ORIGINAL ARTICLE

Examination of Fourteen Elemental Impurities in Levofloxacin Parenteral by Applying ICP-MS Technique

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ABSTRACT: In our work, a process for levofloxacin (LVO) digestion using the microwave digester was proposed. Simultaneous examination of fourteen metal elemental impurities (lithium, vanadium, chromium, manganese, iron, cobalt, nickel, copper, arsenic, molybdenum, cadmium, antimony, mercury, and lead) in digested LVO sample was done by ICP-MS system. Quantification limits vary between 2.7 ppb to 3000 ppb for all studied metal elemental impurities. Linear regression analysis proved linearity from LOQ quantity level to 200% of respective metal specification quantity limitations. The slope and coefficient correlation findings for fourteen metal elemental impurities were reported to be within permissible limit values. These outcomes demonstrated that the recommended ICP-MS methodology is capable of detecting 14 metal elemental impurities. Percentage recoveries for all studied metal elemental impurities were revealed to be satisfactory with recommended ICP-MS methodology conditions. The fully validated ICP-MS technique was finally adopted for batch studies of six different LVO parenteral for the selected fourteen metal elemental impurities.

INTRODUCTION

As metal elemental impurities (MEI) within the medicinal products are linked to significant safety & toxicological hazards, proper analysis of MEI in the medicinal products would be significant [1, 2]. Any components that aren't even intended to be contained in the formulation of the medicinal products are known as MEI. Several phases in the medication manufacturing process can contribute to these MEI. Most drugs are used on an every day or weekly schedule. If MEI is not thoroughly tested in medicinal products the patients may be regularly exposed to harmful components and serious health problems may arise.

According to regulatory advice, MEI can come from two sources: purposefully introduced MEI or unintentionally added MEI. MEI might intrude on the drug product through the catalysts employed throughout the production of APIs [3, 4]. The unintentionally added MEI includes impurities from naturally derived ingredients, manufacturing equipment, dosage container systems, and water used in medication production or formulation [3, 4]. Multiple potentially hazardous metals, including palladium & rhodium, are employed as catalysts and perhaps even as reagents in the manufacture of APIs and therefore should be removed to protect patients. Several metals, including cadmium and lead, are not often found in pharmaceuticals, but they are regulated because they accumulate in patients over time.

The use of catalysts (example - iridium, palladium, osmium, rhodium, platinum, and ruthenium) or embedded metals and metalloids (example - antimicrobial representatives including gold and silver; imaging entities including barium; antipsychotic drugs having lithium, and platinum-based agents) during the formulation of APIs can also result in elemental

contamination [5,6]. Trace substances including arsenic, mercury, cadmium, and lead are poisonous, as well as concentrations greater than those permitted values can be dangerous to one's health. Cobalt, molybdenum, copper, and selenium, on the other hand, are considered necessary elements for humans, although large quantities can be harmful to health [7, 8]. The identification and removal of trace metals in medicines are required due to their toxicity [9].

The regulatory criteria regarding MEI analysis have been modified and standardized, and producers must show conformity using approved instrumental techniques [10-13]. The most important recent modification in all regulatory guidelines is the elimination of the titration technique for the detection of heavy MEI. The MEI testing should now be done employing approved instrumental techniques to guarantee that adequate exposure levels are reached. The strategies for regulating MEI in pharmaceutical goods are being revised.

"Inductively coupled plasma–mass spectrometry" (ICP–MS) [14, 15], or "Inductively coupled plasma–optical emission spectroscopy" (ICP–OES) [16,17] are the greatest widely employed methodologies for analyzing MEI. These methods rely on an elevated energy plasma to ionize the MEI contained in the sample preparation & identify them via elemental masses and perhaps emission bands. ICP has the benefit of being able to identify a wide range of MEI at extremely low amounts. This feature allows the evaluation of product safety criteria for most of the common product types (oral solid dosage, inhaled, and injected).

