Development and Validation of Analytical Method for Quantitative Estimation of Multiple Metal Impurities in Dobutamine Hydrochloride using ICPMS Spectroscopy

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ABSTRACT

Objectives: Primary objective of the present study is to develop and validate an accurate and linear analytical method for precise estimation of Vanadium, Cobalt, Nickel, Arsenic, Cadmium, Mercury, Thallium and Lead elemental impurities present in the Dobutamine Hydrochloride active pharmaceutical ingredient using inductively coupled plasma mass spectrometry. **Materials and Methods:** Argon gas is used as carrier gas and helium gas as collision gas, 5% nitric acid is used as diluent, plasma gas flow rate is 15 l/m, spray chamber temperature is 2°C, helium gas flow rate is 5 ml/m, integration time is 0.3 s and tune mode is He gas. Microwave digester is used to extract the elemental impurities. The developed method was validated according to the Q3D guidelines provided by the International Conference on Harmonization. **Results:** The correlation coefficients for all the eight metals were found to be 1, and their concentration variation (%) in standard check solution was estimated to be less than 20. The system precession was found to be less than 20% of relative standard deviation and the linearity calibration curve was linear over the concentration range of 0.25J to 2.50J specification level. The obtained recoveries are well within the acceptance criteria of 70%-150%. **Conclusion:** The low relative standard deviation and high recoveries of the method confirm the suitability of the method for precise estimation of the above metal impurities in Dobutamine Hydrochloride active pharmaceutical ingredient.

Key words: Inductively Coupled Plasma Mass Spectrometer, Elemental Impurities, Method validation, Dobutamine Hydrochloride, International Conference on Harmonization.

INTRODUCTION

Dobutamine Hydrochloride (DBH) is used as medicine to treat cardiogenic shock and severe heart failure.[1] However, the elemental metal impurities in this drug substance are irresistible due to the fact that it's synthesis often involves the use of reactive substances which may extant in the final drug substances as impurities. Therefore, controlling of such impurities is highly desirable to prevent any unwanted toxicities including several health and genetic problems. Thus the control of elemental metal impurities in such active pharmaceutical ingredient (API) has attracted great interest from both academia and pharmaceutical industries. Although in the recent past, such control is done by specifying the concentration of metal impurities in drug materials, the pharmaceutical manufacturers illustrate that they meet the compendial limits on some drugs by applying pharmacopeial heavy metal tests based on sulphide precipitation as demonstrated in the United States Pharmacopoeia (USP) general chapter <231> heavy metals.[2] However, in 1995, the USP demonstrated several problems with the sulphide precipitation method which includes poor and variable recoveries, lack

of selectivity, loss of volatile elements, and thus the validity of the method is under question.[3] Accordingly, in 1998, European medicines agency (EMA) develops a guideline on such specification limits for residues of metal impurities.[4] The EMA guideline introduced mass-based permitted daily exposures in drug substances rather than concentration limits on it. Several evaluations are also being done to calibrate the modern instrumental methods of analysis for elemental metal impurities in pharmaceutical ingredients.[5-8] In 2008, USP established new chapter <232> which accounts safety based limits on metal impurities in pharmaceutical products as well as suitable criteria for methods for elemental analysis.[9] Later on the International Conference on Harmonization (ICH) provides the Q3D guidelines for elemental impurities as per daily exposure limit of drugs.[10] A general survey of elemental impurity concentrations on commonly used pharmaceutical products and drug substances are provided recently.[11] Subsequently, various researchers have used HPLC,[12] UPLC,[13] LC-MS/MS[14] and GC-MS[15] analysis methods for determining the impurities present in pharmaceutical products. In addition to the above, inductively coupled plasma mass spectrometry is recognised as one of the most sensitive multi-elemental analysis techniques which can detect trace amount of elements ranging from nanogram to picogram per milliliter (ml). Therefore, inductively coupled plasma mass spectrometer (ICPMS) offers an exceptional sensitivity and excellent accuracy for detecting the elemental impurities at trace level. Thus, in the present work, we aim to develop an accurate, precise and linear analytical method for quantitative estimation of Vanadium (V), Cobalt (Co), Nickel (Ni), Arsenic (As), Cadmium (Cd), Mercury (Hg), Thallium (Tl), and Lead (Pb) elemental impurities present in the DBH, using ICPMS spectroscopy. Microwave digester is used to extract such elemental impurities. The specification limits of the elemental impurities are considered as per the Q3D guidelines provided by the ICH.[10] The chemical structure of DBH is shown in Figure 1.

