Multivariate Optimization and Exploratory Analysis Applied to the Internal Standardization of Complex Matrices by Inductively Coupled Plasma Optical Emission Spectrometry

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INTRODUCTION

Trace elements in complex matrices, such as biopharmaceutical drug products, environmental, geochemical, beverages, biological, and food samples, are commonly determined by various spectrometric analytical techniques (1-4). The composition of the matrix may affect the analytical signal, and consequently deteriorate its accuracy and precision. In the analysis of some environmental, food and beverage, geological, drug, and other samples, easily ionized elements (EIEs), such as Na, K, and Ca, are generally present at high concentrations. These elements may promote a stronger interference effect. In the spectrometric analysis of complex matrices, it is common to employ analytical strategies to minimize interference effects. The pretreatment procedures of complex samples include acid digestion under conventional or microwave heating (6,7), dilution with appropriate solvents (2), emulsification (8,9), acid and solid phase extraction (10,11), ultrasound-assisted extraction (12), and others (13). In addition to an increase in experimental time, cost of analysis, and the amount of sample required,

ABSTRACT

The presence of high concentrations of Na, K, Ca, and C in complex matrices such as beverages, foods, and pharmaceutical formulations may interfere in their analysis by inductively coupled plasma optical emission spectrometry (ICP-OES). The interference is amplified when it is associated with large variations in operating conditions. Internal standardization is indicated for the repair of this interference effect. Elements that present comparable behavior in similar conditions may be used as internal standards (IS) for other elements. The behavior of 31 analytical lines in the presence of Ca, K, and Na (250 and 1000 mg L⁻¹) in 8% urea, to simulate pharmaceuticals, beverages, and foods, was evaluated under different operating conditions by hierarchical cluster analysis (HCA) and principal component analysis (PCA). The HCA and PCA methods formed four element groups with similar behavior. In these groups, some elements were tested as IS from the other groups. It was possible to choose the best IS for the element groups, and the recoveries were close to 100% with simulated samples. This study amplified the possibility of selecting internal standards for the analysis of complex matrices, thus promoting better precision and accuracy of the results.

some procedures risk loss of analyte, sample contamination, and poor detection. A good strategy in the analysis of complex matrices is the use of internal standardization to minimize or avoid interference effects, thus increasing precision and accuracy (14-16). Internal standards (IS) are used to allow for the identification and correction of fluctuations during analysis (17).

In inductively coupled plasma optical emission spectrometry (ICP-OES) analysis, these interferences can result in an increase or decrease of the analytical signal. Carbon is just another example of an element commonly found in most complex sample matrices, particularly in foods, drugs, and biological materials, in addition to geological and environmental samples. An increase in carbon concentration may cause an increase in background radiation due to non-specific emissions and, consequently, resulting in poor limits of detection and quantification by ICP-OES measurements. Thus, the direct introduction of a complex sample matrix into an ICP-OES may suffer interference effects.

Multivariate optimization of the experimental conditions makes direct analysis possible. However, if the traditional methods of multivariate optimization are applied for each element, model construction for each element will be necessary. Most applications require matrix

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pre-treatment, because the direct determination of trace elements in complex matrices is difficult as a result of interference effects. Biopharmaceutical drug products consist of multiple inactive ingredients, including monoclonal antibodies (mAbs), antibody drug conjugates (ADCs), protein-conjugated vaccines and others, and the excipients (4). Several kinds of excipients are used in biopharmaceutical drug products to enhance stability, control pH, and adjust tonicity (5). The excipients are diversified, including cations (such as Na, K, and Ca), anions, zwitterions (i.e., amino acids), hydrophobic surfactants, hydrophilic sugars, etc. (5).

Inductively coupled plasma optical emission spectrometry is a technique commonly used to investigate the mineral composition of complex matrices (17-20). Easily ionized elements (EIEs), such as Na, K, and Ca, are generally present in high concentrations in foods, beverages, and drugs (21,22). They may strongly interfere with ICP-OES analysis by either increasing or decreasing the analytical signal. Brenner et al. (21) reported that increasing the Na and Ca concentrations decreased the analytical signals of Mo, Co, Ni, Cd, Be, Pb, and Zn in axial and radial viewing. They also observed that the Ca effect is stronger than that of Na as more energy is required to dissociate the matrix in aqueous solutions with 0–1000 mg L⁻¹ of Na⁺ and Ca²⁺. A single IS [Sc(II), 361.384 nm] was used to compensate for this depressive effect. In another study, Brenner et al. (22) evaluated the interference effects of Ca and Na on the atomic and ionic lines of As, Be, Cd, Co, Cr, Cu, Fe, Li, Mg, Mn, Mo, Ni, Pb, Sb, Se, Sr, Ti, Tl, V, and Zn using both high and low aerosol loadings on spectral line measurements in a 0.1% Ca and Na solution. According to the results, the limits of detection degraded 10- to 16-fold using cross-flow nebulization, and

