drugs should have a standardized composition and provide assurance on quality control and safety matters. Recently, the United States Pharmacopeia (USP) released two new chapters <232> and <233> (The United States Pharmacopeia 2015a, 2015b), concerning elemental impurity limits for 15 elements and recommended procedures based on inductively coupled plasma (ICP) techniques, but the implementation was postponed and it is intended to be established in early 2018 (The United States Pharmacopeia 2015c). The literature has also described procedures for determination of elemental impurities in pharmaceuticals by inductively coupled plasma optical emission spectrometry (ICP OES) and inductively coupled plasma mass spectrometry (ICP-MS) based on the USP chapter protocols (Van Hoecke, Catry, and Vanhaecke 2012; Støving et al. 2013; Fischer et al. 2014).

Among the analytical methods used for trace element analysis of herbal medicines (Yuan, Chapman, and Wu 2011), ICP-MS is attractive due to suitable sensitivity, multi-elemental characteristics, and high sample throughput (Thomas 2013); however, mass analyzers based on quadrupole spectrometers present low resolution (*ca.* 1 amu) and are prone to severe spectral interferences due to polyatomic species and isobaric overlaps. Over the years, several strategies have been used to overcome interferences in quadrupole ICP-MS, including mathematical correction equations, cool plasma technology, and the use of collision/reaction cells (Thomas 2013). In addition, the use of sector field mass spectrometers (SF ICP-MS) with high resolution is a straightforward approach to overcome spectral overlaps; however, this technique is expensive and the limits of detection may be deteriorated due to lower ion transmission when the required resolution is increased.

Recently, ICP tandem mass spectrometry (ICP-MS/MS) was proposed for inorganic analysis, presenting a novel technology to overcome spectral overlaps. The instrument presents an additional quadrupole (quadrupole 1) located before the octopole reaction system (ORS^3), which acts as a mass filter and allows only the target mass to reach the collision/reaction cell. After the cell, the second quadrupole (quadrupole 2) operates as a conventional mass analyzer. Such configuration provides better efficiency and selectivity in collision/reaction processes for the correction of spectral interferences.

The instrument is versatile and may be operated in the on-mass or mass-shift modes (Balcaen et al. 2015). In the on-mass mode, both quadrupoles select the same target mass of the ions entering and leaving the ORS^3 (quadrupole 1 = quadrupole 2). In the mass-shift mode, the precursor ions entering the cell are set in the first quadrupole for a target mass, while the second quadrupole selects the reaction product in specific m/z, which is the analyte's m/z and the mass of the reaction gas used (e.g., quadrupole 2 = quadrupole 1 + 16, in case of oxygen; or quadrupole 2 = quadrupole 1 + 17, in case of ammonia) (Sugiyama and Nakano 2014). The use of mass-shift mode with oxygen (Balcaen et al. 2013; Amais et al. 2014; Balcaen et al. 2014; Amais et al. 2015; Amaral et al. 2015; Jackson, Liba, and Nelson 2015; Virgilio et al. 2015), ammonia (Balcaen et al. 2014), and methyl fluoride (Bolea-Fernandez et al. 2014; Bolea-Fernandez et al. 2015) as the reaction gas for ICP-MS/MS has been reported in the literature. However, the combination of on-mass and mass-shift modes for elements with different reactivities in the same run is an underexplored strategy and requires thorough studies concerning the feasibility and possible effects over the sensitivity and accuracy of methods. Moreover, considering recent legislation for pharmaceutical analysis, the development of sensitive methods based on microwave-assisted digestion and plasma-based techniques are of utmost importance.

In this work, we evaluate the performance of ICP tandem mass spectrometry (ICP-MS/MS) for the determination of As, Cd, Cr, Ni, Pb, and V in phytotherapy medicines. Oxygen was used as a reaction gas into the ORS^3 at different gas flow rates, and the influence of the on-mass and mass-shift modes on sensitivity, accuracy, and precision was studied.

