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DEVELOPMENT AND VALIDATION OF ANALYTICAL METHOD FOR SIMULTANEOUS QUANTITATIVE DETERMINATION OF ELEMENTAL IMPURITIES AS PER ICH Q3D AND USP <232> IN NON-AQUEOUS PARENTERAL FORMULATIONS WITH COMPLEX MATRIX CONTAINING CASTOR OIL BY ICP-MS

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ABSTRACT

Comprehensive studies, control strategies and management of elemental impurities (EIs) in pharmaceutical products are provided by ICH in its Quality Guidelines (ICH Q3D) considering Safety and Quality of drug product for human use. Replacement of historical 'Heavy Metal Test' by introducing more sophisticated analytical methodologies such as AAS, ICP-OES, ICP-MS etc. opened the doors for the quantitative determination of EIs with stringent limits. Performing EI estimation requires sound scientific knowledge and sensitive analytical techniques that can deliver accurate results of each toxic EI present in targeted products. Continuous monitoring of EIs in manufacturing of pharmaceutical products with GLP/GMP compliance in line with regulatory guidelines helps to generate scientific-based risk assessments for over all possibilities for the presence of EIs from different sources (i.e. Drug Substance, Excipients, Solvents, Regents and Chemicals etc). For testing ICH Class 1, Class 2A, Class 2B and Class 3 EIs in single analytical method required samples prepared using microwave digestion technique. Developed methods were validated in-house as per ICH and USP <233>.

***Key words** -Elemental impurities, ICHQ3D, Method development, Method validation, Parenteral formulations, Castor oil*

INTRODUCTION

Considering metal toxicity of EIs enlisted in ICH Q3D[1], it becomes challenging for the analytical R&D laboratories to develop novel and sensitive methods that become suitable to determine the EIs at trace levels and even more difficult to validate the developed method in QC that provides fast, precise and accurate results for the tested article. In previous years, compendial methodologies were applied for the estimation of Heavy metals[2] (now represented as Elemental Impurities), like colorimetry or by the orthodox method that required lengthy solution preparations (i.e. generating and precipitating metal sulfides by chemical reaction) and analysing them against series of standard solutions. These routine methods have inherent limitations like these are unable to differentiate metals in sample and due to low repeatability and accuracy, requires huge sample quantity[3]. To overcome these challenges, fast, robust and highly sensitive analytical methodologies like wavelength based spectroscopic techniques (i.e., ICP-OES or AAS) or mass based spectrometry technique (i.e. ICP-MS) can be used that can accurately determine EIs even present at ultra-trace levels and also distinguish metals in a mixture of EIs in a sample. As EIs testing required quantitation at sub-ppb level, in complex matrices, ICP-MS technique observed more compatible due its sensitivity at very low level concentrations, resolution for isotopic, isomeric elements and having efficiency for removing polyatomic and other interfering species from the sample[4-6].

Approaches to transform methodologies to modern analytical methods and define limits of individual EIs

Based on exceptional patient safety concerns and metal toxicity[7,8], EI classification becomes primary requirement that is set and represented in ICH Q3D guideline by Requirements for Registration of Pharmaceuticals for Human Use (ICH) as well as respecting Pharmacopoeias. As per recommendations[9-11], PDEs are provided in µg/day for 24 elements (segregated in three separate classes) and these classifications are further extrapolated based on route of administration of drug product as well as metal toxicity and likely hood of occurrence. ICHQ3D also provide insight for performing risk based assessments testing of articles by the selection of related elements that should be tested in finished pharmaceutical dosage forms. 30% of PDEs are the control thresholds as per the guideline. If actual results fall below the control threshold then there will be no requirement of further controls and if results go above control thresholds then further line of actions should be executed to confirm that the results will be within acceptance limits.

There are only few literatures provides information for the estimation of EIs in pharmaceuticals as per the current guideline recommendations and regulatory requirements.

