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Evaluation of dilute-and-shoot procedure for determination of inorganic impurities in liquid pharmaceutical samples by ICP OES

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ABSTRACT

This study evaluated a dilute-and-shoot procedure for determination of 23 elemental impurities in liquid pharmaceutical samples by inductively coupled plasma optical emission spectrometry (ICP OES). Two dilution factors were tested for analysis of four liquid drugs (10-fold and 20-fold dilution in 0.14 mol L^{-1} HNO_3). Microwave-assisted digestion using 7.0 and 2.0 mol L^{-1} HNO_3 was used for comparison purposes. The accuracy and precision were evaluated by addition-recovery experiments and satisfactory recoveries were obtained only when matrix effects were corrected for applying internal standardization (IS) or one-point standard addition (OP SA) calibration methods. Bismuth, Ge and Y were evaluated as internal standards and recoveries ranged from 86 to 116% when the best internal standard was employed for each analyte. For OP SA, recoveries varied from 78 to 119%. The relative standard deviations for all elements and samples were lower than 9% for both calibration methods applied. The LODs obtained for IS and OP SA were lower than the lower level of addition suggested by the Chapter 233, except for Pb and Tl, and all samples are within the limits recommended by USP considering the maximum daily dose of each liquid drug and the diluted factor adopted in the analytical procedure. The tailored calibration methods were essential to correct for matrix effects enabling application of dilute-and-shoot procedure for samples 10-fold diluted and making feasible the elemental impurities analysis of liquid drugs by ICP OES.

1. Introduction

After a century of the Chapter 231 validity, which regulated the determination of elemental impurities in pharmaceutical samples using sulfide precipitation and evaluation of the staining resulting from the suspension, the United States Pharmacopeia (USP) has established two news Chapters, 232 [1] and 233 [2]. These Chapters proposed analytical procedures for determination of 24 elemental impurities by either inductively coupled plasma optical emission spectrometry (ICP OES) or inductively coupled plasma mass spectrometry (ICP-MS). It is well known how some of these elements are also critical when present in foods, such as fishes [3]. On the other hand, ICP OES and ICP-MS are largely used for trace analysis and even the combination of both instrumental methods was already demonstrated and recently re-evaluated [4].

Sample preparation methods of pharmaceutical products can include simple dissolution in acids [5] or organic solvents [6,7], and procedures generally used for active pharmaceutical ingredients (APIs) and solid drugs (pills and tablets), such as microwave-induced combustion [8,9] and microwave-assisted digestions [9–14] for elemental determination or, when needed, for speciation analysis of toxic elements [15]. Dilute-and-shoot procedures are interesting for fast routine analysis [16], however, for elemental determination in complex samples by instrumental methods based on plasma, the direct introduction of only diluted samples must be carefully evaluated due to the possibility of matrix effects associated with nebulization, transport and plasma energy. Differences among complex samples properties and standard solutions used for calibration, for instance, viscosities, dissolved carbon compounds, main matrix constituents, such as high concentrations of easily ionizable elements, can cause severe transport or spectral interferences [17,18].

For complex matrices analysis, External Calibration (EC) method may not be effective due to the physical and chemical differences among samples and reference solutions. Some calibration methods alternatives to EC can be used to correct for matrix effects [19], such as standard additions (SA) [20], internal standardization (IS) [13,21], standard dilution analysis (SDA) [22], multi-energy calibration (MEC) [23] and one-point standard addition (OP SA) [24,25].

For MEC and SDA only two calibrations solutions are needed per sample. In the MEC method, the instrument response at several wavelengths is monitored for each analyte [23,26]. On the other hand, SDA is a novel calibration strategy based on combining the methods of IS and SA to simultaneously correct for matrix effects and signal

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Table 1
Function, active principle and excipients for the liquid drug samples analyzed.

Sample	Function	Active principle	Excipient
A	Hepatic metabolic disorders	Choline citrate, betaine and racemetionine	Sorbitol, sodium saccharin dihydrate, quinoline yellow, methylparaben, propylparaben, pineapple aroma and water
B	Antipyretic and analgesic	Dipyrone monohydrate	Sodium phosphate monobasic, sodium phosphate dibasic, sodium saccharin and water
C	Antiallergic	Dexchlorpheniramine maleate	Sucrose, ethyl alcohol, orange flavor, sodium citrate, sodium chloride, menthol, methylparaben, propylparaben, propylene glycol, sorbitol and water
D	Analgesic	Paracetamol	Citric acid, sodium benzoate, sodium cyclamate, sodium saccharin, sodium metabisulphate, macrogol 400, caramel flavor, yellow colorant and water

fluctuations [19,22]. Although both methods are effective for matrix effects correction, a minor difficulty associated to these calibrations strategies is data processing. Probably, the implementation of data processing software to automatically calculate the analyte concentration in the sample would contribute to increase the adoption of both strategies in routine analysis.

In SA calibration, the analyte is added to the sample in increasing concentrations, thus, standard solutions are prepared in the sample medium correcting for matrix effects [19,20]. Usually more than four standard solutions are used to analytical curve construction. Thereby, the use of multi-point SA calibration can be a time-consuming method not interesting for analysis of a high number of samples. This problem can be avoided employing OP SA calibration, since only two standards are used per sample. Proposed by Zhu and Chiba (2012) [27], OP SA calibration was used for elemental analysis by ICP-MS combining gravimetric standard additions method with internal standardization. The analyte concentration is determined considering the signal and mass of analyte using appropriate equation proposed by authors. This calibration strategy was also used to determine As in seawater [24] and Sb in natural waters [25] by photochemical vapor generation ICP-MS. There are no reports in the literature about matrix effects correction using OP SA method for ICP OES analysis.

Other well established calibration method is the IS. In this, the calibration curve is plotting correlating the standard concentrations with the ratio standard signal/internal standard signal. It is expected that internal standard controls the sample processing during the analyses correcting for possible fluctuations [17,19,28]. So, a constant concentration of internal standard is added to all samples, standard solutions and analytical blanks and, preferably, the selected internal standard would present chemical and physical properties similar to the analyte. Thereby, the selected internal standard must not be present in the original samples. In determinations by ICP OES, the use of Y as internal standard is commonly reported in the literature [13,21,29–32]. Yttrium was used as internal standard for determination of As, Cd, V, Cr, Ni, Cu, Mo, Ru, Rh and Pd in two excipients by ICP-MS and Tl was used as internal standard for Os, Ir, Pt, Pb and Hg [13]. However, after harmonization with International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Tl was incorporated as analyte in the Chapter 232 [33].