about 30-fold with ultrasonic nebulization (22). Dubuisson et al. (23) compared axial and radial ICP-OES with and without IS to compensate for the Na effects (10 g L⁻¹) on accuracy. The authors obtained good efficiency with a single IS (Ni²⁺ at the 231-nm line) for radial ICP-OES. The axial view mode (with or without IS) failed to provide the same quality and efficiency as that of the radial measurements with IS. Carbon is another element which is mostly found in foods, drugs, and beverages. An increase in the carbon concentration may increase the background radiation due to non-specific emissions, consequently resulting in inferior limits of detection and quantification (24).

The application of IS is only effective if the IS and analyte behaviors are similar with respect to the interference effects and instrumental noise. Therefore, the proper selection of IS has received considerable attention. The IS may be selected by employing various methods, including a universal IS such as yttrium and scandium (25, 26). An alternative would be the base selection of the response of each analytical line tested as an IS compared to the analyte. Recovery studies of spiked concentrations and the relative standard deviation obtained with or without IS should be observed in IS applications (26).

Recently, chemometric tools have been used for choosing the best element as the internal standard (27). Grotti et al. (27) analyzed the IS efficiency in the reduction of matrix effects caused by Fe, Al, Ca, Na, and K on the analytical signals of As, Cd, Cr, Cu, Mn, Mo, Ni, P, Pb, V, and Zn in ICP-OES and the reduction of acidic effects. Optimal IS was selected based on the set of measurements supplied by the factorial design processed by principal component analysis (PCA). By analogous selection of the IS, Pan et al. (28) developed a

method to determine As, Sb, and Se in synthetic digested plant- and food-based solutions.

The following study evaluates different elements as internal standards based on their similarity of analytical lines obtained by ICP-OES analysis and using multivariate optimization and exploratory analysis.

EXPERIMENTAL

Instrumental Operating Conditions

Measurements were performed using an Optima™ 2000 DV ICP-OES, dual view (PerkinElmer, Inc., Shelton, CT, USA) with axial (AX-ICP-OES) and radial (RD-ICP-OES) configurations. The radio frequency source (40 MHz) provided a power of 0.75–1.5 kW. A 79-nm⁻¹ line Echelle grating, solid-state detector, cross-flow nebulizer, coupled with a double-pass Scott-type spray chamber, and interface shear gas were used. The sample injection system was automated using an AS 90 Plus autosampler (PerkinElmer). The remaining operating conditions are presented in Table I, and the analytical lines and their properties in Table II.

Reagents, Solutions, and Materials

Analytical grade Na, K, and Ca salts (NaCl, KCl, and CaCl₂ from VETEC, São Paulo, Brazil) were used to obtain a 10 g L⁻¹ intermediate solution of each element. Standard solutions, containing 1000 mg L⁻¹ of Al, As, Ba, Be, Cd, Cr, Cu, Fe, Hg, Ir, Li, Mg, Mn, Mo, Ni, Pb, Pt, Rb, Rh, Ru, Sb, Se, Sn, Sr, Ti, Tl, V, W, Y, Zn, and Zr (ICP Standard, Certipur®, Merck, Darmstadt, Germany) were used for this study. A multi-element intermediate solution, containing 100 mg L⁻¹ of the above-mentioned elements in 2% (v/v) HNO₃ (from 70% VETEC, São Paulo, Brazil), was previously prepared and used to obtain the

TABLE I
ICP-OES Operating Conditions

Parameters	
Auxiliary gas flow rate	0.2 L min ⁻¹
Plasma gas flow rate	15 L min ⁻¹
Injector tube diameter	2.0 mm
View	Axial
Interface	Shear gas
Sample flow rate	1.0–1.5 mL min ⁻¹
Applied power	1.1–1.5 kW
Nebulization gas flow rate	0.4–1.1 L min ⁻¹

reference solutions. Urea (QUIMEX, São Paulo, Brazil) was used to prepare a carbon reference solution. Deionized water from a Milli-Q® system (Millipore Corporation, Bedford, MA, USA) was used to prepare all solutions.

