Application Note
Pharmaceuticals

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Analysis of Extractable and Leachable Metals in Plastic Materials used for Drug Products by ICP-OES

Elemental analysis of High Density Polyethylene in accordance with USP <661.1>

Authors

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Verified for Agilent
5800 and 5900 ICP-OES

Introduction

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

Drug products can interact chemically with the packaging system while the product is being manufactured, shipped, stored, and administered. According to United States Pharmacopeia (USP) 39 National Formulary (NF) 34 General Chapters <661.1> and <661.2>, the magnitude of these interactions must not adversely affect the safety of the drug product or the suitability of the packaging system (*1, 2*). Although these two chapters will not be official until December 1, 2025, early adoption of the requirements is permitted by USP. When early adoption is not used, Plastic Packaging Systems and Their Materials of Construction <661> apply (*3*).

The applicant who secures and owns the regulatory approval of a packaging system or packaged drug product is responsible for establishing that the packaging system meets all requirements. To show that any packaging is suitable for its intended use, the packaging system itself and/or the packaged pharmaceutical product must be tested, and the results evaluated. The evaluation of packaging products includes several tests such as physicochemical properties, biocompatibility (biological reactivity), chemical testing, such as extractable or leachable (E&L) profiling, and toxicological assessment of the data. The combination of chemical testing and toxicological assessment is termed "chemical safety assessment". Among the evaluations, profiling of extractable or leachable metals is of prime importance, especially metals that are of potentially harmful such as arsenic, cadmium, mercury, and lead.

In this study, an Agilent 5110 Vertical Dual View (VDV) ICP OES was used for the analysis of extractable metals from plastic packaging materials in accordance with USP <661.1>. USP <661.1> relates to the analysis of the polymers that compose packaging materials and USP <661.2> relates to the whole packaging system (*1, 2*).

Experimental

Standard and sample preparation

The calibration standards for all elements were prepared using multi-element NIST traceable standards. High Density Polyethylene (HDPE) samples were prepared in triplicate following acid extraction procedure described in USP <661.1> for polyethylene (*1*). 100 g of test material was placed in a borosilicate glass flask with a ground glass neck and 250 mL of 0.1 N hydrochloric acid was added. The mixture was boiled using a reflux condenser for 1 h with constant stirring. After cooling, the solution was decanted into a 250 mL volumetric flask and diluted with 0.1 N hydrochloric acid to volume. The diluted solution was then used for elemental analysis by ICP-OES. The spiked samples were prepared at two different levels, 0.025 mg/L (Level 1) and 0.050 µg/L (Level 2), except Ca, which was spiked at 0.250 mg/L (Level 1) and 0.500 mg/L (Level 2). The sample preparation technique is shown in Figure 1.

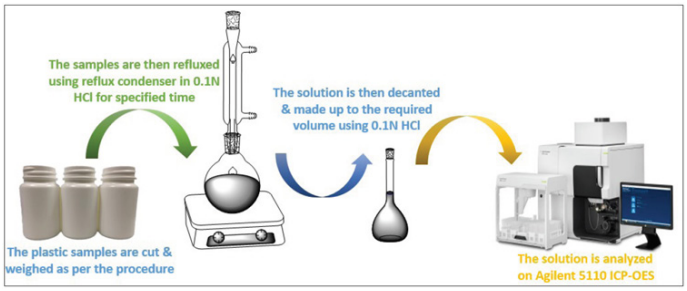

Figure 1. Sample preparation of HDPE samples for analysis of extractable metals by ICP-OES.

Instrumentation

This work was performed using the 5110 VDV ICP-OES, but the method is also compatible with the Agilent 5800 VDV or Agilent 5900 SVDV ICP-OES. The sample introduction system included 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 Agilent Multimode Sample Introduction System (MSIS). An Agilent SPS 4 Autosampler was used for fast, automated, high throughput analysis. The ICP-OES uses a solid-state RF (SSRF) system operating at 27 MHz to deliver a robust plasma capable of excellent long-term analytical stability. The 5110 VDV ICP-OES uses the Vista Chip II detector, while the 5800 and 5900 are fitted with an even faster VistaChip III detector. The detectors are high speed (1 MHz) CCD devices that enable fast warmup, high throughput, and high sensitivity. They also have a large dynamic range of up to eight orders of magnitude and provide full wavelength coverage from 167–785 nm from a single entrance slit. Instrument operating conditions are listed in Table 1 and Table 2.