MATERIALS AND METHODS

Reagent and Materials

Concentrated nitric acid (HNO_3) of 70% v/v was gifted from a reputed laboratory. The purity of this HNO_3 is of trace metal grade. 5% HNO_3 is used as diluent. Deionised water was produced through a millipore water system. Dobutamine Hydrochloride drug substance and impurity standards were gifted from the reputed laboratory.

Instrumentation

The elemental impurity analysis is performed by using the Agilent ICPMS 7800 model. Calibration blank, calibration standard solutions of 0.25J to 2.50J (J = 100 % specification level of impurities), standard check solutions and bracketing standard check solutions aspirated to the nebulizer via peristaltic pump at 1 ml/m. The details of ICPMS instrumentation conditions are as follows: the radio frequency power is 1550 watts, plasma gas flow rate is 15 l/m, spray chamber temperature is 2°C, spectral peak pattern is 3 points, rate of helium gas flow is 5 ml/m, integration time is 0.3s, tune mode is helium gas, number of metal impurities counts per second (CPS) are replicated 3 times. Nebulizer uptake speed is 0.35 revolutions per second, sample uptake time is 45s and sample stabilization time is 45s. The microwave digester is used to extract the elemental impurities whose programme details are as follows: Microwave digester power is 1200 watts, ramp time is set as 30 min to reach the temperature as 160°C and hold the sample at 160°C for 20 min to digest it.

Specification

The specification limit of the Cadmium is 0.5 ppm, Lead is 0.5 ppm, Arsenic is 1.5 ppm, Mercury is 3 ppm, Cobalt is 5 ppm, Vanadium is 10 ppm, Nickel is 20 ppm and Thallium is 0.8 ppm in the sample solution.

Diluent Preparation (5% HNO₃)

Diluent (5% HNO_3) was prepared by transferring 72 ml of the above mentioned 70% v/v nitric acid into a 1000 ml volumetric flask containing about 500 ml of milli-Q-Water and made up to the volume with milli-Q Water.

Preparation of Standard stock solutions

Various standard stock solutions were prepared by transferring the substance into the diluent at various proportions. Stock A, B, D, E, F and I were prepared by transferring 0.1 ml of 1000 ppm of Cd, Pb, As, Hg, Co and Tl standard solution into a 10 ml volumetric flask, respectively, and made up the volume with diluent (5% HNO_3). Similarly, stock G and H were prepared by transferring 1 ml of 1000 ppm of V and Ni standard solutions into 10 ml volumetric flasks, respectively, and by adding 9 ml of the above prepared diluent into the flasks. Moreover, Stock C was prepared by mixing 1 ml of stock A, 1 ml of stock B and 8 mL of the diluent. Whereas stock J was obtained by mixing various above prepared stock solutions in different proportions. The details were tabulated in Table 1. Additionally, Yttrium and Bismuth were added as internal standards to get

Table 1: Various components of the stock solution and the final concentrations of metals in the standard stock solutions.					
Concentration of metal (ppm)	Volume of Stock (ml)	Volume of Diluent (ml)	Final Volume (ml)	Final Concentration (ppm)	Stock Name
Cd = 1000	0.1	9.9	10	10	Stock-A
Pb = 1000	0.1	9.9	10	10	Stock-B
Stock-A + Stock-B	1.0 (each)	8.0	10	1	Stock-C
As = 1000	0.1	9.9	10	10	Stock-D
Hg = 1000	0.1	9.9	10	10	Stock-E
Co = 1000	0.1	9.9	10	10	Stock-F
V = 1000	1.0	9.0	10	100	Stock-G
Ni = 1000	1.0	9.0	10	100	Stock-H
Tl = 1000	0.1	9.9	10	10	Stock-I
Stock-C	1.250			0.125 (Cd and Pb)	
Stock-D	0.375			0.375 (As)	
Stock-E	0.750			0.75 (Hg)	
Stock-F	1.250	5.425	10	1.25 (Co)	Stock-J
Stock-G	0.250			2.5 (V)	
Stock-H	0.500			5 (Ni)	
Stock-I	0.200			0.2 (Tl)	
Yttrium = 1000	0.1	9.8	10	10	Stock-K
Bismuth = 1000	0.1				
Stock-K	1.0	9.0	10	1	Stock-L (Internal Standard)
Aurum = 1000	0.1	9.9	10	10	Stock-M
Stock-M	1.0	9.0	10	1	Stock-N

good recoveries of the elemental impurities. Furthermore, an Aurum standard was added to stabilize the mercury.