Experimental

Instrumentation

All measurements were performed with an Agilent 8800 ICP-MS (Agilent Technologies, Japan) equipped with two quadrupole mass analyzers (quadrupole 1 and quadrupole 2), located in between the ORS^3 as a collision/reaction cell. Pure oxygen (≥99.999%, Air Products, São Paulo, SP, Brazil) was used as a reaction gas to generate the oxide species of the analytes. The ICP-MS/MS operational parameters are shown in Table 1. Sample preparation was performed using an Ethos 1600 microwave oven (Milestone, Sorisole, Italy).

Reagents and standard solutions

Ultrapure water (resistivity $>18.2\ \mathrm{M\Omega\ cm}$) and nitric acid (Merck, Darmstadt, Germany) obtained from a sub-boiling distillation system (Milestone) were used to prepare all analytical solutions. Standard solutions were prepared by adequate dilution of $1000\ \mathrm{mg\ L^{-1}}$ As, Cd, Cr, Ni, Pb, and V stock solutions (Fluka Analytical, St. Gallen, Switzerland) in $1\%\ \mathrm{v\ v^{-1}}$ HNO_3.

Microwave-assisted digestion

Two plant-certified reference materials (CRMs), apple leaves (NIST SRM 1515) and tomato leaves, (NIST SRM 1573a) from the National Institute of Standard and Technology (NIST,

Table 1. Operational conditions for ICP-MS/MS.

Instrument parameter	Operating condition	
Radiofrequency power (kW)	1.55	
Sampling depth (mm)	8.0	
Nebulizer	Concentric nebulizer–glass	
Spray chamber	Scott type–double pass	
Plasma gas flow rate ($\mathrm{L\ min^{-1}}$)	18	
Auxiliary gas flow rate ($\mathrm{L\ min^{-1}}$)	1.8	
Carrier gas flow rate ($\mathrm{L\ min^{-1}}$)	1.09	
Integration time (s)	3.0	
Mass/charge ratios selected in Q1	51 (V); 52 (Cr); 60 (Ni); 75 (As); 112 (Cd); 208 (Pb)	
Operating mode	Single quadrupole	MS/MS
Cell gas	No gas	O2
Gas flow rate ($\mathrm{mL\ min^{-1}}$)	0	0.50 and 0.75
Mass/charge ratios monitored in Q2	On-mass mode	Mass-shift mode
	51 (V)	51 (V); 67 (VO)
	52 (Cr)	52 (Cr); 68 (CrO)
	60 (Ni)	60 (Ni); 76 (NiO)
	75 (As)	75 (As); 91 (AsO)
	112 (Cd)	112 (Cd); 128 (CdO)
	208 (Pb)	208 (Pb); 224 (PbO)

ICP-MS/MS, inductively coupled plasma–tandem mass spectrometry.

Gaithersburg, MD, USA) were used to check the accuracy. Four phytotherapy drugs with labeled concentrations per capsule of 200 mg Boldo (*Peumus boldus*), 300 mg Ginseng *(Panax ginseng)*, 250 mg Green Tea (*Camellia sinensis)*, and 100 mg Kava-kava (*Piper methysticum*) were purchased at a local pharmacy in São Carlos (SP, Brazil).

For sample digestion, masses of approximately 300 mg were accurately weighed directly in the Teflon-PFA digestion vessels, followed by the addition of 3 mL of concentrated HNO_3 (16 mol L^{-1}), 3 mL of distilled and deionized water, and 2 mL of 30% m m^{-1} H_2O_2. The microwave-assisted digestions for CRMs and samples were performed using a two-step heating program, consisting of a 10 min ramp to 200°C followed by a 10 min hold at 200°C. After cooling down to room temperature, the samples were diluted to 50.0 mL with distilled and deionized water. The digestions were made in triplicate.