Hence, to explore the analytical pathways for the estimations of EIs in pharmaceutical products, Non-aqueous formulation with complex matrix has been evaluated. Targeted methods are designed in-house in such a way to encounter challenges like EIs, which are having very low PDEs and sensitivities, polyatomic and isotopic interferences, matrix interference. Test materials were digested using microwaves before further dilution. The developed methods were validated as per the USP Pharmacopoeia chapters <233> and <730>[10-11]

The overall objective behind the study was to develop efficient and reproducible analytical methods for quantification of EIs in Parenteral Pharmaceuticals product with higher amount of matrix that provides simplicity and applicability for sample preparation as well as instrument operations in routine QC testing.

MATERIALS AND METHODS

Reagents and materials

Concentrated nitric acid (69%, v/v, Tracemetal grade) was purchased from Fischer Scientific (Fair Lawn, NJ, USA). Concentrated hydrochloric acid (36%, v/v, Tracemetal grade) was purchased from Fischer Scientific (Fair Lawn, NJ, USA). Acetic acid (99.6%, v/v, Optima grade) was purchased from Fischer Scientific (Fair Lawn, NJ, USA). Ultrapure water used in the experiments was prepared by passing purified water through a Milli-Q Advantage A10 water system (EMD Millipore, Billerica, MA, USA). Standard solutions for calibration and spike solutions for recovery assessment were prepared by diluting commercially available Parenteral Standard stock solution as per ICH Q3D (Sigma Aldrich, Buchs, Switzerland) and Yttrium internal standard solution was prepared using NIST traceable, single element 1000 mg/L stock solutions (Sigma Aldrich, Buchs, Switzerland). Test samples provided for this study consisted formulation development batch from R&D and three submission batches from manufacturing facility (Alembic Pharmaceuticals Limited, Vadodara, INDIA).

Standard preparation

25 mL of Conc. HNO_3, 12.5 mL of Conc. HCl and 2 mL of Acetic Acid were mixed well and diluted up to 500 mL with water. This acidic mixture was used as a diluent for blank and standard solution preparations.

Standards were prepared by mixing and diluting readily available standard stock solution to the desired concentration level mentioned all the samples and standard solution preparations. Concentration range of standards from 25% level to 200 % level were prepared considering calculation of working concentration from sample dilution and maximum daily dose of drug product (Table 1).

Table 1: Concentration levels (ng/mL) of calibration standards of the Class 1, Class 2a and b and Class 3 EIs

Element	Std 1 (ng/mL)	Std 2 (ng/mL)	Std 3 (ng/mL)	Std 4 (ng/mL)	Std 5 (ng/mL)
	Level 1 (25%)	**Level 2 (50%)**	**Level 3 (100%)**	**Level 4 (150%)**	**Level 5 (200%)**
	0.25*J*	**0.5*J***	**1*J***	**1.5*J***	**2*J***
As	2.25	4.5	9	13.5	18
Hg	0.45	0.9	1.8	2.7	3.6
Se	12	24	48	72	96
Cd	0.3	0.6	1.2	1.8	2.4
Pb	0.75	1.5	3	4.5	6
Co	0.75	1.5	3	4.5	6
V	1.5	3	6	9	12
Ni	3	6	12	18	24
Tl	1.2	2.4	4.8	7.2	9.6
Au	15	30	60	90	120
Pd	1.5	3	6	9	12
Ir	1.5	3	6	9	12
Os	1.5	3	6	9	12
Rh	1.5	3	6	9	12
Ru	1.5	3	6	9	12
Ag	1.5	3	6	9	12
Pt	1.5	3	6	9	12
Li	37.5	75	150	225	300
Sb	13.5	27	54	81	108
Ba	105	210	420	630	840
Mo	225	450	900	1350	1800
Cu	45	90	180	270	360
Sn	90	180	360	540	720
Cr	165	330	660	990	1320

Sample preparation

Sample stock solution was prepared carefully by taking about 6 g of sample and diluted it up to 10 mL with Acetic Acid, mixed well. Taken 0.5 mL of sample stock solution in digestion vessel, added 0.5 mL of internal standard stock solution, 2.5 mL of Conc. HNO_3, 1.25 mL of Conc. HCl swirled it gently to mix up the contents in digestion vessel. After adding the content in digestion vessel, sealed it with cap carefully. Then performed closed vessel digestion in microwave digestion system that cause decomposition of sample under high temperature and pressure. Three-step microwave program (mentioned in Table 2) for microwave digestion was used for the digestion of the sample. After digestion, cooled down the digested solution to room temperature for at least 30 min before venting and opening of the digestion vessel, then transferred the digested solution in to a flask, diluted it to 50 mL with water and mixed well. Centrifuged it at 4500 RPM for 10 min and used supernatant solution for analysis. Reagent blank (Digested solution without sample) and Spiked samples (Sample digestion with addition of standard) were prepared with the same procedure.

