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Pharmaceuticals

Analysis of pharmaceuticals for elemental impurities after dissolution in organic solvents using ICP-MS

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Keywords

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Goal

To develop an analytical method using single quadrupole ICP-MS that enables the analysis of pharmaceutical products after dissolution in organic solvents such as dimethyl formamide (DMF) and dimethyl sulfoxide (DMSO), as per the requirements of USP General Chapters <232> and <233> and ICH Guideline Q3-D (R1)

Introduction

The United States Pharmacopeia (USP) has introduced General Chapters <232> and <233> to govern the analysis of elemental impurities in pharmaceutical products. While USP Chapter <232> suggests analytes and their limit concentrations, USP Chapter <233> provides guidelines for the analytical procedures, including instrumentation, sample preparation and validation of analytical methods. It further advises on different approaches of sample preparation, including analysis of the neat sample (for liquid samples), direct aqueous solution (for water soluble or samples soluble in aqueous solvents), direct organic solution (for samples soluble in organic solvents), and indirect solution analysis (for samples that are not soluble in aqueous or organic solvents). USP Chapter <232> does not define a specific sample preparation method unless this is specified in the individual monograph of the substance under examination. A sample can be either a finished product or a single ingredient of a drug product, such as an active pharmaceutical ingredient (API) or an excipient (fillers, colorants, coatings, etc.).

Depending upon the chemical and physical properties of the sample, laboratories can adopt one of the above-mentioned approaches of sample preparation. Indirect dissolution, for example, using a closed vessel microwave-assisted digestion, is often the only way to dissolve a finished product. The analysis of individual ingredients may allow adoption of a simple strategy based on direct dissolution. Although microwave-assisted closed vessel acid digestion is an effective technique of sample preparation for samples insoluble in aqueous solvents, it presents some challenges, such as increased time required for complete digestion of the sample, efforts required for method optimization, requirements of expensive acids and reagents, chances of potential carryover / cross contamination in the digestion vessels, and potential loss of volatile impurities. To overcome these challenges, direct dissolution in organic solvents may be an alternative. Although this option does not completely eliminate the need for microwave digestion (since many inorganic components like TiO_2 cannot be dissolved in either aqueous or organic media), this approach can be easily employed, for example, for organic compounds like APIs, which may be soluble in organic solvents such as alcohols, DMF, DMSO, and acetonitrile.

In general, clear sample solutions without the presence of any suspensions, sediments, or residue are desirable for analysis of elemental impurities with analytical instruments like inductively coupled plasma – optical emission spectroscopy (ICP-OES) or inductively coupled plasma mass spectrometry (ICP-MS). Both techniques are generally capable of performing analysis of organic solvents, but changes need to be made to the configuration of the sample introduction system to facilitate robust and reliable analysis in the long term and avoid frequent interruptions of the productive time of the instrument due to maintenance. Organic solvents are challenging to handle compared to aqueous samples as they can adversely affect plasma stability due to excessive vapor pressure and matrix load. However, use of a solid-state RF generator with dynamic swing frequency matching generates a robust and stable plasma, which allows effective handling of this kind of challenging matrix.

This note discusses a workflow (including instrument configuration and consumables used), for the analysis of pharmaceutical ingredients soluble in organic solvents using a Thermo Scientific™ iCAP™ RQ ICP-MS. Two separate methods were developed for different APIs, each involving sample preparation by direct dissolution of the compound in dimethyl formamide (DMF) and dimethyl sulfoxide (DMSO), respectively.

Each developed method was applied for the quantification of all 24 elements required as per USP Chapter <232> in a single analysis and in accordance with the procedures highlighted in USP Chapter <233>. Thermo Scientific™ Qtegra™ Intelligent Scientific Data Solution™ (ISDS) Software was used to control the ICP-MS instrument and to generate, process, and report analytical data, ensuring that the entire workflow meets the requirements described in Part 11 of Title 21 of the “Code of Federal Regulations; Electronic Records; Electronic Signatures” (21 CFR Part 11).