Therefore, considering the need of simplifying drug analysis aiming routine determinations this work evaluated the application of a dilute-and-shoot approach associated with IS or OP SA for determination of Ag, As, Au, Ba, Cd, Co, Cr, Cu, Hg, Ir, Li, Mo, Ni, Pb, Pd, Pt, Rh, Ru, Sb, Se, Sn, Tl and V in liquid drugs. The applicability of the developed procedure was assessed by comparison of analyte determinations using as reference microwave-assisted digestion as well as by determining dissolved organic carbon and evaluation of carbon effects on plasma signals.

2. Experimental

2.1. Samples and sample preparation

Four drug samples marketed in liquid form (oral administration route) were analyzed (Table 1). Two dilution factors were evaluated using 0.14 mol L^{-1} HNO_3 as diluent: (1) 10-fold and (2) 20-fold diluted. For comparison purposes two sample preparation methods were applied (1) microwave-assisted acid digestion in 2.0 mol L^{-1} HNO_3 and (2) microwave-assisted acid digestion in 7.0 mol L^{-1} HNO_3. For samples digestion, approximately 1.0 mL were placed in the teflon-perfluoroalkoxy alkanes (PFA) digestion vessels and microwave-assisted digested in triplicate (UltraWave, Milestone, Sorisole, Italy) in 7.0 mL of both nitric acid concentrations. Subsequently, digests were diluted to 40.0 mL with distilled-deionized water. Volumes of 150 mL of water and 5 mL of concentrated nitric acid were inserted into the single reaction chamber (SRC) and the chamber was pressurized with nitrogen gas to 40 bar. The microwave heating program was applied as follows: (1) 2.5 min to reach 140 °C, (2) 2.5 min hold at 140 °C, (3) 2.5 min to reach 180 °C, (4) 2.5 min hold at 180 °C, (5) 10 min to reach 220 °C and (6) 10 min hold at 220 °C.

2.2. Instrumentation

Elemental analysis was performed using an iCAP 6000 ICP OES (Thermo Fisher Scientific, EUA) operated in axial view and at robust conditions. Argon (99.996%, White Martins-Praxair, Sertãozinho, SP, Brazil) was used in all measurements. A *V-Groove* nebulizer was used aiming the introduction of samples with high solids contents. Plasma operating conditions are described in Table 2.

2.3. Reagents and standard solutions

Experiments were performed using HNO_3 (Synth, Diadema, SP, Brazil) purified in a sub-boiling distillation system Distillacid™ BSB-939-IR (Berghof, Eningen, Germany) and ultrapure water, resistivity > 18.2 MΩ cm, (Milli-Q®, Millipore, Bedford, MA, USA). Standard solutions used for ICP OES calibration and for addition and recovery experiments were prepared by dilution of 1000 mg L^{-1} of Ag, As, Au, Ba, Cd, Co, Cr, Cu, Hg, Ir, Li, Mo, Ni, Pb, Pd, Pt, Rh, Ru, Sb, Se, Sn, Tl and V (Qhemis, São Paulo, SP, Brazil) in 0.14 mol L^{-1} HNO_3 medium, as well as the internal standards evaluated: Bi, Ge and Y.

For IS method, the concentrations of the solutions used for analytical calibration curve for all elements were 0; 0.010; 0.025; 0.050; 0.10; 0.20; 0.30 and 0.50 mg L^{-1} prepared in 0.14 mol L^{-1} HNO_3 medium and 0.10 mg L^{-1} of each internal standard was added to each solution, analytical blank and diluted and digested samples. The accuracy and precision of the methods were evaluated by addition and recovery experiments in two concentration levels: 0.10 and 0.30 mg L^{-1}. Spikes were added before microwave-assisted digestion.

For OP SA method, calibration curves were obtained using two calibration standards for each sample. Standard 1 is composed of sample + blank and Standard 2 is composed of sample + standard addition [24,25,27]. Thus, Standard 1 was composed of sample 10 or 20-fold diluted in 0.14 mol L^{-1} HNO_3 and Standard 2 contained sample 10 or 20-fold diluted and 0.10 mg L^{-1} of all analytes. The blank was used in the Standard 1 to adjust with the standard addition volume of the Standard 2. Accuracies were evaluated by addition and recovery experiments in concentrations of 0.10 and 0.20 mg L^{-1} and three concentrations of standard addition were evaluated for each level. Thereby,

Table 2
Instrumental parameters for ICP OES determinations.

Instrument parameter	Operating condition
RF applied power (kW)	1.2
Plasma gas flow rate (L min^{-1})	12
Auxiliary gas flow rate (L min^{-1})	0.50
Carrier gas flow rate (L min^{-1})	0.70
Integration time (s)	15
Sample introduction flow rate (mL min^{-1})	1.0
Nebulizer	V-Groove
Spray chamber	Cyclonic
Number of replicates	3

Element	Emission line (nm)	Element	Emission line (nm)	Element	Emission line (nm)
Ag	328.068	Hg	184.950	Pt	214.423
As	189.042	Ga	294.363	Rh	343.489
Au	242.795	Ge	265.118	Ru	267.876
Ba	455.403	Ir	224.268	Sb	217.581
Bi	223.061	Li	670.784	Se	196.090
Cd	226.502	Mo	202.030	Sn	189.989
Co	228.616	Ni	221.647	Tl	190.856
Cr	357.869	Pb	220.353	V	292.402
Cu	324.754	Pd	340.458	Y	371.030

for level 0.10 mg L^{-1} Standard 1 was composed of sample 10 or 20-fold diluted in 0.14 mol L^{-1} HNO_3 and all analytes in the concentration of 0.10 mg L^{-1} and the Standard 2 contained sample 10 or 20-fold diluted and all analytes in the concentrations evaluated (0.20; 0.40 and 0.60 mg L^{-1}). For the concentration 0.20 mg L^{-1} Standard 1 was composed of sample 10 or 20-fold diluted in 0.14 mol L^{-1} HNO_3 and all analytes at 0.20 mg L^{-1} and the Standard 2 contained sample 10 or 20-fold diluted and all analytes in the concentrations evaluated (0.40; 0.60 and 1.0 mg L^{-1}).