Levofloxacin (LVO), a fluoroquinolone antibacterial drug, works against "Gram-positive" & "Gram-negative" kinds of bacteria, as well as respiratory pathogens [18,19]. LVO is being used to cure infections caused by susceptible bacteria in the sinuses, lungs, skin, ears, bones, airways, and joints. LVO is a commonly used/very frequently recommended drug product in India for the treatment of viral infections. In the literature search, it was found that there are no specific methodologies for the estimation of the MEI concerning to the ICH limits. These MEI are having a toxic nature which may interfere with the therapeutic nature of the

parental drugs. So, it was strongly contemplated to develop a novel analytical methodology to determine the MEI that may be associated with the drug product.

The most recent literature review revealed that no published papers were found on the simultaneous examination of fourteen MEI (lithium, vanadium, chromium, manganese, iron, cobalt, nickel, copper, arsenic, molybdenum, cadmium, antimony, mercury, and lead) in LVO. All impurities opted in this research are the heavy metals, that were categorized by ICH as Class-1 (cadmium, lead, arsenic, and mercury), Class-2A (cobalt, vanadium, and nickel), Class-3 (lithium, copper, molybdenum, antimony) and 2B (lithium, chromium, and manganese) which are to be avoided, minimized and exempted. The maximal standard dosage of LVO was used to determine the specification quantity limits for the fourteen MEI selected. The specification quantity limits were 3 ppm (vanadium), 75 ppm (lithium), 330 ppm (chromium), 1000 ppm (iron), 25 ppm (manganese), 1.5 ppm (cobalt), 90 ppm (copper), 6 ppm (nickel), 4.5 ppm (arsenic), 0.6 ppm (cadmium), 450 ppm (molybdenum), 27 ppm (antimony), 1.5 ppm (lead) and 0.9 ppm (mercury).

After a thorough literature search, it is observed that there is an innumerable research articles about to the related substances and residual solvents [20-23]. But, there was no article found for the estimation of MEI (lithium, vanadium, chromium, manganese, iron, cobalt, nickel, copper, arsenic, molybdenum, cadmium, antimony, mercury, and lead) in LVO by ICP-MS, which is a highly sophisticated and superior analytical technique for the estimation of elemental analysis.

In this study, an investigation was performed on the simultaneous evaluation of selected fourteen MEI in LVO using ICP-MS and a microwave digestion sample processing approach. The developed ICP-MS methodology was verified in adherence with the USP Pharmacopoeia [10, 11]. Another advantage of the protocol that we have adopted for the estimation of MEI (lithium, vanadium, chromium, manganese, iron, cobalt, nickel, copper, arsenic, molybdenum, cadmium, antimony, mercury, and lead) in LVO can be used for the other drug products of same therapeutic behaviour.

MATERIALS AND METHODS

Apparatus

The simultaneous examination of fourteen MEI in LVO was accomplished with the ICP-MS system (Agilent Technologies, model number 7700 X). Samples were weighed with an electronic balance device (Sartorius Secura, model number 225D-10 IN). The water utilized in the study experiments was from the Merck water treatment system. LVO sample was digested using a microwave digester (CEM Corporation, MARS 6).

Chemicals

Nitric acid (trace metal category), hydrochloric acid (supra pure category), hydrogen peroxide (ACS reagent category), and single metal element aqueous solutions (NIST traceable quality) at the quantity of 1000 ppm were employed in the simultaneous examination of fourteen MEI in LVO. Arsenic, cadmium, lead, vanadium, cobalt, lithium, manganese, antimony, yttrium, copper, bismuth, and indium were obtained from "Merck, India". Mercury, nickel, rhodium, and gold were obtained from "Sigma, India". Molybdenum, chromium, and iron were obtained from "Inorganic ventures, India".

ICP-MS conditions

In this study, the ICP-MS system was operated in multiple tune acquisition configurations, with reflected as well as forward reflected powers of 1-20 W and 1550 W, respectively. Helium, as well as Argon was used as collision and nebulizer gases, respectively. The plasma gas flow velocity was 15 L min^{-1}, with 6 repeats. The gas flow of collision, auxiliary, and nebulizer were 3.5 mL min^{-1}, 1200 mL min^{-1}, and 900 mL min^{-1}, respectively. Internal standards used were: rhodium for cadmium; indium for lithium and antimony; bismuth for mercury and lead; yttrium for chromium, vanadium, manganese, cobalt, iron, nickel, arsenic, molybdenum, and copper.

