

Application News

Inductively Coupled Plasma Mass Spectrometer ICPMS-2040/2050 Series

Extractable and Leachable Study of Pharmaceutical Packaging Material used to Store Penicillin-V Using ICPMS-2050

Saroj Mataprasad, Amol Ramishte, Hemant Kesarkar, Prashant Hase, Pratap Rasam, Jitendra Kelkar
Shimadzu India Pvt. Ltd.

User Benefits

- ◆ Simultaneous qualitative scanning feature benefits to user in identification of non-targeted elements, supporting the creation of a comprehensive extractable profile.
- ◆ Proprietary Mini-Torch technology enables stable plasma with higher sensitivity and lower gas consumption (11 L/min).
- ◆ LabSolutions™ ICPMS ensures compliance with regulatory norms in spectroscopy products, streamlining data management.

■ Introduction

Extractable and leachable (E & L) studies are becoming increasingly important in the pharmaceutical industry as it is a mandatory requirement from the FDA during filing of the drug product. The purpose of E & L studies is to identify and evaluate possible toxicological risks. In this, the regulatory references aim to identify traces of potential chemical substances. These substances may be harmful to patients due to their toxicity or may impact the activity of the drug product. Hence, to ensure the safety and efficacy of the drug throughout its shelf-life, E & L studies play an important role. Impact of Extractables on efficacy and safety of the drug product is presented in Figure 1.

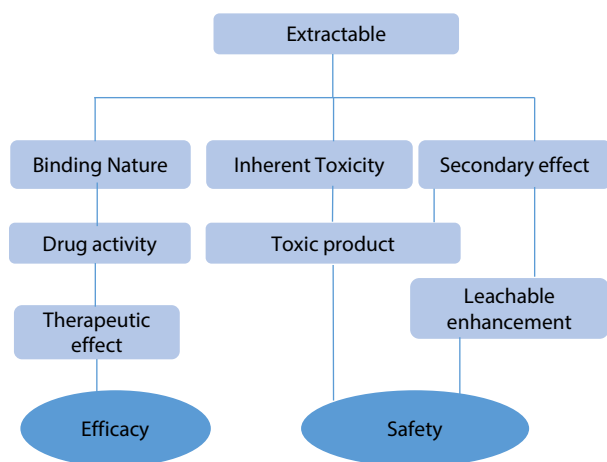


Figure 1: Impact of extractables

What are Extractables and Leachables ?

Extractables are organic and inorganic chemical entities that are released from a pharmaceutical packaging/delivery system, packaging component, or packaging material of construction into an extraction solvent under laboratory conditions^[1].

Leachables are foreign organic and inorganic chemical entities that are present in a packaged drug product because they have leached into the packaged drug product from a packaging/delivery system, packaging component, or packaging material of construction under normal conditions of storage and use or during accelerated drug product stability studies^[1]. The hypothetical relationship between E & L and Drug Degradation products is shown in Figure 2.

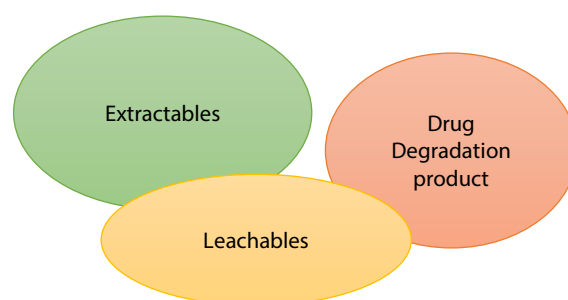


Figure 2 : Relation between E & L and Drug Degradation products.

Sources of extractables

Extractables are derived from a variety of sources and exhibit extensive chemical diversity. Few of the primary sources are listed below.

- Chemical additives in individual polymeric packaging material.
- Chemical entities that are present in the packaging components.
- Monomers and higher molecular mass oligomers derived from incomplete polymerization.
- Migrants from secondary and tertiary packaging materials such as inks, label adhesives etc.
- Surface residues on metal canisters and containers.
- Chemical substances on the surface of components fabrication machinery such as anti-static and anti-slip agents.

Calculation of AET

Safety Concern Threshold (SCT) for elemental/inorganic impurities is not available in any of the regulatory references. Hence, for evaluation purpose, the Analytical Evaluation Threshold (AET) is derived using Permitted Daily Exposure (PDE) values for oral drug product available in ICH Q3D guideline.

$$\text{AET } (\mu\text{g/g}) = \frac{\text{PDE } (\mu\text{g/day})}{\text{Maximum Daily dose (g/day)}}$$

For demonstration purpose AET's for Class 1 elements were calculated using the formula stated above and tabulated in the below Table 1. Similarly, AET's for all other elements were calculated and used for further evaluation.