The dissolved organic carbon concentration was determined in all digests and diluted solutions. Carbon was determined using the atomic emission line 193.090 nm and dehydrated oxalic acid (Mallinckrodt Chemicals, St. Louis, MO, USA) was used as the carbon source for preparing calibrating analytical solutions. Carbon effects were also investigated by determination of all analytes in standard solutions containing increasing concentrations of carbon: 0.50; 1.0; 2.0 and 3.0% m v^{-1}.

3. Results and discussion

3.1. Dilute-and-shoot procedure and matrix effects

For analysis of liquid pharmaceutical samples, application of a dilute-and-shoot strategy is interesting for routine analysis. However, taking into account the solution characteristics for elemental determination by ICP OES, some important aspects must be evaluated, such as residual acidity (RA), total dissolved solids (TDS) and dissolved organic carbon for avoiding matrix effects and also for avoiding wear of equipment [17]. Thus, the dilute-and-shoot procedure was applied for liquid drug samples 10 and 20-fold diluted and microwave-assisted digested using 7.0 and 2.0 mol L^{-1} HNO_3. Dissolved organic carbon was determined in all samples (Fig. 1).

As expected, dissolved organic carbon concentrations were significantly higher for only diluted samples when compared with microwave-assisted digested samples. Additionally, the four samples analyzed have distinct concentrations of dissolved organic carbon since they contain different APIs and excipients (Table 1), characterizing complex and different matrices.

Solutions with high carbon concentrations may cause changes in the plasma characteristics and, consequently, in distribution of species in the argon plasma. Grindlay et al. [34] showed that sensitivities for As, Au, Hg, Sb and Se are higher for carbon-containing solutions than for solutions without carbon. Besides the changes in the plasma characteristics, the authors related the matrix effects for these elements to increase of analytical signals caused by charge transfer reactions between C^+ and the respective element in the plasma. Other elements, such as Cd, Pb, Ir and Pt, could also be involved in carbon based charge transfer reactions. [34,35].

Thus, carbon effects were evaluated monitoring the signal intensities for all analytes in standard solutions containing increasing concentrations of carbon. As expected, increments of signal intensities were observed for As, Au, Sb, Se and Pt, however, this was not observed for Hg neither for the other analytes (Fig. 2). For As, Au, Sb, Se and Pt the signal intensities were normalized when using IS for all concentrations of carbon evaluated.

Bismuth, Ga, Ge and Y were evaluated as internal standards for 23 analytes. Bismuth was the best internal standard for Hg, Mo and Rh; and Ge was the best one for Pd, Se, Sn and Tl. For Ag, As, Au, Ba, Cd, Co, Cr, Cu, Ir, Li, Ni, Pb, Pt, Ru, Sb and V the best internal standard was Y.

Another effective alternative to correct for matrix effects is the SA method, however, the amount of sample consumed and preparation time are drawbacks associated with this method because more than four addition points are needed to obtain analytical calibration curve for each sample and analyte [19,20]. These disadvantages can be avoided

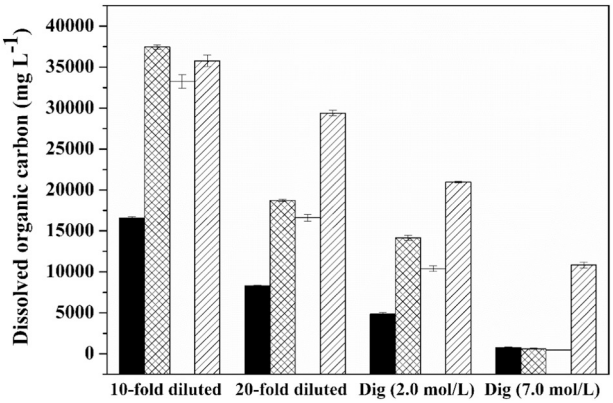

Fig. 1. Dissolved organic carbon in samples (A–D) for each sample preparation procedure (mg L^{-1}, mean ± standard deviations, n = 3). (■) A; (▨) B; (□) C; (*transversal traces*) D. Dig means microwave-assisted digestion.

