

Application News

No. J98

Inductively Coupled Plasma Atomic Emission Spectrometry

Measurement of Elemental Impurities in Pharmaceutical Products by ICP-AES and ETAAS

■ Introduction

Electrothermal atomic absorption spectrometry (ETAAS) and inductively coupled plasma atomic emission spectroscopy (ICP-AES) are widely used as trace metal analytical methods. In addition, they are also effective for analysis of metallic impurities in pharmaceutical products and their raw materials. In Japan, the guidelines for impurities in new drug substances (Notification No. 1216001, issued by Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau; revised December 16, 2002) specify that residual metallic catalysts are to be analyzed according to the test method specified in the Japanese Pharmacopoeia or another appropriate method, and that evaluation be conducted in the development stage. Furthermore, the first revision of the 16th Japanese Pharmacopoeia (September 27, 2012) includes inductively coupled plasma atomic emission spectroscopy (ICP-AES) and inductively coupled plasma mass spectrometry (ICP-MS) as analytical methods under the general test methods.

In addition, The United States Pharmacopeia (USP) added the general chapter <232> Elemental Impurities – Limits, which sets the permissible limits for the so-called Big Four elements (lead, cadmium, arsenic, mercury). Also, the preparation procedures and analytical methods specified in USP <233> Elemental Impurities – Procedures include those for ICP-MS and ICP-AES, respectively.

Here we introduce examples of analysis of metallic impurities in the commonly used anti-inflammatory analgesic acetylsalicylic acid (aspirin) using ICP-AES and ETAAS.

■ Sample Preparation

Sample digestion was conducted using the ETHOS One microwave sample preparation system (Milestone Srl). Digestion conducted in a closed system prevents the volatilization of low-boiling elements, including mercury, arsenic, and cadmium. The digestion process flow is shown in Fig. 1. Since the hydride generation method is used in the case of arsenic, the digested solution was transferred to a tall beaker and heated to near dryness on a hot plate. After nearly all the nitric acid was removed, hydrochloric acid and potassium iodide were added for pre-reduction treatment.

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graph TD
    A[Transfer 0.5 g sample to digestion container] --> B[Add 5 mL nitric acid]
    B --> C[Let stand about 30 min]
    C --> D[Add 9.5 mL nitric acid and 0.5 mL hydrochloric acid]
    D --> E[Set container in ETHOS One microwave digester and digest (Approx. 1 h)]
    E --> F[Refrigerate]
    F --> G[Transfer to volumetric flask, adjust volume to 25 mL (add internal standard elements)]
  
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Fig. 1 Sample Preparation Flow Chart

A spike-and-recovery test solution was prepared to evaluate the validity of the preparation and measurement procedures. The sample was spiked with standard solution prior to sample preparation.

■ Analytical Method and Conditions

(1) ICP-AES

The Shimadzu ICPE-9000 Multitype Inductively Coupled Plasma Emission Spectrometer was used to measure 14 elements, including the Big Four. The standard sample was prepared so that its acidity would be nearly equivalent to that of the sample solution, and an internal standard correction was applied using yttrium. Regarding arsenic, the high-sensitivity hydride generation method was used. Table 1 shows the main ICP measurement conditions that were used.

(2) ETAAS

The Shimadzu AA-7000 Atomic Absorption Spectrophotometer was used to measure arsenic and lead. The standard sample was prepared so that its acidity would be nearly equivalent to that of the sample solution. Table 2 shows the main ETAAS measurement conditions that were used.

Table 1 Analytical Conditions for ICP-AES

Instrument	ICPE-9000		
Radio frequency power	1.2 kw		
Plasma gas flowrate	10 L/min		
Auxiliary gas flowrate	0.6 L/min		
Carrier gas flowrate	0.7 L/min		
Sample introduction	Coaxial nebulizer Arsenic: HVG-1 Hydride Generator		
Misting chamber	Cyclone chamber		
Plasma torch	Mini torch		
Observation method	Axial		
Internal standard element	Y 0.1 mg/L		
Measurement wavelengths (nm)	As 189.042	Cd 226.502	Cr 205.552
	Cu 327.396	Hg 184.950	Ir 212.681
	Mo 202.030	Ni 221.647	Pb 220.353
	Pd 340.458	Pt 203.646	Rh 343.489
	Ru 240.272	V 292.402	

Table 2 Analytical Conditions for ETAAS

Instrument	Main unit: AA-7000 Graphite furnace: GFA-7000	
Measurement element	As	Pb
Measurement wavelength (nm)	193.7	283.3
Background correction	D2 method	
Ashing temperature	800 °C	600 °C
Atomization temperature	2200 °C	2000 °C
Tube type	Pyrolytic graphite tube	
Matrix modifier	Palladium nitrate 50 mg/L	–

■ **Results and Conclusion**

The measurement results for the 14 elements obtained using ICP-AES are shown in Table 3, and the measurement results for lead and arsenic by ETAAS are shown in Table 4. None of the elements were detected in the samples. Excellent results were obtained in the spike-and-recovery test. Figs. 2 and 3 show examples of the peak profiles obtained by ICP-AES and ETAAS, respectively.