Table 1. ICP-OES operating parameters.

Parameter	Setting
Read Time (s)	5
Replicates	3
Viewing Mode	Axial
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

The hydride forming elements, As and Hg, were analyzed by ICP-OES using the MSIS, which is a simple plug and play sample introduction system that replaces the existing spray chamber. MSIS nebulizes liquid samples and creates volatile hydrides, as shown in Figure 2.

Table 2. ICP-OES using MSIS operating parameter.

Parameter	Setting
Read Time (s)	5
Replicates	3
Viewing Mode	Axial
Sample Uptake Delay (s)	25
Stabilization Time (s)	20
Rinse Time (s)	15
Pump Speed (rpm)	12
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

For this work, both hydride elements were analyzed separately from the other elements, for Hg samples & standards were prepared in 10% HCl and analyzed using 0.3% $NaBH_4$ and 0.5% NaOH, while for As samples & standards were prepared in 5% HCl after using the appropriate reduction procedure (1% KI) followed by analysis using 0.3% $NaBH_4$ 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.

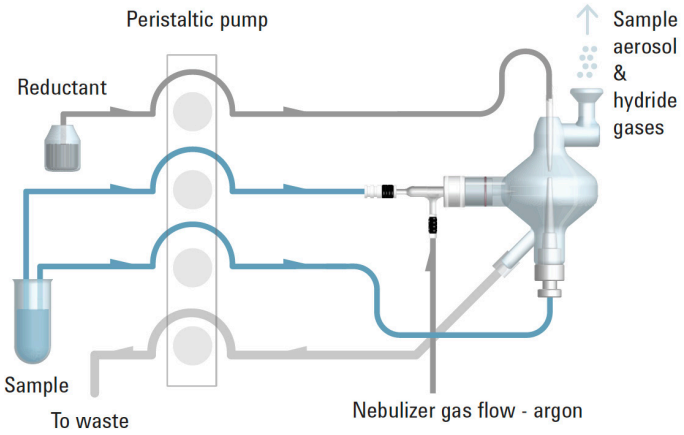

Figure 2. Multimode Sample Introduction System (MSIS) operation.