Experimental

Instrument parameters and experimental conditions

An iCAP RQ ICP-MS, equipped with an additional mass flow controller (MFC) to control and introduce oxygen at a constant flow rate, was used in this study. To allow for unattended operation, the system was operated in conjunction with a Teledyne CETAC ASX-560 autosampler (Teledyne CETAC Technologies, Omaha, NE, USA). A constant flow of pure oxygen (equivalent to a defined percent rate of the specified output of the mass flow controller) was introduced into the spray chamber elbow to ensure complete combustion of carbon, thereby avoiding adverse effects on plasma stability and eliminating carbon deposition on the interface cones. The iCAP RQ ICP-MS was operated in KED mode, using pure helium as the only collision cell gas, to remove potentially occurring polyatomic interferences on various analytes. When analyzing samples containing organic solvents, this is particularly important for analytes affected by carbon containing interferences, such as chromium, which is interfered at ^{52}Cr and $^{53}Cr^+$ by $^{40}Ar^{12}C^+$ and $^{40}Ar^{13}C^+$, respectively. Another important point to consider is the temperature of the spray chamber. For the analysis of samples dissolved in DMSO (with a freezing point of 18 ˚C), the spray chamber temperature was consistently maintained at 20 ˚C using the Peltier controlled temperature settings to avoid solidification of the solvent (and hence blocking of the spray chamber outlet). For the analysis of samples dissolved in DMF, in turn, the spray chamber had to be cooled to 2.7 ˚C. Instrument performance was checked prior to analysis to confirm that it met set criteria. The sample introduction system components and method parameters are summarized in Table 1.

Table 1. Instrument configuration and typical operating parameters

Parameter	Value (Experiment 1; DMF)	Value (Experiment 2; DMSO)
Nebulizer	Micromist nebulizer (400 µL·min^{-1})	
Interface cones	Pt – tipped sample and skimmer	
Skimmer cone insert	High matrix	
Spray chamber	Cyclonic quartz	
Injector	Quartz, 1.0 mm i.d.	
Torch	Quartz torch (organics)	
Auxiliary flow (L·min^{-1})	0.8	
Cool gas flow (L·min^{-1})	16	
Nebulizer flow (L·min^{-1})	0.61	0.65
Oxygen additional gas	5%	7%
RF power (W)	1,550	
Sampling depth (mm)	5	
Number of replicates	3	
Spray chamber temp (˚C)	2.7	20
KED settings (Flow rate in mL·min^{-1})	Helium, 4.5 mL·min^{-1}, 3 V	Helium, 4.8 mL·min^{-1}, 3 V
Number of sweeps	10	
Dwell time (s)	0.05	

Standard and sample preparation

The samples analyzed in this study were active pharmaceutical ingredients (API), used in a drug product that is administered orally. To determine the limit concentrations of all 24 elements, the maximum permitted daily exposures (PDEs) for elemental impurities given in USP Chapter <232> were used as a reference. The limit concentrations were then calculated based on the PDEs, assuming a maximum daily dose of 10 g as suggested by the guidelines. In both experiments, 0.1 g of the available API samples were weighed accurately and then diluted to 20 mL using either 100% pure DMF or 100% pure DMSO as a diluent (further referred to as experiment 1 and experiment 2, respectively). Since DMF and DMSO are easily miscible with water, an initial stock solution corresponding to a concentration level of 200J was prepared in 0.5% (v/v) nitric acid using aqueous certified single element standards, followed by preparation of two separate intermediate stock solutions (each at 50J concentration) using DMF and DMSO respectively as diluents. These two intermediate stock standard solutions were then diluted appropriately using the respective organic solvents to prepare working standards used in two separate experiments. A total of seven linearity standards, covering the range between 0.05J and 2J were prepared (for more details on J-value calculation and concentrations of various analytes in linearity standards, please refer to AN000734[5]).