Digestion procedure

PerkinElmer Titan microwave digestion system and 100 mL Digestion vessel (PerkinElmer, USA) having 40 bar maximum pressure and 300°C maximum temperatures were utilized for sample digestion (Table 2).

Table 2: Typical microwave digestion program (MDS)[@] for sample preparation[#]

Step	Temp (°C)	pressure (p, bar)	Ramp (min)	Hold (min)	Power (P, %)
1	140	30	5	10	60
2	180	30	5	40	60
3	50	30	1	10	0

[@]: MDS programs with different operating conditions were conducted and presented here the most suitable program identified.
[#]: Samples prepared employing different concentration of HNO_3 and HCl while doing digestion. Also screened different centrifuge program to get the clear solution for aspiration into ICPMS system for analysis.

Methods

Thermoscientific centrifuge machine was used to centrifuge the sample solution. PerkinElmer NexION 2000 ICPMS (PerkinElmer, USA) with S10 Auto sampler was employed for sample analysis for EIs. Detailed method parameters are given in Table 3.

Table 3: Method parameters for PerkinElmer NexION 2000 ICP-MS

Instrument settings	
Auxiliary gas flow (mL/min)	1.20
Plasma Gas Flow (mL/min)	15
ICP RF Power (W)	1600
Torch	2 mm ID
Injector	2 mm ID
Timing Parameters	
Sweeps/Reading	30
Readings/Replicates	1
Number of Replicates	3
Scan Mode	Peak Hopping
MCA Channels	1
Dwell Time (ms)	50
Mode	KED
RPq	0.25
RPa	0

IS	Analyte	Mass	Cell Gas (Helium) (mL/min)
-	As	74.922	3
-	Hg	201.971	1
-	Se	81.917	2
Y	Cd	110.904	1
Y	Pb	207.977	3
Y	Co	58.933	3
Y	V	50.944	4
Y	Ni	59.933	3
Y	Tl	204.975	3
Y	Au	196.967	5
Y	Pd	105.903	3
Y	Ir	192.963	3
Y	Os	191.962	3
Y	Rh	102.905	3
Y	Ru	101.904	3
Y	Ag	106.905	5
Y	Pt	194.965	3
Y	Li	7.016	3
Y	Sb	120.904	3
Y	Ba	137.905	5

Y	Mo	97.906	5
Y	Cu	62.93	5
Y	Sn	117.902	5
Y	Cr	51.941	5
-	Y	88.905	4

Signal Processing

Detector Mode	Dual
Measurement Units	cps
QID	On
Spectral Peak Processing	Average
Signal Profile Processing	Average
Blank Subtraction	Subtracted after internal standard
Baseline Readings	0
Smoothing	Factor 5