Conditions for LVO digestion

The conditions in the microwave digester were arranged at a power of 1600 W, the temperature of 210°C,

holding 25 min, and ramp 20 min for digesting LVO sample.

Metal elemental impurities solution

The diluent used for MEI solution preparation is a mix of 1% HCl with 25% HNO$_3$. Working MEI solutions were prepared by successive dilution of single metal element aqueous solutions (1000 ppm) with diluent. These solutions covered the range of quantities 1.8 – 12 ppb (cadmium), 13.5 – 90 ppb (arsenic), 2.7 – 18 ppb (mercury), 4.5 – 30 ppb (lead), 4.5 – 30 ppb (cobalt), 9 – 60 ppb (vanadium), 18 – 120 ppb (nickel), 225 – 1500 ppb (lithium), 81 – 540 ppb (antimony), 1350 –9000 ppb (molybdenum), 75 - 500 ppb (manganese), 990 – 6600 ppb (chromium), 270 – 1800 ppb (copper), 3000 – 20000 ppb (iron). The internal standards were included in all working metal elemental impurities solutions at a quantity of 0.5 ppm each of rhodium, indium, bismuth, and yttrium.

Blank sample

Placed 8 mL of H$_2$O$_2$, 5 mL of HNO$_3$, and 0.2 mL of HCl in the microwave digester container. After waiting for 10 min, included 0.2 mL of internal standard solution (0.5 ppm quantity each of rhodium, indium, bismuth, and yttrium) and 4 mL of H$_2$O in the microwave digester container. Then continued digestion using conditions directed in section "Conditions for LVO digestion" for LVO sample. After execution of digestion, transferred the contents to a 20 mL flask, water diluted the sample to volume and mixed thoroughly.

LVO sample

200 mg of LVO sample was weighed carefully into a microwave digester container. Digestion of the LVO sample was executed by the cautious addition of 8 mL of H$_2$O$_2$, 5 mL of HNO$_3$, and 0.2 mL of HCl. Then waited 10 min for the reaction to proceed. Placed 0.2 ml of internal standard solution (0.5 ppm quantity each of rhodium, indium, bismuth, and yttrium) and 4 mL of H$_2$O in the microwave digester container. The container

was carefully assembled and sealed. The sample was thereafter exposed to microwave digestion, which allowed for LVO sample decomposition at higher temperature as well as pressure using conditions cited in segment "Conditions for LVO digestion". Digested LVO samples were now appropriately placed in a 20 mL flask, water diluted to volume, and well mixed to have a quantity of 0.01 g L^{-1}.

General ICP-MS procedure for MEI assessment in LVO sample

Suctioned the blank sample followed by six working MEI solutions. Analyzed six working MEI solutions using recommended ICP-MS methodology conditions. The response (counts sec^{-1}) ratio of elements to internal standard were measured. The response (counts/sec) ratio of opted elements as the y-axis values and quantities of opted elements as the x-axis values yielded linearity curves of opted fourteen MEI. Suctioned the blank sample followed by digested LVO sample. Analyzed digested LVO sample using recommended ICP-MS methodology conditions. The response (counts sec^{-1}) ratio of MEI to internal standard in the LVO sample was measured. Using response ratio, the content of opted fourteen MEI in LVO sample was quantified.

RESULTS AND DISCUSSION

Digestion condition optimization

Microwave digester aided LVO sample preparation approach was optimized for analysis of LVO parenteral

