

Multi-element determination in pharmaceutical preparations using the Thermo Scientific iCAP Q ICP-MS

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Key Words

- iCAP Q
- Pharmaceutical preparations
- ICP-MS
- USP 232
- USP 233



Introduction

Monitoring and control of metal impurities in medicinal preparations is of importance to the pharmaceutical industry as drug production and formulation processes often involve either direct addition of metals (as catalysts) or non-intentional addition via contaminated reagents or contact of the pharmaceutical ingredients with metal surfaces during production. Historically, qualitative methods based on subjective tests such as visually detecting metal sulphides via colorimetry (the US Pharmacopeia 231 method (USP 231)) were used, but these have been recognized to be inaccurate and insufficiently comprehensive in terms of detecting all metals of concern. In August 2008, at a workshop organized by and conducted at the Institute of Medicine (IOM) of the US National Academy of Sciences, plans were put in place to develop improved methods and to harmonize analytical approaches to these measurements. The result was a revised impurities list (USP 232) and a new analysis procedure (USP 233), that described the use of ICP-OES and ICP-MS for determining metal impurities in pharmaceutical products. Following comments and feedback from the pharmaceutical industry, both USP 232 and USP 233 were further revised in 2011 to improve their clarity and flexibility and these documents are now in the process of being officially implemented.

In addition to the requirements described in the USP documents, any method used for the analysis of pharmaceuticals must also comply with the US Food and Drug Administration's 21 CFR Part 11 regulations regarding electronic records and validation of electronic signatures. These regulations are concerned with ensuring the integrity and authenticity of any 'electronic records and electronic signatures that persons create, modify, maintain, archive, retrieve or transmit'. This means that the control software of analytical instruments used in

pharmaceutical production must include tools to maintain the integrity of the analysis method and results, allow audit trailing and electronic signatures as well as provide security features to ensure that alterations cannot be made without clear indication of what has been changed, who changed it and why.

This note describes the application of a new quadrupole ICP-MS, the Thermo Scientific iCAP Q, to the detection and quantification of the 16 target elements specified in USP 232 in accordance with the ICP-MS procedures described in USP 233. In order to comply with the requirements described above for 21 CFR Part 11 compliance, the Thermo Scientific Qtegra software suite of the iCAP Q ICP-MS has been specifically developed to provide comprehensive features for the pharmaceutical industry, such as audit trails, support for electronic signatures and tools for integrated data management.

Sample and calibration solution preparation

Three pharmaceutical samples were selected for this work, namely:

- Sample A - Soluble aspirin product (in tablet form)
- Sample B - Cold and flu remedy (in powder form)
- Sample C - Children's cough syrup (in liquid form)

Each sample ($5.00 \pm 0.05\text{g}$) was dissolved into 500 mL of a diluent containing 1% (v/v) HNO_3 , 0.5% (v/v) HCl and 200 ppb Au, prior to a further 1:10 dilution in the same diluent for analysis.

The samples were measured using an external calibration approach against calibration solutions prepared in the same diluent as the samples. The calibration solutions contained all 16 of the elements listed in "USP 232, Elemental Impurities - Limits". Internal standardization was used, with Ga, In and Tl as internal standards at 10, 5 and 5 ppb respectively, added on-line via a T-piece.

Method

Sample analysis was carried out in accordance with the requirements described in "USP 233, Elemental Impurities – Procedures". This document specifies that the elements to be measured should be calibrated at a level of blank, 0.5J and 2J where J = the concentration (w/w) of the element(s) of interest at the Target limit, appropriately diluted to the working range of the instrument. For this work, a blank and three standards (at 0.5J, J and 2J) were measured. The Target limits (in the original, undiluted samples) for each element are presented in Table 1.

Element	Daily Dose PDE* (µg/day)	Target Limit (J) (per dose at 4 doses per day) (µg)
Inorganic arsenic	15	3.75
Cadmium	5	1.25
Lead	10	2.5
Inorganic mercury	15	3.75
Chromium	250	62.5
Copper	2500	625
Manganese	2500	625
Molybdenum	250	62.5
Nickel	250	62.5
Palladium	100	25
Platinum	100	25
Vanadium	250	62.5
Osmium		
Rhodium	100 (Combination not to exceed)	100 (Combination not to exceed)
Ruthenium		
Iridium		

* PDE = permitted daily exposure based on a 50 kg person

Table 1: Target Limit (J) for the elements specified in USP 232.

