

MATERIALS ANALYSIS

ANALYSIS OF EXTRACTABLE AND LEACHABLE METALS IN PLASTIC MATERIALS OF CONSTRUCTION AS PER USP <661.1> ACID EXTRACTION PROCEDURE USING THE AGILENT 5110 VDV ICP-OES

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ABSTRACT

This solution note highlights a complete solution for the quantitation of trace and toxic extractable and leachable metals in plastic materials of construction, as per the United States Pharmacopeia (USP) <661.1> acid extraction procedure, using Agilent's 5110 Vertical Dual View (VDV) ICP-OES. The ICP-OES demonstrates excellent sensitivity, repeatability & precision, along with good spike and recovery results for all elements at trace levels..

INTRODUCTION

Plastic packaging systems for pharmaceutical use include, but are not limited to bags, bottles, vials, ampoules, cartridges, dry powder and metered dose inhalers, syringes, blisters, pouches and their associated closures and secondary components like labels and printing overpouches. Plastic materials that are commonly used in packaging systems include polyethylene, polypropylene, cyclic olefins, polyethylene terephthalate, polyethylene terephthalate G, and plasticized polyvinyl chloride, among others.

Drug products can chemically interact with their associated packaging systems and/or the system's plastic materials and components of construction while the product is being manufactured, shipped, stored and administered.

As per USP <661.1> the magnitude of these interactions must not be such that the interactions adversely affect the suitability for use of the drug product or the packaging system. Suitability for use includes several quality aspects of the packaged drug product and its performance and directly impact the patient safety. Also as per USP <661.1> the applicant who secures and owns the regulatory approval of a packaging system or packaged drug product is responsible for establishing that the product's packaging system meets these expectations, and thus is suited for its intended use, by ensuring that the packaging system itself and/or the packaged pharmaceutical product has been appropriately tested and that the test results have been appropriately evaluated. The evaluation of packaging products includes several tests such as physicochemical properties, biocompatibility (biological reactivity), chemical testing such as extractable or leachable profiling and toxicological assessment of the test data. This combination of chemical testing and toxicological assessment is termed "chemical safety assessment". Among these evaluations, extractable or leachable trace & toxic metals profiling is of prime importance. Agilent's 5110 VDV ICP-OES is perfect for this, providing a complete end-to-end solution for the analysis of extractable & leachable metals from plastic packaging materials of construction as per USP <661.1>.



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ANALYTICAL TECHNIQUE

Instrumentation:

Analysis was performed using Agilent's 5110 VDV Inductively Coupled Plasma-Optical Emission Spectrometer (ICP-OES). The sample introduction system used was a single-pass glass cyclonic spray chamber, a seaspray nebulizer, white-white peristaltic pump tubing and a standard 1.8 mm injector torch. The hydride forming elements were analyzed using the Multimode Sample Introduction System (MSIS). An SPS 4 Autosampler was used for fast, automated, high throughput analysis. The instrument uses a solid state RF (SSRF) system operating at 27 MHz to deliver robust plasma capable of excellent long term analytical stability. The Agilent 5110 VDV ICP-OES uses the VistaChip II detector. This is a high speed (1MHz) CCD detector that enables fast warmup, high throughput, high sensitivity, has a large dynamic range of up to 8 orders of magnitude and provides full wavelength coverage from 167–785nm from a single entrance slit. The instrument operating conditions used are listed in Table 1.

Parameter	Setting/Value
Read time (s)	5
Replicates	3
Sample uptake delay (s)	15
Stabilization time (s)	10
Rinse time (s)	15
Pump Speed (rpm)	12
Fast pump (rpm)	80
RF power (kW)	1.20
Aux flow (L/min)	1.0
Plasma flow (L/min)	12.0
Nebulizer flow (L/min)	0.7
Background Correction	Fitted

Table 1. Agilent 5110 VDV ICP-OES operating parameters

Sample and Standard Preparation:

The calibration standards for all mentioned elements, irrespective of plastic material of construction as per the USP <661.1> acid extraction procedure, were prepared using multi-element NIST traceable standards. The samples were prepared in triplicate as per the procedure described in USP <661.1>. For this study, High Density Polyethylene (HDPE) material was chosen and prepared as per the USP <661.1> acid extraction procedure for polyethylene. 100g of test material was placed in a borosilicate glass flask with a ground glass neck, 250 mL of 0.1 N hydrochloric acid added and boiled under a reflux condenser for 1 h with constant stirring. After cooling, the solution was then decanted into a 250 mL volumetric flask and diluted with 0.1 N hydrochloric acid to volume. This diluted solution was then used for elemental analysis. The sample preparation technique is depicted in Figure 1.

