

ICP-Optical Emission Spectroscopy

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Analysis of SiO_2 - and TiO_2 - Containing Medications Using ICP-OES Following USP 232/233 Guidelines with Software Designed to Aid in 21 CFR Part 11 Compliance

Introduction

Since early 2018, manufacturers of pharmaceutical products are mandated to comply with USP <232>/<233> requirements around the analysis of elemental impurities in medications.^{1,2}

A detailed description of the requirements of USP <232>/<233>

is available,³ so only a brief description is given here. Elements are categorized into four classes, with Class 1 being the most toxic and Class 2A elements being likely contaminants from the manufacturing process (i.e. from mixing equipment, stainless steel vessels, etc.). Therefore, these are the most important elements to measure in pharmaceutical products. Their oral maximum permitted daily exposures (PDEs) are shown in Table 1.

Table 1. Maximum Oral Daily Exposures for Elements Defined in USP <232>.

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

*PDE = permissible daily exposure based on a 50 kg person.

The actual concentrations which must be measured in solution are dependent on the J value, which is based on the maximum PDE of the element, the maximum daily dose of the medication, and the dilution factor used in sample preparation.

Pharmaceutical tablets are complex mixtures which can contain a wide variety of excipients. Because of the variation and complexity, closed-vessel microwave digestion is the most efficient technique to get the tablets into solution without losing volatile elements, such as mercury (Hg). However, when tablets contain silica (SiO₂) and titanium dioxide (TiO₂) as excipients, digestion becomes more complex as hydrofluoric acid (HF) must be used. The presence of HF also requires the use of non-glass sample introduction components, unless the HF is dealt with during the digestion process.

When analyzing pharmaceutical materials, it is important to comply with 21 CFR Part 11, which is mandatory for companies and their suppliers that operate in regulated environments to sell products into the United States. This regulation puts forward the criteria for electronic records, electronic signatures, and audit trails to ensure data integrity and reliability during the analytical testing. Syngistix™ for ICP Enhanced Security™ software (version 4.0 or higher) was developed to help companies comply with regulations and sustain best practices delineated in 21 CFR Part 11.

This work focuses on the sample preparation and analysis of Class 1 and 2A elements in SiO₂- and TiO₂-containing tablets using a PerkinElmer Avio® 200 ICP-OES with Syngistix™ for ICP Enhanced Security software (version 4.0) to aid in compliance of the 21 CFR Part 11 regulations.

Experimental

Samples and Sample Preparation

All samples, purchased locally and summarized in Table 2, were tablets (i.e. oral administration) containing either SiO₂ or TiO₂ as inactive ingredients. The presence of these compounds requires the use of hydrofluoric acid (HF) for a complete digestion, which was accomplished with the Titan MPS™ Microwave Sample Preparation System (PerkinElmer, Shelton, Connecticut, USA) using the samples and reagents in Table 3. Hydrochloric acid (HCl) was required to stabilize mercury (Hg). One tablet of each medication was added to each vessel, followed by pre-digestion spikes, as required. Next, the nitric, hydrochloric, and hydrofluoric acids were added, followed by deionized water. The vessels were allowed to sit uncapped for 10 minutes before sealing and placing in the microwave for digestion.

The Titan MPS microwave digestion program used is shown in Table 4. The digestion itself is accomplished in the first two steps, with Step 3 being incorporated to rapidly cool the vessels for safe handling. If this step were eliminated, the vessels would require a significantly longer cooling time.

The use of HF requires alternate sample introduction components (i.e. spray chamber, nebulizer) which are not made of glass or quartz, unless the HF is complexed. This was accomplished by adding 3 mL of a saturated boric acid solution to each vessel and digesting again, following the Titan program in Table 5. The resulting solutions were clear, transferred to autosampler tubes, and diluted to 50 mL with deionized water. This final solution was analyzed with a glass nebulizer and spray chamber.

Table 2. Sample Information.