Preparation of Calibration blank solution

Calibration blank solution was prepared by transferring 0.1 ml of Stock-L and 0.1 ml of Stock-N into 10 ml volumetric flask and diluted to volume with diluent (5% HNO_3).

Preparation of calibration standard solutions

Six calibration standard solutions were prepared to comply with the system (ICPMS) suitability. These were prepared with different specifications by mixing the above prepared standard stock solutions at various proportions. The final volumes of such solutions were made to 10 ml with the diluents. The various proportions of stock solutions and the final concentrations of metals are tabulated in Table 2. It can be seen from the Table 2 that the standard check solution was obtained by mixing 0.4 ml Stock J, 0.1 ml of Stock L and 0.1 ml of Stock N and made the total volume to 10 by adding 9.4 ml of diluent.

Sample Blank Preparation

5 ml of HNO_3 was taken into the digestion vessel and 0.25 ml of Stock-N solution was added into it. It was then kept for 15 min and allowed the reaction to occur at atmospheric condition. Then the sample is digested in the microwave digester system. After completion of digestion, it was allowed to cool. Subsequently, 0.25 ml

Stock Concentration (ppm)	Volume of Stock (ml)	Volume of Diluent (ml)	Final Volume (ml)	Final Concentration (ppb)							Label	Level
				Cd and Pb	As	Hg	Co	V	Ni	Tl		
Stock-J+L+N	0.1+0.1+0.1	9.7	10	1.25	3.75	7.5	12.5	25	50	2	CC-1	0.25J
Stock-J+L+N	0.2+0.1+0.1	9.6	10	2.5	7.5	15	25	50	100	4	CC-2	0.50J
Stock-J+L+N	0.4+0.1+0.1	9.4	10	5	15	30	50	100	200	8	CC-3	1.00J
Stock-J+L+N	0.6+0.1+0.1	9.8	10	7.5	22.5	45	75	150	300	12	CC-4	1.50J
Stock-J+L+N	0.8+0.1+0.1	9.0	10	10	30	60	100	200	400	16	CC-5	2.00J
Stock-J+L+N	1.0+0.1+0.1	8.8	10	12.5	37.5	75	125	250	500	20	CC-6	2.50J
Stock-J+L+N	0.4+0.1+0.1	9.4	10	5	15	30	50	100	200	8	Standard check	1.00J

Table 2: Various components of the standard stock solutions and the final concentrations of metals in the calibration standard solutions.

Note: J= 100% Specification level.

of Stock-L Solution (Internal standard) was added and diluted the solution up to 25 ml with milli-Q Water. Finally, the solution was vortexes for 5 min to get the Sample blank.

Sample Preparation

250 mg of sample was transferred into the digestion vessel. Then 5 ml of HNO_3 and 0.25 ml of Stock-N solution were added into it. It was then kept for 15 min to allow the reaction to occur at atmospheric conditions. Such a sample is then digested in the microwave digester system. After completion of digestion, it was allowed to cool and then 0.25 ml of Stock-L Solution (Internal standard) was added and finally made up the solution to 25 ml with milli-Q Water. At the end the final solution was vortexes for 5 min to get the sample.

Spiked Sample Preparation

250 mg of sample was transferred into the digestion vessel. Then 5 ml of HNO_3, 0.25 ml of Stock-N solution and 1 ml of Stock-J solution were added into it. It was then kept for 15 min to allow the reaction to occur at atmospheric conditions. Next, the sample was digested in the microwave digester system. After completion of digestion, it was allowed to cool and then 0.25 ml of Stock-L solution (Internal standard) was added. This mixture was finally diluted by making the volume 25 ml with milli-Q Water. At the end the final solution was vortexes for 5 min to get the spiked sample.