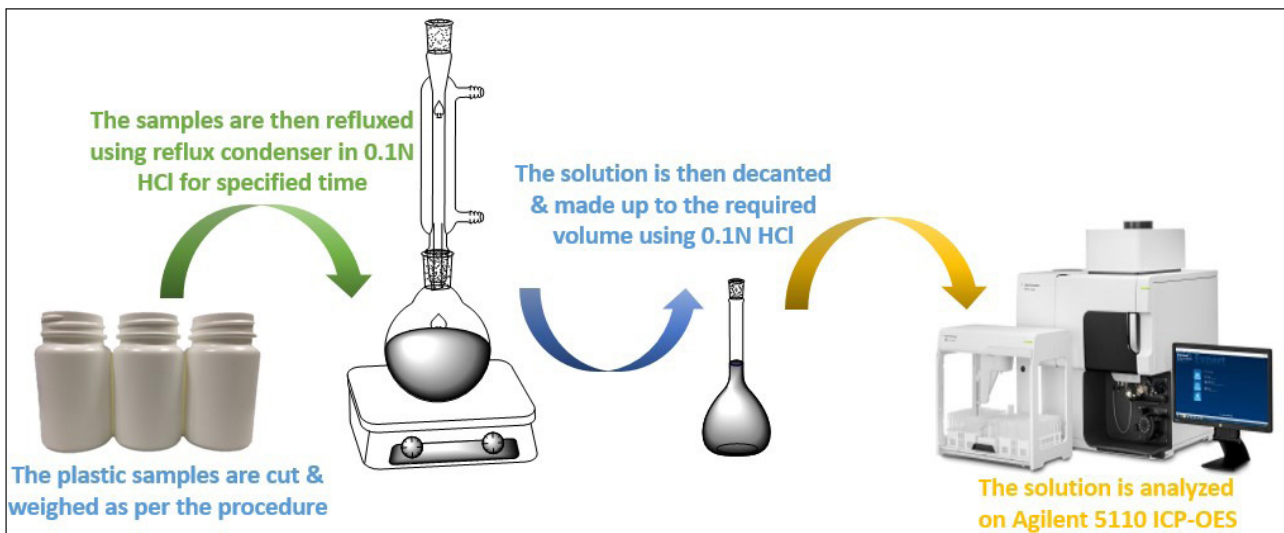


Figure 1. Sample Preparation & Analysis Workflow.

The hydride forming elements As & Hg were analyzed on the Agilent 5110 VDV ICP-OES using the Multimode Sample Introduction System (MSIS). MSIS is a simple plug and play sample introduction system that replaces the existing spray chamber and has the ability to nebulize liquid sample and create volatile hydrides simultaneously. It can be used in one of three modes, as shown in Figure 2.

- A. Liquid Nebulization Only
- B. Hydride Generation Only
- C. Simultaneous Liquid Nebulization and Hydride Generation

For this work, both hydride elements were analyzed using the MSIS but separately from the other elements, after using the appropriate reduction procedure for As (1% KI, followed by 0.3% NaBH₄ and 0.5% NaOH). Black-Black (Agilent catalog # 3710027200) peristaltic pump tubing was used for the sample and reductant, and Black-White (Agilent catalog # 3710068900) for the drain.

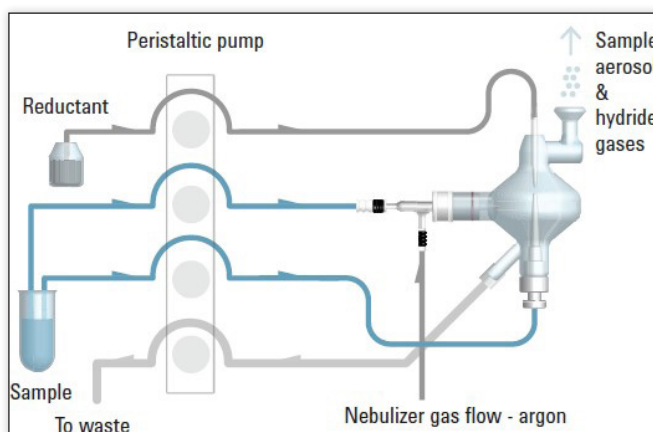


Figure 2. The Multimode Sample Introduction System (MSIS) Operation.

