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Application News

Inductively Coupled Plasma Mass Spectrometer ICPMS-2030

Extractables Analysis of Elements in Plastic Pharmaceutical Packaging

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User Benefits

- Extracted elements can be examined based on extractables and leachables (E&L) guidelines.
- Elements extracted from packaging materials can be evaluated using ICPMS-2030.
- The ICPMS-2030 is capable of high-sensitivity analysis of multiple elements simultaneously.

■ Introduction

The extractables and leachables from packaging into pharmaceuticals is a critical issue that must be addressed. This Application News uses inductively coupled plasma mass spectrometry (ICP-MS) to perform a detailed analysis of packaging extractables that targets the elements listed in the ICH Q3D guideline on elemental impurities in pharmaceuticals. ICP-MS offers a detailed breakdown as it can simultaneously analyze an extracted solution for multiple elements with high sensitivity.

■ Extractables and Leachables (E&L)

Biopharmaceuticals and other high molecular weight pharmaceuticals are not easily absorbed into the body as oral formulations, thus they are stored in a solution such as in the case of injectables. The area of contact between a tablet formulation and its packaging is very small, while pharmaceuticals formulated in solution have a very large contact area with their packaging material, and thus leachables become an important concern. Single-use technologies play an increasingly common role in biopharmaceutical production, and leachables from plastic products used in manufacturing also pose a major issue.

Substances that transfer from packaging to a pharmaceutical product under normal conditions are typically called leachables, while substances that occur under conditions more extreme than during normal storage are called extractables. Leachables are normally identified by analyzing the pharmaceutical product itself for substances transferred under normal storage conditions. By contrast, analyzing for extractables aims to reveal potential hazards and identify which leachables occur in worst-case scenarios, thus extractables are identified by analyzing an extraction solution of the packaging material.

Standards for the measurement of extractables and leachables (E&L) include guidance issued by the FDA[1)] and other private organizations such as the PQRI[2)] and BPOG[3)], though these standards and guidelines are not harmonized. The ICH is currently developing Q3E guidelines on the assessment and control of extractables and leachables[4)], of which the current goal as of January 2023 is to reach Step 4 in 2025. The scope of ICH Q3E is anticipated to include small-molecule pharmaceuticals as well as biopharmaceutical products.

Elemental impurities must be considered among extractables and leachables. In the already-implemented ICH Q3D[5)], section 5.3 (Identification of Potential Elemental Impurities) states the following about the need for a risk assessment of the probability of elemental impurities leaching from the container closure system into the drug substance.

"For liquid and semi-solid dosage forms there is a higher probability that elemental impurities could leach from the container closure system during the shelf-life of the product. Studies to understand potential leachables from the container closure system (after washing, sterilization, irradiation, etc.) should be performed."

■ Assay of Elemental Extractables

The objective of this Application News is to measure elemental impurities in packaging extractables. The Japanese Pharmacopoeia 18th Edition, USP<233>, and Ph. Eur. Chapter 2.4.20 use ICP optical emission spectrometry (ICP-AES/OES) and ICP-MS in assay methods for the elemental impurities cited in ICH Q3D, methods that can also be used to assay elemental impurities in extractables. ICP-MS is particularly useful as it can analyze multiple elements simultaneously with high sensitivity.

The Shimadzu ICPMS-2030 (Fig. 1) used in this application is a highly sensitive and efficient analytical instrument that can operate with reduced argon gas consumption and low-purity argon gas for reduced running costs.

Fig. 1 ICPMS-2030

■ Samples for Analysis

This study performed a risk assessment of potential elemental leaching from three common infusion bags (Table 1).

Table 1 Infusion Bag Materials

Polyvinyl chloride (PVC, DEHP-free)
Polyethylene (PE)
Ethylene-vinyl acetate (EVA) copolymer

■ Experimental Method

• Preparation of Extraction Solvents

Many standards and guidelines note that the choice of extraction solvent is important for predicting which potential hazards may occur in the actual pharmaceutical product. Extraction solvents must be selected with care since E&L analyses performed under too extreme extraction conditions will not give meaningful results.

For aqueous systems, the PRQI uses water at pH 2.5 and pH 9.5 because, in general, few aqueous solvents are lower than pH 2.5 or higher than pH 9.5. The PRQI also mentions using 50 % IPA in an extraction solvent to simulate aqueous formulations containing solubilizing agents.[2)] The extraction solvents used in this study are shown in Table 2.

Table 2 Extraction Solvents and Reagents

Extraction Solvent	Reagents
pH 2.5 solution	0.01 M KCl: FUJIFILM Wako Chemicals 0.003 M HCl: Kanto Chemical
pH 9.5 solution	0.0045 M sodium dihydrogen phosphate: FUJIFILM Wako Chemicals 0.007 M disodium hydrogen phosphate: Sigma-Aldrich (pH adjusted with 1 M NaOH)
50 % IPA	High purity IPA: Kanto Chemical (diluted with pure water)

• Extraction Method

An unprinted section was cut from a transfusion bag, the surface area and weight of the section of bag were measured, and the section of bag was washed with pure water and cut into small pieces with ceramic scissors. Small pieces with a total surface area of approx. 100 cm^2 were placed into a DigiTUBE (SCP SCIENCE), 30 mL of extraction solvent was added, and the mixture was heated (70 °C for 24 H). After cooling, the liquid contents of the DigiTUBE were transferred to an empty container and used as the extraction solution. This extraction process was performed six times (n = 6) for each transfusion bag.