for all desired MEI. Optimization was executed with MEI spiked LVO solution. The quantities of fourteen MEI spiked were 3 ppm vanadium, 75 ppm lithium, 330 ppm chromium, 1000 ppm iron, 25 ppm manganese, 1.5 ppm cobalt, 90 ppm copper, 6 ppm nickel, 4.5 ppm arsenic, 0.6 ppm cadmium, 450 ppm molybdenum, 27 ppm antimony, 1.5 ppm lead and 0.9 ppm mercury. Internal standards of quantity 0.5 ppm each of rhodium, indium, bismuth, and yttrium was also added. MEI spiked LVO solution was digested using of adding different volumes of H_2O_2 (6, 7, 8, 9 and 10 mL), HNO_3 (3, 4, 5, 6 and 7 mL) and 0.2 mL HCl (0.1 0.15, 0.2, 0.25 and 0.3 mL). The ICP-MS system was then deployed to examine the digested LVO solution for fourteen metal elemental impurities. A better response ratio for fourteen MEI was attained with 8 mL H_2O_2, 5 mL HNO_3, and 0.2 mL HCl. Therefore, for completely subsequent LVO digestion and fourteen MEI measurements, 8 mL H_2O_2, 5 mL HNO_3, and 0.2 mL HCl was affixed.

Validation of developed ICP-MS methodology conditions

System suitability

Working MEI solutions were assessed for system suitability as specified in recommended ICP-MS methodology conditions. The slope and coefficient correlation for opted fourteen MEI were measured (Table 1). The findings were reported to be within permissible limitations, demonstrating that the ICP-MS device system is capable of detecting 14 MEI.

Table 1. ICP-MS system device suitability, LOD, and LOQ.

Impurities	Slope	Correlation coefficient	LOD		LOQ		
			Measure (ppb)	RSD (%)	Measure(ppb)[*]	RSD (%)[*]	Regained (%)[**]
Lithium	0.0371	0.9997	74.25	0.64	225	0.47	114.48
Vanadium	0.1466	0.9992	2.97	1.24	9	0.64	92.23
Chromium	0.0147	1.0000	326.7	0.30	990	0.32	102.30
Manganese	0.1569	1.0000	24.75	0.29	75	0.36	101.64
Iron	0.1357	1.0000	990	0.31	3000	0.25	99.38
Cobalt	0.1377	0.9995	1.485	0.30	4.5	0.34	93.12
Nickel	0.0294	0.9993	5.94	0.32	18	0.29	91.75
Copper	0.0662	1.0000	89.1	0.16	270	0.23	99.89
Arsenic	0.0182	0.9998	4.455	0.54	13.5	0.34	102.21
Molybdenum	0.0505	1.0000	445.5	0.23	1350	0.25	101.80
Cadmium	0.0302	1.0000	0.594	0.87	1.8	0.51	103.54
Antimony	0.0721	1.0000	26.73	0.26	81	0.36	89.22
Mercury	0.0214	0.9999	0.891	0.60	2.7	0.39	83.83
Lead	0.1316	0.9981	1.485	0.13	4.5	0.05	95.25

[*]RSD of 6 measures; [*]Mean of 3 recovered measures

LOD and LOQ

Ten blank samples were assessed as specified in recommended ICP-MS methodology conditions. Computed the SD for ten blank counts. Using the slope values quantified in system suitability, gauged the LOD and LOQ for each opted impurity as follows.

$$LOD = 3.3 \times Standard\ deviation\ /\ Slop$$
$$LOQ = 10 \times Standard\ deviation\ /\ Slop$$

Precision tests with a solution of fourteen opted MEI at the quantities of LOD levels were used to verify the LOD measures obtained. Precision and accuracy tests with a solution of fourteen opted MEI at the quantities of LOQ levels were used to verify the LOQ measures obtained. The RSD measures and recovery measures (Table 1) of fourteen opted MEI indicated effective LOD and LOQ sensitivity, respectively for recommended ICP-MS methodology conditions.

Selectivity

Two blank samples and two opted MEI solutions (LOD quantity level) were assessed as specified in recommended ICP-MS methodology conditions. Compared the MEI response ratio of the blank sample with MEI solution (LOD quantity level). The higher response ratio values of opted fourteen elements in MEI solution (LOD quantity level), evidenced selectivity of recommended ICP-MS methodology conditions.