RESULTS

Method Validation

Validation of the above method is verified in this section as per the Q2 (R1) and ICH guidelines. Such verifications were done by estimating the system

suitability, specificity, limit of quantification, system precision, linearity, method precision, intermediate precision, accuracy and robustness and the results are given in Table 3. The procedure of these measurements is developed by injecting calibration blank, calibration standards, standard check solution, sample solution and spiked sample solution and bracketing standard solution into ICPMS. The amount of Vanadium, Cobalt, Nickel, Arsenic, Cadmium, Mercury, Thallium and Lead content present in sample solution is then calculated by using the below formula.

$$ppm = \frac{\text{Instrument Reading (ppb)}}{\text{Sample weight in grams}} \times \frac{\text{Dilution}}{1000}$$

System Suitability

System suitability is established by measuring the system performance before the analysis. The response of system suitability was obtained by aspirating standard solutions with concentrations in the range from 0.25J to 2.50J of specification level. Subsequently, correlation coefficient and concentration of percent variation in standard check solution were calculated. As per the acceptance criteria provided by the ICH guidelines the correlation coefficient for all the eight metals should be 0.99 or above, and their concentrations in standard check solution should not vary more than ± 20% of actual concentration. Our results are shown in Table 3. As can be seen from Table 3 that the correlation coefficients for Vanadium, Cobalt, Nickel, Arsenic, Cadmium, Mercury, Thallium and Lead were found to be 1.0. And concentration variations of the above metal impurities in standard check solution were found to be 0.2, 0.0, 0.9, 0.9, 1.8, 0.1, 0.1 and 0.8 percent in the same order.

Table 3: Method validation results.

Parameters	Results							
System suitability	Correlation Coefficient (r)							
	V=1.0	Co=1.0	Ni=1.0	As=1.0	Cd=1.0	Hg=1.0	Tl=1.0	Pb=1.0
	Concentration of % Variation in standard check solution							
	V=0.2	Co=0.0	Ni=0.9	As=0.9	Cd=1.8	Hg=0.1	Tl=0.1	Pb=0.8
Specificity	No Calibration blank interference was observed.							
LOQ (ppm)	V=2.5	Co=1.3	Ni=5.0	As=0.4	Cd=0.1	Hg=0.8	Tl=0.2	Pb=0.1
System Precision (% RSD)	V=2.3	Co=2.5	Ni=2.5	As=0.8	Cd=2.9	Hg=3.5	Tl=1.8	Pb=1.9
Linearity	Correlation Coefficient (r)							
	V=1.0	Co=1.0	Ni=1.0	As=1.0	Cd=1.0	Hg=1.0	Tl=1.0	Pb=1.0
Method Precision (% RSD)	V=0.3	Co=0.3	Ni=0.5	As=0.4	Cd=0.7	Hg=0.4	Tl=1.4	Pb=1.1
Intermediate precision (% RSD)	V=0.6	Co=0.3	Ni=0.5	As=0.4	Cd=0.3	Hg=0.3	Tl=1.5	Pb=1.9
Accuracy (% Recovery)	V	Co	Ni	AS	Cd	Hg	Tl	Pb
	97-109	97-106	98-107	91-108	94-106	82-103	93-102	91-93
Robustness Acid (+5%)	V=0.3	Co=0.2	Ni=0.4	AS=0.3	Cd=0.6	Hg=0.4	Tl=1.4	Pb=1.3
Robustness Acid (-5%) (% RSD)	V=0.2	Co=0.2	Ni=0.4	AS=0.3	Cd=0.8	Hg=0.4	Tl=1.5	Pb=1.3
Robustness 0.45rps (% RSD)	V=0.3	Co=0.2	Ni=0.4	AS=0.4	Cd=1.3	Hg=0.4	Tl=1.3	Pb=1.6
Robustness 0.25rps (% RSD)	V=0.3	Co=0.2	Ni=0.4	AS=0.5	Cd=1.3	Hg=0.5	Tl=1.3	Pb=1.5

rps: revolution per second, RSD: Relative standard deviation, LOQ: Limit of quantification.

