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Multielemental Screening and Analytical Method Validation for Determination of Elemental Impurity in Sucroferric Oxyhydroxide by Using (ICP-MS)

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

A highly selective, specific, precise sensitive and reliable ICPMS method has been developed and validated by using ICP-MS for the determination of multielement in Sucroferric oxyhydroxide. The described ICP-MS method provides specific detection and quantification of minor and trace elements from 0.3J(30%) to 2J(200%) of its individual specification of each element i.e Ag, As, Au, Ba, Cd, Co, Cr, Cu, Hg, Ir, Li, Mo, Ni, Os, Pb, Pd, Pt, Rh, Ru, Sb, Se, Sn, Tl, and V.The analytical method found to be Linear for each individual element with working concentration range from 30%, 50%, 100%, 150% and 200% i.e 0.3J, 0.5J, 1J, 1.5J and 2J with correlation coefficient not less than 0.990.The % recoveries of elemental impurities of each individual elements at three different concentrations with spiking in samples were found to be an acceptable range as 70% to 150%.The method was found to be precise and robust and its relative standard deviation was below 20%.The actual observed relative standard deviation in Precision was found to be in an acceptable range. Therefore developed method can be use for routine quantitative analysis of elemental impurities like Ag, As, Au, Ba, Cd, Co, Cr, Cu, Hg, Ir, Li, Mo, Ni, Os, Pb, Pd, Pt, Rh, Ru, Sb, Se, Sn, Tl, and V to ensure the quality of drug product.

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1. INTRODUCTION

Sucroferric oxyhydroxide is a non-calcium, iron-based phosphate binder used for the control of serum phosphorus levels in adult patients with chronic kidneydisease (CKD) on haemodialysis (HD)or peritoneal dialysis (PD) [1]. It is used in form of chewable tablets.It has a molecular formula of $C_{12}H_{29}Fe_5Na_2O_{23}$ and a molecular weight of 866.5g/mol.

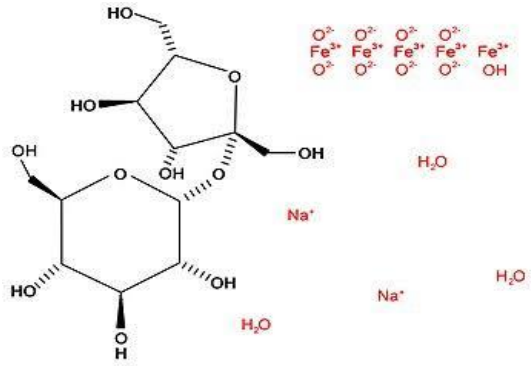

Fig. 1. Chemical structure of Sucroferric oxyhydroxide [2]

Sucroferric oxyhydroxide is chemically as disodium;(2*R*,3*R*,4*S*,5*S*,6*R*)-2-[(2*S*,3*S*,4*S*,5*R*)-3,4-dihydroxy-2,5-bis(hydroxymethyl)oxolan-2-yl]oxy-6-(hydroxymethyl)oxane-3,4,5-triol;iron(3+);oxygen(2-);hydroxide;trihydrate. Iron saccharate (Sucroferric oxyhydroxide or Iron Sucrose) is used as a source of iron in patients with iron deficiency anemia with chronic kidney disease (CKD), including those who are undergoing dialysis (hemodialysis or peritoneal) and those who do not require dialysis. Due to less side effects than iron dextran, iron saccharate is more preferred in chronic kidney disease patients. Heavy metals are widespread pollutants of great environmental concern as they are nondegradable, toxic and persistent [3].

The USP current method, (231) “heavy metals limit test” is recognized to be insufficient and is due to be replaced with USP (232) & (233) new general chapters. On the subject of the constraint of elemental impurities like heavy metals & catalyst residue, bring into being an urgent requirement for robust and competent ICP-MS analytical method [4]. Permitted daily exposure (PDE) limits for a extensive assortment of inorganic elemental impurities defined in USP (232):

1.1 Aim

Our main aim and objective of research work is to develop and validate method to make sure efficient control of the levels of elemental impurities in the different pharmaceuticals .An approach based on assessing and controlling potential sources of elemental impurities, coupled with focused, limited testing, is preferable to exhaustive testing on the different Pharmaceuticals drugs and APIs.A scientific, risk-based approach combined with knowledge and control of the key sources of elemental impurities in the different active pharmaceutical ingredients(APIs) manufacturing processsuch as catalysts, provides an efficient and comprehensive elemental impurity control strategy for different Pharmaceuticals.