Table 1. AET Calculation details

Elements	As	Cd	Hg	Pb
Oral PDE (µg/day)	15	5	30	5
AET as per option-1 (µg/mL)	1.5	0.5	3.0	0.5

Note: Daily dose is as per option-1 i.e. 10 g

■ Typical Images of CCP

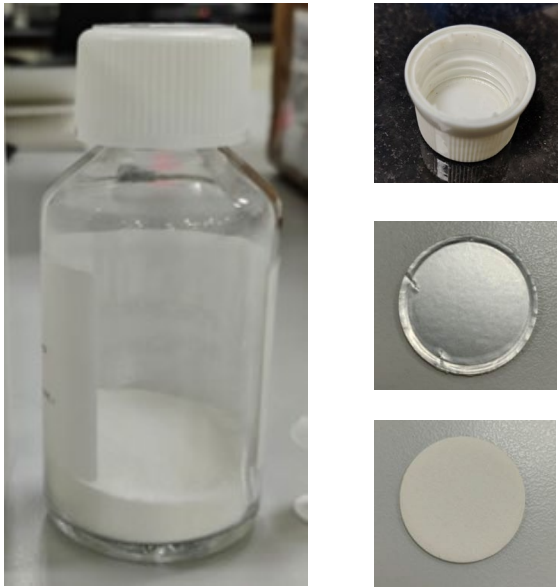


Figure 3 : Typical Images of Container Closure Pack (CCP)

■ Experimental Design

Various methodologies exist for designing extractable studies, including solvent-mediated maceration, reflux, soxhlet extraction, and sonication, as well as microwave acid digestion. The physical and chemical properties of the sample such as the polarity, pH, and chemical components of the drug product must be considered when designing the extraction experiment. Typically, extractable studies are performed under accelerated temperature conditions to represent the worst-case scenario for drug product storage.

In this study, we conducted an extractable analysis using various acids and by refluxing CCPs at variable temperatures. Empty CCPs intended for Penicillin-V storage were sourced from a local supplier. Using these CCPs, multiple experiments were performed, and the resulting data were evaluated to identify potential extractables. Figure 3 depicts a typical image of CCP.

To evaluate the potential extractables, two specific experimental designs were utilized Experiment-A and Experiment-B, in which the CCPs were incubated in nitric acid and hydrochloric acid, respectively. Details for both experiments are provided below.

Experiment-A

In this experiment CCP was filled with 100 mL of 5 % (v/v) nitric acid solution prepared in Type-I water, sealed with cap, and placed in an inverted orientation within a thermostatically controlled oven at 85°C for 72 hours. The mixture was homogenized and subjected to ultrasonication for 10 minutes.

Experiment-B

The experiment-B was executed in a similar way as mentioned under experiment-A, except incubation medium. i.e. instead of 5 % nitric acid solution, 5 % hydrochloric acid was selected for incubation.

To ensure exhaustive extraction, the vessel was subjected to intermittent manual agitation. Following the incubation period, all CCPs were removed and kept at ambient temperature. The resulting extract was transferred into separate ICP-MS grade volumetric flasks for subsequent analysis (Figure 4).

These extracts from Experiments A and B were directly infused into the ICP-MS using QualAll mode (qualitative scanning). Based on the findings from the qualitative scan, any elements detected beyond the 24 elements classified in ICH Q3D were additionally quantified using QuanAll mode (Analysis).

After evaluating the extractable profile of the CCP, potential extractable elements including those classified in ICH Q3D were analyzed as Leachables within the drug product. For the drug product analysis, sample preparation was performed via microwave acid digestion. Experimental design is shown in Figure 5.