For the purposes of this work, the Target Limit was taken as the limit per dose, based on 4 doses of the selected pharmaceuticals per day, as 4 was the maximum number of doses prescribed for each medicine per day. With this Target Limit taken into account, and as the samples were diluted by 1000x from the original sample, the calibration solutions were prepared at the concentrations given in Table 2.

Element	Calibration solution 1	Calibration solution 2	Calibration solution 3
Arsenic	1.875	3.75	7.5
Cadmium	0.625	1.25	2.5
Lead	1.25	2.5	5
Mercury	1.875	3.75	7.5
Chromium	31.25	62.5	125
Copper	312.5	625	1250
Manganese	312.5	625	1250
Molybdenum	31.25	62.5	125
Nickel	31.25	62.5	125
Palladium	12.5	25	50
Platinum	12.5	25	50
Vanadium	31.25	62.5	125
Osmium	3.125	6.25	12.5
Rhodium	3.125	6.25	12.5
Ruthenium	3.125	6.25	12.5
Iridium	3.125	6.25	12.5

Table 2: Calibration solution concentrations (ppb).

USP 233 specifies that spike recoveries should be performed on each of the pharmaceutical preparations under test at the Target limit (J) and at 80% of the Target limit (0.8J). These spike tests are required to be carried out on a minimum of three separate samples of each preparation at both spike levels. Three samples of each of the three materials under test were therefore prepared at spike levels of 0.8J and J accordingly, and analyzed against the calibration solutions.

USP 233 also requires that the analysis be precision tested. For this, the protocol specifies that six independent samples of the material under test, spiked with the target elements at the indicated levels should be measured. As the protocol does not explicitly state what ‘the indicated levels’ means, it was decided in this work to measure one of the materials (sample B – the cold and flu remedy) at spike level J as described earlier. Finally, instrument detection limits for all the USP 232 target elements (based on 3 x the standard deviation of the calibration blank) and method detection limits (based on 3 x the standard deviation of the mean of 5 consecutive independent blanks) were determined.

Instrument configuration

The Thermo Scientific iCAP Qc ICP-MS was used for all measurements. The sample introduction system used consisted of the standard Peltier cooled, quartz cyclonic spray chamber, PFA concentric nebulizer and demountable quartz torch with a 2.5 mm ID quartz injector. Standard Ni sample and skimmer cones were also used. The instrument was operated in a single collision cell mode with kinetic energy discrimination (KED), using pure He as collision gas. All samples were presented for analysis using a SC4 DX autosampler from Elemental Scientific (Omaha, NE, USA).

General analytical conditions

Parameter	Value
Forward power	1550 W
Nebulizer gas	0.89 L/min
Auxiliary gas	0.8 L/min
Cool gas	14.0 L/min
Collision cell gas	He at 7 mL/min
Sample uptake/wash time	45s each
Dwell times	Optimized per analyte
Number of points per peak	1
Number of repeats per sample	3
Total acquisition time	3.5 mins

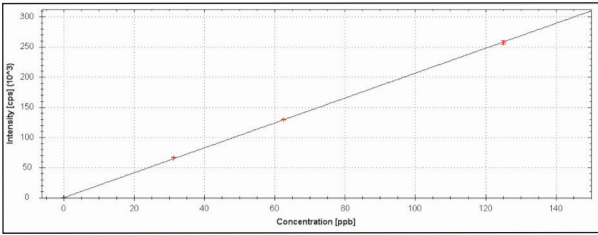
Table 3: Instrument operating parameters.

Results and Discussion

1. Calibration performance.

Linear calibrations with low (sub-ppb) blanks were obtained for all 16 of the elements specified in USP 232 as shown by the examples of ⁵¹V and ²⁰⁸Pb in Figure 1 and by the calibration data presented in Table 4.

(a) ⁵¹V.



(b) ²⁰⁸Pb.

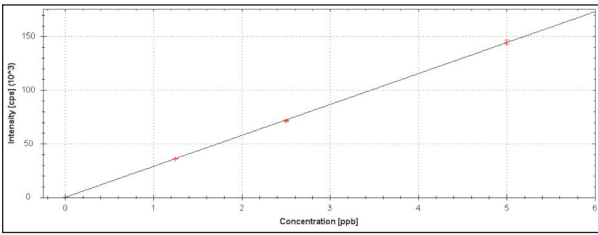


Figure 1: Example calibrations.