Extraction blanks were also created by performing the same extraction process but adding only 30 mL of extraction solvent to the DigiTUBE. This blank extraction process was performed three times (n = 3).

The extraction conditions used are shown in Table 3. This process of adding extraction solvent and sample to a test tube is based on the PQRI document, though the temperature and duration of extraction used are not identical. This is because the conditions described in this Application News represent a single trial run from a larger number of runs performed to derive a best practice for this study, an approach that is also outlined in the PQRI document[2)].

Table 3 Extraction Conditions

Total Sample Surface Area	Approx. 100 cm^2
Extraction Solvent Volume	30 mL
Heating Temperature	70 °C
Heating Time	24 hr

• Preparation of Samples for Analysis

The extraction solutions obtained from each solvent were prepared for analysis by diluting 10-fold with pure water. Nitric acid and hydrochloric acid were also added to 1 % (v/v) and 0.5 % (v/v), respectively, to stabilize the elements in the sample.

A fixed concentration of standard solution was also added to the extraction solutions to prepare samples for spike recovery analysis.

• Preparation of Standard Samples

Standard samples were prepared to create calibration curves for each targeted element. Standard samples were prepared by diluting and mixing XSTC-22 (general-purpose mixed standard solution, SPEX CertiPrep), XSTC-2071A (ICH Q3D-compatible mixed standard solution, SPEX CertiPrep), and commercially available single-element standard solutions as appropriate. Nitric acid and hydrochloric acid were also added to the standard samples to 1 % (v/v) and 0.5 % (v/v), respectively. A 50 % IPA standard sample was also prepared by adding IPA to 5 % (v/v) in the above standard solution.

The objective of this study was to primarily to target elements specified by ICH Q3D, but since no commercially available standard solution containing all these elements was available, multiple standard solutions were used to create calibration curves for all the elements.

• Analysis

The analytical conditions shown in Table 4 and calibration curves were used to simultaneously analyze extraction samples for the 24 Class 1 to 3 elements listed in ICH Q3D as well as Fe and Zn.

Be, Sc, Ga, Y, In, Te, and Bi were used as internal standard elements, and an automatic internal standard addition kit was used to add an internal standard element solution to each sample in a ratio of 1 to 9 (internal standard element solution to sample) for analysis.

The validity of results was verified by analyzing spike recovery samples and calculating spike recovery.

Table 4 ICP-MS Analytical Conditions

Instrument:	ICPMS-2030
RF Power:	1.2 kW
Plasma Gas Flowrate:	9.0 L/min
Auxiliary Gas Flowrate:	1.1 L/min
Carrier Gas Flowrate:	0.7 L/min
Nebulizer:	Nebulizer 07 UES
Pump Speed:	20 rpm
Chamber:	Electric cooled Cyclone chamber
Plasma Torch:	Mini torch
Sampling Cone/Skimmer Cone:	Cu
Collision Gas:	He
Internal Standard Element Addition Method:	Automatic addition

■ Results of PVC Sample Analysis

• Results of PVC Extractables Analysis

Tables 5 and 6 show the extraction data obtained from PVC for the three extraction solvents. All three solvents extracted Tl and Zn. Pb and Ba were extracted with pH 2.5 and 50 % IPA, showing the amount of Pb and Ba extracted from PVC increases under acidic conditions and with 50 % IPA.

Tables 5 and 6 show the concentration of elements extracted in ng/cm^2 indicating how much of each element was extracted per 1 cm^2 of packaging material. The amount of material in contact with the drug substance must be considered when calculating the amount of elemental impurities extracted from packaging.

• Spike Recovery and Limit of Quantitation

Table 5 shows the limit of quantitation and spike recovery for measurements from the pH 2.5 extraction solution. Spike recovery results were good at between 95 and 108 %.

The packaging-adjusted PDE*1 in Table 5 is the parenteral PDE listed in ICH Q3D divided by the surface area of the inside of the transfusion bag, assuming administration of one transfusion bag per day. The measurements using ICPMS-2030 confirmed that the limit of quantitation was sufficient to measure PDE.

*1:ICH Q3D sets permitted daily exposure (PDE) limits for 24 elements in pharmaceutical products and requires valid analytical methods are used to control levels of these 24 elements.