System suitability – Correlation coefficients (R)

The correlation coefficient is an important figure of merit and often considered as a useful system suitability criterion in many regulated methods. As per the guideline given in USP General Chapter <730> on plasma spectrochemistry, the correlation coefficient (R) should at least be above 0.99, which needs to be confirmed and recorded appropriately before proceeding with the analysis of unknown samples. Details of analytes, *m/z* ratio used, and typically obtained correlation coefficient in both the experiments are summarized in Table 2. The correlation coefficients obtained for all analytes were well above 0.995 for the concentration range investigated in this study, indicating fulfillment of this system suitability criterion.

Table 2. List of analytes, *m/z*, and correlation coefficients obtained in both the experiments (values presented here are the lower R values obtained for each analyte in the respective experiments)

Element	*m/z*	Correlation coefficient (R)	Element	*m/z*	Correlation coefficient (R)
Li	7	≥ 0.9987	**Ag**	107	≥0.9987
V	51	≥0.9989	**Cd**	111	≥0.9992
Cr	52	≥0.9992	**Sn**	118	≥0.9991
Co	59	≥0.9997	**Sb**	121	≥0.9996
Ni	60	≥0.9988	**Ba**	137	≥0.9998
Cu	63	≥0.9999	**Os**	189	≥0.9988
As	75	≥0.9980	**Ir**	193	≥0.9984
Se	77	≥0.9981	**Pt**	195	≥0.9998
Mo	95	≥0.9987	**Au**	197	≥0.9993
Ru	101	≥0.9989	**Hg**	202	≥0.9990
Rh	103	≥0.9978	**Tl**	205	≥0.9996
Pd	105	≥0.9992	**Pb**	208	≥0.9998

Sample analysis

The analysis of two different APIs (Sample A and Sample B) was carried out in experiment 1 after direct dissolution using DMF as diluent. Both API samples were analyzed in duplicate by measuring two independently prepared sample aliquots. In experiment 2, one API (named as Sample C) was prepared in triplicate by direct dissolution using DMSO as a diluent. As described in USP Chapter <233>, method accuracy was assessed and confirmed in both experiments. In experiment 1, the lowest concentration tested to demonstrate the accuracy was 0.05J, or 5% of the limit concentration of each analyte, whereas in experiment 2, accuracy was checked by spiking 0.1J (10% of the limit concentration) as a lowest concentration. Although the developed method is suitable for accurate and precise quantification at trace levels, the method quantification limits presented here were calculated based on the targeted limit of quantification established in both experiments (0.05J in experiment 1 and 0.1J in experiment 2). Method quantification limits (MQL) were calculated following the equation below:

Method quantification limit = Instrument quantification limit × total dilution factor

Analysis results obtained in both the experiments are presented in Table 3. The reported concentrations of all analytes in the analyzed samples are average values calculated from replicate measurements as mentioned above.

Method accuracy

In addition to the complete validation performed before putting the method into production, an accuracy test needed to be performed in alignment with applicable regulations to ensure that the developed method is suitable for the intended purpose of impurity analysis in a specific sample material. In experiment 1, both the API samples (sample A and sample B) were spiked with an appropriate volume of stock standard solution before solubilization of the samples. The samples were spiked at three different concentration levels, equating to 0.05J, 1J, and 2J using the same standard stock solution used for the preparation of the working linearity standards. Samples were prepared in triplicate for each level of spiked concentrations. The accuracy of each sample measurement was then calculated based on the spiked and observed concentrations in spiked and unspiked samples. Accuracy data obtained for all spiked samples was found to be in the range of 85 to 115%, which is well within the acceptance criteria of 70 to 150% specified in USP Chapter <233>. Sample C, analyzed in experiment 2, was also spiked at three different concentration levels, equating to 0.1J, 1J, and 2J, using the same standard stock solution used for preparation of the linearity standards. This sample was also prepared in triplicate for each spiked concentration level. Percent accuracy data obtained for each spiked sample was found to be in the range of 85 to 115%, indicating that the performance again met the specified acceptance criteria.