Precision

Six replicate analyses of a newly produced MEI spiked LVO solution (0.01 g L^{-1}) using the same ICP-MS apparatus on the same day revealed the precision. The quantities of fourteen MEI spiked were 3 ppm (vanadium), 75 ppm (lithium), 330 ppm (chromium), 1000 ppm (iron), 25 ppm (manganese), 1.5 ppm (cobalt), 90 ppm (copper), 6 ppm (nickel), 4.5 ppm (arsenic), 0.6 ppm (cadmium), 450 ppm (molybdenum), 27 ppm (antimony), 1.5 ppm (lead) and 0.9 ppm (mercury). Internal standards of quantity 0.5 ppm each of rhodium, indium, bismuth, and yttrium was also spiked. The RSD of a set of measurements was applied to demonstrate precision (Table 2). The outcomes evidenced the precision of recommended ICP-MS methodology conditions.

Table 2. ICP-MS methodology conditions precision.

Impurities	Added (ppm)	Measured (ppm)*	Regained (%)*	RSD (%)
Lithium	75.00	76.96	102.61	1.47
Vanadium	3.00	2.81	93.62	1.53
Chromium	330.00	320.31	97.06	1.02
Manganese	25.00	24.37	97.48	0.90
Iron	1000.00	973.06	97.31	0.96
Cobalt	1.50	1.50	99.91	1.84
Nickel	6.00	5.36	89.30	1.60
Copper	90.00	86.51	96.12	0.91
Arsenic	4.50	4.49	99.71	2.96
Molybdenum	450.00	464.50	103.22	0.96
Cadmium	0.60	0.60	99.53	1.03
Antimony	27.00	23.88	88.42	0.77
Mercury	0.90	0.79	87.37	0.37
Lead	1.50	1.42	94.75	0.35

*Mean of six score

Linearity

Calibration curves for fourteen opted MEI in recommended ICP-MS methodology were obtained by analysing the working MEI solutions with series of quantities 1.8 – 12 ppb (cadmium), 13.5 – 90 ppb (arsenic), 2.7 – 18 ppb (mercury), 4.5 – 30 ppb (lead), 4.5 – 30 ppb (cobalt), 9 – 60 ppb (vanadium), 18 – 120 ppb (nickel), 225 – 1500 ppb (lithium), 81 – 540 ppb (antimony), 1350 –9000 ppb (molybdenum), 75 - 500 ppb (manganese), 990 – 6600 ppb (chromium), 270 – 1800 ppb (copper), 3000 – 20000 ppb (iron). Concerning

to their respective specification quantity limitations, each element's concentration range is LOQ, 50%, 75%, 100%, 150%, and 200%. Linear regression investigation was performed to demonstrate linearity (Table 3). Correlation

coefficient measures, percent Y-intercept measures, and regression equation evidenced linearity of recommended ICP-MS methodology conditions.

Table 3. Recommended ICP-MS methodology linearity.

Impurities	Linearity range (ppb)	Correlation coefficient (R^2)	Y-intercept(%)	Regression equation
Lithium	225 – 1500	0.9996	1.00	Rr = 0.028386 x + 0.257378
Vanadium	9 – 60 ppb	0.9988	5.92	Rr = 0.134332 x + 0.257546
Chromium	990 – 6600	1.0000	0.32	Rr = 0.013433 x + 0.140675
Manganese	75 - 500	1.0000	1.67	Rr = 0.146141 x + 0.620883
Iron	3000 – 20000	1.0000	0.52	Rr = 0.126168 x + 6.635002
Cobalt	4.5 – 30	0.9996	-0.22	Rr = 0.127427 x - 0.004386
Nickel	18 – 120	0.9997	-0.07	Rr = 0.027166 x - 0.001131
Copper	270 – 1800	1.0000	0.53	Rr = 0.062380 x + 0.300733
Arsenic	13.5 – 90	0.9996	2.98	Rr = 0.017531 x + 0.024520
Molybdenum	1350 –9000	1.0000	-0.23	Rr = 0.047719 x - 0.497046
Cadmium	1.8 – 12	0.9999	0.52	Rr = 0.027432 x + 0.000849
Antimony	81 – 540	1.0000	0.71	Rr = 0.062782 x + 0.121347
Mercury	2.7 – 18	1.0000	-0.40	Rr = 0.021358 x - 0.000775
Lead	4.5 – 30	0.9991	-2.21	Rr = 0.127481 x - 0.040071