Figure 4 : Shimadzu ICPMS-2050 with AS-20s System

■ Analytical Conditions

Instrument	: ICPMS-2050 with AS-20s
RF Power	: 1.2 kW
Sampling depth	: 5 mm
Plasma gas	: 9.0 L/min
Auxiliary gas	: 1.1 L/min
Carrier gas	: 0.85 L/min
Chamber temp.	: 5 °C
Plasma Torch	: Mini torch
Pump Speed	: 20 rpm
Cell Gas	: He
Total Flow	: 6 mL/min
Sample introduction	: Aqueous kit
Acq. Mode	: QualAll & QuanAll

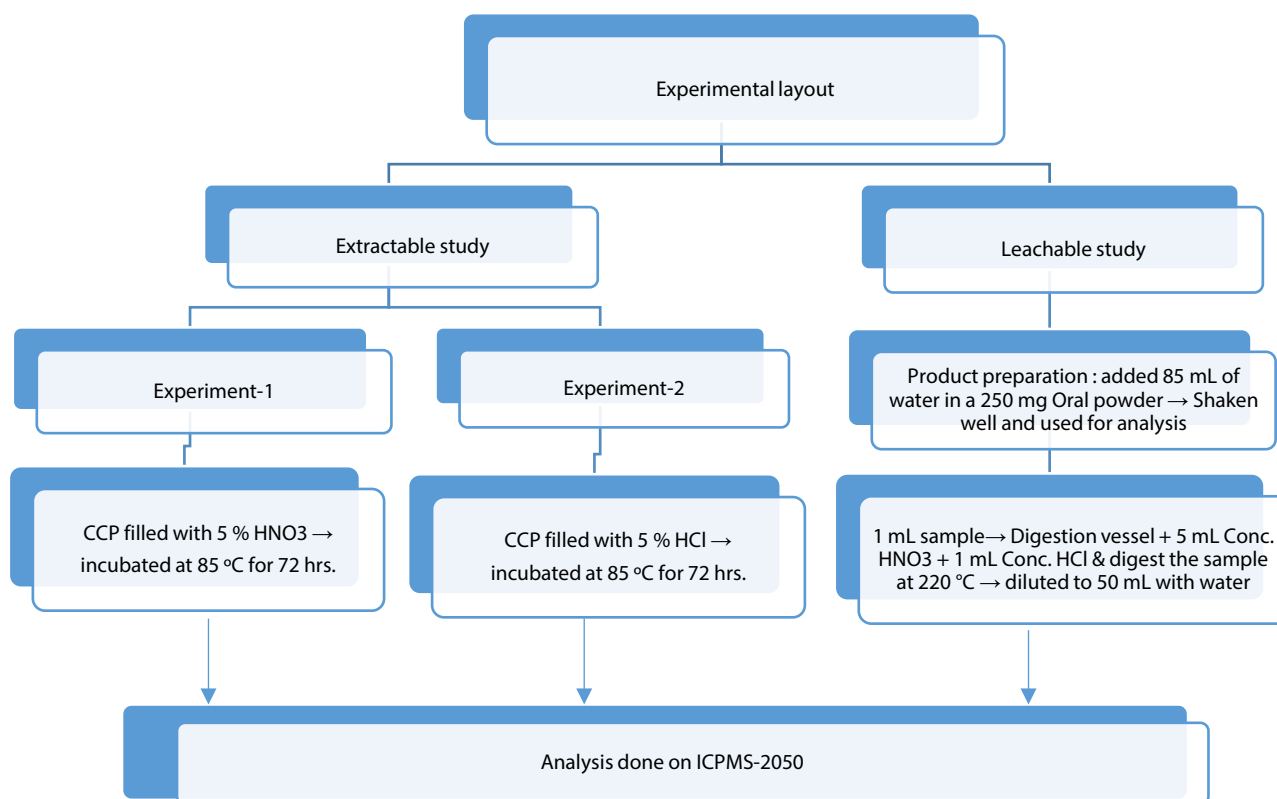


Figure 5 : Detailed layout of the experimental design for sample preparation

■ Extractables Study

Qualitative study for non-targeted elements

Samples collected from both Experiment A and B were analyzed by using the specialized 'QualAll' feature, which enables the user to obtain a complete profile for non-targeted elements. Only those elements exhibiting a signal intensity at tenfold (10X) greater than the intensity in the blank, were included in the 'QuanAll' analysis. Table 2 depicts the results of qualitative acquisition for extractable study in µg/L.

Quantification of targeted elements

Quantification study was conducted in accordance with ICH Q3D guidelines for 24 classified elements. Additionally, 8 elements identified during the qualitative study for non-targeted elements were also used for assessment.

Standard preparation

AET for the classified elements was calculated as stated under AET calculation section. For elements other than ICH Q3D classification AET was targeted based on best possible quantitation level on instrument. The concentration limits were then calculated using the AET formula, as given in Table-1. Seven individual calibration linearity levels were prepared, covering a range of 0.05X to 1.5X of working concentration (J). Two Quality Control (QC) solutions were prepared at the 0.5J level, along with a blank solution. Continuing Calibration Verification (CCV) preparations and analyses were done using the ICPMS-2050 instrument with an AS-20s auto-sampler. All preparations were done by using 5% nitric acid diluent.