Table 3. List of analytes, apparent concentrations, and MQL (all results are expressed as $mg \cdot kg^{-1}$)*

Analyte	Experiment 1			Experiment 2	
	Sample A	Sample B	MQL	Sample C	MQL
Li	<MQL	<MQL	2.75	<MQL	5.5
V	<MQL	<MQL	0.5	<MQL	1.0
Cr	<MQL	<MQL	55	<MQL	110
Co	<MQL	<MQL	0.25	<MQL	0.5
Ni	<MQL	<MQL	1	<MQL	2
Cu	<MQL	<MQL	15	<MQL	30
As	<MQL	<MQL	0.075	<MQL	0.15
Se	<MQL	<MQL	0.75	<MQL	1.5
Mo	<MQL	<MQL	15	<MQL	30
Ru	<MQL	<MQL	0.5	<MQL	1
Rh	<MQL	<MQL	0.5	<MQL	1
Pd	<MQL	<MQL	0.5	<MQL	1
Ag	<MQL	<MQL	0.75	<MQL	1.5
Cd	<MQL	<MQL	0.025	<MQL	0.05
Sn	<MQL	<MQL	30	<MQL	60
Sb	<MQL	<MQL	6	<MQL	12
Ba	<MQL	<MQL	7	<MQL	14
Os	<MQL	<MQL	0.5	<MQL	1
Ir	<MQL	<MQL	0.5	<MQL	1
Pt	<MQL	<MQL	0.5	<MQL	1
Au	<MQL	<MQL	0.5	<MQL	1
Hg	<MQL	<MQL	0.15	<MQL	0.3
Tl	<MQL	<MQL	0.04	<MQL	0.08
Pb	<MQL	<MQL	0.025	<MQL	0.05

*Although the iCAP RQ ICP-MS can quantify significantly lower concentrations of each analyte ($\mu g \cdot kg^{-1}$ or lower) with the required degree of accuracy and precision, the MQLs presented in the table are based on the targeted LOQ of 0.05J and 0.1J (or 5% and 10% of limit concentration) of each analyte.

Figures 1 and 2 represent the results obtained for the accuracy test for different spiked levels of 0.05J, 1J, and 2J in sample A and sample B. Figure 3 presents the accuracy results obtained for spiked levels of 0.1J, 1J, and 2J in sample C, which was analyzed in experiment 2 using DMSO as the diluent. The reported accuracy values correspond to the average calculated from three independently prepared spiked samples at each level of spiked concentration.