The objective contains three main aspects:

1. An evaluation of the toxicity data for potential elemental impurities.
2. The establishment of permitted daily exposure (PDE) for each element of toxicological concern.
3. Development of controls to limit the inclusion of elemental impurities in drug products to levels at or below the PDE.

Multielements to be determined in Sucroferric oxyhydroxide by ICPMS																							
Ag	Au	As	B	Ba	Cd	Co	Cr	Cu	Hg	Ir	Li	Mo	Ni	Os	Pb	Pd	Pt	Rh	Ru	Sb	Sn	Tl	V

2. METHOD

For multi-metal screening of 24 elements in pharmaceutical API .There is no single standard solution having all elements of interest, because some specific elements require specific conditions for producing stable solution.

Therefore the desired standard solution have been made by using comercially available single element standard by reference standard material.Working standard solutions were prepared by diluting individul stock standard solutions.The tuning solution used for the ICP-MS instruements contained 1µg/L Ce,Co,Li,Mg,Tl and Y.

The nonspectral matrix effects were resolved by the addition of internal standards.The internal standard stock solution was prepared by diluting single element stock solutions of Sc(1000 ppm) and Dy (1000 ppm) into 10 mL volumetric flask made of polypropylene or polymethylpentene, added 100 µL of concentrated nitric acid, than added Sc (100 µL) and Dy (100 µL) and dilute the volume up to mark with Milli-Q water.

2.1 ICP-MS Instrument and Equipment

The elemental impurity (heavy metal) analysis was carried out by using Agilent technologies 7700 Series (ICPMS MODEL 7700X) with Mass Hunter Workstation Software for ICP-MS with Milestone Microwave Reactor Milestone, model Ultra WAVE.

The Agilent 7700x ICP-MS provides unparalleled accuracy in high matrix samples redefining cell performance in helium mode with revolutionary 3rd generation cell design-ORS (Octapole Reaction System), it includes a standard helium (He) mode cell gas line which provides removal of polyatomic interference. The advanced high energy helium mode (He) was used in this method. The instrument equipped with standard nickel sampling and skimmer cones and concentric nebulizer of glass, quartz spray chamber and quartz torch with 2.5 mm id injector. An agilent ASX-500 ICP-MS auto-sampler was used to deliver the samples.It can measure trace metals as low as one part per trillion (ppt) and have capability to quick scan more than 80 elements to determine the composition of unknown samples with MassHunter Workstation Software that automates the analysis and accurately interprets the analysed data.

For accurate quantitative determination of trace elements in sample matrix, an Internal standard method was used using a internal standard and a multistandard calibration method. The operating conditions of ICPMS method are as follows: carrier gas (argon)flow rate 15L\min,collision gas Helium flow rate 4mL/min, Nebulizer pump / rps 0.10, Spray chamber temperature 2ºC , Nebulizer pump 0.10 rps, RF forward power 1550 W, Sampling depth 10mm,Quartz Torch. Microwave reactor temperature program: t(min) 00:15:00,T1 100ºC, T2 70ºC P 100bar, t(min) 00:20:00,T1 100ºC, T2 70ºC ,P 100bar.

Acquistion Mode is Spectrum, Peak Pattern1Point Replicates, 3 Sweep/Replicates 100, Stabilization time 20sec, He mode, Stabilization time 20sec, No gas mode.

2.2 Selection of Matrix Solvent

The matrix solvent composition plays very crucial role for elemental analysis .Sample digestion is mainly done by common mineral acids like nitric acid, hydrochloric acid ,perchloric acid and sulphuric acid.By using microwave assisted digestion procedures with 0.1 g of sample and simplified reagent with mixture of HNO_3/ HCl in ratio of 1:3 v/v were used for quantitative determination of 27 elements(Ag,As, Au, Ba, Cd, Co, Cr, Cu, Hg, Ir, Li, Mo, Ni,Os, Pb, Pd, Pt, Rh, Ru, Sb, Se, Sn, Tl and V) and observed minimal contribution to ICP-MS spectral intrferences.