Calibration

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

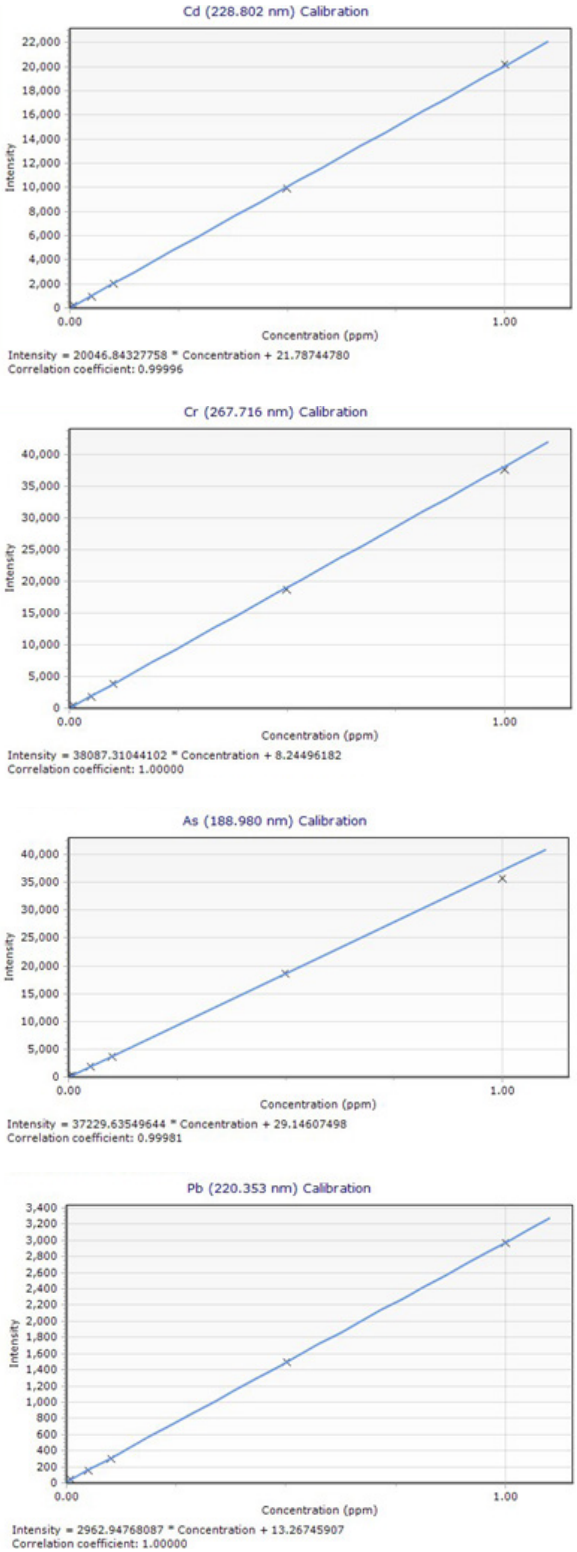

Figure 3. Calibration curves for Cd, Cr, As, and Pb, showing excellent linearity (R > 0.999) across the calibration range.

Results and discussion

Method Detection Limits (MDL)

The Method Detection Limits (MDL) for each element are shown in Table 2. The MDLs were calculated by analyzing 10 replicates of the calibration blank and multiplying the standard deviation by three. The USP <661.1> method for HDPE doesn't require the measurement of Ba, Mn, Ca, and Sn, so the MDLs are included for information only.

Analysis of HDPE samples

Each of the three replicate digests of the HDPE sample was analyzed by ICP-OES and the average of the measured concentrations is given in Table 3. None of the measured elements exceeded the Not More Than (NMT) concentration limits specified in the USP 39-NF 34 661.1 General Chapter (*1*).

Table 3. Method detection limits, quantitative results for HDPE samples, and not more than (NMT) limits, per USP 39-NF 34 <661.1>.

Element	Wavelength (nm)	MDL (µg/mL)	Average Concentration (mg/L)	Limit NMT (mg/L)
Aluminum	396.152	0.9	0.09	0.4
Arsenic*	188.980	0.5	<MDL	0.01
Cadmium	228.802	0.3	<MDL	0.01
Chromium	267.716	0.3	0.01	0.02
Cobalt	238.892	0.4	<MDL	0.01
Lead	220.353	1.5	<MDL	0.01
Mercury*	194.164	0.2	<MDL	0.01
Nickel	231.604	1.4	0.01	0.01
Titanium	336.122	0.4	<MDL	0.4
Vanadium	292.401	0.3	<MDL	0.04
Zinc	213.857	0.9	0.11	0.4
Zirconium	343.823	0.2	<MDL	0.04
Barium	455.403	0.3	<MDL	0.25
Manganese	257.610	0.1	<MDL	0.4
Calcium	422.673	4.0	0.68	35
Tin	189.925	2.1	<MDL	1

**Using MSIS. NMT: Not More Than limits and corresponding concentration per USP 39-NF 34, 666.1*

Spike recoveries

The accuracy and precision of the method were assessed by analyzing the HDPE samples spiked at two different concentration levels. The percentage recoveries of the spiked HDPE samples are shown in Tables 4 and 5.

Excellent recoveries of between 95–110% were obtained for all elements, with RSDs below 3.5%. The results demonstrate the suitability of the 5110 VDV ICP-OES for the measurement of elemental impurities in plastic packaging materials.

Table 4. HDPE sample spike recovery results (Level 1 spike).