Specificity

In specificity, the procedure must be able to unequivocally assess each target element in the presence of components that may expect to be present, including matrix components. The calibration blank solution and calibration curve standards are injected in to the ICPMS to measure the specificity parameters. Blank interference was evaluated by measuring the percent of interference of six replicate injections of calibration blank solutions and comparing the response with respect to calibration standard solution-1 (CC-1) response. The acceptance criteria for this are as follows: the interference of calibration blank for all the eight metal impurities shouldn't be more than 20% of response (counts per second) of the CC-1. In the present study the calibration blank average counts per second (CPS) for Vanadium, Cobalt, Nickel, Arsenic, Cadmium, Mercury, Thallium and Lead found to be less than the 20% of counts per second of the CC-1. Therefore, no calibration blank interference was observed indicating that the specificity parameters are well within the acceptance criteria provided by ICH.
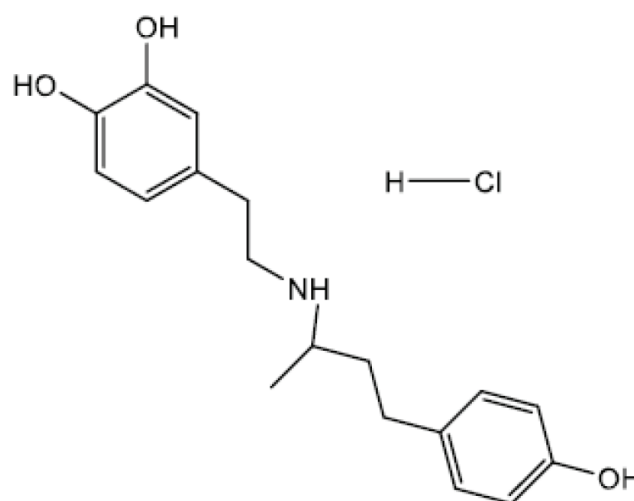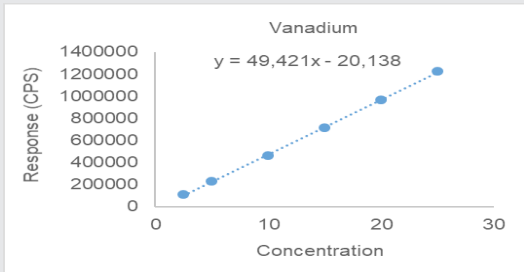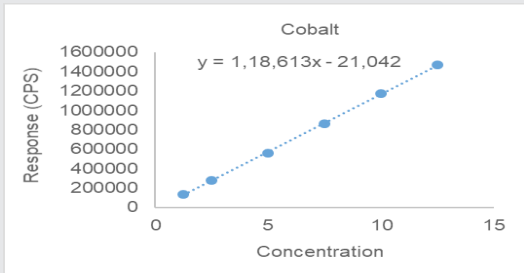
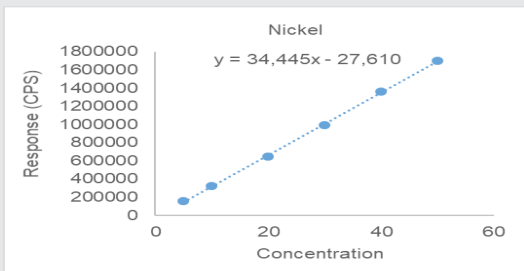**Figure 1: Chemical structure of Dobutamine hydrochloride.**
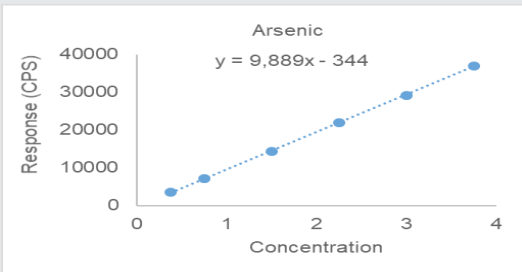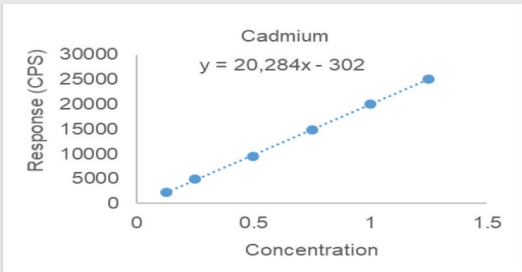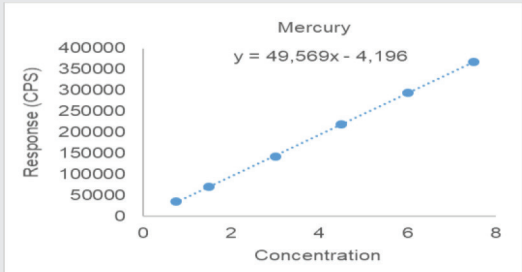
Limit of Quantification