Calibration information

Analyte	Mass	Curve Type	Sample Units	Std Units	Std 1	Std 2	Std 3	Std 4	Std 5
As	74.922	Linear Thru Zero	ng/mL	ng/mL	2.25	4.5	9	13.5	18
Hg	201.971	Linear Thru Zero	ng/mL	ng/mL	0.45	0.9	1.8	2.7	3.6
Se	81.917	Linear Thru Zero	ng/mL	ng/mL	12	24	48	72	96
Cd	110.904	Linear Thru Zero	ng/mL	ng/mL	0.3	0.6	1.2	1.8	2.4
Pb	207.977	Linear Thru Zero	ng/mL	ng/mL	0.75	1.5	3	4.5	6
Co	58.933	Linear Thru Zero	ng/mL	ng/mL	0.75	1.5	3	4.5	6
V	50.944	Linear Thru Zero	ng/mL	ng/mL	1.5	3	6	9	12
Ni	59.933	Linear Thru Zero	ng/mL	ng/mL	3	6	12	18	24
Tl	204.975	Linear Thru Zero	ng/mL	ng/mL	1.2	2.4	4.8	7.2	9.6
Au	196.967	Linear Thru Zero	ng/mL	ng/mL	15	30	60	90	120
Pd	105.903	Linear Thru Zero	ng/mL	ng/mL	1.5	3	6	9	12
Ir	192.963	Linear Thru Zero	ng/mL	ng/mL	1.5	3	6	9	12
Os	191.962	Linear Thru Zero	ng/mL	ng/mL	1.5	3	6	9	12
Rh	102.905	Linear Thru Zero	ng/mL	ng/mL	1.5	3	6	9	12
Ru	101.904	Linear Thru Zero	ng/mL	ng/mL	1.5	3	6	9	12
Ag	106.905	Linear Thru Zero	ng/mL	ng/mL	1.5	3	6	9	12
Pt	194.965	Linear Thru Zero	ng/mL	ng/mL	1.5	3	6	9	12
Li	7.016	Linear Thru Zero	ng/mL	ng/mL	37.5	75	150	225	300
Sb	120.904	Linear Thru Zero	ng/mL	ng/mL	13.5	27	54	81	108
Ba	137.905	Linear Thru Zero	ng/mL	ng/mL	105	210	420	630	840
Mo	97.906	Linear Thru Zero	ng/mL	ng/mL	225	450	900	1350	1800
Cu	62.930	Linear Thru Zero	ng/mL	ng/mL	45	90	180	270	360
Sn	117.902	Linear Thru Zero	ng/mL	ng/mL	90	180	360	540	720
Cr	51.941	Linear Thru Zero	ng/mL	ng/mL	165	330	660	990	1320
Y	88.905	Linear Thru Zero	ng/mL	ng/mL	5	5	5	5	5

Sampling devices

Peristaltic Pump Control	Yes
Sample Flush Time (s)	120
Sample Flush Speed (rpm)	-35
Read Delay Time (s)	60
Read Delay and Analysis Speed (rpm)	-35
Wash Time (s)	120
Wash Speed (rpm)	-35
Auto Sampler	S10

RESULTS AND DISCUSSION

As per ICH Q3D and USP <232> requirements, analytical method has been developed and validated as per regulatory requirements for the parameters mentioned in Table 4. Further the test article was tested using validated analytical method for the estimation of EIs Class 1, Class 2a and b and Class 3. Considering the PDE value mentioned in the ICHQ3D and USP <232> for parenteral formulation and maximum daily dose of the drug product i.e. 10 mL/day, specification has been mentioned.

Test sample contains commercial alcohol, benzylalcohol, benzylbenzoate and castor oil as excipients along with 50 mg/mL of an API. Castor oil is the major component of the drug product. Presence of higher amount of matrices in the drug product as well as insolubility of drug product in strong inorganic acidic (Nitric acid and Hydrochloric acid) environment impacted the sample preparation which was major challenge to prepare the sample using direct dilution. Further the insolubility in strong inorganic acidic medium gave challenge to dissolve the sample in the regular acids used for ICP-MS analysis, which made compulsion to prepare higher stock of sample in organic acid (acetic acid). This stock was used for further sample preparation using microwave digestion.

Multielement analysis of EIs as per ICHQ3D and USP<232> requires the analytical method, which can work on wider range of concentration. Applying MDD of drug product, *J* value varied from 1.2 ng/mL for Cd to 900 ng/mL for Mo. KED mode has been selected for analysis to tackle the issue of interferences from the polyatomic or Isobaric interferences during multielement analysis in drug product with complex matrix as well as simultaneous determination of elements with varied mass range i.e. 7 amu (Li) to 208 amu (Pb). Mass for elements has been carefully selected to avoid any isotopic interference during analysis. Due to matrix interference, several method development trials were taken for sample preparation, which can give consistent output. Developed method has been further validated as per USP general chapter USP <730> “Plasma Spectrometry” and USP <233> “Elemental Impurities-Procedures” for the parameters mentioned in Tables 4 and 5.