The ICPE-9000 used for measurement is equipped with an Echelle spectrometer and CCD detector, making it possible to conduct simultaneous analysis of all elements at all wavelengths, thereby permitting high-throughput measurement even for multiple analytes, such as in impurity elemental analysis in pharmaceutical products. Further, compared to a conventional torch, the mini torch offers lower consumption of argon gas, thereby reducing running costs. The ETAAS method using the AA-7000 provides high-sensitivity analysis of small-volume samples.

Table 3 Measurement Results by ICP-AES

	As	Cd	Cr	Cu	Hg	Ir	Mo
Permissible limit value (μg/g)	0.15 ^{*1}	2.5	2.5 ^{*2}	100	1.5 ^{*1}	10	10
Measurement value (μg/g)	<0.003 ^{*3}	<0.007	<0.03	<0.03	<0.4	<0.07	<0.05
Recovery rate (%)	97	91	101	109	95	93	106
	Ni	Pb	Pd	Pt	Rh	Ru	V
Permissible limit value (μg/g)	50	0.5	10	10	10	10	10
Measurement value (μg/g)	<0.04	<0.2	<0.05	<0.3	<0.07	<0.03	<0.01
Recovery rate (%)	94	95	109	98	109	95	100

The permissible limit for oral intake is a concentration less than 10 g per day in pharmaceutical products as indicated in USP <232>.

*1: Concentrations of inorganic arsenic and mercury, respectively

*2: Concentration in an inhalant drug

*3: Concentration obtained using the hydride generator method

Table 4 Results by ETAAS

	As	Pb
Permissible limit value (μg/g)	0.15	0.5
Measurement value (μg/g)	<0.06	<0.02
Recovery rate (%)	95	100

The permissible limit for oral intake is a concentration less than 10 g per day in pharmaceutical products as indicated in USP <232>. For arsenic, content in inorganic form was measured.

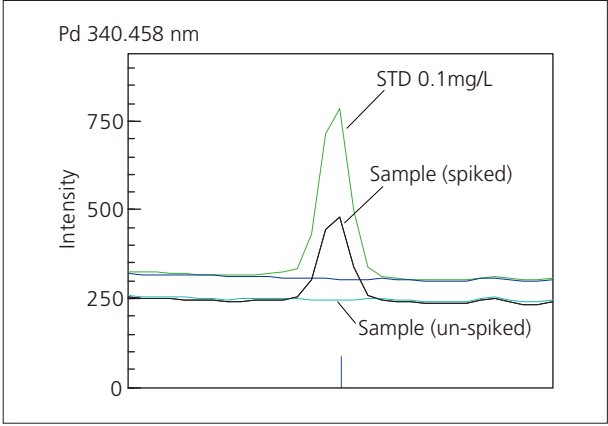


Fig. 2 Peak Profile of Pd 340.458 nm by ICP-AES

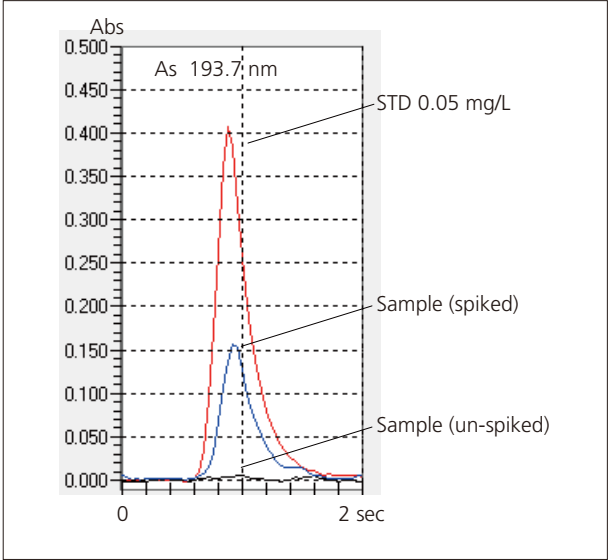


Fig. 3 Peak Profile of As 193.7 nm by ETAAS

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