To valid the limit of quantification, first six replicates of sample blank solution are injected into ICPMS. Subsequently, limit of quantification is estimated by
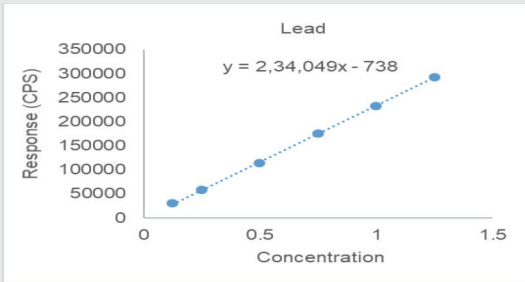
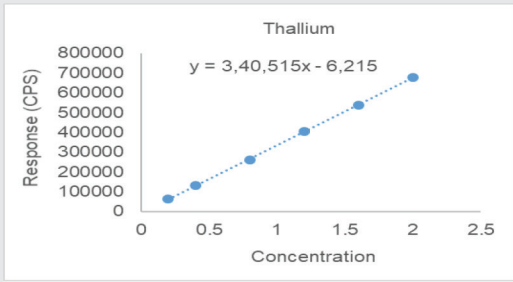## Table 4: Linearity Graphs for Vanadium, Cobalt, Nickel, Arsenic, Cadmium, Mercury, Lead and Thallium.

Linearity for Vanadium

Concentration (ppm)	Response (CPS)	
2.5	111335.75	
5	231560.93	
10	461954.44	
15	712938.21	
20	967096.44	
25	1224417.99	
Slope	49421	
Y-Intercept	-20138	
Correlation coefficient	1.0	

Vanadium

y = 49,421x - 20,138

Linearity for Cobalt

Concentration (ppm)	Response (CPS)	
1.25	134996.77	
2.5	280563.13	
5	557125.65	
7.5	860332.42	
10	1170980.56	
12.5	1466019.62	
Slope	118613	
Y-Intercept	-21042	
Correlation coefficient	1.0	

Cobalt

y = 1,18,613x - 21,042

Linearity for Nickel

Concentration (ppm)	Response (CPS)	
5	156502.79	
10	322953.21	
20	642481.95	
30	989201.66	
40	1361831.56	
50	1700405.84	
Slope	34445	
Y-Intercept	-27610	
Correlation coefficient	1.0	

Nickel

y = 34,445x - 27,610

Linearity for Arsenic		
Concentration (ppm)	**Response (CPS)**	
0.375	3510.57	
0.75	7065.36	
1.5	14359.99	
2.25	21836.37	
3	29208.63	
3.75	36906.6	
Slope	9889	
Y-Intercept	-344	
Correlation coefficient	1.0	

Arsenic

y = 9,889x - 344

Linearity for Cadmium		
Concentration (ppm)	**Response (CPS)**	
0.125	2328.07	
0.25	4926.6	
0.5	9530.28	
0.75	14797.29	
1	20085.18	
1.25	25122.36	
Slope	20284	
Y-Intercept	-302	
Correlation coefficient	1.0	

Cadmium

y = 20,284x - 302

Linearity for Mercury		
Concentration (ppm)	**Response (CPS)**	
0.75	2328.07	
1.5	4926.6	
3	9530.28	
4.5	14797.29	
6	20085.18	
7.5	25122.36	
Slope	49569	
Y-Intercept	-4196	
Correlation coefficient	1.0	

Mercury

y = 49,569x - 4,196

Linearity for Lead		
Concentration (ppm)	**Response (CPS)**	
0.125	30436.4	
0.25	57482.07	
0.5	113388.56	
0.75	175546.99	
1	233047.64	
1.25	292611.52	
Slope	234049	
Y-Intercept	-738	
Correlation coefficient	1.0	

Lead

$y = 2,34,049x - 738$

Linearity for Thallium		
Concentration (ppm)	**Response (CPS)**	
0.2	63871.51	
0.4	132025.97	
0.8	259841.23	
1.2	403524.17	
1.6	538369.95	
2	676270.89	
Slope	340515	
Y-Intercept	-6215	
Correlation coefficient	1.0	

Thallium

$y = 3,40,515x - 6,215$

taking the ratio of impurity CPS in sample blank solution with internal standard CPS. Such a ratio for the above mentioned eight metal impurities are found to be less than the 0.25J of the specification level and 0.25J level is considered as the limit of quantification in the present study.