For the other elements, standards were prepared from multi element NIST traceable standards. They were introduced onto the system using the single-pass glass cyclonic spray chamber fitted with the sea-spray nebulizer and analyzed in axial mode on the 5110 VDV ICP-OES.

RESULTS AND DISCUSSION

Calibrations:

Calibration curves for As, Cr, Cd, and Pb are shown in Figure 3.

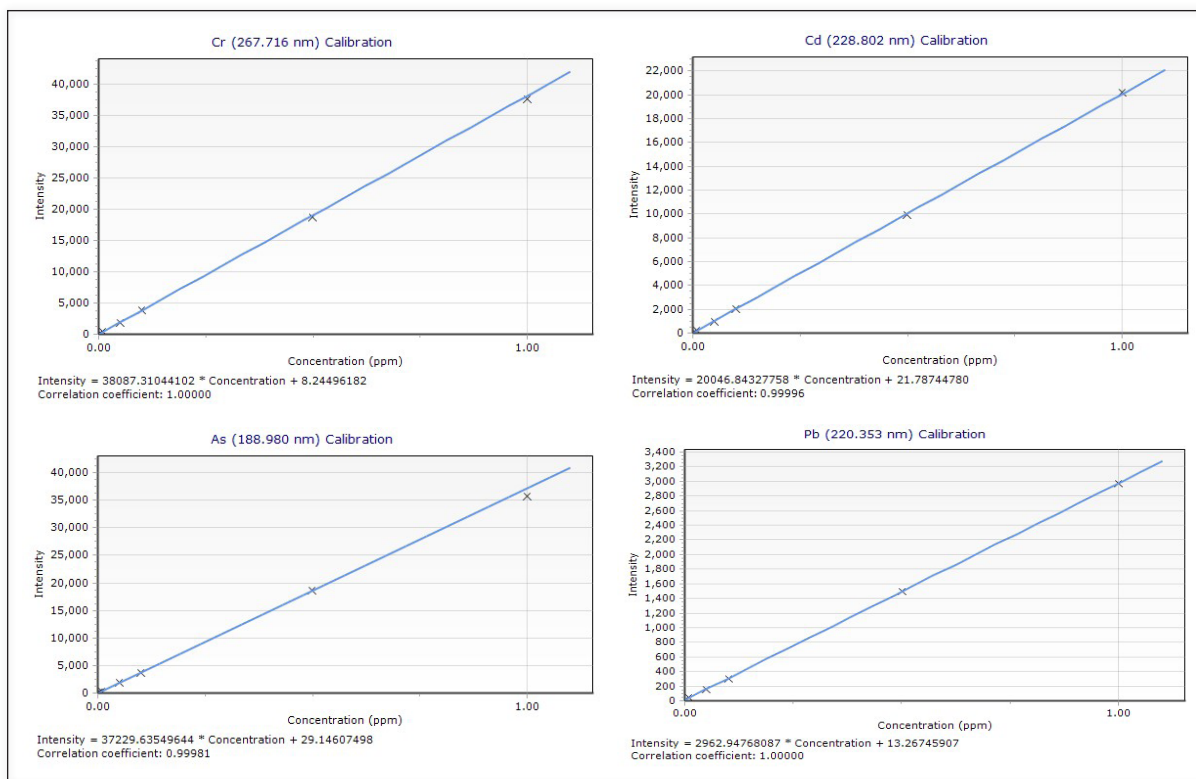


Figure 3. Calibration curves for As, Cr, Cd and Pb.

Element	Wavelength (nm)	Element ($\mu\text{g/L}$)
Aluminum	396.152 nm	0.9
Arsenic*	188.980 nm	0.5
Cadmium	228.802 nm	0.3
Chromium	267.716 nm	0.3
Cobalt	238.892 nm	0.4
Lead	220.353 nm	1.5
Mercury*	194.164 nm	0.2
Nickel	231.604 nm	1.4
Titanium	336.122 nm	0.4
Vanadium	292.401 nm	0.3
Zinc	213.857 nm	0.9
Zirconium	343.823 nm	0.2
<i>Barium</i>	455.403 nm	0.3
<i>Calcium</i>	422.673 nm	4.0
<i>Manganese</i>	257.610 nm	0.1
<i>Tin</i>	189.925 nm	2.1

Table 2. Method Detection limits ($\mu\text{g/L}$)

Method Detection Limits (MDL):

The Method Detection Limits (MDL) for each element are shown in Table 2. Method detection limits (MDLs) were established by analyzing ten replicate injections of the calibration blank and multiplying the obtained standard deviation by three.