Table 4: Validation parameters performed for the study

Validation Parameter	Acceptance Criteria[@]
Specificity	Demonstrated by meeting the accuracy requirement[#]
Linearity	r^2 (Correlation coefficient) $\geq$ 0.99
Precision	%RSD $\leq$ 20.0%[$]
Accuracy	Mean Recovery 70.0% -150.0%
Range	Demonstrated by meeting the precision, accuracy and linearity requirement[#]
Quantitation Limit	Precision and Accuracy at 50% level should comply[#]
System Suitability	%Drift $\leq$ 20%

[@]: Combination of acceptance criteria given in USP <730> and <233>.
[#]: Parameters omitted as these were already demonstrated by the of other validation parameter.
[$]: For System precision stringent criteria has been followed i.e., %RSD $\leq$ 15.0%
% RSD: % Relative Standard Deviation;
% Drift: % Difference between initial and bracketing standard results.

Table 5: Maximum permitted concentration limits (Specification) for EIs in test article

Class	Element	Parenteral PDEs[@] (µg/day)	Specification[#](µg/mL)	Control Threshold[$] (µg/mL)	*J* Value* (ng/mL)	LOQ level (ng/mL)
1	Cd	2	0.2	0.06	1.2	0.3
	Pb	5	0.5	0.15	3	0.75
	As	15	1.5	0.45	9	2.25
	Hg	3	0.3	0.09	1.8	0.45
2a	Co	5	0.5	0.15	3	0.75
	V	10	1	0.3	6	1.5
	Ni	20	2	0.6	12	3
2b	Tl	8	0.8	0.24	4.8	1.2
	Au	100	10	3	60	15
	Pd	10	1	0.3	6	1.5
	Ir	10	1	0.3	6	1.5
	Os	10	1	0.3	6	1.5
	Rh	10	1	0.3	6	1.5
	Ru	10	1	0.3	6	1.5
	Se	80	8	2.4	48	12
	Ag	10	1	0.3	6	1.5
	Pt	10	1	0.3	6	1.5
3	Li	250	25	7.5	150	37.5
	Sb	90	9	2.7	54	13.5
	Ba	700	70	21	420	105
	Mo	1500	150	45	900	225
	Cu	300	30	9	180	45
	Sn	600	60	18	360	90
	Cr	1100	110	33	660	165

[@]: Permitted daily exposures for parenteral elemental impurities considered from USP <232> elemental impurities-limits
[#]: Specification value (µg/mL)=PDE/MDD; where PDE is EIs limit in µg/day and MDD is Maximum Daily Dose of drug product in mL/day.
[$]**:** Control threshold (µg/mL)=0.3 × Specification value in µg/mL
[*]: Working concentration (*J* value)=Specification value in µg/mL × Sample dilution

Method validation

Linearity and LOQ: Linearity was performed by selecting calibration standards mentioned as in Table 1. Correlation coefficients (r) calculated by extrapolating intensity counts or intensity count ratios against standard concentrations and the linearity was plotted through linear through zero formula. Results from the calibration curves obtained within acceptance criteria for all the targeted elements ($r \geq 0.99$). R values calculated are almost near to 1.00. Hence, it could be summarise that the instrument response is linear throughout the entire concentration range defined for this method. LOQ (0.25*J* standard) considered as lowest linearity level which is also below control threshold (i.e., 30% of specification level).

Precision: System precision carried out by continuous aspirations of 1*J* standard. Six consecutive aspirations from a single standard preparation were monitored and %RSD for the intensity counts or intensity ratios for all the standard aspiration for individual element found within acceptance criteria. From %RSD calculation, results obtained in the range of 0.3%-1.72%. This proves the method consistency and suitability.

Method precision was conducted by preparing and aspirating six individual preparations of spiked samples at 1*J* value (100% level standard spiking study). Intensity counts or intensity counts ration %RSD for six discrete spiked samples declares results in the range of 0.51-10.42. Results of method precision demonstrate stable responses for all the target analytes that shows uniform decomposition of sample matrix during sample digestions without the loss of analytes during sample digestion and sample dilution after completion of digestion.