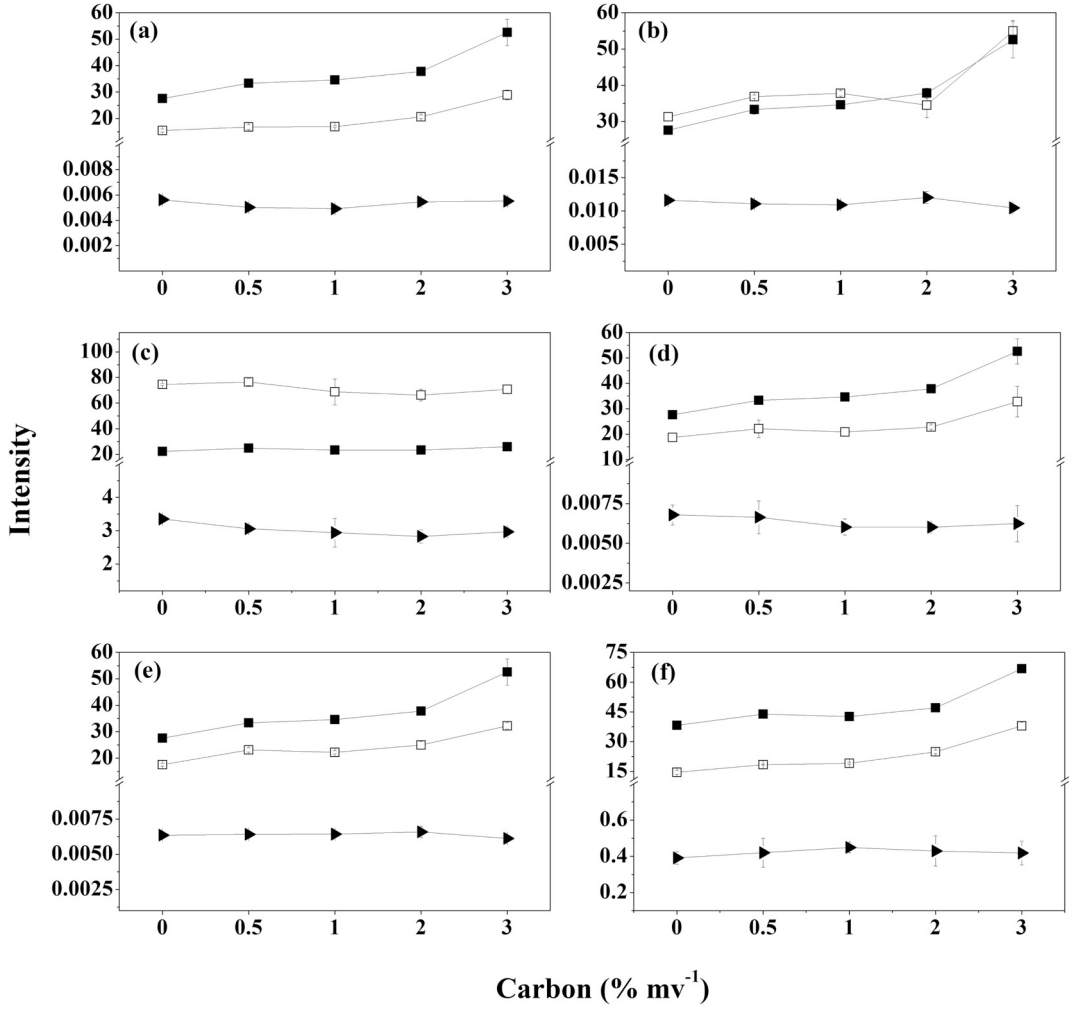

Fig. 2. Signal intensities for (a) As, (b) Au, (c) Hg, (d) Pt, (e) Sb and (f) Se in standard solutions containing increasing concentrations of carbon. (■) Internal standard signal; (□) Analyte signal; (►) Ratio of the analyte signal/internal standard signal.

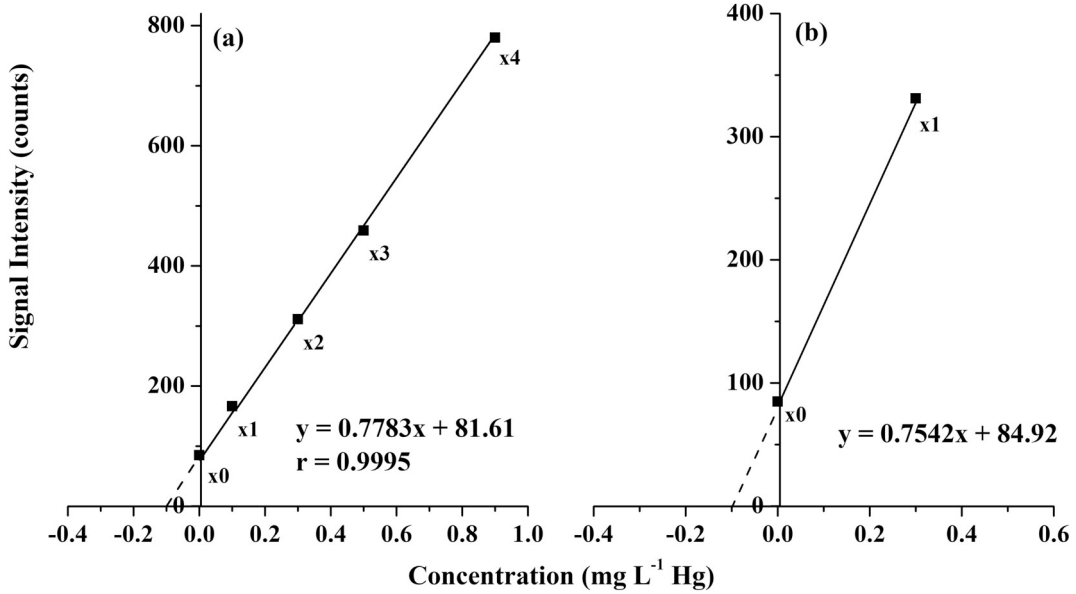

Fig. 3. Linear model for SA (a) and OP SA curve (b) for Hg determination in drug sample A 10-fold diluted. (a) x0 = 0.10, x1 = 0.20 and x2 = 0.40 mg L^{-1} of Hg. (b) x0 = 0.10 and x1 = 0.40 mg L^{-1} of Hg.

Table 3
Evaluation of calibration methods used for Ag, As, Au, Ba, Cd, Co, Cr, Cu, Hg, Ir, Li, Mo, Ni, Pb, Pd, Pt, Rh, Ru, Sb, Se, Sn, Tl and V determination by ICP OES in liquid drug samples (A–D) 10-fold diluted. Recovery (relative standard deviation, n = 3) for addition level of 0.10 mg L^{-1}.