Internal standard preparation:

The internal standard solution containing 10 ng/mL of Sc, Ge, Y, In, Ce and Bi was added continuously during the analysis with the help of on-line internal standard kit.

The ratio between sample and internal standard was maintained at approximately 9:1.

■ Results of Extractable Study

From QualAll analysis eight elements (Al, B, Ca, Fe, K, Mg, Na and Si) were identified based on their response in blank and sample solution. Table 3 shows the results for extractable study quantitative acquisition in (µg/L)

System suitability was evaluated by linearity, Continuing Calibration Verification (CCV) and LOQ precision. All the elements comply the correlation coefficient (R) criteria of not less than 0.995. The % RSD of intensity in six replicates of LOQ standard as well as CCV injections throughout the analysis were found to be below 10%. Figure 6 depicts calibration curves of representative elements.

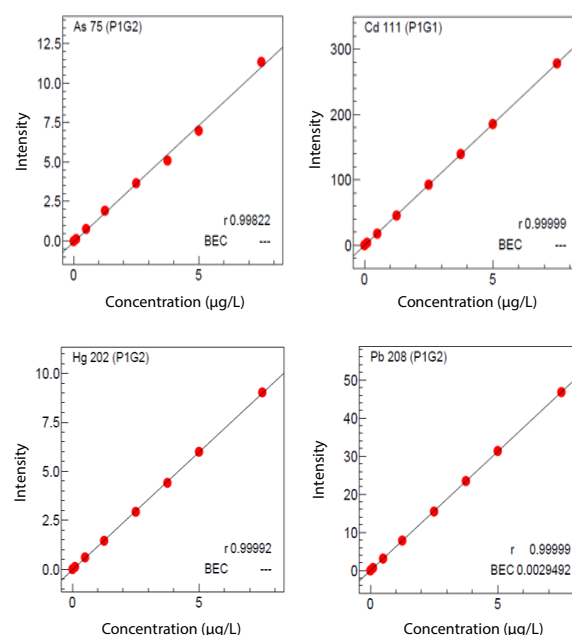


Figure 6 : Calibration curves for As, Cd, Hg, and Pb

Table 2. Results of Qualitative Acquisition for Extractable Study in µg/L

Sr. No.	Element	Expt-A BLK	Expt-A SPL	Expt-B BLK	Expt-B SPL
1	Ag	< 0.033	< 0.033	< 0.033	< 0.033
2	Al	(0.52) +	72 +	< 0.024	50 +
3	As	< 0.960	< 0.960	< 0.960	< 0.960
4	Au	< 0.016	< 0.016	< 0.016	-0.030
5	B	26.00	24.00	-0.730	13.00
6	Ba	< 0.038	(3.2) +	< 0.038	(2.7) +
7	Be	< 0.058	< 0.058	< 0.058	< 0.058
8	Bi	< 0.005	< 0.005	< 0.005	-0.005
9	Br	< 15	< 15	< 15	(120) +
10	Ca	< 160	(870) +	< 160	(620) +
11	Cd	< 0.079	< 0.079	< 0.079	< 0.079
12	Ce	< 0.011	-0.013	< 0.011	-0.016
13	Co	< 0.043	-0.056	< 0.043	-0.082
14	Cr	< 0.160	-1.500	< 0.160	-1.000
15	Cs	< 0.068	< 0.068	< 0.068	< 0.068
16	Cu	< 0.062	-0.270	< 0.062	-0.330
17	Dy	< 0.026	< 0.026	< 0.026	< 0.026
18	Er	< 0.019	< 0.019	< 0.019	< 0.019
19	Eu	< 0.020	< 0.020	< 0.020	< 0.020
20	Fe	-0.420	21 +	-0.520	(14) +
21	Ga	< 0.430	< 0.540	< 0.430	< 0.540
22	Gd	< 0.022	< 0.022	< 0.022	< 0.022
23	Ge	< 0.490	< 0.490	< 0.490	< 0.490
24	Hf	< 0.014	< 0.014	< 0.014	< 0.014
25	Hg	< 0.062	< 0.062	< 0.062	< 0.062
26	Ho	< 0.006	< 0.006	< 0.006	< 0.006
27	In	< 0.058	< 0.058	< 0.058	< 0.058
28	Ir	< 0.008	< 0.008	< 0.008	< 0.008
29	K	(100) +	(110) +	560 +	(140) +
30	La	< 0.016	< 0.016	< 0.016	< 0.016
31	Li	19.00	18.00	22.00	23.00
32	Lu	< 0.009	< 0.009	< 0.009	< 0.009
33	Mg	(0.30) +	190 +	< 0.019	120 +