* Using MSIS

Italic, elements not required for High Density Polyethylene as per USP <661.1>

Analysis of Real Samples & Spiked Samples:

The accuracy and precision of the method were assessed by analyzing the spike & recovery studies at two different levels in the samples.

Samples of HDPE were analyzed, (Table 3), these samples were also spiked with known concentrations: 25 µg/L (Level 1) and 50 µg/L (Level 2) for all elements [except Ca which was spiked with 250 µg/L (Level 1) and 500 µg/L (Level 2)]. The percentage recoveries were calculated and are shown in Table 4. Excellent recoveries of between 95-110% were obtained for all elements, demonstrating good method repeatability and capability using the Agilent 5110 VDV ICP-OES.

Element	Wavelength (nm)	Average (mg/L)	Limit NMT** (mg/L)	Corresponding to
Aluminum	396.152 nm	0.09	0.4	1.00 (µg/g)
Arsenic	188.980 nm	ND*	0.01	0.025 (µg/g)
Cadmium	228.802 nm	ND*	0.01	0.025 (µg/g)
Chromium	267.716 nm	0.01	0.02	0.050 (µg/g)
Cobalt	238.892 nm	ND*	0.01	0.025 (µg/g)
Lead	220.353 nm	ND*	0.01	0.025 (µg/g)
Mercury	194.164 nm	ND*	0.01	0.025 (µg/g)
Nickel	231.604 nm	0.01	0.01	0.025 (µg/g)
Titanium	336.122 nm	ND*	0.4	1.00 (µg/g)
Vanadium	292.401 nm	ND*	0.04	0.100 (µg/g)
Zinc	213.857 nm	0.11	0.4	1.00 (µg/g)
Zirconium	343.823 nm	ND*	0.04	1.00 (µg/g)
Barium	455.403 nm	ND*	0.25	5.00 (µg/g)
Manganese	257.610 nm	ND*	0.4	1.00 (µg/g)
Calcium	422.673 nm	0.68	35	0.070 (Wt. %)
Tin	189.925 nm	ND*	1	20.00 (µg/g)

Table 3. Real Sample Results & Limits as per USP <661.1>

ND*: Not Detected

NMT: Not More Than, as per definition of USP 34, General notices

Element	Spike Level 1		Spike Level 2	
	(n=3)			
	% Average Recovery	% RSD	% Average Recovery	% RSD
Aluminum	97.1	0.43	98.4	0.37
Arsenic	105.3	1.79	108.0	2.31
Cadmium	108.7	1.70	103.6	0.85
Chromium	102.7	1.22	101.0	1.48
Cobalt	109.3	1.72	108.0	0.87
Lead	102.7	1.79	106.2	0.88
Mercury	104.0	3.14	106.5	0.89
Nickel	102.2	1.63	100.6	0.63
Titanium	104.3	0.83	108.5	0.43
Vanadium	109.3	1.72	103.5	2.58
Zinc	99.1	0.78	101.4	0.35
Zirconium	106.7	1.77	104.5	1.80
Barium	109.7	1.49	109.5	0.80
Manganese	102.4	0.58	103.5	0.32
Calcium	106.0	1.22	104.2	0.96
Tin	102.7	1.84	104.0	1.81

Table 4. Spike & Recovery Results (%)

CONCLUSIONS

The Agilent 5110 VDV ICP-OES with vertical torch feature provides the sensitivity benefits of axial plasma with the robust qualities of radial plasma, along with greater precision, faster analysis times and reduced argon gas consumption. For extractable and leachable trace & toxic metals, as per USP <661.1> acid extraction procedure, Agilent's 5110 VDV ICP-OES in combination with the MSIS, offers a complete solution with good repeatability, precision & recovery. It demonstrates excellent method detection limits, along with good spike and recovery results at trace levels with %RSDs of less than 5%.

REFERENCES

1. USP <661.1>, Plastic Materials of Construction, Official from May 1, 2016.
2. USP <661.2>, Plastic Packaging Systems for Pharmaceutical Use, Official from May 1, 2016.
3. USP <1663>, Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems.
4. USP 34, General Notices and Requirements, Applying to Standards, Tests, Assays and Other Specifications of the United States Pharmacopeia, Official from May 1, 2011.



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