2.3 Reagents and Chemicals

The reagents used to prepare the samples and standard for the method, trace metal grade ultrapure concentrated nitric acid, hydrochloric acid (J.T.Baker), thiourea for metal analysis (Sigma Aldrich),multielement standard of Ag,As, Au, Ba, Cd, Co, Cr, Cu, Hg, Ir, Li, Mo, Ni,Os, Pb, Pd, Pt, Rh, Ru, Sb, Se, Sn, Tl, and V are from inorganic venture.Ultrapure de-ionized water from a Milli-Q analytical reagent grade water purification system(Millipore) was used.All volumetric flasks used in preperations were made up of polypropylene (PP)and polymethyl pentane (PMP).

2.4 Diluent (0.076% Thiourea w/v)

Transferred into 1000 mL of volumetric flask made of polypropylene or polymethylpentene add about 0.76 g of thiourea and 25 mL of concentrated hydrochloric acid. Diluted to volume with de-ionised water.

The (0.076% thiourea) diluents selected to overcome the problem of low osmium recoveries due to formation of volatile Os oxide in the nitric acid medium,to prevent formation of osmium tetraoxide 0.076% thiourea used which

yield acceptable osmium recoveries around 97%-99%.

2.5 Calibration Blank Solution (Blank)

Transfer into 50 mL volumetric flask made of polypropylene or polymethylpentene 3 mL of concentrated nitric acid, 1 mL of concentrated hydrochloric acid and 100 µL of ISTD solution as internal standard. Dilute to volume with diluent.

2.6 Internal Standard Stock Solution

A 10 ppm mixed internal standard solution contaning (Scandium and Dysporium) was introduced online into the spraychamber by using peristaltic pump.

2.7 Standard Stock Solution 1 Preparation

Transferred into 50 mL volumetric flask made of polypropylene or polymethylpentene.1 mL of concentrated nitric acid, respective volume of Cd 165µL ,Pb 165µL,Co 165 µL,As 500 µL,Hg 1000 µL,Ni 660 µL,Tl 265 µL elements solution and diluted the volume up to mark with de-ionized water.

2.8 Stock Solution-2 (SS-2)

Transferred into 50 mL volumetric flask made of polypropylene or polymethylpentene 1 mL of concentrated nitric acid, 2 mL of concentrated hydrochloric acid, respective volume of Stock solution-1(SS-1) 1000 µL,Li 366.7 µL,Cr733.33 µL,Cu 2000 µL,Mo 200 µL,Sn 4000 µL,Sb 800 µL,Ba 933.3 µL,Se 100 µL,Ag 100 µL,V 66 Ml,Pd 66.7 µL,Ir 66.7 µL,Pt 66.7 µL,Rh 66.7 µL, Ru 66.7 µLAu 66.7 µL and Os 66.7 µL elements solution and diluted the volume up to mark with de-ionized water.

2.9 Preparation of Calibration Working Standard Solutions

The calibration standards were prepared at 30% (0.3J), 150% (1.5J) and 200% (2J) the target limit for each elemental impurities in the final analysis solution.

2.10 Sample Preparation

Duplicate replicates were prepared by weighing accurately about 100 mg of the substance and transferred into digestion tube quartz than added 3 mL of concentrated nitric acid, 1 mL of concentrated hydrochloric acid and 100 µL of ISTD solution as internal standard. Shaked each mixture carefully upto dissolving, Wait at least 30 min before the vessels are closed. Than sample was heated in the microwave reactor, when the microwave reactor temperature program finished, allowed the digestion vessels to cool down and then transfer sample solutions into a 50 mL volumetric flasks made of polypropylene or polymethylpentene and dilute to volume with diluent.