Results and discussion

Analytical performance

The occurrence and extension of the reactions in reaction cells are intimately related to the physical–chemical properties of the analytes and cell gas used. The efficiency of oxygen reactions into the ORS^3 is also dependent upon the gas flow rate. In mass-shift mode, the reaction of analyte ions from plasma with the oxygen usually occurs through the transfer of oxygen atoms, resulting in an oxide-based ion with m/z dislocated by 16 atomic mass units from the original analyte's m/z. For some reactive elements such as As and P, the activation energy required for ionic reactions in gas phase is negligible, so exothermic ($\Delta H_r < 0$) and spontaneous reactions take place. Hence, the oxides of the elements are the major products. For less reactive elements such as Cu and Pb, the monitoring of oxide ions is not recommended due to energetically unfavorable reactions ($\Delta H_r > 0$) or the occurrence of charge transfer reactions with oxygen, which results in neutral species of the analyte (Agilent Technologies 2015). Therefore, the on-mass mode is more useful for these elements. In addition, the use of oxygen into the cell may also promote reactions with polyatomic species, and the use of on-mass mode may lead to interference-free determinations (Amais et al. 2015).

Considering the distinct reactivity of the elements with O_2, the analytical performance of an ICP-MS/MS operating in both single quadrupole mode in absence of cell gas and MS/MS mode with O_2 into the ORS^3 under different gas flow rates (0.50 and 0.75 mL min^{-1} O_2) was evaluated for As, Cd, Cr, Ni, Pb, and V. In each case, linear analytical curves ($r^2 > 0.99$) in 0.1–100 μg L^{-1} were obtained for the evaluation of figures of merit. Results for sensitivity, as the slope of analytical curves, and limits of detection and quantification, as 3 or 10 times the standard deviation of blank ($n = 12$) divided by the slope, respectively, were obtained for on-mass (quadrupole $1 =$ quadrupole 2) and mass-shift (quadrupole $2 =$ quadrupole $1 + 16$) modes. The results are shown in Table 2.

In general, sensitivities decreased when O_2 was used and also when the gas flow rate is increased. In MS/MS mode, As and V presented better sensitivities and lower limits of detection when mass-shift mode was used, and the oxides ($^{75}As^{16}O^+$ and $^{51}V^{16}O^+$) were monitored in comparison with the on-mass mode ($^{75}As^+$ and $^{51}V^+$). On the other hand, the sensitivity and limits of detection were improved for Cd, Cr, Ni, and Pb when the same target masses were selected in both quadrupoles (on-mass mode). According to the

Table 2. Sensitivities and limits of detection and quantification for As, Cd, Cr, Ni, Pb, and V for various oxygen flow rates into the octopole reaction system using on-mass (quadrupole 1 = quadrupole 2) and mass-shift (quadrupole 2 = quadrupole 1 + 16) ICP-MS/MS.

		No gas			0.50 mL min^{-1} O_2			0.75 mL min^{-1} O_2		
Analyte	Mode	Sensitivity	Limit of detection (ng L^{-1})	Limit of quantitation (ng L^{-1})	Sensitivity	Limit of detection (ng L^{-1})	Limit of quantitation (ng L^{-1})	Sensitivity	Limit of detection (ng L^{-1})	Limit of quantitation (ng L^{-1})
As	On-mass	2.8×10^4	5	17	36	500	1.7×10^3	1	8×10^3	2.7×10^4
	Mass-shift	–	–	–	7.9×10^3	60	200	3.7×10^3	6	20
Cd	On-mass	5.2×10^4	1	3	1.5×10^4	1	3	9.8×10^3	5	17
	Mass-shift	–	–	–	2	1×10^3	3.3×10^3	0.3	9×10^3	3×10^4
Cr	On-mass	1.6×10^5	40	133	2.4×10^4	50	167	1.9×10^4	20	67
	Mass-shift	–	–	–	2.9×10^3	70	233	1.1×10^3	50	167
Ni	On-mass	4.8×10^4	100	333	1.0×10^4	50	167	4.8×10^3	20	67
	Mass-shift	–	–	–	249	100	333	98	200	667
Pb	On-mass	1.2×10^5	10	33	5.9×10^4	20	67	3.3×10^4	90	300
	Mass-shift	–	–	–	52	400	1.3×10^3	17	300	1×10^3
V	On-mass	1.8×10^5	4	13	260	1×10^3	3.3×10^3	7	2×10^4	6.7×10^4
	Mass-shift	–	–	–	4.3×10^4	10	33	1.9×10^4	5	17

ICP-MS/MS, inductively coupled plasma–tandem mass spectrometry.

literature (Agilent Technologies 2015), the reactions of As and V with oxygen are thermodynamically favorable ($\Delta H_r = -0.63$ eV for As and -0.85 eV for V) while for Cd, Cr, Ni, and Pb, endothermic and less favorable reactions with O_2 are generally observed ($\Delta H_r = +1.38$ eV, $+2.36$ eV, $+2.9$ eV for Cr, Ni, and Pb, respectively).