Analyte	IS	Samples															
		A				B				C				D			
		EC	IS	SA	OP SA	EC	IS	SA	OP SA	EC	IS	SA	OP SA	EC	IS	SA	OP SA
Ag	Y	92	102	125	108	81	108.0	94	104	91	99	65	78	140	104	144	92
		(2)	(1)	(6)	(8)	(1)	(0.3)	(4)	(8)	(7)	(8)	(7)	(9)	(4)	(2)	(6)	(6)
As	Y	130	98,0	93	91	132	98	92	97	152	96	97	101	141	109	93.1	84
		(2)	(0.2)	(4)	(6)	(4)	(6)	(4)	(7)	(3)	(1)	(4)	(2)	(5)	(3)	(0.4)	(2)
Au	Y	81	108	97	107	125	99	103	112	83	95	64	94	135	98	97	96
		(6)	(2)	(4)	(6)	(2)	(1)	(1)	(6)	(1)	(2)	(8)	(3)	(2)	(2)	(4)	(5)
Ba	Y	81	92	97	94	85	96	103	98	78	96	102	97	121	98	97	94
		(2)	(3)	(4)	(4)	(2)	(4)	(2)	(5)	(3)	(4)	(3)	(7)	(5)	(3)	(2)	(2)
Cd	Y	84	100	97.0	95	87	99	101	98	82	102.0	99	97	125	102	97	96
		(3)	(1)	(0.7)	(4)	(2)	(4)	(1)	(4)	(1)	(0.2)	(2)	(7)	(3)	(1)	(2)	(3)
Co	Y	90	100	96	96	95	95	100	98	87.1	95.0	99	97	133	95	97.0	95
		(4)	(2)	(1)	(2)	(2)	(5)	(1)	(4)	(0.4)	(0.4)	(2)	(7)	(3)	(1)	(0.6)	(3)
Cr	Y	81.2	111	97	94	97	103	95	97	79	92	102	99	119	92	98	96
		(0.2)	(6)	(3)	(2)	(3)	(5)	(10)	(5)	(4)	(5)	(6)	(7)	(5)	(3)	(2)	(2)
Cu	Y	83.1	103	97	93	84	94	96	98	78	94	103	98	119	95	97	94
		(0.2)	(6)	(4)	(4)	(2)	(5)	(10)	(4)	(2)	(3)	(3)	(7)	(5)	(3)	(2)	(2)
Hg	Bi	81	92	92	95	60	81	95	99	83	90	98	95	120	89	66	107
		(2)	(6)	(2)	(4)	(5)	(4)	(9)	(3)	(1)	(9)	(1)	(7)	(2)	(8)	(2)	(6)
Ir	Y	85	101	94	100	87	98	97	98	82.1	101.0	93	101	126	103.0	86	93
		(4)	(1)	(2)	(4)	(1)	(4)	(5)	(3)	(0.3)	(0.7)	(4)	(9)	(2)	(0.3)	(5)	(3)
Li	Y	80	110	93	95	143	106	104	100	83.2	100	103	98	147	116	98	97
		(2)	(5)	(3)	(2)	(2)	(4)	(1)	(3)	(0.3)	(4)	(3)	(6)	(5)	(3)	(1.4)	(3)
Mo	Bi	82	100	93	96	92	99	97	95	81	88.0	97	97	123	87	96	92
		(4)	(1)	(1)	(2)	(2)	(1)	(3)	(3)	(6)	(0.3)	(3)	(9)	(18)	(9)	(1)	(3)
Ni	Y	81	100	95	95	85	93	99	101	79.5	95.0	97	96	121	96	93	94
		(4)	(2)	(2)	(3)	(3)	(5)	(2)	(1)	(0.3)	(0.3)	(3)	(8)	(2)	(1)	(4)	(3)
Pb	Y	79	91	94	95	77	94	99	97	78.0	105	97	96	112	98	91	93
		(3)	(3)	(2)	(6)	(1)	(3)	(3)	(3)	(0.3)	(7)	(4)	(9)	(4)	(3)	(3)	(6)
Pd	Ge	101	100	98	104	65	102	91	101	85	119.1	99	103	86	108	99.2	88
		(4)	(1)	(6)	(6)	(5)	(8)	(9)	(7)	(6)	(0.3)	(3)	(9)	(25)	(1)	(0.2)	(2)
Pt	Y	86	92	97	96	68	87	91	109	83.5	96	87	94	127	94	89	88
		(1)	(3)	(6)	(8)	(3)	(2)	(8)	(4)	(0.3)	(3)	(2)	(9)	(3)	(1)	(2)	(2)
Rh	Bi	83	94	80	86	93	94	90	84	79.0	91	87	96	121	106	69	81
		(5)	(7)	(1)	(9)	(4)	(8)	(4)	(6)	(0.3)	(6)	(7)	(8)	(7)	(1)	(5)	(7)
Ru	Y	85	95	94	91	85	95	102	99	81.2	99	102	101	121	97.0	92	93
		(3)	(4)	(3)	(2)	(1)	(2)	(2)	(5)	(0.3)	(5)	(5)	(9)	(2)	(0.2)	(4)	(4)
Sb	Y	86	91	92	97	84	97	95	95	80.1	100	100	109	112.0	92	97	94
		(5)	(5)	(3)	(4)	(2)	(4)	(1)	(6)	(0.3)	(3)	(6)	(7)	(0.5)	(2)	(2)	(7)
Se	Ge	80	116	94	99	75	80	93	119	84	95.1	98	91	135	103	86	80
		(15)	(1)	(4)	(9)	(5)	(8)	(6)	(8)	(4)	(0.3)	(4)	(6)	(18)	(7)	(4)	(8)
Sn	Ge	86	100	89.0	94	97	98	99	95	76.0	105	99	102	117	111	89	84
		(5)	(1)	(0.4)	(2)	(8)	(7)	(5)	(6)	(0.3)	(3)	(9)	(6)	(10)	(4)	(9)	(4)
Tl	Ge	78	102	< SE[a]	< SE[a]	74	87.1	< SE[a]	< SE[a]	69.1	91	< SE[a]	< SE[a]	84	86	< SE[a]	< SE[a]
		(1)	(1)			(2)	(0.5)			(0.3)	(4.1)			(16)	(5)		
V	Y	81	96	95	93	88	103	102	99	82.1	105	102	98	128	107	95	93
		(2)	(5)	(2)	(2)	(2)	(4)	(2)	(4)	(0.3)	(4)	(2)	(8)	(5)	(3)	(3)	(2)

[a] SE: Standard error.

using OP SA calibration, since only two standards are used for sample. However, for proper accuracy of this method, the concentration of the addition point must be evaluated because the added standard concentration cannot be too higher compared to the analyte concentration [27,36,37]. Thus, OP SA also was evaluated in the study to correct for matrix effects. For comparison purposes, EC and SA were evaluated.

3.2. Analytical performance for each calibration method

The main figures of merit for evaluating analytical performance (accuracy, linear correlation coefficient and standard error) were calculated for all calibrations methods evaluated. For EC, the calibration curve was built by plotting the analyte concentration on the x-axis with the signal intensity (SI) on the y-axis and the analyte concentration in the sample ($C_{analyte}$) is obtained using the relationship $C_{analyte} = (SI - b) / a$, where (b) is the intercept of the regression line and (a) is the slope of straight line.