Isotope	R	BEC
⁵¹ V	0.99994	0.012
⁵² Cr	0.99993	0.102
⁵⁵ Mn	0.99993	0.102
⁶⁰ Ni	0.99999	0.034
⁶³ Cu	0.99997	0.070
⁷⁵ As	0.99993	0.009
⁹⁸ Mo	0.99983	0.088
¹⁰² Ru	0.99985	0.001
¹⁰³ Rh	1.00000	0.001
¹⁰⁶ Pd	0.99989	0.022
¹¹¹ Cd	0.99968	0.003
¹⁸⁹ Os	0.99998	0.008
¹⁹³ Ir	0.99979	0.020
¹⁹⁵ Pt	0.99991	0.001
²⁰² Hg	0.99989	0.019
²⁰⁸ Pb	0.99996	0.003

Table 4: Calibration correlation coefficient (R) and BEC (ppb) data.

Table 4 shows that for most of the target elements, low ppt BEC (background equivalent concentration) values were obtained. However, traces of Cr, Mn and Cu were detected, as a result of trace contamination of the blank reagents. The very low ⁵¹V and ⁷⁵As blanks obtained demonstrate the excellent collision cell performance of the iCAP Qc ICP-MS in removing the ³⁵Cl¹⁶O and ⁴⁰Ar³⁵Cl interferences generated on ⁵¹V and ⁷⁵As respectively by the HCl used in this analysis.

2. Sample analysis results.

The concentration determined for each target element in the pharmaceutical materials under investigation (three repeat analyses per sample) is shown in Table 5. The results shown here have been corrected for the 1000x sample dilution, and show the concentrations measured in the original 5g sample (in µg).

Sample	⁵¹ V	⁵² Cr	⁵⁵ Mn	⁶⁰ Ni	⁶³ Cu	⁷⁵ As	⁹⁸ Mo	¹⁰² Ru
Soluble aspirin #1	n.d.	0.04	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Soluble aspirin #2	n.d.	0.03	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Soluble aspirin #3	n.d.	0.03	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Cold and flu remedy #1	0.012	0.03	n.d.	n.d.	0.01	n.d.	n.d.	n.d.
Cold and flu remedy #2	0.012	0.03	n.d.	n.d.	0.02	n.d.	n.d.	n.d.
Cold and flu remedy #3	0.015	0.02	n.d.	n.d.	0.01	n.d.	n.d.	n.d.
Cough syrup #1	n.d.	n.d.	1.00	n.d.	0.05	n.d.	n.d.	n.d.
Cough syrup #2	n.d.	n.d.	0.97	n.d.	0.05	n.d.	n.d.	n.d.
Cough syrup #3	n.d.	n.d.	1.01	n.d.	0.06	n.d.	n.d.	n.d.

Sample	¹⁰³ Rh	¹⁰⁶ Pd	¹¹¹ Cd	¹⁸⁹ Os	¹⁹³ Ir	¹⁹⁵ Pt	²⁰² Hg	²⁰⁸ Pb
Soluble aspirin #1	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Soluble aspirin #2	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Soluble aspirin #3	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Cold and flu remedy #1	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Cold and flu remedy #2	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Cold and flu remedy #3	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Cough syrup #1	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	0.019
Cough syrup #2	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	0.017
Cough syrup #3	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	0.018

n.d. = not detected

Table 5: Sample analysis results (µg in the original 5g sample).

Table 5 shows that, in all three samples, most of the target elements were either present at low concentrations or not detected at all (i.e. present at concentrations lower than the detection limit). The cough syrup however, was found to contain around 1 µg of Mn, 0.05 µg of Cu and almost 0.02 µg of Pb (in the 5g sample dose), while 0.03 to 0.04 µg of Cr was detected in the soluble aspirin and cold / flu remedy samples (also in 5g of sample). These levels, although easily detectable with the iCAP Qc ICP-MS, are far below the Target Limit values for these elements (i.e. Cr – 62.5 µg, Mn – 625 µg, Cu - 625 µg and Pb – 2.5 µg per 5g dose, with 4 doses per day for each of the three samples tested in this work).

3. Detection limits.

The instrumental detection limits (I.d.L) for the target elements, calculated for the original undiluted sample are presented in Table 6. These limits are calculated from 3 x the standard deviation of the calibration blank.

Element	⁵¹ V	⁵² Cr	⁵⁵ Mn	⁶⁰ Ni	⁶³ Cu	⁷⁵ As	⁹⁸ Mo	¹⁰² Ru
I.d.L	0.0006	0.009	0.01	0.01	0.01	0.003	0.01	0.0005

Element	¹⁰³ Rh	¹⁰⁶ Pd	¹¹¹ Cd	¹⁸⁹ Os	¹⁹³ Ir	¹⁹⁵ Pt	²⁰² Hg	²⁰⁸ Pb
I.d.L	0.0001	0.0007	0.001	0.002	0.003	0.001	0.003	0.0008

Table 6: Instrument detection limits (in µg, relative to the original 5g sample).