System Precision

System precision is measured by injecting six replicates of calibration standard solution-3 into ICPMS and measuring the percentage of relative standard deviation (RSD) of their CPS. We note that the acceptance criteria of the percentage of RSD for the above metal impurities given by USP <233> should be less than 20%. In the present study, the percentage of RSD in terms of CPS of the Vanadium, Cobalt, Nickel, Arsenic, Cadmium, Mercury, Thallium and Lead are found to be 2.3, 2.5, 2.5, 0.8, 2.9, 3.5, 1.8 and 1.9, respectively.

Linearity

Linearity of the curve in response (CPS) vs concentration plots for calibration standard solutions were established with concentration ranging from 0.25J to 2.50J specification level. These results are shown in Table 4. The correlation coefficients for all the metal impurities were found to be 1.0.

Method Precision

To validate the method precision, sample blank, samples and six different 100% spiked samples were injected in to ICPMS and recorded the percentage of RSD of impurities content (ppm) for all the six 100% spiked samples. The percentage of RSD for those six spiked samples of the Vanadium, Cobalt, Nickel, Arsenic, Cadmium, Mercury, Thallium and Lead found to be 0.3, 0.3, 0.5, 0.4, 0.7, 0.4, 1.4 and 1.1, respectively which are well within the acceptance criteria of the metal impurities provided by USP <233>. The intermediate precision is also validated by different analyst on different day. Such a results for the above metal impurities are found to be 0.6, 0.3, 0.5, 0.4, 0.3, 0.3, 1.5 and 1.9 in the same order as above.

Accuracy

The accuracy is also established by injecting sample blank, sample and spike samples with 25%, 50%, 100%, 150%, 250% specification levels. The percentage of recovery (Minimum - Maximum) for Vanadium, Cobalt, Nickel, Arsenic, Cadmium, Mercury, Thallium and Lead are found to be 97-109%, 97-106%, 98-107%, 91-108%, 94-106%, 82-103%, 93-102% and 91-93%, respectively which are within the acceptance criteria of 70-150%, as provided by ICH guidelines.

Robustness

The robustness shows the reliability of an analysis with respect to deliberate variations in method parameters. To check the robustness of the method, ± 5% of HNO_3 are added to the sample blank, sample and spike samples. And then the peristaltic uptake speeds in ICPMS are varied by ± 0.1 rotation per second (RPS). The percentage of RSD for spiked samples of the Vanadium, Cobalt, Nickel, Arsenic, Cadmium, Mercury, Thallium and Lead found to be 0.3, 0.2, 0.4, 0.3, 0.6, 0.4, 1.4 and 1.3, respectively, when the concentration of HNO_3 are varied by +5%. Similarly, the percentages of RSD are found to be 0.2, 0.2, 0.4, 0.3, 0.8, 0.4, 1.5 and 1.3, respectively, when the concentration of the acid is varied by -5%. The Robustness of the method is also established by varying peristaltic uptake speed by ±0.1 RPS. The percentages of RSD for spiked samples of the Vanadium, Cobalt, Nickel, Arsenic, Cadmium, Mercury, Thallium and Lead are found to be 0.3, 0.2, 0.4, 0.4, 1.3, 0.4, 1.3 and 1.6, respectively, when peristaltic uptake speed is varied by +0.1 RPS. Subsequently percentages of RSD for spiked samples of the above metal impurities are found to be 0.3, 0.2, 0.4, 0.5, 1.3, 0.5, 1.3 and 1.5, respectively, in the same order as above upon variation of peristaltic uptake speed by +0.1 RPS.

DISCUSSION

As can be inferred from above sections that the present method is developed by injecting calibration blank, calibration standards, standard check solution, sample blank solution, sample solution, spiked sample solution and bracketing standard solution. The validation of the method is done by performing system suitability, specificity (Blank interference), limit of quantification, system precision, method precision, intermediate precision, linearity, accuracy and robustness. It can also be seen from the method validation result tables, that all the results are well within the acceptance criteria provided by the ICH Guidelines and USP <232> and <233> guidelines. The calibration blank CPS are less than 20% of the CC-1 CPS. The correlation coefficient of all the elements was more than 0.99. The recoveries of spiked samples were within the limit of 70% to 150%. Therefore, the present method is in very good compliance with the ICH Guidelines, USP <232> and <233> guidelines, and can be used routinely to estimate the above mentioned metal impurities in Dobutamine Hydrochloride drug substance at trace level.