It was demonstrated by Sugiyama and Nakano (2014) that when the ORS^3 was pressurized with O_2, the prevalent forms for the evaluated analytes were $^{75}As^{16}O^{+}$, $^{112}Cd^{+}$, $^{52}Cr^{+}$, $^{60}Ni^{+}$, $^{208}Pb^{+}$, and $^{51}V^{16}O^{+}$. In these cases, the lowest limits were obtained for Cd (1 ng L^{-1}) and Pb (20 ng L^{-1}) at 0.5 mL min^{-1} and for As (6 ng L^{-1}), Cr (20 ng L^{-1}), Ni (20 ng L^{-1}), and V (5 ng L^{-1}) at 0.75 mL min^{-1} O_2. It is important to consider that despite sensitivity losses caused by the use of O_2 into the cell, background signals and the standard deviation for the blank were also significantly lower. Thus the limits of detection were generally better or similar to those obtained in single quadrupole mode. In spite of the possibility of the instrument operation using O_2 into the ORS^3 for single quadrupole mode, the reaction processes presented low selectivity and may lead to inaccurate results, and hence this strategy was not evaluated in this work.

Accuracy and practical analysis

The accuracy of procedures using on-mass and mass-shift modes for different oxygen flow rates was checked by analysis of two plant-CRMs. Recoveries for NIST SRM 1515 apple leaves and NIST SRM 1573a tomato leaves are shown in Tables 3 and 4, respectively. In the single mode, the appropriate recoveries were only obtained for Cd and Pb in NIST SRM 1515 apple leaves and Ni in NIST SRM 1573a tomato leaves. For the MS/MS mode, the use of O_2 as reaction gas combined with mass-shift mode for As and V (AsO^{+} and VO^{+}) and on-mass mode for Cd, Cr, Ni, and Pb (Cd^{+}, Cr^{+}, Ni^{+}, and Pb^{+}) provided recoveries of 85–113% for 0.5 mL min^{-1} O_2 and 68–112% for 0.75 mL min^{-1} in both CRMs. Under these conditions, for 0.5 mL min^{-1} $O_{2,}$ no statistically significant differences (*t*-test) were observed at 95% confidence level, and the calculated *t* values were lower than 4.3 (Tables 3 and 4). However, for 0.75 mL min^{-1} O_2, the determined concentrations for V in NIST SRM 1515 apple leaves and of Cd, Cr, and V in NIST SRM 1573a tomato leaves were not in agreement with the certified values at the same confidence level, and *t* values were up to 33.8.

It is worth noting that when O_2 was used in mass-shift mode for elements with lower reactivity, inaccurate results (e.g., Ni recoveries up to 173%) or inadequate sensitivity (as for Cd in the apple leaves) were generally obtained and the determined values were statistically distinct. The same effect is observed for more reactive elements monitored in on-mass mode, where low sensitivities impaired the determination of As and V. The combination of both on-mass and mass-shift modes for different elements in the same run is an interesting strategy for sensitive and accurate analysis by ICP-MS/MS. Average precision values, as the relative standard deviation, were lower for the MS/MS mode (8%) in comparison with single quadrupole mode (11%). Furthermore, the average precision for all analytes in mass-shift mode (7.5%) was lower than for the on-mass mode (9.1%).