Table 6 shows that the iCAP Qc ICP-MS provides exceptionally low detection capability for all 16 of the USP 232 target elements. These results give an indication of the instrumental detection limits achievable with the instrument but, as such, are not indicative of what would be practically achieved on a routine basis. To determine the detection limits that would be routinely achievable for this analysis, method detection limits have to be calculated. Therefore, method detection limits based on 5 separate consecutive blanks were measured. These were calculated from 3 x the standard deviation of the mean of the 5 blanks and are presented in Table 7.

Isotope	⁵¹ V	⁵² Cr	⁵⁵ Mn	⁶⁰ Ni	⁶³ Cu	⁷⁵ As	⁹⁸ Mo	¹⁰² Ru
M.d.L	0.011	0.01	0.03	0.03	0.01	0.01	0.07	0.002

Isotope	¹⁰³ Rh	¹⁰⁶ Pd	¹¹¹ Cd	¹⁸⁹ Os	¹⁹³ Ir	¹⁹⁵ Pt	²⁰² Hg	²⁰⁸ Pb
M.d.L	0.005	0.03	0.001	0.01	0.07	0.01	0.03	0.007

Table 7: Method detection limits (in µg, relative to the original 5g sample).

The method detection limits shown in Table 7 provide a robust indication of the iCAP Qc's performance for the USP 233 method as they allow for blank to blank variation, caused by random contamination in the sample tubes or during sample preparation. As shown in this Table, sub-µg method detection limits relative to the original, undiluted samples were obtained for all 16 target elements, demonstrating that the iCAP Qc far exceeds the performance required to meet the analytical criteria required by USP 233.



4. Spike recoveries.

The spike recoveries for each repeat of all three samples at the 0.8J and J spike levels are shown in Figures 2 and 3.

USP 233 states that the acceptance criteria for this test are recoveries of between 70 and 150% for the mean of the three repeat analyses of each sample at both spike levels. Figures 2 and 3 show that these criteria (indicated by the red lines) are easily achieved using the iCAP Qc ICP-MS, with average recoveries at both spike levels ranging from 91 to 113%.

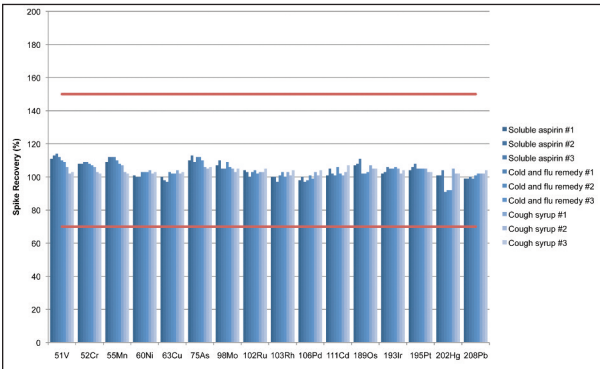


Figure 2: Recoveries (in %) at the 0.8J spike level

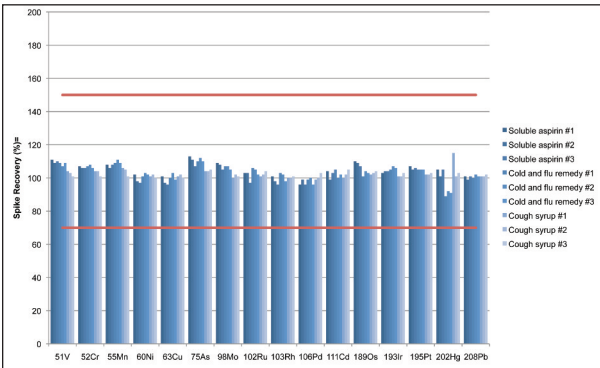


Figure 3: Recoveries (in %) at the J spike level.

5. Repeatability.

Results for the analysis of 6 independent aliquots of sample B (the cold / flu remedy) spiked at the Target Limit, J, with the 16 USP 232 elements are shown in Table 8 below.