The IS calibration curve was built using the same approach, however with the ratio analyte signal/internal standard signal on the y-axis. However, for SA calibration, the $C_{analyte}$ was obtained by extrapolation of the x axis at y = 0, (i.e. $C_{analyte} = b / a$) and for OP SA, the $C_{analyte}$ was also obtained by extrapolation of the x axis at y = 0, however only two calibrations points, (i.e. x0 and x1) were used. For SA, at least four calibration points are needed, (i.e. x0 and x1-x4), where (x0) is a point without any analyte added and (x1–x4) are additions points with increasing concentrations [19,37], as shown in Fig. 3 for Hg determination.

3.3. Methods accuracy

For evaluation of the methods accuracy, addition and recovery experiments in two concentration levels were applied in digested samples using 7.0 and 2.0 mol L^{-1} HNO_3 and samples 10 and 20-fold diluted in 0.14 mol L^{-1} HNO_3 using EC, IS, SA and OP SA. For determinations

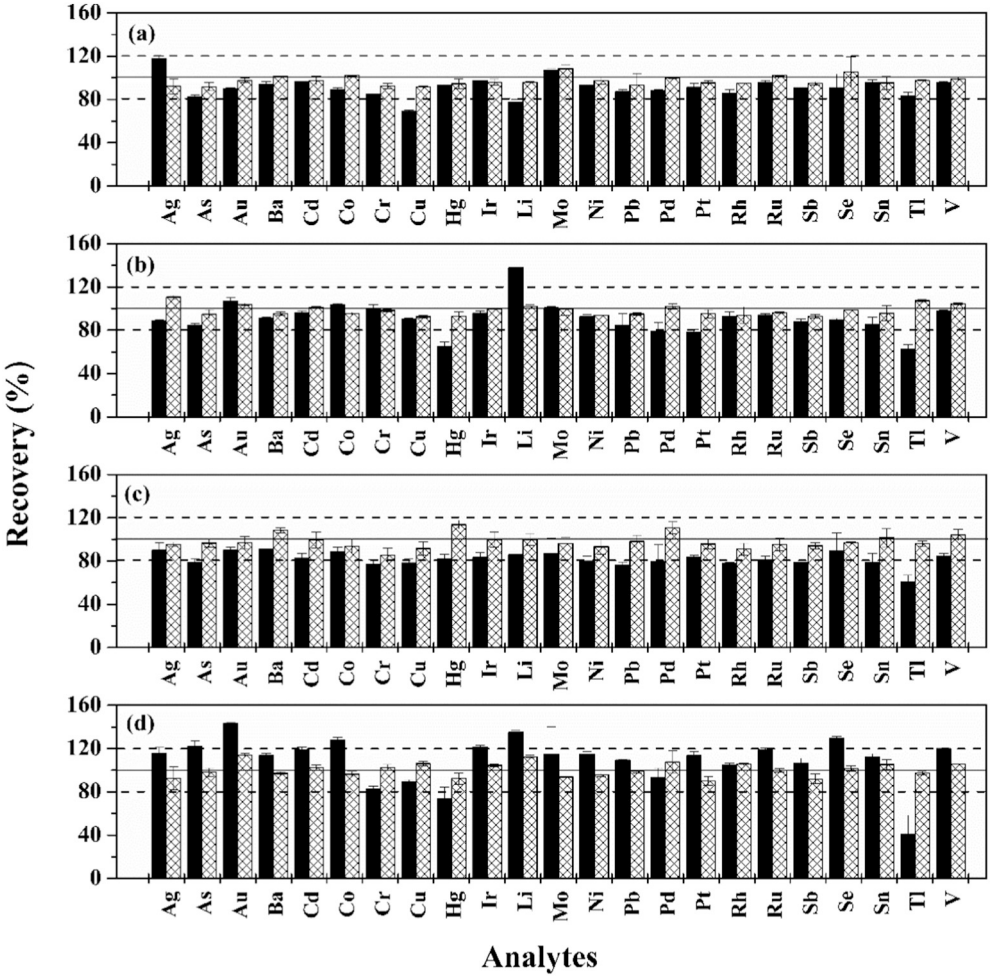

Fig. 4. Percentage recoveries for addition 0.10 mg L^{-1} in samples (a) A; (b) B; (c) C and (d) D; 20-fold diluted with and without internal standard by ICP OES. (▒) With internal standard; (■) Without internal standard.

using EC, recoveries lower than 80% were observed for most analytes for samples A, B and C and positive errors (recoveries > 120%) for sample D 10-fold diluted (Table 3) were observed. However, when using the IS method, best recoveries were obtained ranging from 91 to 116% for sample A; 81 to 107% for sample B; 89 to 118% for sample C; and 87 to 115% for sample D. The same behavior was observed for samples 20-fold diluted (Fig. 4).

Due to the large matrix differences among the samples, it can be observed different behaviors for some recoveries of analytes without using internal standard. For instance, for samples 10-fold diluted, Ag, As and Co showed recoveries higher than 120% only for sample D, for Li the same was observed for samples B and D, however, positive errors were observed for Au in all samples. On the other hand, recovery was lower than 60% for Hg in sample B, and for Tl recoveries were lower than 80% for all samples.

Matrix effects were also observed for sample D digested in both nitric acid concentrations (Fig. 5). Positive errors (recoveries > 115%) were obtained for all analytes in samples digested using 7.0 mol L^{-1} HNO_3 and recoveries higher than 120% were obtained in samples digested using 2.0 mol L^{-1} HNO_3, except for Cu, Sn and Tl in both cases. When using internal standard best recoveries were obtained ranging from 93 to 115% for samples digested using 7.0 mol L^{-1} HNO_3 and ranging from 92 to 115% samples digested using 2.0 mol L^{-1} HNO_3. In addition to carbon effects, probably the observed matrix effects were originated by differences in viscosities for digests, diluted samples, and standards solutions. The use of IS led to more accurate recoveries due to correction of matrix effects associated with transport, nebulization, and/or energetic effects in the argon plasma [17,21].