2.11 Reference Formula of Metal Content (ppm) in Sample

Metal content in ppm is calculated using the following formula:

Metal content (ppm) in Sample = $\frac{c\left(\frac{ng}{mL}\right)\times V(mL)}{m(mg)}$

c (ng/mL) = instrument read-out concentration
V (mL) = final volume of dissolved sample (50 mL)
m (mg) = sample weight (100 mg).

2.12 Spiked Sample Preparation

Spiked samples were prepared by spiking reference standard materials of the target limit concentration at 50 %(0.5J), 100 %(1J)and 150 %(1.5J) with 250 µL, 500 µL and 750 µL of the standard stock solution 2 (SS-2) alongwith 100 µL of internal stock standard solution.

Three preperations at each spiking level were prepared and each solution was analysed in triplicate measurement.

Table 1.Preparation of Calibration working standard solutions

Label	WS-1	WS-2	WS-3
SS-2	150 µL	750 µL	1000 µL
ISTD	100 µL	100 µL	100 µL
Diluent	Dilute to the Volume with diluent		

3. RESULT AND DISCUSSION

3.1 Method Validation

The purpose of this work to demonstrate method validation for determination of elemental impurity in Sucroferric Oxyhydroxide. Content of Ag, As, Au, Ba, Cd, Co, Cr, Cu, Hg, Ir, Li, Mo, Ni,Os, Pb, Pd, Pt, Rh, Ru, Sb, Se, Sn, Tl, and V in with Sc and Dy as internal standard will be determined by Inductively Coupled Plasma Mass Spectrometry.

The following parameters have been tested during this study:

I. Linearity & Range
II. Accuracy and Recovery
III. Specificity
IV. Precision (Repeatability) & Intermediate Precision.

The validation was performed according to ICH Q3D guidelines [5,6,7].

3.2 Linearity and Range

3.2.1 Working standard solutions for linearity

To demonstrate Linearity, five (5) solutions at different concentrations were prepared, WS-1 Solution, WS-2 Solution, WS-3 Solution, WS-4 Solution and WS-5 Solutions. Transfered into five separate 50 mL volumetric flasks made of polypropylene or polymethylpentene added 3 mL of concentrated nitric acid, and 1 mL of concentrated hydrochloric acid and added as per below table.Each solution was analyzed in triplicate measurements.

3.3 Accuracy/Recovery

To demonstrate Accuracy, a single un-spiked sample and samples spiked with reference material, prepared in triplicate (3x), at concentrations of 0.5J, 1.0J and 1.5J were prepared. Each solution was analyzed in triplicate measurements. A Standard stock solution was added to nine sample solutions as shown in the table below.

During method development stage before the addition of Thiourea to the analysis matrix,osmium recoveries were in the range of 55-65%.Excellent Osmium spike recoveries ranging from 97% to 99 % were obtained due to thiourea addition as it prevents the formation of volatile osmium tetraoxide and this helped balance the accuracy of the analysis of osmium response in the calibration standards and will compensate for matrix effect.

The spiked sample solution recoveries was analysed by ICP-MS.Prior to ICP-MS analysis internal standard solution was was added to each solution. The endogeneous content of the unspiked sample was subtracted from the results of the spiked samples. before accuracy and precision were determined. A close inspection of the results from all nine sample matrices indicated that excellent average recoveries were obtained for each of the 24 elements (Ag, As, Au, Ba, Cd, Co, Cr, Cu, Hg, Ir, Li, Mo, Ni, Os, Pb, Pd, Pt, Rh, Ru, Sb, Se, Sn, Tl, and V) was within 70% to 150%.

All acceptance criteria described for accuracy were met as the spike recoveries for the mean of all six preperations at each spiking concentration for each element was within specification criteria i.e 70% -150% and the % RSD for each six replicates at each of the spiking concentrations for each element was ≤ 20%.

3.4 Specificity

To evaluate specificity of the method for the contents of Ag, As, Au, Ba, Cd, Co, Cr, Cu, Hg, Ir, Li, Mo,Ni, Os, Pb, Pd, Pt, Rh, Ru, Sb, Se, Sn, Tl and V in Sucroferric oxyhydroxide were compared with contents of Ag, As, Au, Ba, Cd, Co, Cr, Cu, Hg, Ir, Li, Mo, Ni, Os, Pb, Pd, Pt, Rh, Ru, Sb, Se, Sn, Tl, and V contents in Sucroferric oxyhydroxide in Accuracy test (Level 2).