Sample	51V	52Cr	55Mn	60Ni	63Cu	75As	98Mo	102Ru
Cold / flu remedy run 1	65.2	63.6	642	62.6	627	4.03	63.9	6.11
Cold / flu remedy run 2	64.8	63.3	636	61.5	613	4.04	64.1	6.28
Cold / flu remedy run 3	65.8	64.1	651	62.3	620	4.10	66.7	6.31
Cold / flu remedy run 4	66.3	64.8	649	62.9	627	4.09	66.2	6.46
Cold / flu remedy run 5	66.4	65.1	656	63.1	634	4.07	65.0	6.39
Cold / flu remedy run 6	66.0	64.7	655	62.2	623	4.01	63.5	6.21
Mean	65.8	64.3	648	62.4	624	4.06	64.9	6.29
Std. Dev.	0.62	0.70	8	0.56	7.06	0.03	1.32	0.12
%RSD	0.9	1.1	1.2	0.9	1.1	0.8	2.0	2.0

Sample	103Rh	106Pd	111Cd	180Os	193Ir	195Pt	202Hg	208Pb
Cold / flu remedy run 1	6.07	23.9	1.24	6.40	6.41	25.6	3.66	2.49
Cold / flu remedy run 2	6.13	24.2	1.27	6.17	6.39	25.3	3.68	2.43
Cold / flu remedy run 3	6.30	25.1	1.18	6.19	6.45	25.5	3.75	2.46
Cold / flu remedy run 4	6.35	25.5	1.27	6.21	6.48	26.2	3.77	2.43
Cold / flu remedy run 5	6.24	24.6	1.22	6.10	6.33	25.2	3.71	2.37
Cold / flu remedy run 6	6.04	24.2	1.22	6.27	6.54	26.0	3.78	2.48
Mean	6.19	24.6	1.23	6.22	6.43	25.6	3.73	2.44
Std. Dev.	0.13	0.62	0.03	0.10	0.07	0.38	0.05	0.05
%RSD	2.0	2.5	2.8	1.6	1.1	1.5	1.3	1.9

Table 8: Repeatability test results for the cold / flu remedy sample (spiked at the Target Limit, J). All concentrations are shown in µg.

Table 8 shows that excellent repeatability (< 3% RSD for all 16 elements and < 2% RSD for 14 of them) for 6 separate analyses of the spiked cold / flu remedy sample was obtained, illustrating the robustness and reliability of the tested method using the iCAP Qc ICP-MS.

6. Internal standard stability.

The robustness of the iCAP Qc ICP-MS in meeting the USP 232 and 233 requirements was assessed by monitoring the absolute suppression and relative drift of the internal standards throughout the analysis. The response (in %) of all three internal standards relative to the initial calibration blank for all blanks, standards and samples analyzed in this work is shown in Figure 4.

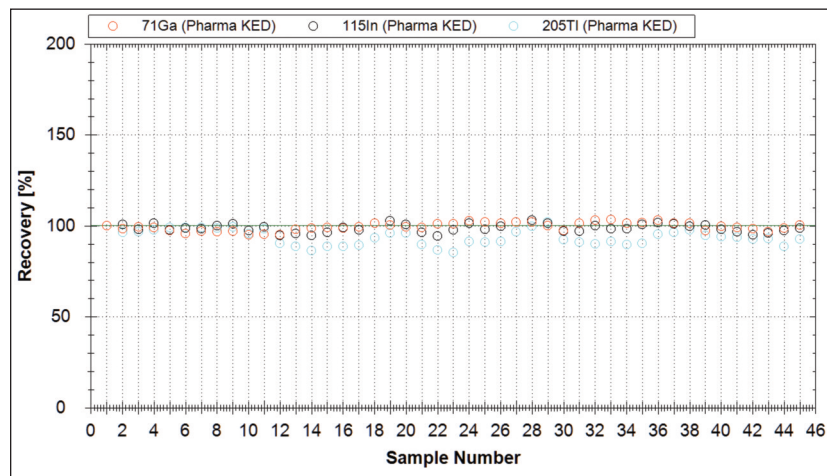


Figure 4: Internal standard response throughout the analysis.

Figure 4 shows that no drift was observed throughout the duration of the run (2.75 hours), with the final sample giving internal standard responses of 106%, 101% and 97% for ^{71}Ga , ^{115}In and ^{205}Tl respectively. The range in response of the internal standards was 89% to 109%, illustrating the robustness of the iCAP Qc for this analysis.

Conclusions.

This application note has shown that the Thermo Scientific iCAP Qc ICP-MS is an ideal tool for elemental determination in pharmaceutical preparations. With its high sensitivity and robustness, the instrument is easily capable of accurately and precisely measuring all 16 of the specified elements in a single analysis mode at the Target Limits currently listed in USP 232 and in accordance with the analytical performance criteria described in USP 233. Finally, the range of security features, data management and audit trailing tools included in the advanced and flexible Qtegra software provide the necessary support to meet the demands of 21 CFR Part 11 compliance for the highly regulated pharmaceutical industry.

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