For OP SA, accuracies were evaluated by addition and recovery experiments in two concentration levels (0.10 and 0.20 mg L^{-1}) and three concentrations of addition point concentrations were evaluated for each level: 0.20; 0.40 and 0.60 mg L^{-1} for addition level 0.10 mg L^{-1} and 0.40; 0.60 and 1.0 mg L^{-1} for addition level 0.20 mg L^{-1}. For both levels of addition, the three addition point concentrations were effective to obtain satisfactory recoveries (80 to 120%), showing that good results can be obtained when adding concentrations equivalent to twice the analyte concentrations. Table 3 shows the recoveries obtained for addition level of 0.10 mg L^{-1} for all samples in each calibration method. The recoveries obtained for Ag in all samples were better using OP SA than SA. For sample D, better recoveries were obtained using OP SA than SA for Hg and Rh. Recoveries were similar for others analytes and samples.

3.4. Limits of detection and concentrations limits based on J values

For EC and IS, limits of detection (LOD) and quantification (LOQ) were calculated considering background equivalent concentration (BEC), signal-to-background ratio (SBR) and relative standard deviation (RSD) for 10 measurements of blank solutions [38]. For OP SA and SA, the accuracy was evaluated based on the standard error (SE), according to Eq. (1):

$$SE = \sqrt{\frac{\sum_i^n (y_i - \hat{y})^2}{n-1}} \quad (1)$$

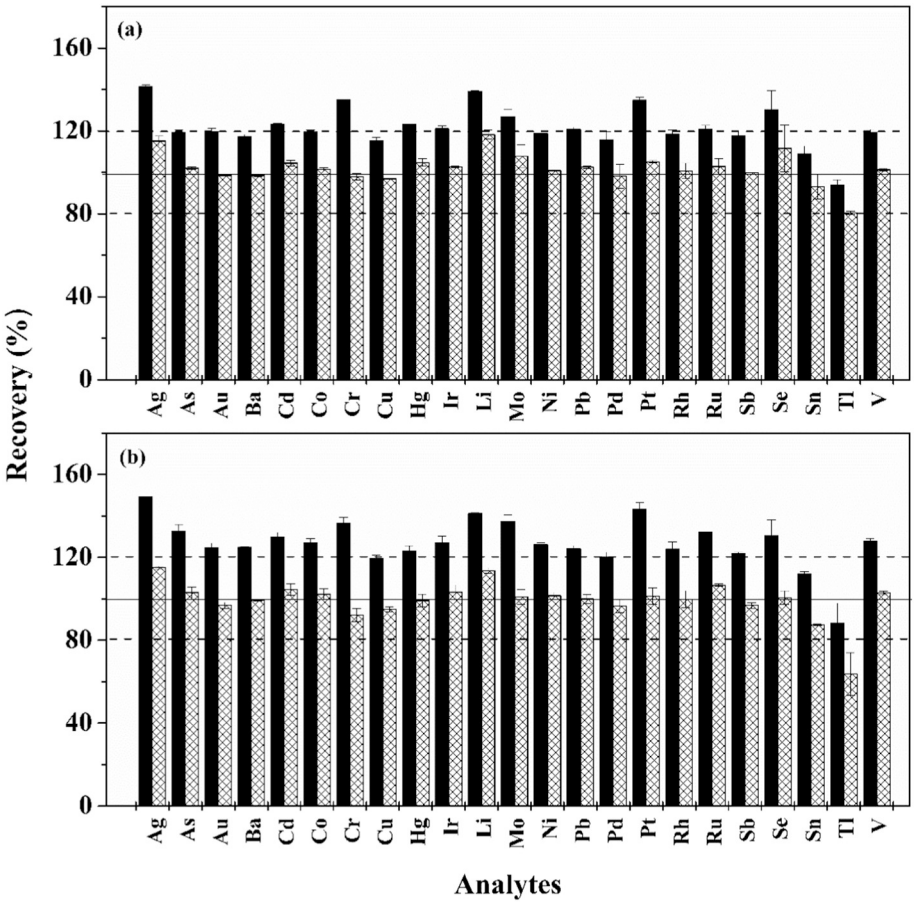

Fig. 5. Percentage recoveries for addition 0.10 mg L^{-1} in sample D with and without internal standard by ICP OES. (a) Digested using 7.0 mol L^{-1} HNO_3; (b) Digested using 2.0 mol L^{-1} HNO_3. (▒) With IS; (■) Without IS.

Table 4
Analytical performance parameters for the determination of Ag, As, Au, Ba, Cd, Co, Cr, Cu, Hg, Ir, Li, Mo, Ni, Pb, Pd, Pt, Rh, Ru, Sb, Se, Sn, Tl and V in liquid drug samples by ICP OES using the calibration methods EC, IS, SA and OP SA.