Medication Type	Excipient	Active Ingredient	Daily Dose	Mass Per Tablet (g)
Acid Reducer	TiO ₂	Ranitidine, 75 mg	2 tablets	0.13
		Ranitidine, 150 mg	2 tablets	0.32
		Famotidine, 20 mg	2 tablets	0.21
Sleep Aid	SiO ₂	Diphenylhydramine, 25 mg	2 tablets	0.43
		Diphenylhydramine, 25 mg	2 tablets	0.42
Motion Sickness	SiO ₂	Meclizine, 25 mg	2 tablets	0.20

Table 3. Sample Amounts and Acids Used per Digestion Vessel.

Sample	HNO ₃ 70% (mL)	HCl 35% (mL)	HF 49% (mL)	Water (mL)
Tablet	1.5	0.5	0.5	7.5

Table 4. Titan MPS Digestion Program.

Step	Temperature (°C)	Pressure (Bar)	Ramp (Min)	Hold (Min)	Power (%)
1	160	35	5	1	90
2	190	35	5	5	100
3*	50	35	1	15	0

*Cooling step

Table 5. Titan MPS Program to Complex Hydrofluoric Acid.

Step	Temperature (°C)	Pressure (Bar)	Ramp (Min)	Hold (Min)	Power (%)
1	190	35	5	10	90
2*	50	35	1	15	0

*Cooling step

Calibrations

According to USP <233>, calibration curves must be constructed of standards at the 0.5J and 1.5J levels. Because half of the daily dose was used for sample preparation, the J values across all medications were equivalent, although they differed by analyte. The PerkinElmer J-Value Calculator was used to determine the appropriate concentrations.

The calibration blank and standards were prepared in 3% HNO₃ + 1% HCl (v/v) to matrix-match the digested samples. All measurements were made against external calibration curves. To evaluate potential interferences, single-element standards of each analyte were prepared at the J value, analyzed individually, and the spectra observed. Table 6 shows the concentrations of the analytes at the various J values used in this work.

Table 6. Analyte Concentrations at Different J Values.

Element	0.5J (mg/L)	1J (mg/L)	1.5J (mg/L)
Cd	0.025	0.05	0.075
Pb	0.025	0.05	0.075
As	0.075	0.15	0.225
Hg	0.15	0.3	0.45
Co	0.25	0.5	0.75
V	0.50	1	1.5
Ni	1	2	3

Instrumental Conditions

All analyses were performed on an Avio 200 ICP-OES system (PerkinElmer) using the conditions and parameters in Table 7, along with the analytical wavelengths listed in Table 8. Standard sample introduction components and conditions were used, including a total argon consumption of 9 L/min. All measurements were made against external calibration curves prepared in 3% HNO₃ and 1% HCl. Yttrium (Y) was added to all blanks, standards, and samples as an internal standard. Optimized sample-to-sample times are approximately 1.5 minutes.

Table 7. Avio 200 ICP-OES Instrumental Parameters.

Parameter	Value
Nebulizer	MEINHARD® Type K, glass
Spray Chamber	Baffled glass cyclonic
Sample Uptake Rate	1.0 mL/min
RF Power	1500 W
Injector	2.0 mm id Alumina
Nebulizer Gas Flow	0.70 mL/min
Auxiliary Gas Flow	0.2 L/min
Plasma Gas Flow	8 L/min
Torch Position	-3
Plasma View Mode	Axial
Replicates	3

Table 8. Elements and Wavelengths.

Element	Wavelength (nm)
As	193.696
Cd	214.440
Co	238.892
Hg	194.168
Ni	231.604
Pb	220.353
V	309.310
Y (Int std)	371.029

To satisfy the data integrity requirements of the pharmaceutical industry, Syngistix for ICP Enhanced Security software version 4.0 was used. This software features all of the power of Syngistix for ICP, with the additional features required for 21 CFR Part 11 compliance for the regulated industry, including electronic signatures, electronic data review, the ability to set up different users and groups with different permissions, audit trail, version tracking, and much more.⁴ Examples of the audit trail, version tracking, and electronic data review are shown in Figures 1-3, respectively.