Synthetic reference solutions, simulating several beverages, some pharmaceutical products and foods, were prepared with 250 and 1000 mg L⁻¹ Na, K, and Ca, 8% (w/v) urea, and 1.0 mg L⁻¹ Al, As, Ba, Be, Cd, Cr, Cu, Fe, Hg, Ir, Li, Mg, Mn, Mo, Ni, Pb, Pt, Rb, Rh, Ru, Sb, Se, Sn, Sr, Ti, Tl, V, W, Y, Zn, and Zr. These solutions were used in the multivariate optimization experiments and recovery studies.

Data Collection and Treatment

Multivariate optimization is an appropriate data collection method because it allows for evaluation of the responses to many variables and their interactions (29, 30). A 2³ factorial design was employed to obtain the response of 31 analytical lines in a synthetic reference solution. The behavior of the analytical lines, submitted to several different operating conditions, were evaluated. The factors and levels that were employed included nebulization gas flow rate (0.4–1.1 L min⁻¹), applied power (1.1–1.5 kW), and sample flow rate (1.0–1.5 mL min⁻¹). The resulting responses were evaluated by exploratory methods of analysis known as Hierarchical

Cluster Analysis (HCA) and Principal Component Analysis (PCA). The same methodology was used by Penteadó et al. (31) in the optimization of solid-phase microextraction conditions for gas chromatography-mass spectrometry analysis of linear alkylbenzenes in detergents. The authors evaluated the operating conditions and determined the optimum analysis conditions.

Recovery studies were used to evaluate the accuracy and precision of the applied method to select the IS for each analyte.

RESULTS AND DISCUSSION

Experimental Consideration

Internal standardization (IS) efficiency depends on the operating conditions. Elements that show similar behavior when submitted to different experimental conditions may be employed as IS for a group of elements that also exhibit similar behavior under the same conditions (14,19,20,26). The behavior of 31 analytical lines in the presence of high Na, K, Ca, and C concentrations, under different experimental conditions, was evaluated. Table III lists the experimental and analytical responses of each element according to this design. The matrix data with the analytical signal, obtained by a 2³ factorial design, were evaluated by exploratory analysis.

TABLE II
Analytical Lines, Respective Wavelengths, and Ionization Energy

Element	Wavelength (nm)	Ionization Energy (eV)
Al I	396.153	5.99
As I	193.696	9.81
Ba II	493.408	5.21
Be II	313.042	9.32
Cd II	214.440	8.99
Cr II	267.716	6.77
Cu I	324.752	7.73
Fe II	238.204	7.87
Hg I	253.652	10.4
Ir II	224.268	9.00
Li I	610.362	5.39
Mg II	280.271	7.65
Mn II	257.610	7.44
Mo II	202.031	7.1
Ni II	221.648	7.64
Pb II	220.353	7.42
Pt I	265.945	9.00
Rb I	780.023	4.18
Rh II	343.489	7.45
Ru II	240.272	7.37
Sb I	206.836	8.64
Se I	196.026	9.75
Sn I	235.485	7.34
Sr II	407.771	5.70
Ti II	334.940	6.82
Tl I	276.787	6.11
V II	292.464	6.74
W II	207.912	7.98
Y II	371.029	6.38
Zn II	213.857	9.39
Zr II	343.823	6.84

The dendrogram obtained by hierarchical cluster analysis (HCA) is shown in Figure 1. The 31 analytical lines were separated into four groups. Variations in the experimental conditions are grouped by analytical lines according to line type: either ionic or atomic, and according to potential energy values (excitation for atomic lines and sum of