34	Mn	< 0.290	(0.48) +	< 0.290	(0.63) +
35	Zn	< 0.500	< 0.510	< 0.500	(2.1) +
36	Zr	< 0.086	-0.400	< 0.086	-0.170
37	Mo	< 0.090	< 0.090	< 0.090	< 0.090
38	Na	5.2 +	2900 +	6.4 +	2400 +
39	Nb	< 0.046	< 0.046	< 0.046	< 0.046
40	Nd	< 0.051	< 0.051	< 0.051	< 0.051
41	Ni	< 0.430	(0.56) +	< 0.430	< 0.590
42	Os	< 0.014	< 0.014	< 0.014	< 0.014
43	P	< 180.0	< 180.0	< 180.0	< 180.0
44	Pb	-0.007	-0.058	< 0.007	-0.059
45	Pd	< 0.067	< 0.067	< 0.067	< 0.067
46	Pr	< 0.013	< 0.013	< 0.013	< 0.013
47	Pt	< 0.024	< 0.024	< 0.024	< 0.024
48	Rb	< 0.380	< 0.380	< 0.380	< 0.380
49	Re	< 0.005	< 0.005	< 0.005	< 0.005
50	Rh	< 0.011	< 0.011	< 0.011	< 0.011
51	Ru	< 0.059	< 0.059	< 0.059	< 0.059
52	S	< 990	< 990	< 990	< 990
53	Sb	< 0.220	< 0.220	< 0.220	< 0.220
54	Sc	< 0.880	< 0.880	< 0.880	< 0.880
55	Se	< 20.00	< 20.00	< 20.00	< 20.00
56	Si	< 120	(940) +	(270) +	(600) +
57	Sm	< 0.045	< 0.045	< 0.045	< 0.045
58	Sn	< 0.180	< 0.180	< 0.180	< 0.180
59	Sr	< 0.350	-0.610	< 0.350	< 0.350
60	Ta	< 0.005	< 0.005	< 0.005	< 0.005
61	Tb	< 0.007	< 0.007	< 0.007	< 0.007
62	Te	< 1.00	< 1.00	< 1.00	< 1.00
63	Th	< 0.003	-0.003	< 0.003	-0.003
64	Ti	< 1.2	< 3.8 +	< 1.2	< 3.0 +
65	Tl	< 0.005	< 0.005	< 0.005	< 0.005
66	Tm	< 0.005	< 0.005	< 0.005	< 0.005
67	U	< 0.003	< 0.003	< 0.003	-0.003
68	V	< 0.160	< 0.160	< 0.160	-0.170
69	W	< 0.027	< 0.027	< 0.027	< 0.027
70	Y	< 0.100	< 0.100	< 0.100	< 0.100
71	Yb	< 0.015	< 0.015	< 0.015	< 0.015

***Note:** Elements highlighted in green colour (Al, B, Ca, Fe, K, Mg, Na and Si) were detected w.r.t diluent response in qualitative mode. These elements were included in the analysis mode along with ICH Q3D elements during E & L study.

Table 3. Results for Extractable Study Acquisition in µg/L

Sr. No.	Element	Mass	J (µg/L)	R	LOQ (µg/L)	LOQ* Precision RSD (%)	CCV* Mean Recovery (%)	Expt-1	Expt-2
1	Li	7	50	0.9998	5.0	2.0	103.2	<LOQ	<LOQ
2	B	11	50	0.9995	12.5	1.1	101.8	<LOQ	<LOQ
3	Na	23	50	0.9999	200.0	1.1	104.8	1835	1830
4	Mg	24	50	0.9999	40.0	1.0	104.55	187	131
5	Al	27	50	0.9998	200.0	0.8	104.45	<LOQ	<LOQ
6	Si	28	1500	0.9986	250.0	1.6	102.05	764.5	521
7	K	39	50	0.9999	12.5	3.9	100.45	6.54	9.1
8	Ca	44	1500	0.9999	100	6.2	105.35	694	609
9	V	51	5.0	0.9995	0.5	4.8	101.35	<LOQ	<LOQ
10	Cr	52	50	0.9999	1.0	1.8	100.85	3.46	1.63
11	Fe	56	50	0.9998	1.0	2.9	100.2	33.6	16.4
12	Co	59	5.0	0.9999	0.1	2.1	101.0	<LOQ	0.2