Accuracy (Recovery): Accuracy perfumed on three different levels (0.25*J*, 1*J* and 1.5*J*) considering three different preparation of spiked samples at each spiking concentration level. Recovery at LOQ (0.25*J*) level express that the method is sensitive enough to determine the EIs at and below the control threshold. Additional, accuracy experiments (1*J* and 1.5*J*) describe that spiking at level below and above the working level concentration of the standard was also suitable for the analysis.

System suitability: % Drift was supervised over entire validation parameter execution on ICP-MS. Absolute % Difference of concentration of each analyte between initial and bracketing aspiration of system suitability standard (1.5*J*) were calculated. % Drift calculated falls within the acceptance criteria (%Drift ≤ 20%) which present that even in the presence of complex samples aspirations, response of the system stay constant and stable (Tables 6 and 7).

Table 6: Results for linearity, precision and accuracy

Element	Linearity (R)[@]	System Precision[#]	Method Precision[$]	Accuracy[*]		
				at 25% level	at 50% level	at 100% level
Cd	0.99995	1.23	1.03	94.45	96.92	99.78
Pb	0.99997	1.14	3.55	110.07	115.78	115.16
As	0.99997	1.74	2.02	82.14	88.97	87.75
Hg	0.99998	0.79	2.16	93.37	92.95	89.34
Co	0.99999	0.96	0.62	103.53	103.93	106.36
V	0.99995	0.74	1.27	107.25	109.52	109.93
Ni	0.99998	0.96	10.42	105.57	114.89	107.93
Tl	0.99997	0.93	0.81	109.28	110.79	112.93
Au	0.99999	1.41	1.53	119.15	120.83	121.53
Pd	0.99999	1.08	0.74	99.03	100.28	102.2
Ir	0.99999	0.88	0.97	108.05	109.94	112.2
Os	0.99998	0.89	1.41	105.33	105.2	108.9
Rh	0.99999	1.02	0.81	98.71	100.14	102.36
Ru	1	0.85	0.84	98.45	99.68	101.61
Se	0.99999	1.29	1.16	96.08	94.39	92
Ag	1	1.09	1.09	96.93	98.03	98.14
Pt	0.99999	1.04	0.95	112.09	114.12	115.92
Li	0.99999	0.71	0.51	96.79	97.75	99.7
Sb	1	1.16	1.08	111.15	112.79	114.1
Ba	0.99998	1.11	1.05	101.53	101.8	100.81
Mo	0.99953	0.3	0.85	95.56	96.87	95.88
Cu	1	0.94	0.64	103.71	104.13	104.43
Sn	1	0.78	1.14	101.68	103.34	102.57
Cr	1	0.98	0.88	110.06	110.19	109.64

[@]: Linearity calculated using intensity counts or ratio as a function over entire concentration range.
[#]: System Precision (%RSD) for six consecutive aspiration of a 100% level standard
[$]: Method Precision (%RSD) for six individual aspiration of 100% level spiked samples
[*]: Average Accuracy (%) of three individual aspirations for each 25%, 100% and 150% level spiked samples

Table 7: System suitability (%Drift)

Element	System Suitability[@]			
	%Diff.	%Diff.	%Diff.	%Diff.
Cd	0.94	2.43	2.87	0.5
Pb	0.09	5.62	9.43	9.61
As	0.64	5	5.28	4.2
Hg	1.93	6.81	6.47	11.39
Co	1.26	2.15	3.41	4.16
V	0.15	6.4	8.45	7.8
Ni	0.15	3.61	4.83	5.41
Tl	1	5.07	8.4	8.92
Au	1.04	9.23	14.1	10.15
Pd	0.09	1.71	1.77	2.43
Ir	1.03	5.06	7.17	8.38
Os	0.74	3.14	5.65	6.44
Rh	0.55	2.14	2.21	2.51
Ru	1.62	2.07	2.35	3.09
Se	1.69	3.75	8.9	2.71
Ag	0.27	3.49	3.35	4.8
Pt	0.62	6.02	8.92	9.93
Li	1.19	1.96	1.12	3.66
Sb	1.28	5.67	10.37	9.49
Ba	0.69	0.54	0.23	2.2
Mo	0.16	8.97	5.41	7.65
Cu	0.19	1.23	1.67	1.1
Sn	0.99	1.09	1.31	0.33
Cr	1.53	3.84	5.94	4.42

[@]: %Drift calculated between initial and bracketing standard aspirated using 150% level standard. System suitability was observed with 3 bracketing standard aspirated after individual validation parameter.