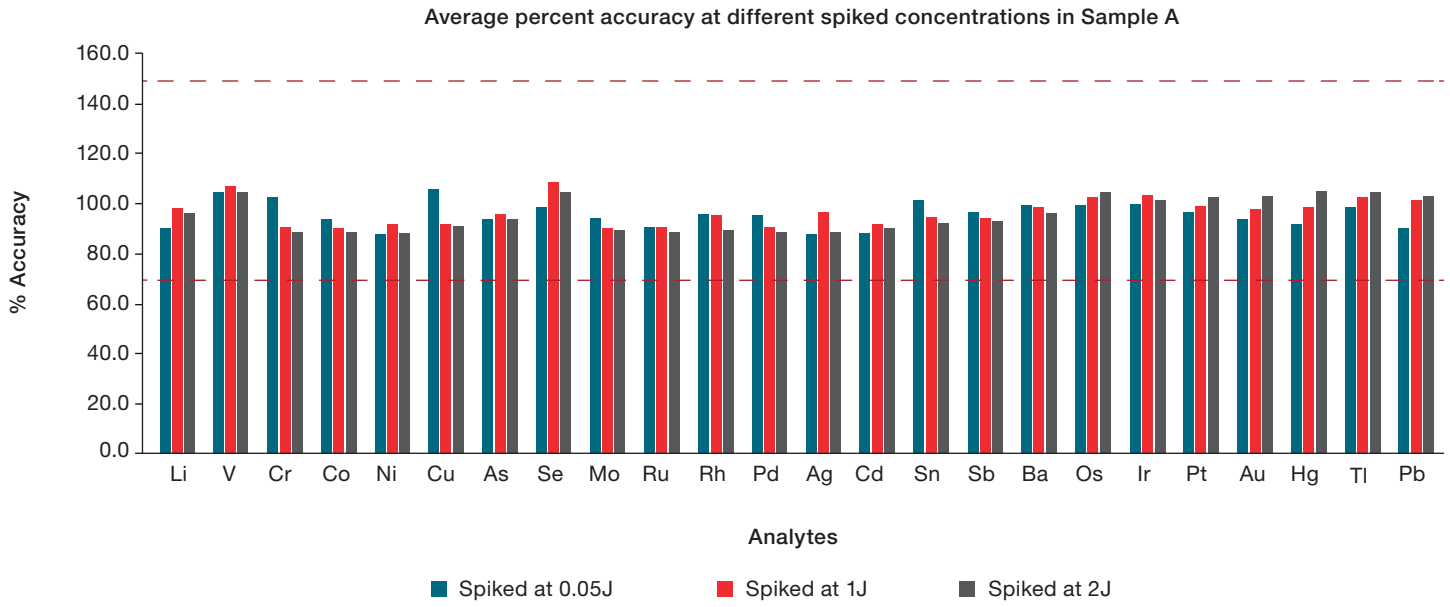

Figure 1. Average percent accuracy at 0.05J, 1J, and 2J spiked concentrations in sample A

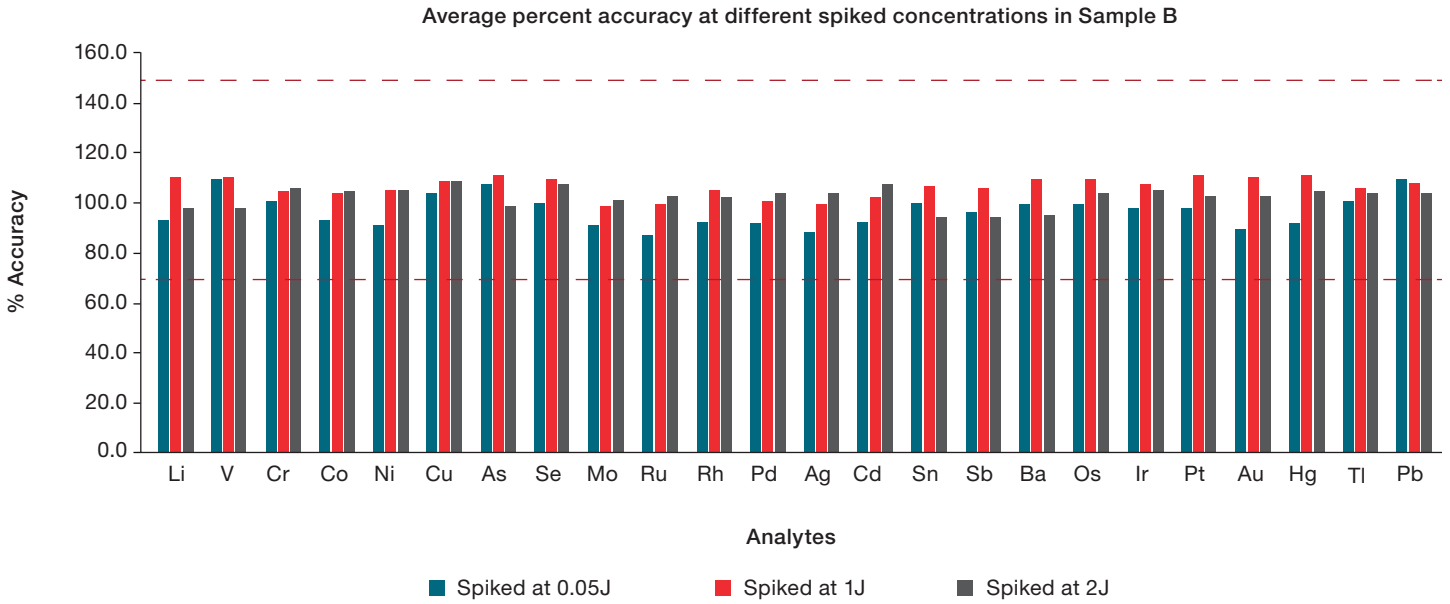

Figure 2. Average percent accuracy at 0.05J, 1J, and 2J spiked concentrations in sample B