Rr = response ratio of impurity; x = concentration of element (ppb)

Accuracy

To bring out the accuracy, the recoveries of opted fourteen MEI were determined with recommended ICP-MS methodology conditions after known quantities of MEI were added differently to the LVO sample (0.01 g L^{-1}). Internal standards of quantity 0.5 ppm each of

rhodium, indium, bismuth, and yttrium was also spiked in the LVO sample. Percentage recoveries for fourteen MEI were revealed to be satisfactory under recommended ICP-MS methodology conditions (Table 4).

Table 4. Recommended ICP-MS methodology accuracy.

Impurity	50% spiking level		100% spiking level		200% spiking level	
	Added (ppm)	Regained (%)*	Added (ppm)	Regained (%)*	Added (ppm)	Regained (%)*
Lithium	37.50	110.34	75.00	102.61	150.00	112.79
Vanadium	1.50	95.75	3.00	93.62	6.00	98.51
Chromium	165.00	97.23	330.00	97.06	660.00	100.37
Manganese	12.50	96.58	25.00	97.48	50.00	99.96
Iron	500.00	95.29	1000.00	97.31	2000.00	99.79
Cobalt	0.75	88.08	1.50	99.91	3.00	97.90
Nickel	3.00	87.47	6.00	89.30	12.00	97.68
Copper	45.00	94.99	90.00	96.12	180.00	97.43
Arsenic	2.25	97.42	4.50	99.71	9.00	98.49
Molybdenum	225.00	97.69	450.00	103.22	900.00	102.86
Cadmium	0.30	97.31	0.600	99.53	1.20	101.23
Antimony	13.50	84.50	27.00	88.42	54.00	87.66
Mercury	0.45	81.87	0.90	87.37	1.80	89.54
Lead	0.75	90.09	1.50	94.75	3.00	104.30

*Mean of 3 recovered measures

Robustness

The robustness was executed with afresh-produced MEI spiked LVO solution (0.01 g L^{-1}) by doing negligible modifications in concentrations of nitric acid and HCl. The quantities of fourteen MEI spiked were 3 ppm (vanadium), 75 ppm (lithium), 330 ppm (chromium), 1000 ppm (iron), 25 ppm (manganese), 1.5 ppm (cobalt), 90 ppm (copper), 6 ppm (nickel), 4.5 ppm (arsenic), 0.6 ppm (cadmium), 450 ppm (molybdenum), 27 ppm

(antimony), 1.5 ppm (lead) and 0.9 ppm (mercury). Internal standards of quantity 0.5 ppm each of rhodium, indium, bismuth, and yttrium was also spiked. Table 5 shows an overview of the findings. As can be revealed, the RSD estimates for all tested and changed parameters were between 0.95% to 5.49%, representing the recommended ICP-MS methodology's robustness.

Table 5. Recommended ICP-MS methodology accuracy robustness.

| Impurity | Added (ppm) | Conditions put on | | | RSD (%) ** |
| | | 22.5% v/v HNO$_3$ +0.9 % v/v HCl | 27.5% v/v HNO$_3$ +1.1 % v/v HCl | 25% v/v HNO$_3$ +1.0% v/v HCl | |
		Regained (%)*	Regained (%)*	Regained (%)*	
Lithium	75.00	108.03	110.75	102.61	3.44
Vanadium	3.00	97.71	96.46	93.62	2.04
Chromium	330.00	100.14	99.31	97.06	1.50
Manganese	25.00	100.12	98.75	97.48	1.26
Iron	1000.00	100.20	98.70	97.31	1.35
Cobalt	1.50	94.55	88.90	99.91	5.02
Nickel	6.00	93.19	88.09	89.30	2.64
Copper	90.00	98.34	96.88	96.12	1.12
Arsenic	4.50	105.94	94.52	99.71	5.49
Molybdenum	450.00	102.24	101.48	103.22	0.95
Cadmium	0.60	99.61	100.82	99.53	1.07
Antimony	27.00	88.12	84.56	88.42	2.13
Mercury	0.90	89.01	86.16	87.37	2.21
Lead	1.50	96.63	91.02	94.75	2.69