Element	Wavelength (nm)	Sample Concentration (mg/L)	Spiked Concentration (mg/L)	Measured Spiked Concentration (mg/L)	% Recovery	% RSD
Aluminum	396.152	0.09	0.025	0.11	97	0.4
Arsenic*	188.980	<MDL	0.025	0.026	105	1.8
Cadmium	228.802	<MDL	0.025	0.027	109	1.7
Chromium	267.716	0.01	0.025	0.036	103	1.2
Cobalt	238.892	<MDL	0.025	0.027	109	1.7
Lead	220.353	<MDL	0.025	0.026	103	1.8
Mercury*	194.164	<MDL	0.025	0.026	104	3.1
Nickel	231.604	0.01	0.025	0.036	102	1.6
Titanium	336.122	<MDL	0.025	0.026	104	0.8
Vanadium	292.401	<MDL	0.025	0.027	109	1.7
Zinc	213.857	0.11	0.025	0.14	99	0.8
Zirconium	343.823	<MDL	0.025	0.027	107	1.8
Barium	455.403	<MDL	0.025	0.027	110	1.5
Manganese	257.610	<MDL	0.025	0.026	102	0.6
Calcium	422.673	0.68	0.250	0.95	106	1.2
Tin	189.925	<MDL	0.025	0.026	103	1.8

** Using MSIS.*

Table 5. HDPE sample spike recovery results (Level 2 spike).

Element	Wavelength (nm)	Sample Concentration (mg/L)	Spiked Concentration (mg/L)	Measured Spiked Concentration (mg/L)	% Recovery	% RSD
Aluminum	396.152	0.09	0.05	0.14	98	0.4
Arsenic*	188.980	<MDL	0.05	0.05	108	2.3
Cadmium	228.802	<MDL	0.05	0.052	104	0.9
Chromium	267.716	0.01	0.05	0.061	101	1.5
Cobalt	238.892	<MDL	0.05	0.054	108	0.9
Lead	220.353	<MDL	0.05	0.053	106	0.9
Mercury*	194.164	<MDL	0.05	0.053	107	0.9
Nickel	231.604	0.01	0.05	0.060	101	0.6
Titanium	336.122	<MDL	0.05	0.054	109	0.4
Vanadium	292.401	<MDL	0.05	0.052	104	2.6
Zinc	213.857	0.11	0.05	0.16	101	0.4
Zirconium	343.823	<MDL	0.05	0.052	105	1.8
Barium	455.403	<MDL	0.05	0.055	110	0.8
Manganese	257.610	<MDL	0.05	0.052	104	0.3
Calcium	422.673	0.68	0.5	1.20	104	1.0
Tin	189.925	<MDL	0.05	0.052	104	1.8

** Using MSIS.*

Conclusion

The Agilent 5110 VDV ICP-OES with vertical torch provides the sensitivity benefits of an axial plasma and the fast analysis times needed for the cost-effective analysis of pharmaceutical samples. The method is also compatible with the Agilent 5800 VDV or Agilent 5900 SVDV ICP-OES.

The study has demonstrated the sensitivity, accuracy, and precision of the ICP-OES method for the determination of trace elements in HDPE. The ICP-OES was fitted with an Agilent Multimode Sample Introduction System (MSIS) for the analysis of hydride forming elements, As and Hg. The samples were prepared using an acid extraction procedure specified in USP <661.1>. The MDLs were significantly lower than the 'not more than' limits given in USP 39-NF 34 <661.1>. Also, recoveries of all elements spiked at trace levels in HDPE samples were within 97–110%, with RSDs ranging from 0.3 to 3.1%.

Agilent ICP-OES instruments with MSIS offer a complete solution for the quantitation of trace and ultra-trace E&L metals in materials used in the construction of drug packaging systems.

References

1. USP 39-NF 34 <661.1>, Plastic Materials of Construction, May 1, 2016, 496–506
2. USP 39-NF 34 <661.2>, Plastic Packaging Systems for Pharmaceutical Use, May 1, 2016, 506
3. USP Revision Bulletin, Plastic Materials of Construction, March 2021, accessed September 2021, https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/revisions/gc-661-1-rb-notice-20210226.pdf

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Printed in the USA, October 7, 2021
5994-4199EN

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