Ver.	Section Changed	Parameter Changed	Old Value	New Value	Changed By	Timestamp
5	Calibration Page Equation and...	Calb Units for analyte ICP Cont...	As 193.696	ug/L	Jane Smith - JcdSmith	6/13/2018 11:08:13 AM
5	Calibration Page Equation and...	Calb Units for analyte ICP Cont...	Hg 194.185	ug/L	Jane Smith - JcdSmith	6/13/2018 11:08:13 AM
5	Calibration Page Equation and...	Calb Units for analyte ICP Cont...	Cd 214.440	ug/L	Jane Smith - JcdSmith	6/13/2018 11:08:13 AM
5	Calibration Page Equation and...	Calb Units for analyte ICP Cont...	Pb 220.353	ug/L	Jane Smith - JcdSmith	6/13/2018 11:08:13 AM
5	Calibration Page Equation and...	Calb Units for analyte ICP Cont...	Ni 231.604	ug/L	Jane Smith - JcdSmith	6/13/2018 11:08:13 AM
5	Calibration Page Equation and...	Calb Units for analyte ICP Cont...	Co 238.892	ug/L	Jane Smith - JcdSmith	6/13/2018 11:08:13 AM
5	Calibration Page Equation and...	Calb Units for analyte ICP Cont...	V 230.310	ug/L	Jane Smith - JcdSmith	6/13/2018 11:08:13 AM

Figure 1. Example of an audit trail in Syngistix for ICP Enhanced Security software version 4.0. The audit trail shows any changes made to the method (in this example) and, for data security, can be printed to PDF in a human-readable format.

Version	Status	Logged in user	Signed by	Timestamp	Reason	Comment
5	Original	PNL - JPNL	Jane Smith - JcdSmith	6/13/2018 11:08:13 AM	Changed calibration units and values	
4	Original	PNL - JPNL	Jane Smith - JcdSmith	6/13/2018 11:05:13 AM	Changed limits on internal standards	
3	Original	PNL - JPNL	Jane Smith - JcdSmith	6/13/2018 11:04:21 AM		
2	Original	PNL - JPNL	Jane Smith - JcdSmith	6/13/2018 11:02:43 AM	Added Sc as Internal Standard	
1	Original	PNL - JPNL	PNL - JPNL	6/13/2018 10:12:04 AM		

Figure 2. Example of version tracking in Syngistix for ICP Enhanced Security software version 4.0. The Method icon in the ribbon allows the Method Report, Audit Trail, and Signatures and Comments to be sorted and viewed. Version tracking allows one to quickly and easily see when a method has been changed and approved. Those with appropriate permissions can approve or reject new or altered methods.

Sample ID	Y 217.1091 (Cu)	As 193.696 (As)	Hg 194.185 (Hg)	Cd 214.440 (Cd)	Pb 220.353 (Pb)	Ni 231.604 (Ni)	Co 238.892 (Co)	V 230.310 (V)
3 Cal 1.5J	105.5	223.462	444.489	79.926	79.926	297.090	789.086	1479.988
4 1.5J Std	100.0	2.022	-5.103	0.110	-4.888	-37.496	-6.814	12.488
5 5.24J Std	94.1	79.295	142.903	23.461	20.555	914.907	238.728	522.990
7 5.24J Std	89.6	222.182	419.811	69.193	64.420	2742.955	694.852	1505.454
8 5.24J-1	97.7	153.353	281.185	45.358	42.765	1506.589	478.407	1081.429
9 5.24J-2	86.3	164.658	284.214	46.216	43.291	1522.079	481.456	1042.027
10 5.24J-3	93.8	187.271	291.469	47.295	45.267	1515.546	487.215	1088.190
11 5.24J-4	95.3	181.032	290.539	48.893	46.444	1514.790	489.254	1039.125
12 5.24J-5	96.1	191.296	293.423	49.787	47.146	1504.228	479.688	1033.903
13 5.24J-6	96.9	184.794	289.874	49.794	47.942	1504.194	479.690	1033.174

Figure 3. Example of electronic data review in Syngistix for ICP Enhanced Security software version 4.0. Data Review Mode allows for side-by-side comparison of results, spectra, and calibrations, as well as the ability to review and add signatures and comments in customizable windows. This is an easy and quick way to view data. Those with appropriate permissions can approve or reject data.