Analyte (nm)	PDE (μg dia^{-1})	0.5*J* adition (μg L^{-1})[a]	LOD (μg L^{-1})			r		Standard error (μg L^{-1})		ratio $F_{experimental}/F_{tabulated}$
			EC_D[c]	EC	IS	EC	IS	SA	OP SA	OP SA
Ag (328.068)	150	250	2.7	3.5	3.3	0.9982	0.9991	43	27	1979–57,323
As (189.042)	15	25.0	5.3	2.8	3.0	0.9969	0.9997	7.8	10	180,846–6,295,551
Au (242.795)	100	167	11	13	17	0.8994	0.9909	21	7.8	46,485–902,266
Ba (455.403)	1400	2.33[b]	0.20	0.74	0.90	0.9973	1.0000	3.1	4.8	128,974–4,691,952
Cd (226.502)	5	8.00	0.40	0.20	0.30	0.9968	0.9997	2.6	3.4	213,855–2,558,852
Co (228.616)	50	83.0	0.94	0.71	0.82	0.9981	0.9996	3.0	3.7	229,547–2,926,340
Cr (357.869)	11,000	18.3[b]	9.1	3.8	4.4	0.9957	0.9995	3.7	3.2	99,779–2,416,358
Cu (324.754)	3000	5.00[b]	4.3	1.1	1.2	0.9974	0.9996	3.8	4.2	119,394–7,320,281
Hg (184.950)	30	50.0	2.0	1.8	2.2	0.9977	0.9991	20	12	211,974–1,643,246
Ir (224.268)	100	167	3.9	2.0	3.0	0.9969	0.9997	9.8	4.8	168,441–2,749,456
Li (670.784)	550	917	0.50	0.21	0.31	0.9962	0.9998	5.3	2.9	115,832–6,977,673
Mo (202.030)	3000	5.00[b]	1.4	4.2	4.2	0.9894	0.9991	5.5	5.7	197,914–1,962,392
Ni (221.647)	200	333	2.8	1.5	1.8	0.9975	0.9995	5.1	4.2	226,272–2,925,675
Pb (220.353)	5	8.00	7.2	4.7	5.4	0.9956	0.9991	6.6	4.1	273,123–2,904,947
Pd (340.458)	100	167	7.0	5.8	6.2	0.9997	0.9994	5.1	10	93,015–2,468,047
Pt (214.423)	100	167	15	5.8	6.8	0.9981	0.9994	11	10	210,479–6,883,870
Rh (343.489)	100	167	12	9.6	13	0.9933	0.9992	23	17	86,304–1,753,669
Ru (267.876)	100	167	6.7	4.4	5.6	0.9978	0.9989	6.1	5.5	123,226–3,145,053
Sb (217.581)	1200	2.00[b]	12	6.4	8.5	0.9970	0.9994	5.6	7.0	230,038–897,978
Se (196.090)	150	250	18	12	13	0.9949	0.9990	9.5	18	236,189–1,018,746
Sn (283.997)	6000	10.0[b]	16	6.0	10	0.9956	0.9979	9.0	9.7	268,225–830,041
Tl (190.856)	8	13.0	7.9	4.3	6.5	0.9982	0.9998	113	104	278,019–2,639,911
V (292.402)	100	167	2.0	1.6	2.0	0.9968	0.9998	4.5	4.8	113,599–5,545,457

[a] Based in the higher MDD for all drugs, 30 mL day^{-1}.
[b] Values in mg L^{-1}.
[c] LOD for sample digested determinations by external calibration.

where y_i is the analyte reference concentration (from the lower addition level value), $\hat{y}$ is the concentration determined by calibration strategy, and n is the number of samples analyzed (n = 4). For OP SA, the linearity was tested applying the test F, and in this case the ratio $F_{experimental}/F_{tabulated}$ was calculated. This ratio ≥10 demonstrated that the variances are statistically different (the quadratic mean of the regression is statistically different when compared with the quadratic mean of the residues) and the model can be considered linear [27,39].

The concentrations limits (known as J values) defined by Chapter 232 [1] is calculated by dividing the permissible daily exposures value (PDE) for each element by the maximum daily dose (MDD) of the drug and multiplied by the dilution factor (DF) adopted in the analytical procedure, as shown in Eq. (2):

$$J = \frac{PDE\left(\frac{\mu g}{dia}\right)}{\mathrm{MDD}\left(\frac{\mathrm{mL}}{\mathrm{dia}}\right)\mathrm{x\ FD}} \quad (2)$$

According to the Chapter 233 [2] the accuracy must be evaluated by addition and recovery experiments with concentrations from 0.5J to 1.5J values. Thus, for evaluating if the respective LODs obtained for each calibration method are adequate in terms of sensitivities, it was calculated the lower level of addition 0.5J considering 10-fold dilution (lower dilution adopted in this procedure) and MDD of 30 mL day^{-1} (MDD for sample A). The specific MDD for other samples are 8 mL day^{-1} for sample B, 20 mL day^{-1} for sample C and 4.3 mL day^{-1} for sample D. Higher MDD was chosen because it led to lower J values, and consequently, higher strictness to evaluate sensitivities. Table 4 shows the PDE values specific to oral administration, the addition level 0.5J, limit of detection, linear correlation coefficient, standard error and ratio $F_{experimental}/F_{tabulated}$ obtained for determination of all analytes using each calibration method.

The analyte LODs obtained for EC and IS and the standard errors calculated for SA and OP SA were lower than the lower level of addition suggested by the Chapter 233, considering the dilution factor of 10-fold adopted in the analytical procedure, except for Pb and Tl. For Pb, the 0.5J value is 8.00 μg L^{-1} and the LOQs obtained for EC and IS were 15.7 and 18.0 μg L^{-1}, respectively. However, the standard errors calculated for SA and OP SA are lower, 6.60 and 4.10 μg L^{-1}, respectively. For Tl, with 13 μg L^{-1} as 0.5J value, the LOQs were 14.3 and 21.6 μg L^{-1} for EC and IS, and the standard errors were 113 and 104 μg L^{-1} for SA and OP SA, respectively. The high standard errors for Tl can be explained due to the recovery < 70% obtained for samples C and D for SA and OP SA methods. However, for the addition level of 0.20 mg L^{-1} all recoveries ranged from 80 to 110%.

3.5. Determination of inorganic impurities in liquid drug samples

All analytes were below the respective LODs for the calibration methods EC and IS and below the respective standard errors for SA and OP SA methods for all drug samples in both sample preparation procedures (microwave-assisted digestion and nitric acid dilution). Consequently, all samples are within the limits suggested by USP taking into account the maximum daily dose of each liquid drug indicated in the package insert.

4. Conclusion

The dilute-and-shoot procedure is a simple strategy, less expensive and faster than the traditional sample preparation procedure using microwave-assisted digestion. Calibration strategies as IS and OP SA were effective to correct for matrix effects and allowed the adoption of the dilute-and-shoot procedure for determination of 23 elemental impurities in liquid pharmaceutical samples by ICP OES. The LODs and standard errors obtained for IS and OP SA, respectively, were suitable to meet USP requirements considering the adopted factor of dilution and the specific MDD for each drug. The low dilution factor of the procedure led to higher J values, allowing suitable LODs using ICP OES. Consequently, this procedure can be easily used for pharmaceutical laboratories to control elemental impurities contamination in liquid drugs.

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Conflict of interest

All authors declared that they have no conflict of interest.

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