Table 2. Working Standard Solution preparation for Linearity for Multielements to be determined in Sucroferric oxyhydroxide by ICPMS"

Label	WS-1	WS-2	WS-3	WS-4	WS-5
Added Volume of SS-2	150 µL	250 µL	500 µL	750 µL	1000 µL
Added Volume of ISTD	100 µL	100 µL	100 µL	100 µL	100 µL
Diluent	Dilute to the volume with diluents				

Table 3."Linearity Summary Results of Multielements to be determined in Sucroferric oxyhydroxide by ICPMS"

Sr.No.	Elemental metal	Correlation Coefficient	Sr.No.	Elemental metal	Correlation Coefficient
1	Lithium	0.9997	13	Silver	0.9999
2	Vanadium	0.9999	14	Cadmium	0.9999
3	Chromium	0.9999	15	Tin	1.0000
4	Cobalt	0.9999	16	Antimony	0.9991
5	Nickel	0.9999	17	Barium	1.0000
6	Copper	0.9997	18	Iridium	1.0000
7	Arsenic	0.9990	19	Platinum	1.0000
8	Selenium	0.9962	20	Gold	1.0000
9	Molybdenum	0.9995	21	Mercury	1.0000
10	Ruthenium	0.9999	22	Thallium	1.0000
11	Rhodium	1.0000	23	Lead	0.9998
12	Palladium	1.0000	24	Osmium	1.0000
Acceptance criterion		**Correlation Coefficient($r^2 \geq 0.99$)**			

Hence Linearity result meets the Acceptance Criteria.

Table 4."Concentration levels for Accuracy testof Multielements to bedetermined in Sucroferric oxyhydroxide by ICPMS"

Flask No.	1-3	4-6	7-9	10-12
Added Volume of SS-2	_	250 µL	500 µL	750 µL
Added Volume of ISTD	_	100 µL	100 µL	100 µL
Diluent	Dilute to the volume with diluent			

Table 5. " % Recovery for all USP restricted elements analysed in this study at three different concentration levels for Multielements to be determined in Sucroferric oxyhydroxide by ICPMS"

Element	% Recovery at 0.5 J		% Recovery at 1.0 J		% Recovery at 1.5 J	
	Mean %	RSD%	Mean %	RSD%	Mean %	RSD%
Li	96	0.6	97	2.1	99	1.6
V	101	5.9	98	2.7	100	2.6
Cr	101	2.1	99	3.3	99	2.5
Co	100	2.0	98	2.5	98	2.0
Ni	95	4.0	99	4.7	99	3.8
Cu	96	1.7	96	4.0	97	2.5
As	114	0.6	106	4.3	109	3.1
Se	111	9.2	113	5.4	112	1.4
Mo	101	0.7	104	3.5	103	1.8
Ru	98	0.9	100	1.9	101	1.8
Rh	97	0.9	100	1.9	100	1.8
Pd	96	0.7	99	1.8	99	1.8
Ag	95	0.8	98	1.9	98	2.3
Cd	99	0.8	103	3.5	102	0.2
Sn	102	0.5	104	1.1	105	2.3
Sb	100	0.4	102	1.8	103	2.3
Ba	99	0.5	103	2.1	105	2.2
Ir	100	0.7	100	1.9	100	2.9
Os	97	3.0	99	1.0	99	2.0
Pt	97	1.00	98	1.9	99	2.6
Au	96	0.9	97	1.7	97	2.8
Hg	96	0.3	99	1.6	100	3.1
Tl	99	0.6	101	1.9	101	2.7
Pb	117	1.0	121	3.4	116	6.9

Table 6. ‘‘Summarized results ofPrecision &Intermediate Precision for Multielements to be determined in Sucroferric oxyhydroxide by ICPMS''