Considering sensitivities, limits of detection, quantification, and accuracy, the procedure using 0.5 mL min^{-1} O_2 and monitoring of $^{75}As^{16}O^{+}$, $^{112}Cd^{+}$, $^{52}Cr^{+}$, $^{60}Ni^{+}$, $^{208}Pb^{+}$, and $^{51}V^{16}O^{+}$ species was used for the analysis of phytotherapic drugs (Table 5). Concentrations ranging <0.01–0.168 µg g^{-1} As, <0.0002–0.03 µg g^{-1} Cd, 0.27–0.82 µg g^{-1} Cr, 0.25–1.18 µg g^{-1} Ni,

Table 3. Determination of As, Cd, Cr, Ni, Pb, and V in NIST SRM 1515 apple leaves (in µg g^{-1}, $n = 3$), recovery (in %), and calculated t value (t_{calc}) at the 95% confidence level (tabulated t value = 4.303) under various O_2 flow rates by on-mass (quadrupole 1 = quadrupole 2) and mass-shift (quadrupole 2 = quadrupole 1 + 16) ICP-MS/MS.

			No gas			0.50 mL min^{-1} O_2			0.75 mL min^{-1} O_2		
Analyte	Certified value (µg g^{-1})	Mode	Determined (µg g^{-1})	Recovery (%)	*t* value	Determined (µg g^{-1})	Recovery (%)	*t* value	Determined (µg g^{-1})	Recovery (%)	*t* value
As	0.038 ± 0.007	On-mass	0.13 ± 0.01	3×10^3	15.9	<0.8	–	–	<1.3	–	–
		Mass-shift	–	–	–	0.033 ± 0.002	88	4.2	0.035 ± 0.003	93	1.7
Cd	0.013 ± 0.002	On-mass	0.01 ± 0.01	108	0.5	0.011 ± 0.001	85	3.5	0.015 ± 0.001	112	3.5
		Mass-shift	–	–	–	<0.2	–	–	<1.5	–	–
Cr	0.3	On-mass	0.58 ± 0.08	193	6.1	0.33 ± 0.06	112	0.9	0.28 ± 0.02	94	1.7
		Mass-shift	–	–	–	0.22 ± 0.02	72	6.9	0.34 ± 0.05	113	1.4
Ni	0.91 ± 0.12	On-mass	1.3 ± 0.6	142	1.1	0.89 ± 0.09	98	0.3	0.93 ± 0.09	102	0.4
		Mass-shift	–	–	–	0.93 ± 0.08	103	0.4	1.56 ± 0.08	171	14.7
Pb	0.470 ± 0.024	On-mass	0.45 ± 0.08	95	0.4	0.46 ± 0.07	99	0.2	0.48 ± 0.04	102	0.4
		Mass-shift	–	–	–	0.29 ± 0.01	61	31.2	0.36 ± 0.02	77	9.5
V	0.26 ± 0.03	On-mass	0.19 ± 0.01	74	12.1	<1	–	–	<3	–	–
		Mass-shift	–	–	–	0.24 ± 0.01	94	3.4	0.177 ± 0.005	68	28.8

ICP-MS/MS, inductively coupled plasma–tandem mass spectrometry.

Table 4. Determination of As, Cd, Cr, Ni, Pb, and V in NIST SRM 1573a tomato leaves ($n = 3$), recovery (%), and calculated t value at the 95% confidence level (tabulated t value $= 4.303$) under various O_2 gas flow rates for on-mass (quadrupole 1 = quadrupole 2) and mass-shift (quadrupole 2 = quadrupole 1 + 16) ICP-MS/MS.