*Mean of 6 recovered measures; **RSD for eighteen recovered measures

Ruggedness

Ruggedness was determined by analyzing LVO solution (0.01 g L^{-1}) spiked with 3 ppm (vanadium), 75 ppm (lithium), 330 ppm (chromium), 1000 ppm (iron), 25 ppm (manganese), 1.5 ppm (cobalt), 90 ppm (copper), 6 ppm (nickel), 4.5 ppm (arsenic), 0.6 ppm (cadmium), 450 ppm (molybdenum), 27 ppm (antimony), 1.5 ppm (lead), 0.9 ppm (mercury) and internal standards of

quantity 0.5 ppm each of rhodium, indium, bismuth, and yttrium by two analysts in the same and different day with identical recommended ICP-MS methodology. The recoveries of fourteen opted MEI and cumulative RSD was calculated (Table 6). The RSD estimates were flanked by 0.95% to 5.49%, representing the recommended ICP-MS methodology's ruggedness.

Table 6. Recommended ICP-MS methodology accuracy ruggedness.

Impurity	Added (ppm)	1st day 1st analyst Regained (%)*	2nd day 2nd analyst Regained (%)*	RSD (%)**
Lithium	75.00	102.61	105.83	1.91
Vanadium	3.00	93.62	96.73	2.00
Chromium	330.00	97.06	99.98	1.70
Manganese	25.00	97.48	99.94	1.46
Iron	1000.00	97.31	99.93	1.54
Cobalt	1.50	99.91	94.36	3.26
Nickel	6.00	89.30	93.75	2.76
Copper	90.00	96.12	98.32	1.35
Arsenic	4.50	99.71	98.87	2.31
Molybdenum	450.00	103.22	102.81	0.72
Cadmium	0.60	99.53	101.50	1.52
Antimony	27.00	88.42	87.30	0.88
Mercury	0.90	87.37	90.54	1.91
Lead	1.50	94.75	97.41	1.47

*Mean of 6 recovered measures; **RSD for twelve recovered measures

Batch analysis

Six batches of LVO parenteral such as LV217003, LV217004, LV217005, LV217006, LV217008, and LV217010 were evaluated for fourteen opted MEI with recommended ICP-MS methodology. Table 7 shows an overview of the findings.

Table 7. Analysis of batches of LVO parenteral with recommended ICP-MS methodology.

Impurity	Measured content of MEI (ppm) in					
	LV217003	LV217004	LV217005	LV217006	LV217008	LV217010
Lithium	ND	ND	ND	ND	ND	ND
Vanadium	ND	ND	ND	ND	ND	ND
Chromium	ND	ND	ND	ND	ND	BDQ
Manganese	BDQ	BDQ	BDQ	BDQ	BDQ	BDQ
Iron	BDQ	BDQ	BDQ	BDQ	BDQ	BDQ
Cobalt	BDQ	BDQ	BDQ	BDQ	BDQ	BDQ
Nickel	BDQ	BDQ	BDQ	BDQ	BDQ	BDQ
Copper	BDQ	BDQ	ND	BDQ	ND	BDQ
Arsenic	ND	ND	ND	ND	ND	ND
Molybdenum	ND	ND	ND	ND	ND	ND
Cadmium	ND	ND	ND	ND	BDQ	ND
Antimony	ND	BDQ	ND	ND	ND	ND
Mercury	ND	ND	ND	ND	ND	ND
Lead	BDQ	BDQ	BDQ	BDQ	BDQ	BDQ

ND - not detected; BDQ – below detection quantity

CONCLUSIONS

The current study recommended utilizing an ICP-MS technique to simultaneously estimate fourteen different MEI in LVO parenteral batch samples. According to USP standards, the recommended ICP-MS methodology

was proven to be easy, relatively sensitive, consistent, and effective. The recommended ICP-MS methodology, furthermore, showed a superior degree of practical exploit in LVO parenteral batch samples.

Conflict of interests

The authors declared none.

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