Results and Discussion

Evaluation of Interferences

To evaluate the potential of analytes interfering with each other, single element standards of each analyte at their J concentration were analyzed. Examination of the resulting spectra showed no spectral interferences at the selected wavelengths.

Sample Analysis

The concentrations for all elements in all samples analyzed were less than the 0.3J, a common actionable threshold which is more than three times lower than the PDE.

Meeting the USP <233> Criteria

In order to validate analyses, USP <233> defines several criteria which must be met, as summarized in Table 9. These validation parameters were evaluated using one of the TiO₂- and one of SiO₂-containing medications.

Table 9. Analytical Criteria Defined in USP <233> for Quantitative Procedures.

Criteria	Description
Accuracy	Spike recoveries at 0.5J, J, and 1.5J must be between 70-150%
Repeatability	The RSDs of measurements of six independent samples spiked at J must be less than 20%
Ruggedness	Six solutions must be analyzed on different days, with different instruments, or with different analysts. The RSDs over the 12 measurements must be less than 25%
System Suitability	The difference in the results of the high calibration standard (1.5J) measured at the beginning and end of a batch must be < 20%

First, the system suitability was determined by measuring the 1.5J standard at the beginning (after the calibration) and end of a batch analysis for both the tablets and sprays. With a drift of less than 5% (Figure 4), the methodology easily surpasses the acceptance limit of 20%.

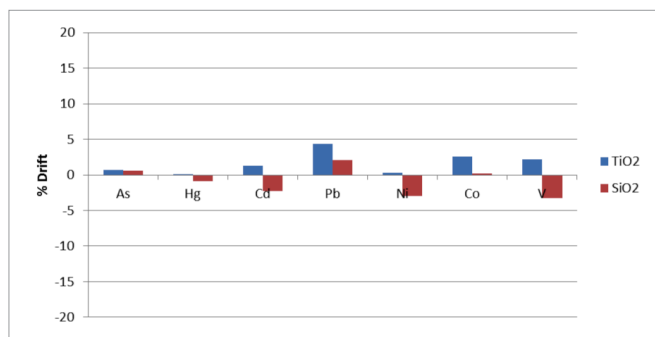


Figure 4. System suitability: drift of a 1.5J standard at the beginning and end of batch analyses of TiO₂- (blue) and SiO₂- (red) containing tablets.

After meeting the suitability criterion, the accuracy of the methodology was assessed. As defined in USP <233>, the accuracy must be evaluated by measuring 0.5J, 1J, and 1.5J analyte spikes, with recoveries being between 70-150%. The spikes were added to the microwave digestion vessels prior to addition of the acids so they were carried through the complete sample preparation procedure to evaluate potential contamination or analyte loss. Figure 5 shows recoveries in both the TiO₂- and SiO₂-containing tablets. With all recoveries within 10% of their true values, the requirement is met.

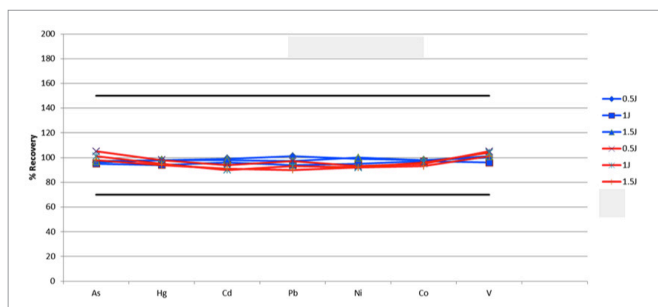


Figure 5. 0.5J, 1J, and 1.5J spike recoveries in TiO_2 - (blue) and SiO_2 - (red) containing medications. Black lines show USP <233> limits.

With the accuracy of the methodology established, the consistency of the sample preparation and measurements was evaluated next by analysis of six tablets of the same medication (for both TiO_2 - and SiO_2 -containing tablets) spiked at the J level prior to digestion. The samples were then analyzed, and the RSDs of the six measurements calculated. With RSDs less than 5% (Figure 6), the methodology easily meets the method criteria of not more than (NMT) 20%.