Sr. No.	Element	Mass	J (µg/L)	R	LOQ (µg/L)	LOQ* Precision RSD (%)	CCV* Mean Recovery (%)	Expt-1	Expt-2
13	Ni	60	5.0	1.000	0.5	1.4	104.15	1.49	0.98
14	Cu	63	50	0.9995	5.0	1.0	106.85	<LOQ	<LOQ
15	As	75	5.0	0.9982	0.5	6.1	107.4	<LOQ	<LOQ
16	Se	78	50	1.000	1.0	2.6	101.45	<LOQ	<LOQ
17	Mo	95	50	0.9999	5.0	1.9	101.85	<LOQ	<LOQ
18	Ru	101	50	1.000	1.0	2.5	99.35	<LOQ	<LOQ
19	Rh	103	50	0.9999	5.0	0.4	101.05	<LOQ	<LOQ
20	Pd	105	50	0.9999	5.0	1.5	107.1	<LOQ	<LOQ
21	Ag	109	50	1.000	1.0	0.8	101.75	<LOQ	<LOQ
22	Cd	111	5.0	1.000	0.1	3.8	101.55	<LOQ	<LOQ
23	Sn	118	50	1.000	1.0	3.2	99.95	<LOQ	<LOQ
24	Sb	121	50	1.000	1.0	3.3	99.95	<LOQ	<LOQ
25	Ba	138	50	1.000	1.0	2.0	96.55	6.18	5.54
26	Os	189	50	1.000	5.0	2.1	95.15	<LOQ	<LOQ
27	Ir	193	50	0.9999	1.0	1.0	98.65	<LOQ	<LOQ
28	Pt	195	50	1.000	1.0	1.1	99.55	<LOQ	<LOQ
29	Au	197	50	0.9984	1.0	2.8	81.7	<LOQ	<LOQ
30	Hg	202	5.0	0.9999	0.5	2.2	99.25	<LOQ	<LOQ
31	Tl	205	50	0.9999	5.0	1.8	101.95	<LOQ	<LOQ
32	Pb	208	5.0	1.000	0.5	1.9	101.2	<LOQ	<LOQ

LOQ (Limit of Quantification) , *CCV (Continuous Calibration verification Standard)

Internal standards intensity deviation response profile

Stable internal standard recovery with the Mini torch throughout the extractables study sequence is shown in Figure 7.

Internal standard solutions containing 10 ng/mL of Sc, Ge, Y, In, Ce and Bi were added continuously during analysis with the help of on-line internal standard kit.

The ratio between sample and internal standard was maintained at approximately 9:1.

The internal standard recovery values remained between the 80–120 %.

■ Conclusion on Extractable Study

The extractable study revealed no elements exceeding the Analytical Evaluation Threshold (AET). The Limit of Quantitation (LOQ) precision and bracketing standard solution (CCV) recoveries were within 90-110%. Consequently, only Class 1 and 2A elements were evaluated in leachable experiment. The acquisition results of extractable study are shown in Table 3.