TABLE III
2³ Factorial Design Factors, Levels, and Conditions

		-	+	-	+	-	0	-	-	+	-
		-	-	+	+	-	0	-	+	+	-
		-	-	-	-	+	0	+	+	+	-
Analytical Response/ cps	Al	75807	230466	28879	235711	44335	395806	321357	35193	362997	
	As	235	86	161	128	161	478	89	143	151	
	Ba	4486457	3390065	1070884	6289600	2233762	18305189	3679330	2666885	7271193	
	Be	1090794	368692	654801	476088	667044	2694446	420639	759922	553035	
	Cd	23896	827	10602	1310	14092	21672	1006	9973	1793	
	Cr	46008	4000	37639	7465	35991	87014	4625	35350	10021	
	Cu	160380	494824	70540	570172	87885	888342	680763	94865	789001	
	Fe	44717	5558	19039	10002	23570	81495	6268	32274	12593	
	Hg	1453	674	702	934	1020	3380	785	972	1193	
	Ir	4244	1684	1854	2842	2212	13406	1676	2199	3486	
	Li	-1527330	1771296	-2072276	1874621	-1671860	3175236	2472473	-2256805	2677295	
	Mg	1434576	92192	853016	202210	911738	2748587	98554	1039446	250623	
	Mn	428104	40666	170420	85666	206956	860425	45651	331198	106388	
	Mo	2434	333	1090	605	1211	4957	343	1139	733	
	Ni	7980	1500	4023	2160	5210	12098	1686	4121	2698	
	PB	1753	798	1135	1081	1078	3647	864	1096	1318	
	PT	5369	4648	2043	5808	3823	14270	6029	2908	7899	
	Rb	-2465379	2342803	-2799561	2231019	-2550532	1349497	3979005	-2945194	3122788	
	Rh	46308	130068	23315	132463	31324	246566	196317	25654	194578	
	Ru	6039	2050	2754	3057	4420	14676	2216	4115	3786	
	Sb	513	353	78	451	215	1454	426	246	577	
	Se	233	334	107	396	161	740	370	148	491	
	Sn	3511	3797	3719	4448	2897	8290	4535	3523	5832	
	Sr	9595192	4536423	2945455	9442754	6471904	41644163	4833005	4846860	11122532	
	Ti	313715	97388	151063	186957	216968	1146956	109711	181365	231509	
	Tl	1904	2136	1408	2714	1533	7944	2844	1444	3575	
	V	-12638	6448	-2542	5072	-3424	-20277	7031	-5393	6094	
	W	1090	-1	591	107	659	2053	-49	741	101	
	Y	1000590	272468	472989	552745	540013	3635307	304894	563316	684378	
	Zn	20804	5657	10748	7049	12943	37753	6978	12861	9423	
	Zr	277306	70347	70546	138946	163862	683503	76568	133575	165333	
(-)	(+)	Variables									
0.4	1.1	Nebulization gas flow rate (L min ⁻¹)									
1.1	1.5	Applied power (kW)									
1.0	1.5	Sample flow rate (mL min ⁻¹)									

excitation and first ionization for ionic lines). The first group was composed of the atomic lines Al, Cu, Li, Rh, and Rb with intermediate and low potential energy values, with the exception of Rh, which has an intermediate potential energy ionic line. The second group was formed by Cd, Fe, Mn, Zn, Mo, Ni, Cr, Mg, and W, which has high potential energy ionic lines. Cadmium was considered in this group, even though it was somewhat dissimilar from the others. The third group consisted of Pb, As, Ru, Be, Hg, Zr, Ti, Y, Ir, and Sr, which has intermediate and high potential energy ionic lines, with the exception of As and Hg, which possess high potential energy atomic lines. The fourth group of elements was formed by the atomic lines of Sn, Se, Sb, Ba, Pt, and Tl, which has intermediate and high potential energy, except for Ba, which has a low potential energy ionic line.

The first three principal components explain 97.3% of the total variance. The object scores and variable loadings for these components are plotted in Figure 2. The same groups of elements obtained in HCA were observed in PCA. PC1, which represents 80% of the total variance, separates the ionic lines from the atomic lines.

IS Selection per Group

Theoretically, the best IS for one element is that which shows the same behavior under identical conditions. Each element group that was created was evaluated separately. Yttrium was used as a universal IS (11,28) and was tested for all analyzed elements. The IS efficiency was evaluated via recovery value of the solutions spiked with 1.0 mg L^{-1} of Al, As, Ba, Be, Cd, Cr, Cu, Fe, Hg, Ir, Li, Mg, Mn, Mo, Ni, Pb, Pt, Rb, Rh, Ru, Sb, Se, Sn, Sr, Ti, Tl, V, W, Y, Zn, and Zr in two interference levels (250 mg L^{-1} and

Fig. 1. Dendrogram of analytical signal of the elements.

Fig. 2. Score plots of elements in synthetic sample.