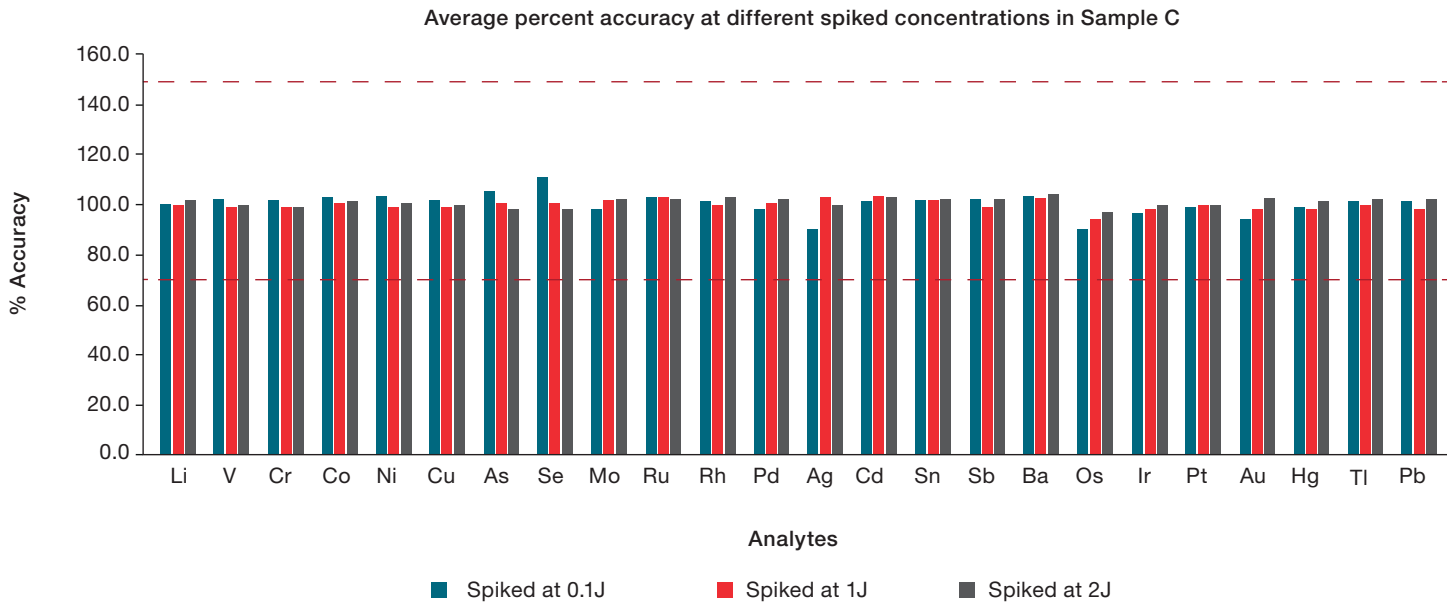

Figure 3. Average percent accuracy at 0.1J, 1J, and 2J spiked concentrations in sample C

System suitability – signal drift for 1.5J standard solution

Another system suitability requirement that needs to be fulfilled during each analysis is the assessment of the percent drift, typically using a standard of 1.5J concentration measured before and after analysis of the sample batch. The results obtained in both analyses should not differ from each other by more than the set limit of 20%. The results obtained in both measurements were compared to determine the percent variation for each analyte, and all data were found to be well within the acceptance criteria, indicating that this system suitability requirement was fulfilled in both experiments. Figure 4 presents the percent drift in the signal observed for all analytes in the 1.5J standard solution measured before and after sample analysis.