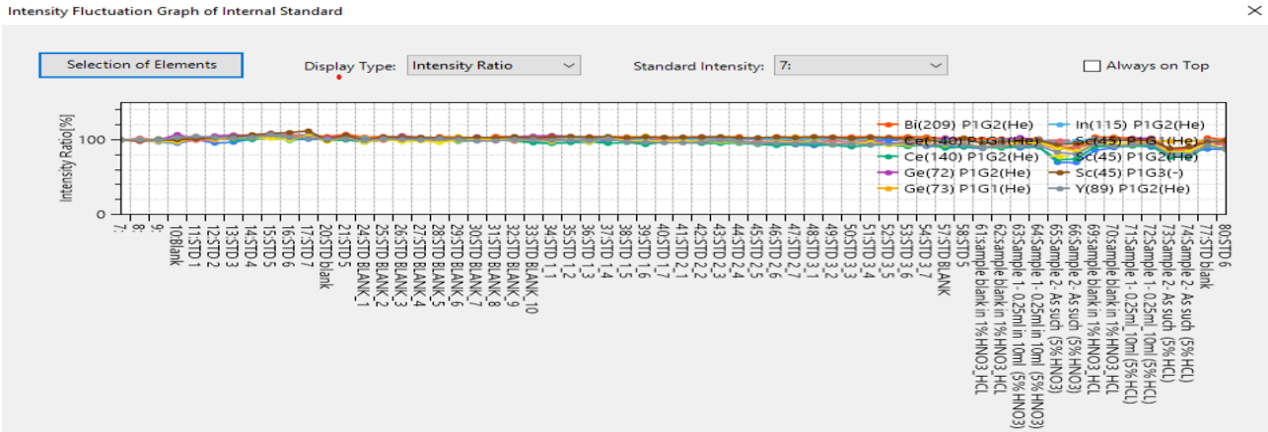


Figure 7 : Recovery data of internal standards from LabSolutions ICPMS Software

■ Leachable study

Based on the extractable study, Class 1 and 2A elements were selected for leachable monitoring. Given that the Penicillin V product is highly complex, the leachable experiment was performed using a microwave-assisted acid digestion technique to ensure accurate results.

Sample preparation:

The lyophilized penicillin V powder was used as sample. It was diluted with 85 mL of Type-I water for leachable study. Transferred accurately 1.0 mL of sample into a cleaned and dried microwave vessel, added ICP-MS grade 5 mL of concentrated nitric acid and 1.0 mL concentrated hydrochloric acid. Kept the vessels at room temperature for 15 minutes. After that closed the vessel with plug followed by cap and placed the vessel in the rotor and digested under the conditions which are mentioned microwave digestion system program in Table 4. After digestion allowed the sample to cool, then transferred into 50 mL volumetric flask and make the final volume with Type-I water.

Standard preparation :

The concentration limits were calculated using the AET formula, as given in Table 1. Standards were prepared in the same way as stated under extractable study.

Seven calibration linearity levels (0.05-1.5 J) and two quality control (QC) solutions (0.5 J) were prepared, along with a blank and CCV was done.

Table 4 . Microwave Digestion System Program Details

Sr. No.	Ramp Time (Min)	Temperatures (°C)	Hold Time (Min)
1	5	130	5
2	5	220	30

■ Results of leachable Analysis

All elements complied with the correlation coefficient (R) criterion of more than 0.995. Representative calibration curves for the toxic heavy metals Arsenic (As), Cadmium (Cd), Mercury (Hg), and Lead (Pb) are illustrated in Figure 8.

System suitability was evaluated by linearity , Continuing Calibration Verification (CCV) and LOQ precision. % RSD of LOQ standard as well as CCV injections throughout the analysis were found to be below 10 % and matrix recovery observed between 70-130 % criteria. Figure 8 depicts calibration curves of representative elements.

Subsequent analysis of the final processed sample showed quantifiable concentrations of 601 Sodium, 0.57 Magnesium , and 272.5 for Silicon in µg/L. Table 5 shows the results of leachable study acquisition in µg/L.