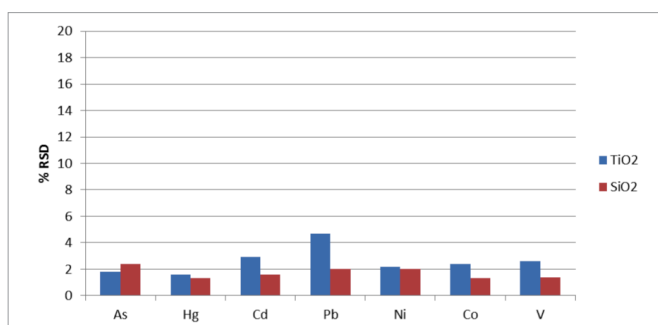


Figure 6. RSDs of six pre-digestion spikes of individual TiO_2 - (blue) and SiO_2 - (red) containing tablets.

The final validation criterion is the ruggedness of the methodology, which was evaluated by measuring the six samples used for the reliability study on different days. With the RSDs for all elements being less than 5% over the 12 samples (as shown in Figure 7), the limit of NMT 25% is easily surpassed.

Conclusion

This work demonstrates the ability of the Avio 200 ICP-OES to meet the USP <232>/<233> criteria for Class 1 and 2A elements in tablets containing TiO_2 or SiO_2 as excipients using Syngistix for ICP Enhanced Security software version 4.0 for 21 CFR Part 11 compliance. Closed-vessel microwave digestion with the Titan MPS prevented analyte loss and resulted in rapid, complete digestions, with the use of minimal acids. Although HF was required during the digestion to completely digest the TiO_2 and SiO_2 , standard sample introduction components could be used since the HF

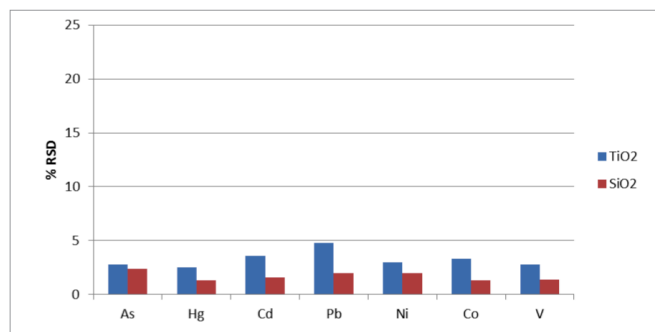


Figure 7. RSDs of six pre-digestion spikes of individual TiO_2 - (blue) and SiO_2 - (red) containing tablets analyzed over two days (12 total measurements).

was complexed post-digestion. The developed methodology demonstrates that both sample types easily meet the USP criteria for system suitability, accuracy, repeatability, and ruggedness.

21 CFR Part 11 compliance is mandatory for pharmaceutical companies and their suppliers to sell products into the United States. Syngistix for ICP Enhanced Security software version 4.0 provides the features necessary that are outlined in 21 CFR Part 11, such as data integrity, electronic signatures and records, and secure audit trails, to keep regulated laboratories' data secure and traceable.

References

1. General Chapter <232> Elemental Impurities – Limits: 2nd Supplement of USP 35-NF 30
2. General Chapter <233> Elemental Impurities – Procedures: 2nd Supplement of USP 35-NF 30
3. "Implementation of USP New Chapters <232> and <233> of Elemental Impurities in Pharmaceutical Products", white paper, PerkinElmer, 2013.
4. "Syngistix for ICP Enhanced Security Software for 21 CFR Part 11 Compliance", product note, PerkinElmer 2018.

Consumables Used

Component	Part Number
Drain Tubing: Red/Red (1.14 mm id) PVC	09908585
Sample Uptake Tubing: Black/Black (0.76 mm id), flared	N0777043
Autosampler Tubes	B0193233 (15 mL) B0193234 (50 mL)
ICH Class 1 Elements + TI – Oral PDE	N9304362
ICH Class 2A Elements – Oral & Parenteral PDEs	N9304363
Pure Grade Yttrium Standard (1000 mg/L)	N9303810 (125 mL) N9300167 (500 mL)