Analysis of test sample

Three different submission batches of test sample at initial time point as well as stored stability condition (5°C ± 3°C (Hor izontal Placement), 3 months) were analysed with in-house validated method. From the results expressed and presented in Table 8, it is evident that all the 24 EIs found below LOQ (e.g. below control thresholds) of individual EIs (Table 8).

Table 8: Analysis of test samples

Element	Specification Limit (µg/mL)	Results (µg/mL)						LOQ
		Initial	3rd Month	Initial	3rd Month	Initial	3rd Month	(ng/mL)
Cd	0.2	0	0	0	0	0	0	0.3
Pb	0.5	0.01	0.01	0	0.04	0	0	0.75
As	1.5	0	0	0.08	0	0.07	0	2.25
Hg	0.3	0	0	0	0	0	0	0.45
Co	0.5	0	0	0	0	0	0	0.75
V	1	0	0	0.02	0	0.02	0	1.5
Ni	2	0	0	0	0	0	0	3
Tl	0.8	0	0	0	0	0	0	1.2
Au	10	0.04	0.05	0	0.06	0	0.05	15
Pd	1	0	0	0	0	0	0	1.5
Ir	1	0	0	0	0	0	0	1.5
Os	1	0	0	0	0	0	0	1.5
Rh	1	0	0	0	0	0	0	1.5
Ru	1	0	0	0	0	0	0	1.5
Se	8	0	0	0.02	0	0.02	0	12
Ag	1	0.01	0	0.01	0.01	0.04	0	1.5
Pt	1	0	0	0	0	0	0	1.5
Li	25	0	0	0	0	0	0	37.5
Sb	9	0	0	0	0	0	0	13.5
Ba	70	0.04	0.23	0	0.21	0	0	105
Mo	150	0	0	0	0	0	0	225
Cu	30	0.01	0	0	0	0	0	45
Sn	60	0	0	0	0	0	0	90
Cr	110	0	0	0	0	0	0	165

Risk assessment

In addition to current study, EIs risk assessment was conducted to ensure the complete evaluation of overall possible EIs from Container closures and Raw materials used in finished drug products as EIs may arise from several sources; they may be residual catalysts that were added intentionally in synthesis or may be present as impurities (e.g., through interactions with processing equipment or container/closure systems or by being present in components of the drug product). Because elemental impurities do not provide any therapeutic benefit to the patient, their levels in the drug product should be controlled within acceptable limits. Before the sample testing, EIs risk assessment prepared considering EIs data available from respective vendors of Container Closure System (CCS) (e.g. Prefilled syringes, plunger stopper), Manufacturing Components (MFC) (e.g. Filters, Tubings) and Raw Material (e.g. API, Excipients). Considering worst case approach for EIs calculated from available data and as a part of USP <232> and ICH Q3D compliance for elemental impurities in drug product, drug product has been analysed using validated method.

CONCLUSION

With the help of emerging technology and modern instruments, estimation/quantitation of EIs become easy and more accurate than the conventional methods which were unable to alert the presence of potential EIs and hence were unable to establish controls over specified EIs in pharmaceutical products. Now, having high-tech machines like ICP-MS, manufacturing of EIs free drug products become practical. Apart from cost and challenges associated, determination of EIs at sub-ppb levels becomes quite possible with ICPMS and other comparative analytical techniques (ICP-OES, AAS). Herein, samples having complex matrices and analysis of multi elements (24 EIs as per ICH Q3D and USP <232>) in single method, ICP-MS technique was employed and the validated analytical test method proven to be precise, accurate and sensitive for its objective.

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