APPLICATION NOTE

ICP - Mass Spectrometry

Author:

Aaron Hineman

PerkinElmer Inc.
Shelton, CT

Testing and Validation of Various Antacids for Class 1 and 2A Elemental Impurities in Pharmaceutical Products Following ICH Q3D and USP <232>/<233> Using the NexION 2000 ICP-MS

Introduction

The United States Pharmacopeia (USP) has announced that its new standards for elemental impurities in drug products will be implemented on January 1, 2018. General Chapters <232> and <2232> specify the list of elements and their permissible daily exposure (PDE) limits based on the route of administration[1]. USP has now harmonized the list of elemental impurities, as well as their PDEs, with the International Conference on Harmonization (ICH) Q3D Step 4 document[2]. In June 2016, the FDA issued guidance on elemental impurities covering ICH Q3D in drug products[3].

As the deadline for assessing and monitoring elemental impurities approaches, pharmaceutical manufacturers and their service laboratories need to act now or risk not being in compliance with the new regulations. Compliance requires that the analytical methodology be capable of accurately measuring low concentrations of elemental impurities in drug products or its components, as necessary, to ensure patient safety.

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A list of Class 1 and 2A impurities[4] and their PDEs appears in Table 1. USP General Chapter <232> outlines two analytical procedures for the determination of elemental impurities in finished drug products: inductively coupled plasma mass spectrometry (ICP-MS) or inductively coupled plasma optical emission spectroscopy (ICP-OES), along with associated sample preparation steps. The analytical capabilities of ICP-MS make it the most suitable technique for performing determinations of the Class 1 elements at these low levels on a routine basis – especially with drug products for which there is a large daily dosage (>10 g/day). Among this category of medications and supplements, antacids present a unique set of analytical challenges due to their extremely high calcium content. However, as shown in this work, these challenges can easily be overcome with correct sample preparation and instrumental design considerations.

In this paper, we present data to illustrate the successful validation of the NexION® 2000 ICP Mass Spectrometer for the determination of Class 1 and 2A elemental impurities in antacids according to USP General Chapter <233>.

Table 1. ICH Class 1 and 2A PDEs.

Element	Class	Oral Daily Dose PDE (µg/day)
Cd	1	5
Pb	1	5
As	1	15
Hg	1	30
Co	2A	50
V	2A	100
Ni	2A	200

Experimental

Sample Preparation

The eight different antacids chosen for the evaluation represent a typical cross section of antacids available over-the-counter and are presented in Table 2.

Table 2. Antacids used in this study.

Type	Quantity	Description
Calcium based	2	Over-the-counter antacid tablet, containing only calcium
Magnesium based	1	Over-the-counter antacid tablet, containing only magnesium
Calcium and Magnesium based	2	Over-the-counter antacid tablet, containing both calcium and magnesium
Other	3	Over-the-counter antacid tablets, containing other combinations of calcium, magnesium, sodium, or aluminum

Most antacids require digestion in order to solubilize all of the material. A typical digestion uses nitric and hydrochloric acids, but, since silica (SiO_2) is present in some of the samples, a source of fluoride is required to completely solubilize the sample. Typically hydrofluoric acid or tetraethylfluoroboric acid is used.

All samples were digested using PerkinElmer's Titan MPS™ Microwave Sample Preparation System with standard 75 mL TFM vessels.

With the exception of the powdered antacid, approximately 3-5 grams of material was crushed and homogenized. Then 0.30 ± 0.01 g of each sample was added to a digestion cup and dropped into a digestion vessel. Next, 5 mL of nitric acid (70%), 1 mL of hydrochloric acid (35%), 1 mL of hydrogen peroxide (30%), and 0.5 mL of HF (49%) were added to the digestion vessel. The vessels were allowed to sit uncapped for ten minutes to allow for any pre-reactions to occur safely before being capped and digested following the program in Table 3. When the digestion was complete, all samples were diluted with deionized water to a final volume of 50 mL, resulting in a total dilution factor of 167x with a reagent matrix of 10% HNO_3, 2% HCl, and 1% HF. Calibration standards were prepared in this same matrix. To stabilize mercury, 200 ppb Au was added to each sample, standard and blank.

Table 3. Titan MPS digestion program.

Step	Temperature (°C)	Pressure Max (bar)	Ramp (min)	Hold (min)	Power (%)
1	190	20	10	0	90
2	170	20	0	15	90
Cooling	50	20	1	15	0

Instrumentation

A NexION 2000 ICP-MS (PerkinElmer Inc., Shelton, CT) was validated in this work for the analysis of antacid tablets in accordance with USP <232> and ICH Q3D. The NexION technology has been described previously[5], so only a brief description will be given here. The NexION is a quadrupole-based ICP-MS system that offers the simplicity and convenience of a traditional collision cell together with the exceptional detection limits of a true reaction cell. Using the patented Universal Cell Technology™ (UCT), the most appropriate collision or reaction cell technique can be chosen for a specific application. By virtue of NexION's Triple Cone Interface (TCI), Quadrupole Ion Deflector (QID) technology, and All Matrix Solution (AMS) system, productivity and ease-of-use result from minimized drift, reduced contamination of the interface region, and an absolute minimum of routine maintenance and cleaning.