			No gas			0.50 mL min^{-1} O_2			0.75 mL min^{-1} O_2		
Analyte	Certified Value (µg g^{-1})	Mode	Determined (µg g^{-1})	Recovery (%)	*t* value	Determined (µg g^{-1})	Recovery (%)	*t* value	Determined (µg g^{-1})	Recovery (%)	*t* value
As	0.112 ± 0.004	On-mass	0.15 ± 0.01	134	6.6	<0.8	–	–	<1.3	–	–
		Mass-shift	–	–	–	0.11 ± 0.03	96	0.1	0.10 ± 0.01	90	2
Cd	1.52 ± 0.04	On-mass	1.22 ± 0.02	80	26	1.57 ± 0.06	103	1.4	1.13 ± 0.02	75	33.8
		Mass-shift	–	–	–	1.9 ± 0.3	126	2.2	1.58 ± 0.07	104	1.5
Cr	1.99 ± 0.06	On-mass	1.62 ± 0.1	81	6.4	2.24 ± 0.02	113	21.6	1.5 ± 0.1	76	8.5
		Mass-shift	–	–	–	1.94 ± 0.05	98	1.7	2.00 ± 0.02	101	0.9
Ni	1.59 ± 0.07	On-mass	1.7 ± 0.1	104	1.9	1.5 ± 0.3	93	0.5	1.7 ± 0.3	104	0.6
		Mass-shift	–	–	–	2.0 ± 0.1	126	7.1	2.5 ± 0.3	155	5.3
Pb	–	On-mass	0.55 ± 0.01	–	–	0.49 ± 0.03	–	–	0.61 ± 0.05	–	–
		Mass-shift	–	–	–	0.42 ± 0.01	–	–	0.47 ± 0.05	–	–
V	0.835 ± 0.010	On-mass	0.64 ± 0.02	77	16.9	<1	–	–	<3	–	–
		Mass-shift	–	–	–	0.84 ± 0.03	100	0.3	0.60 ± 0.02	72	20.4

ICP-MS/MS, inductively coupled plasma–tandem mass spectrometry.

Table 5. Determination of As, Cd, Cr, Ni, Pb, and V in phytotherapic drugs by ICP-MS/MS ($n = 3$).

Sample	As (μg g^{-1})	Cd (μg g^{-1})	Cr (μg g^{-1})	Ni (μg g^{-1})	Pb (μg g^{-1})	V (μg g^{-1})
Green tea	<0.01	0.023 ± 0.001	0.48 ± 0.04	1.18 ± 0.03	0.52 ± 0.02	0.19 ± 0.05
Boldo	0.168 ± 0.004	0.006 ± 0.001	0.82 ± 0.04	0.87 ± 0.06	0.40 ± 0.04	2.4 ± 0.2
Kava-kava	<0.01	<0.0002	0.27 ± 0.02	0.25 ± 0.01	<0.003	0.026 ± 0.001
Ginseng	<0.01	0.03 ± 0.01	0.43 ± 0.03	0.50 ± 0.03	0.22 ± 0.08	0.92 ± 0.05
Limit of detection	0.01	0.0002	0.008	0.008	0.003	0.002
International Conference on Harmonization limits	1.5	0.5	1100	20	0.5	10
The United States Pharmacopeia limits	0.15	2.5	–	50	0.5	10

<0.003–0.52 μg g^{-1} Pb, and 0.026–2.4 μg g^{-1} V were found in Boldo 200 mg, Ginseng 300 mg, Green Tea 250 mg, and Kava-kava 100 mg medication. According to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and The USP guidelines, the impurity concentrations were below the maximum limits allowed in most cases, except for the samples Boldo (for As) and green tea (for Pb), which presented values slightly higher than the established limits. (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use 2016; The United States Pharmacopeia 2015a). In all cases, the limits of detection of this procedure were sufficiently lower compared to values specified in the legislation.

Higher concentrations of toxic metals such as As (<0.005–3.77 μg g^{-1}), Cd (<0.01–0.368 μg g^{-1}), and Pb (<0.02–48.6 μg g^{-1}) were described in the literature, but still within the range found in the this work (Dolan et al. 2003). In another paper, 19 elements were determined in three types of herbal products from different Asian countries by ICP-MS (Nookabkaew, Rangkadilok, and Satayavivad 2006). The determined concentrations of As (0.01–0.75 μg g^{-1}), Cd (0.001–4.77 μg g^{-1}), Cr (0.205–12.42 μg g^{-1}), Ni (0.368–9.19 μg g^{-1}), Pb (0.06–64.4 μg g^{-1}), and V (0.06–7.72 μg g^{-1}) were in a wide range and are consistent with the values obtained in the present work.

Conclusion

The use of tandem mass spectrometry with oxygen into the ORS^3 and the combination of on-mass and mass-shift modes for different analytes was demonstrated as efficient strategies to correct for spectral overlaps and provide accurate determinations. Due to its high sensitivity and compliance with the most recent international legislations, the reported procedure may be considered adequate for the determination of inorganic impurities in phytotherapic drugs and pharmaceutical preparations.

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