Table 5 PDE Values and Extraction Limit of Quantitation, Spike Recovery, and Extracted Element Concentration for pH 2.5 Extraction

Class	Element	Parenteral PDE	Packaging-Adjusted PDE*2	Packaging-Adjusted Limit of Quantitation*3	Spike Recovery	Extracted Element Concentration with pH 2.5 Solvent
		µg/day	ng/cm^2	ng/cm^2	%	ng/cm^2 (n = 6)
1	Cd	2	3	0.008	100	< 0.008
	Pb	5	8	0.01	99	0.18 ± 0.04
	As	15	23	0.02	104	< 0.02
	Hg	3	5	0.05	103	< 0.05
2A	Co	5	8	0.003	101	< 0.003
	V	10	15	0.7	95	< 0.7
	Ni	20	30	0.2	102	< 0.2
2B	Tl	8	12	0.01	99	0.053 ± 0.010
	Au	300	452	0.05	95	< 0.05
	Pd	10	15	0.2	98	< 0.2
	Ir	10	15	0.01	102	< 0.01
	Os	10	15	0.02	103	< 0.02
	Rh	10	15	0.008	98	< 0.008
	Ru	10	15	0.006	102	< 0.006
	Se	80	121	0.1	95	< 0.1
	Ag	15	23	0.01	99	< 0.01
	Pt	10	15	0.03	97	< 0.03
3	Li	250	377	0.02	97	< 0.02
	Sb	90	136	0.01	101	< 0.01
	Ba	700	1056	0.008	101	0.16 ± 0.05
	Mo	1500	2262	0.009	100	< 0.009
	Cu	300	452	0.2	108	< 0.2
	Sn	600	905	0.02	101	< 0.02
	Cr	1100	1659	0.1	104	< 0.1
Other	Zn			0.2	101	148 ± 44

Table 6 Effect of Extraction Solvent on Elements Extracted from PVC

Element	Extracted Element Concentration with pH 9.5 Solvent	Extracted Element Concentration with 50 % IPA Solvent
	ng/cm^2 (n = 6)	ng/cm^2 (n = 6)
Cd	< 0.01	< 0.02
Pb	< 0.05	0.083 ± 0.02
As	< 0.03	< 0.01
Hg	< 0.1	< 0.05
Co	< 0.01	< 0.02
V	< 0.2	< 0.3
Ni	< 0.1	< 0.2
Tl	0.054 ± 0.002	0.082 ± 0.003
Au	< 0.09	< 0.03
Pd	< 0.3	< 0.2
Ir	< 0.03	< 0.03
Os	< 0.05	< 0.09
Rh	< 0.005	< 0.008
Ru	< 0.007	< 0.02
Se	< 0.2	< 0.07
Ag	< 0.006	< 0.01
Pt	< 0.05	< 0.01
Li	< 0.01	< 0.009
Sb	< 0.02	< 0.02
Ba	< 0.01	0.21 ± 0.03
Mo	< 0.006	< 0.04
Cu	< 0.1	< 0.1
Sn	< 0.02	< 0.1
Cr	< 0.2	< 0.1
Zn	70.0 ± 4.0	562 ± 95

*2:Packaging-adjusted PDE = Parenteral PDE/Internal surface area of the bag (assuming 1 bag administered per day)

*3:Packaging-adjusted limit of quantitation = Limit of quantitation in assayed sample (10σ) × 30 (extraction solvent volume) × 10 (dilution factor)/ Material surface area (100 cm^2)

*4:Extracted element concentration = (Element concentration in extraction solution - Element concentration in extraction blank) × 30 (extraction solvent volume) × 10 (dilution factor)/Material surface area

<X: Under limit of quantitation, X: Limit of quantitation

■ Results Specific to PE and EVA

Similar to PVC, almost all elements were detected in PE and EVA extraction solutions at levels below the limit of quantitation. Table 7 shows the results for elements detected in PE and EVA. The same amount of Sb was extracted from PE regardless of the solvent used and Zn was extracted from PE under basic conditions and with the 50 % IPA solvent. Fe was extracted from EVA under acidic conditions.

■ Conclusion

This study shows that the ICPMS-2030 is sensitive enough to identify and quantitate extractables at the permissible limits set by ICH Q3D. This study also reveals that the extraction behavior of different elements varies depending on the extraction solvent.

Table 7 Element Concentrations Extracted from PE and EVA and Spike Recovery

Sample	Element	pH 2.5		pH 9.5		50 %IPA	
		Extracted Element Concentration (n = 6) ng/cm^2	Spike Recovery %	Extracted Element Concentration (n = 6) ng/cm^2	Spike Recovery %	Extracted Element Concentration (n = 6) ng/cm^2	Spike Recovery %
PE	Sb	3.35 ± 0.68	102	2.48 ± 0.28	106	6.8 ± 1.3	111
	Zn	< 0.2		0.52 ± 0.29	102	0.72 ± 0.32	89
EVA	Fe	0.88 ± 0.40	107	< 0.3		< 0.5	

<X: Under limit of quantitation, X: Limit of quantitation
Packaging-adjusted limit of quantitation = Limit of quantitation in assayed sample (10σ) × 30 (extraction solvent volume) × 10 (dilution factor)/ Material surface area (100 cm^2)

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