For this validation, all analyses were performed on a PerkinElmer NexION 2000 ICP-MS Productivity configuration, utilizing the SMARTintro™ High Throughput/High Matrix sample introduction system in its standard operating conditions. This configuration of the NexION 2000 offers enhanced speed of analysis through the use of an in-line flow-switching valve and superior matrix tolerance using the AMS sample introduction system. The NexION's Universal Cell was operated in helium Collision mode for all analytes and samples, demonstrating simple method setup for this analysis. The instrument conditions are shown in Table 4, and the elements and masses appear in Table 5.

Table 4. NexION 2000 ICP-MS Conditions.

Parameter	Value
RF Power	1600 W
Plasma Flow	15 L/min
Aux Flow	1.2 L/min
Nebulizer Gas Flow	0.9 L/min
AMS Dilution	3x

Table 5. Elements and Masses.

Element	Mass	Universal Cell Mode	Internal Standard
Na	23	Collision - Helium	^{71}Ga
Mg	24	Collision - Helium	^{71}Ga
Al	27	Collision - Helium	^{71}Ga
Ca	43	Collision - Helium	^{71}Ga
V	51	Collision - Helium	^{71}Ga
Co	59	Collision - Helium	^{71}Ga
Ni	60	Collision - Helium	^{71}Ga
As	75	Collision - Helium	^{72}Ge
Cd	111	Collision - Helium	^{115}In
Hg	202	Collision - Helium	^{159}Tb
Pb	206 + 207 + 208	Collision - Helium	^{159}Tb

Calibration

USP General Chapter <233> outlines the requirement to calibrate using a matrix-matched blank and calibration standards with concentrations of 0.5J and 1.5J. The J value is defined as the maximum per-daily exposure of the analyte divided by the product of the medication's maximum daily dose and dilution factor used in the sample preparation. In the case of antacids, large daily dosages are possible – for the eight samples in this study, the largest maximum daily dosage was 30 g of the drug product. Therefore, in order to test all samples using one set of calibration standards, a 30 g/day dosage was used in calculating the calibration range (0.5J and 1.5J). The elements and standard concentrations were calculated using the PerkinElmer J Value Calculator, as shown in Figure 1.

Compound Name: Antacids
Doses Per Day: 1
Weight Per Dose: 30 g
Amount Digested: 0.3 g
Final Volume: 50 mL
Dilution: 1

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Element	Oral Daily Dose PDE (µg/day)	J value (µg/L in solution)	Standard 1 (1.5 J [µg/L])	Standard 2 (0.5 J [µg/L])
Cd	5	1.0	1.5	0.5
Pb	5	1.0	1.5	0.5
Inorganic arsenic	15	3.0	4.5	1.5
Inorganic mercury	30	6	9	3
Co	50	10	15	5
V	100	20	30	10
Ni	200	40	60	20

Figure 1. PerkinElmer J Value Calculator applied to antacids.

Results

USP General Chapter <233> also contains requirements for validation of the method, which include the following tests:

- **Accuracy:** Spiking the matrix and material under investigation with target elements at concentrations that are 50%, 100%, and 150% of the target limits (i.e. maximum PDE). Mean spike recoveries for each target element must be within 70%-150% of the theoretical concentrations.
- **Repeatability:** Measuring six independent samples of the material under investigation, spiked at 100% of the target limits defined. The measured percent relative standard deviation (%RSD) must be not more than 20% for each target element.
- **Ruggedness:** Carrying out repeatability measurement testing by analyzing the six repeatability test solutions either on different days, with a different instrument, or by a different analyst – measuring the precision of the measurements. The %RSD of the 12 replicates must be not more than 25% for each target element.
- **System Suitability:** Measuring the high standard before and at the end of analyzing a batch of samples. The difference between the two results must be not more than 20% for each target element.

All sample results were less than the 0.5J standard, therefore less than the target limits for the elemental impurities. For the purposes of this study, we chose to report the method validation results for the sample that had the greatest internal standard suppression. A calcium- and magnesium-based over-the-counter tablet formulation is presented, as it represents the toughest analytical challenge due to the fact that it contained the highest total dissolved solids (TDS) of the samples examined.

Accuracy

The accuracy data shown in Table 6 clearly shows that the spike recovery in the sample matrix passes for this antacid at all three spike levels (50%, 100%, and 150% of the target limits). The mean spike recoveries for each target element were well within the 70%-150% acceptance criteria.

Table 6. Ca/Mg Antacid Accuracy Study.