Element	ForPrecision%RSD(for n=6 Preperations)	ForIntermediate Precision%RSD(for n=6 Preperations)	Overall%RSD(for n=12 Preperations)
Li	2.1	1.5	2.2
V	3.1	3.5	3.2
Cr	2.2	2.5	3.5
Co	2.1	2.4	2.2
Ni	1.8	2.5	2.1
Cu	2.1	2.3	2.2
As	3.4	3.4	3.7
Se	3.0	2.8	3.8
Mo	2.1	2.1	5.4
Ru	2.6	2.3	2.4
Rh	2.2	2.3	2.3
Pd	2.1	2.4	2.3
Ag	2.3	2.2	2.2
Cd	3.3	1.6	3.0
Sn	2.2	1.8	3.0
Sb	2.1	1.9	6.5
Ba	2.2	1.6	2.7
Ir	2.9	2.0	2.1
Os	2.3	2.0	2.4
Pt	2.1	1.8	1.8
Au	2.0	1.9	1.9
Hg	2.3	1.9	2.2
Tl	2.2	2.1	2.0
Pb	3.1	3.7	3.3

Specificity was assessed to show the absence of isobaric and polyatomic interference via quantifying the spiked samples against the calibration standard solution and meeting the the requirements of accuracy.No interference observed the measured mass of any target element from the elements from the elements present in specificity solutions.

3.5 Precision (including Repeatability) & Intermediate Precision

A second analyst on a different day prepared and analysed six preperations of approximately 100% target limit spiked samples (J) with freshly prepared spiking solutions.The samples were quantified against fresh calibration standards.

The result determine for Intermediate Precision /Ruggedness are summarised in (Table 6). For each element the second analyst/day mean for all six preparations was within$\pm$20% of the mean result for the first analysis. The % RSD for all preparations (n=12) for each target element was $\leq$25%.All acceptance criteria described in USP Chapters <233/232> for ruggedness were met.

4. DISCUSSION

This method is developed to be cost effective and less hazardous method which is consider for safety assessment, so it is therefore essential to develop such kind of chromatographic methods which will characterize and determine identified as well as unidentified impurities present in active pharmaceutical ingredients. Identification of identified as well as unidentified impurities. This method is used to analyze and determine the probability of possible degradational impurities.

All pharmacopoeias include a test for heavy metals, the current heavy metals limit test as stated in pharmacopoeias EP 2.4.8 and USP 231 method has been the main reference for more than hundred years; the method has basically a limit of 10 ppm. The basic reaction is between metal impurities and thioacetamide to form sulphides. The intensity of the colored sulphide precipitate is compared with a lead reference standard.

The compendial method is nonspecific, less sensitive, non-specific, and time-consuming,

labour intensive and mostly yield low recoveries and does not provide adequate recovery of the elements being tested., whereas in developed research method all these gaps are covered without any loopholes.

Further serious limitations of the visual heavy metals test are the lack of selectivity and the inability to detect some metals as platinum, iron, palladium, or nickel (frequently used as catalysts) which have to be determined. The color comparison test is difficult to conduct, time consuming and it is not able to detect some toxic elements. Therefore, great effort is currently being devoted for the multimetal screening development and validation of new procedures to control metals in pharmaceuticals that rely on modern advance analytical methodologies.Color comparison of test will be replaced by (ICP-MS) inductively coupled plasma mass spectrometry is a highly sensitive that achieves low detection limits for almost all elements.

5. CONCLUSION

Method for determination of Ag, As, Au, Ba, Cd, Co, Cr, Cu, Hg, Ir, Li, Mo,Ni, Os, Pb, Pd, Pt, Rh, Ru, Sb, Se, Sn, Tl,and V contents in Sucroferric oxyhydroxide is specific. All results met Acceptance Criteria for Specificity. Method adequately demonstrated Specificity for elemental Ag, As, Au, Ba, Cd, Co, Cr, Cu, Hg, Ir, Li, Mo, Ni, Os, Pb, Pd, Pt, Rh, Ru, Sb, Se, Sn, Tl, and V contents in Sucroferric oxyhydroxide. All system suitability parametersare with in range and satisfactory as per ICH guidelines [8].

CONTENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

DISCLAIMER

I have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest from producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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