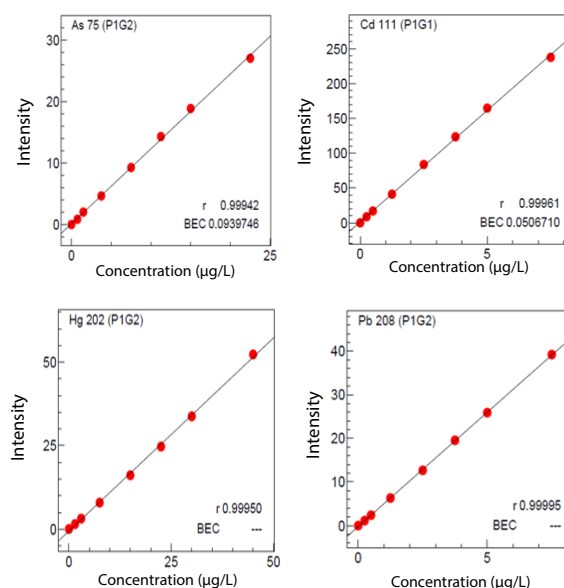


Figure 8 : Calibration curves for As, Cd, Hg, and Pb

Table 5. Experimental Results for Leachable Study Acquisition in µg/L

Sr. No	Element	Mass	J Value (µg/L)	R	LOQ* Conc. w.r.t sample	CCV* Mean Recovery (%)	Sample Results	Spike Mean Recovery (%)
1	B	11	50	0.999	0.25	99.8	<LOQ	99.9
2	Na	23	20000	1.000	125	102.5	601.5	NA
3	Mg	24	50	0.999	0.25	103.9	0.57	116.3
4	Al	27	50	0.996	0.25	105.9	<LOQ	111.1
5	Si	28	15000	0.999	125	101.75	272.5	NA
6	Ca	44	1500	0.999	12.5	102	<LOQ	NA
7	V	51	100	0.999	0.50	102.1	<LOQ	100.5
8	Fe	56	50	0.999	0.25	100.5	<LOQ	111.4
9	Co	59	50	0.999	0.25	100.8	<LOQ	109.6
10	Ni	60	200	0.999	1.00	103.7	<LOQ	102.2
11	As	75	15	0.999	0.075	101.75	<LOQ	72.4
12	Cd	111	5	0.999	0.025	102.7	<LOQ	77.0
13	Hg	202	30	0.999	0.15	97.1	<LOQ	73.1
14	Pb	208	5	1.000	0.025	99.2	<LOQ	113.0

*CCV - Continuous Calibration Verification Standard , # LOQ (Limit of Quantification)

■ Conclusion

- ❖ A Shimadzu ICPMS-2050 spectrometer was utilized to evaluate elemental impurities leached from a Container Closure Pack (CCP) under various acidified extraction environments. To simulate accelerated leaching, extraction was performed at elevated temperatures. Initial qualitative screening revealed the presence of several key analytes specifically aluminum, boron, calcium, iron, potassium, magnesium, sodium, and silicon which showed a significant response relative to the diluent.
- ❖ This study shows that the ICPMS-2050 is sensitive enough to identify and quantify extractables at the permissible limits set by ICH Q3D targeted as well as non targeted elements by using Scan mode feature.
- ❖ Shimadzu ICPMS Series adopted total 11 L/min argon gas consumption by implementing Mini torch accessory attachment is help to minimize the operation cost without compromising the sensitivity and plasma stability.
- ❖ LabSolutions software: Shimadzu ICPMS ensures compliance with regulatory norms in spectroscopy products, streamlining data management and analysis.

■ References

- [1] Product Quality Research Institute "Safety Thresholds and Best Demonstrated Practices for Extractables and Leachables in Parenteral Drug Products (Intravenous, Subcutaneous, and Intramuscular)
<https://pqri.org/wp-content/uploads/2022/03/PQRI-PDP-Recommendation-2022.pdf>
- [2] Final Concept Paper, ICH Q3E: Guideline for Extractables and Leachables(E&L).
https://database.ich.org/sites/default/files/ICH_Q3E_ConceptPaper_2020_0710.pdf
- [3] USP <1663> Assessment of extractables associated with pharmaceutical packaging/delivery systems.

LabSolutions is a trademark of Shimadzu Corporation or its affiliated companies in Japan and/or other countries.



SHIMADZU

Shimadzu Corporation

www.shimadzu.com/an/

Shimadzu India Pvt. Ltd.

www.shimadzu.in

For Research Use Only. Not for use in diagnostic procedure.

This publication may contain references to products that are not available in your country. Please contact us to check the availability of these products in your country.

The content of this publication shall not be reproduced, altered or sold for any commercial purpose without the written approval of Shimadzu. See <http://www.shimadzu.com/about/trademarks/index.html> for details.

Third party trademarks and trade names may be used in this publication to refer to either the entities or their products/services, whether or not they are used with trademark symbol "TM" or "®".

The information contained herein is provided to you "as is" without warranty of any kind including without limitation warranties as to its accuracy or completeness. Shimadzu does not assume any responsibility or liability for any damage, whether direct or indirect, relating to the use of this publication. This publication is based upon the information available to Shimadzu on or before the date of publication, and subject to change without notice.

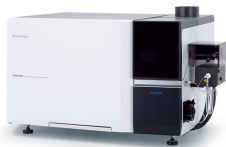
06-SIP-SP-079-EN

First Edition: Oct. 2026

➤ Please fill out the survey

Related Products

Some products may be updated to newer models.



➤ ICPMS-2040 Series
/ ICPMS-2050 Series
Inductively Coupled Plasma Mass
Spectrometry

Related Solutions

➤ Pharmaceutical and
Biopharmaceutical

➤ Small Molecule
Pharmaceutical

➤ Price Inquiry

➤ Product Inquiry

➤ Technical Service /
Support Inquiry

➤ Other Inquiry