CONCLUSION

We have developed an analytical method for simultaneous estimation of multiple elemental metal impurities in Dobutamine Hydrochloride using inductively coupled plasma mass spectrometry. Microwave digester is used to extract the elemental impurities. This method is validated linearly, precisely and accurately for Vanadium, Cobalt, Nickel, Arsenic, Cadmium, Mercury, Thallium and Lead elemental impurities in DBH as per the Q3D guidelines provided by ICH, USP <232> and <233>. Therefore, the above method may be used routinely for quantitative analysis of Vanadium, Cobalt, Nickel, Arsenic, Cadmium, Mercury, Thallium and Lead elemental impurities in DBH.

CONFLICT OF INTEREST

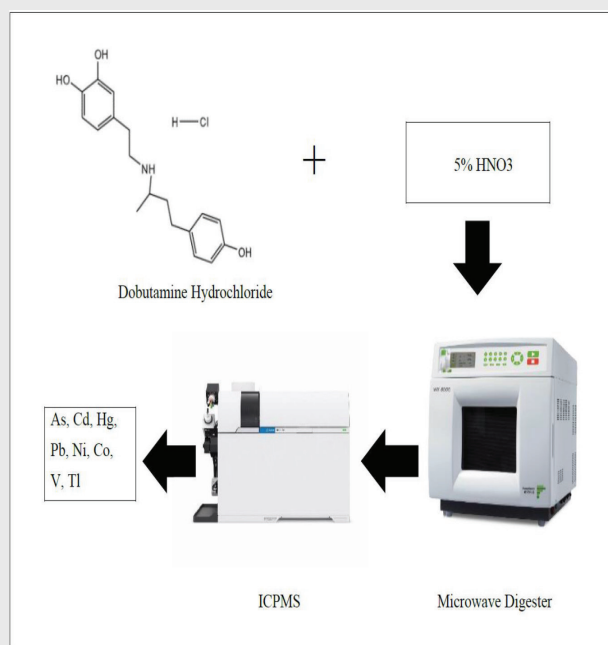The authors declare no conflict of interest.

ABBREVIATIONS

ICP-MS: Inductively Coupled Plasma Mass Spectrometer; **DBH:** Dobutamine Hydrochloride; **HPLC:** High Performance Liquid Chromatography; **UV:** Ultraviolet; **ICH:** International Conference on Harmonization; **USP:** United States of Pharmacopoeia; **LOQ:** Limit of Quantification; **RSD:** Relative Standard Deviation; **RPS:** Rotation per Second; **CPS:** Counts per Second; **V:** Vanadium; **Co:** Cobalt; **Ni:** Nickel; **As:** Arsenic; **Cd:** Cadmium; **Hg:** Mercury; **Tl:** Thallium; **Pb:** Lead.

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PICTORIAL ABSTRACT

Dobutamine Hydrochloride + 5% HNO3

As, Cd, Hg, Pb, Ni, Co, V, Tl

ICPMS   Microwave Digester

SUMMARY

An accurate and linear analytical method was developed for quantitative estimation of trace level of Vanadium, Cobalt, Nickel, Arsenic, Cadmium, Mercury, Thallium and Lead elemental impurities present in Dobutamine Hydrochloride drug by using inductively coupled plasma mass spectrometer (ICPMS). While the ICPMS identifies the trace metal impurities by their mass number up to parts per trillion levels, such a trace level cannot provide good response in HPLC or UV detection. In the present method 5% nitric acid was used as diluent, Yttrium and Bismuth was used as internal standards. The ICPMS specifications were set up as follows: plasma gas flow rate is 15 l/m, spray chamber temperature is 2°C, helium gas flow rate is 5 ml/m, integration time is 0.3s and tune mode is helium gas. This method was further validated by guidelines provided by Q3D(R1), ICH, USP <232> and USP <233>. Our developed method is specific, linear, precise, accurate and robust. Thus the present method can be used routinely for regular analysis in quality control and research laboratory.

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