Fig. 3 (a,b,c,d). Recovery study for the internal standardization in element groups found in HCA and PCA with 250.0 mg L⁻¹ spiked solution.

1000 mg L⁻¹ of K, Na, and Ca in 8% urea). In accordance with scientific literature (32), the acceptable recovery values should be between 80 and 120%. The best IS for each group were the recoveries considered closest to 100% of the spiked values. The results obtained are shown in Figure 3 (250 mg L⁻¹) and Figure 4 (1000 mg L⁻¹).

The analytes measured in each group were elements with the greatest significance for food, drug, and beverage analysis. In the first group, Li, Rh, and Rb were evaluated as IS for Al and Cu. In the presence of 250 mg L⁻¹ of concomitants (Figure 3a), Y was the best IS for Al, with a recovery value of 102.6%. For Cu, the best IS was Rh, with a

97.8% recovery value. When the concentration of concomitants was 1000 mg L⁻¹ (Figure 4a), the best IS for Al was Li (87.4%), and for Cu, it was Rh (94.4%).

In the second group (Cd, Fe, Mn, Zn, Mo, Ni, Cr, Mg, and W), Mo, W, and Y were evaluated as IS. For 250 mg L⁻¹ of concomitants (Figure 3b), Y was the best IS for almost every element, excluding Zn (W 101.0%) and Cr (Mo 97.0%). The obtained recovery values were: Fe 99.3%, Mn 99.7%, Ni 101.5%, Cd 100.5%, and Mg 105.7%. For 1000 mg L⁻¹ of concomitants (Figure 4b), Y remained the best IS for almost every element with the following percent recovery values: Mn 95.4%, Zn 95.8%, Ni 96.3%, Cd 92.5%, Cr 100.7%, and

Mg 103.4%. For Fe, under the same conditions, the best IS was W at 107.2% recovery.

In examining the third group, Ru, Be, Zr, Ti, Ir, and Sr were evaluated as IS for Pb, As, and Hg. For 250 mg L⁻¹ of concomitants (Figure 3c), Y was the best IS for Pb (99.2%) and Hg (96.5%). For As, a 100.4% recovery was obtained when Ru was employed as IS, and 103% with Y as IS. For higher concentrations of concomitants (1000 mg L⁻¹, Figure 4c), Ru was the best IS for Pb (97.2%), Zr for As (101.2%), and Y for Hg (92.9%). However, the recovery values for Pb and As with Y as IS was 93% and 106%, respectively. Platinum, thallium, and yttrium were tested as IS

Fig. 4 (a,b,c,d). Recovery study for the internal standardization in element groups found in HCA and PCA with 1000.0 mg L⁻¹ spiked solution.

for the group formed by Sn, Se, Sb, Ba, Pt, and Tl in concomitant concentrations of 250 and 1000 mg L⁻¹ (Figures 3d and 4d). The best IS for Sn was Pt, with 100.8% and 99.9% recoveries, respectively. For Se, the best IS was Tl, with 104.3% and 102.7% recoveries, respectively. Y was the best IS for Sb and Ba in 250 mg L⁻¹ of concomitants, with 99.2% and 103.5% recoveries, respectively, and 93.1% and 101.3% for 1000 mg L⁻¹ of concomitants, respectively. For most elements, more than one reference line yielded good recovery values according to some studies (33,34), which ranged between 80% and 120%. Therefore, the selection of an appropriate IS depends on the investigative interest, the sample

type, and the absence of possible IS in the matrix composition.

CONCLUSION

The use of exploratory analysis methods associated with multivariate optimization allowed for the evaluation of 31 analytical lines in a synthetic complex matrix subjected to different experimental conditions and groupings according to the similarity of their behavior. The best internal standard (IS) was successfully selected according to the behavior of similarity and analytical interest of each element in each group, yielding recovery values close to 100%. In addition to the universal internal standards, any analytical line in the group of simi-

larity may be used as an internal standard, depending on the presence of the element in the sample, the analytical interest, and the recovery assay of the potential IS. In this study, we observed that at concentrations of 250 mg L⁻¹ of interference studied, Rh was the best IS for Cu; Ru for As; Tl for Se; Pt for Sn; and Y for Al, Pb, Hg, Sb, and Ba. For the concentrations of the interferents at 1000 mg L⁻¹, Li was the best IS for Al; Rh for Cu; W for Fe; Ru for Pb; Zr for As; and Y for Hg.

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