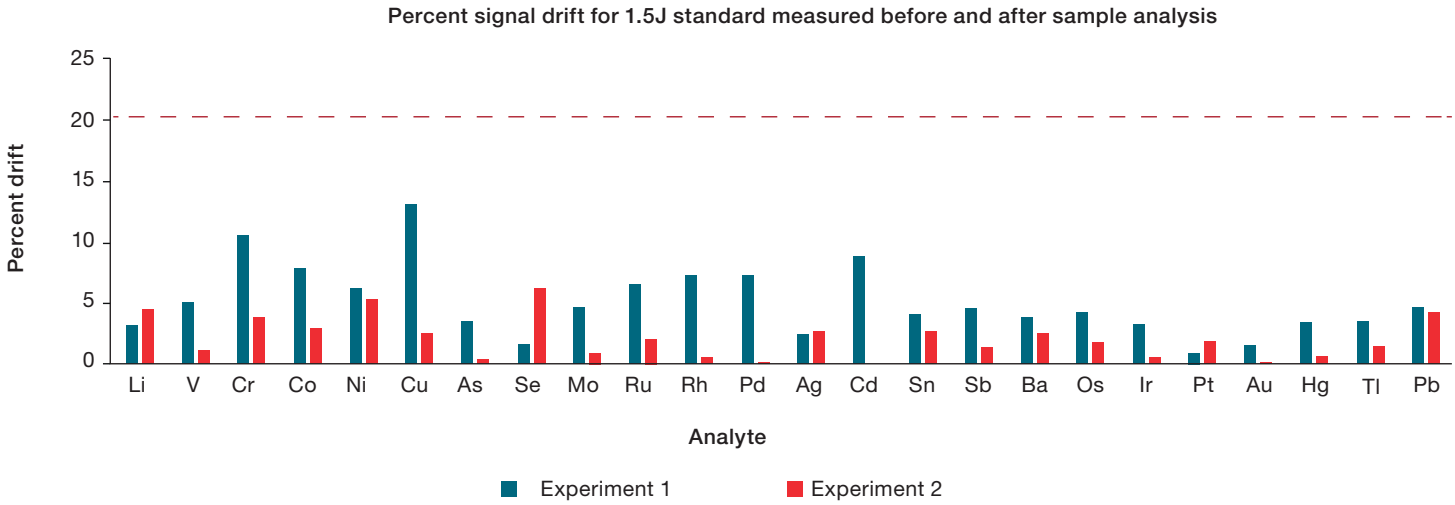

Figure 4. Analytes and percent signal drift observed for the 1.5J standard measured before and after sample analysis in both experiments (DMF as diluent in experiment 1 and DMSO as diluent in experiment 2)

Summary

This work describes a simple approach for analysis of elemental impurities in pharmaceutical products using direct dissolution of the sample in different organic solvents. The described method of sample preparation is in accordance with USP Chapter <233> and applicable for samples that are insoluble in aqueous solvents but soluble in organic solvents such as DMSO, DMF, acetonitrile, and isopropyl alcohol. Some of the important aspects of this work are summarized as follows:

- A single analytical method for interference-free quantification of the entire set of impurities defined in USP Chapter <232> was developed using KED mode with helium as the cell gas. This enables laboratories to avoid development and validation of multiple methods using different reaction gases and eliminates the additional time required to switch between different cell gases in the same method, reducing analysis time and improving overall productivity.
- The suggested approach of sample preparation using direct dissolution of samples in organic solvents allows significant reduction of the required time and cost associated with alternative sample preparation methods such as microwave-assisted closed vessel digestion.
- The accuracy and precision obtained for all three samples, spiked at three different concentration levels and analyzed in two different experiments, indicate that the developed method is suitable for accurate, precise, and reliable quantification of trace as well as relatively higher concentrations of analytes.
- The outcome of the system suitability study involving drift calculation suggests that the iCAP RQ ICP-MS delivers stable and consistent performance over a long period while analyzing samples dissolved in pure organic solvents, minimizing the need for re-calibration and re-analysis of the analytical batch.
- The Qtegra ISDS Software used for instrument control, data acquisition, data processing, and data reporting is equipped with a powerful toolset to ensure reliable instrument operation and easy data handling, fully meeting the requirements given in 21 CFR Part 11.

References

1. USP General Chapter <232>.
2. USP General Chapter <233>.
3. ICH guideline Q3-D (R1).
4. USP General Chapter <730> Plasma Spectrochemistry
5. Thermo Scientific Application Note 000734: Analysis of elemental impurities in pharmaceutical products in accordance with USP General Chapters <232> and <233>.

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