Element / Mass	Mean Unspiked Sample		Mean Spiked Sample as % of Target (ppb)			Mean Recovery (%)			Pass/Fail
	(µg/g)	(J)	50%	100%	150%	50%	100%	150%	
V 51	0.218	<0.3J	10.9	20.1	29.1	96 %	94 %	97 %	Pass
Co 59	0.039	<0.3J	4.79	9.09	13.2	91 %	89 %	88 %	Pass
Ni 60	0.729	<0.3J	21.1	37.1	51.8	84 %	82 %	86 %	Pass
As 75	0.102	<0.3J	2.07	3.51	4.90	97 %	97 %	109 %	Pass
Cd 111	0.123	<0.3J	1.14	1.55	1.93	80 %	81 %	127 %	Pass
Hg 202	0.005	<0.3J	2.77	5.42	7.79	91 %	90 %	86 %	Pass
Pb 208	0.083	<0.3J	0.93	1.34	1.68	86 %	84 %	111 %	Pass

Repeatability

Six independently prepared samples of the Ca/Mg antacid were digested and then spiked at the 100% of the target limit. As shown in Table 7, the %RSDs for all target elements were within 2% - well under the 20% acceptance limit.

Table 7. Ca/Mg Antacid Repeatability Study (units in ppb).

Element/ Mass	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	Sample 6	Mean	% RSD	Pass/Fail
V 51	3367	3424	3374	3370	3250	3342	3354	1.7 %	Pass
Co 59	1524	1522	1536	1514	1497	1494	1515	1.1 %	Pass
Ni 60	6285	6213	6231	6157	6081	6163	6188	1.1 %	Pass
As 75	591	584	580	582	577	595	585	1.2 %	Pass
Cd 111	265	257	257	250	260	264	259	2.0 %	Pass
Hg 202	900	915	902	893	890	920	903	1.3 %	Pass
Pb 208	225	225	222	218	221	228	223	1.6 %	Pass

Ruggedness

The six samples used for the repeatability study above were analyzed on two different days. The RSDs for these twelve measurements are all < 2.5% (as shown in Table 8), well below the method requirement of 25%.

Table 8. Ca/Mg Antacid Ruggedness Study (units in ppb).

Element/ Mass	Event 1 – Spiked Sample at 100% of Target (ppb)						Event 2 – Spiked Sample at 100% of Target (ppb)						Overall		
	1	2	3	4	5	6	7	8	9	10	11	12	Mean	%RSD	Pass/ Fail
V 51	3367	3424	3374	3370	3250	3342	3247	3418	3327	3359	3276	3412	3347	1.8 %	Pass
Co 59	1524	1522	1536	1514	1497	1494	1580	1525	1558	1519	1485	1463	1518	2.1 %	Pass
Ni 60	6285	6213	6231	6157	6081	6163	6061	6202	6145	6137	6130	6293	6175	1.2 %	Pass
As 75	591	584	580	582	577	595	613	585	588	584	572	582	586	1.8 %	Pass
Cd 111	265	257	257	250	260	264	256	256	253	250	262	269	258	2.3 %	Pass
Hg 202	900	915	902	893	890	920	933	917	914	896	883	901	905	1.6 %	Pass
Pb 208	225	225	222	218	221	228	217	225	219	218	222	233	223	2.1 %	Pass

System Suitability

In order to accept the sample validation data, instrument drift is determined by measuring the high standard at the beginning and at the end of the analyses. The difference between the two results for each target element was not more than 6% for each which is below the acceptance limit of 20%, as shown in Table 9.

Table 9. Ca/Mg Antacid Validation Drift Study (units in ppb).

Element/ Mass	Event 1				Event 2			
	Initial Standardization Solution 1	Final Standardization Solution 1	Percentage Drift	Pass/ Fail	Initial Standardization Solution 1	Final Standardization Solution 1	Percentage Drift	Pass/ Fail
V 51	29.8	29.6	0.6 %	Pass	30.4	30.2	0.5 %	Pass
Co 59	14.9	15.4	-3.2 %	Pass	15.1	14.6	2.9 %	Pass
Ni 60	60.0	62.2	-3.5 %	Pass	59.8	57.5	3.9 %	Pass
As 75	4.44	4.68	-5.6 %	Pass	4.53	4.59	-1.2 %	Pass
Cd 111	1.47	1.48	-0.2 %	Pass	1.53	1.57	-2.6 %	Pass
Hg 202	9.17	9.19	-0.2 %	Pass	8.87	8.86	0.0 %	Pass
Pb 208	1.55	1.59	-2.2 %	Pass	1.48	1.51	-2.2 %	Pass

Conclusion

The PerkinElmer NexION 2000 ICP-MS with AMS was easily able to handle some of the highest-matrix drug products that will be encountered for testing. The AMS aerosol-dilution technology helps generate robust and accurate ICP-MS analysis of complex drug products such as the antacids described in this paper. The simple use of AMS reduces the total sample loading introduced to the plasma by accurately and reproducibly controlling aerosol dilution, eliminating reruns and reducing system maintenance. For the validation of the antacids, the most difficult sample material was chosen and all validation tests as per USP General Chapter <233> passed the acceptance criteria without any problems.

References

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PerkinElmer, Inc.
940 Winter Street
Waltham, MA 02451 USA
P: (800) 762-4000 or
(+1) 203-925-4602
www.perkinelmer.com

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