

Application Note

Application Note No.6 (Medicine)



Medicine

Analysis of Residual Catalysts in Pharmaceuticals Using ICP Atomic Emission Spectrometry

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1. Introduction

In addition to containing active ingredients, pharmaceuticals contain a number of components that are intentionally added to improve their properties, as well as residual non-intentional components such as starting materials and intermediates, byproducts, products of decomposition, and reagents and solvents used in the production process. One such component is metallic catalysts, which have been classified as inorganic impurities in the Revised Guidelines on Impurities in New Drug Substances (No. 1216001, issued by the Evaluation and Licensing Division, the Pharmaceutical and Food Safety Bureau (Iyaku Shokuhinkyoku Shinsa Kanri) on December 16, 2002)¹. Testing methods and other appropriate methods found in the Japanese Pharmacopoeia were directed towards evaluation at the drug development stage. On the other hand, turning to overseas, the European Medicines Agency (EMA) published guidelines² on February 21, 2008 that

specified the limits for residual metal catalysts or metal reagents that derive from the pharmaceutical production process; it set the permissible limits for 14 types of metals. Further, the United States Pharmacopeia (USP) proposed a new metal testing method and the permissible limits for 31 types of metals in the Pharmacopeial Forum 34(5) (September-October 2008)³, all of which is indicative of the growing interest in metal impurities in pharmaceuticals. Testing methods that are often used for analysis of metal elements include atomic absorption spectrometry, ICP atomic emission spectrometry, and ICP mass spectrometry, but from the perspectives of speed and simplicity for multi-elemental analysis, using the ICP analytical method is most convenient. Here, the analysis of the 14 types of metals subject to the EMA guidelines will be used to introduce the inductively coupled plasma atomic emission spectrometry method.

2. ICP Atomic Emission Spectrometry Method



Multichannel type (ICPE-9000)

2-1 What Is ICP?

ICP stands for high frequency inductively coupled plasma. Figure 1 shows the theory behind plasma. A high frequency coil is wound around a three-layered coaxial tube (normally made of quartz) called a plasma torch, and a high frequency current (I) of 27.12 MHz (or 40.68 MHz) is applied to the coil to generate an electromagnetic induction magnetic field (H) inside of the plasma torch. Argon (Ar) gas flows through the inside of the plasma torch, while high voltage electrical discharges cause the ionization of the argon gas. This generates the plasma (in this case argon gas plasma). This plasma can also be called an ionized gas, and here, the cations and electrons, in equal numbers, are maintained in balance. The plasmas used in ICP instruments are generated by the high frequency current, 27 MHz (or 40 MHz), and in the center of its donut structure, where the samples are introduced, the temperature is lower. The central part of the plasma reaches high temperatures of from 6000 to 8000 K. Figure 2 shows a general view of ICP. The sample is misted into the central part of the plasma together with a carrier gas, and any elements in the sample gain energy from the plasma and become excited, but upon return to a stable, lower energy level, the energy differential is emitted (as light). Figure 3 shows the principle behind emission spectrometry. Since this light has a wavelength that is specific to the element, detecting the spectrum enables the elemental analysis. Thus, the ICP is termed Inductively Coupled Plasma Atomic (Optical) Emission Spectrometry (ICP-AES or ICP-OES).

The elements introduced to ICP are efficiently ionized. Since these elements have a mass number specific to the element, mass spectrometry allows determination of the elements present in the sample and their concentrations. Thus, the ICP can be used as an ion source for mass spectrometry, hence, it is called ICP Mass Spectrometry (Inductively Coupled Plasma Mass Spectrometry, ICP-MS).

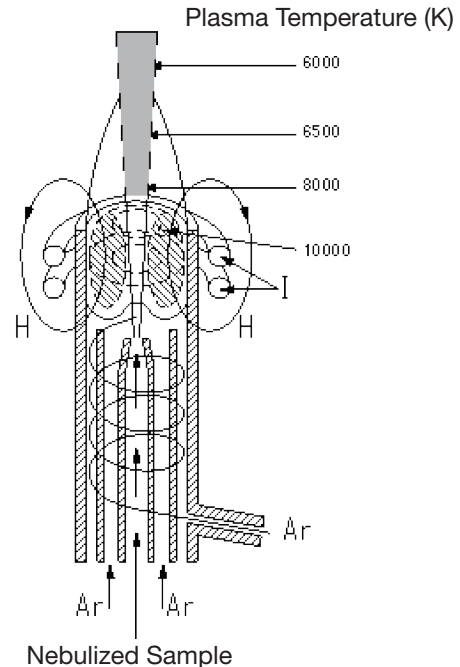


Figure 1: Plasma Theory

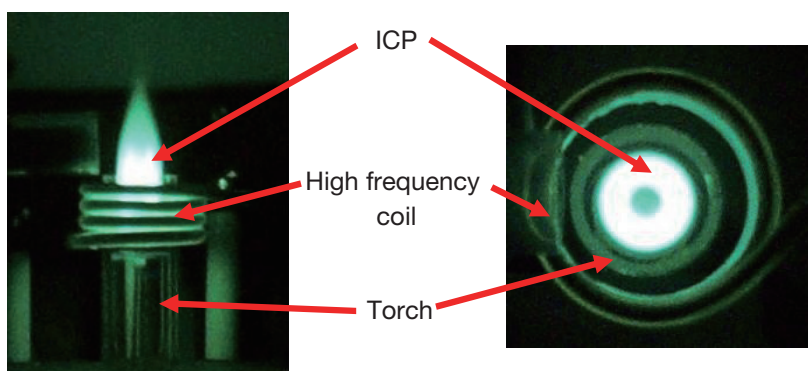


Figure 2: External View of ICP
(left: Photo from the radial view; right: Photo from axial view)

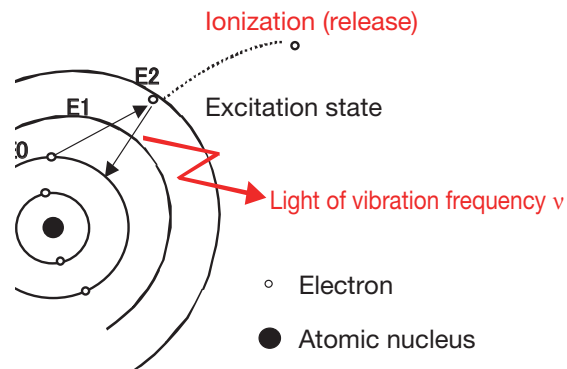


Figure 3: Principle of Emission Spectrometry

2-2 The ICP Atomic Emission Spectrometry Instrument

An ICP Atomic Emission Spectrometer (ICP-AES) uses the high frequency inductively coupled plasma as the means to obtain emissions from the elements in the sample. Since the emission spectrum itself is a mixture of a variety of spectra, a spectrometer is used to isolate the spectra and detect each of the elements. The spectrometer used in emission spectrometry must be one that can separate multiple spectral peaks or lines. Different techniques require different types of spectrophotometers. For example UV-VIS absorption spectrophotometers measure broader molecular peaks than atomic absorption spectrophotometers. On the other hand, atomic emission spectrophotometers measure narrower lines than those of atomic absorption methods. Thus ICP requires a higher performance spectrophotometer for isolating these closely spaced emission lines.

ICP-AES is classified into sequential and multichannel (simultaneous) types. The sequential type generally uses the planar diffraction grating and the wavelength is scanned based upon the diffraction grating angle and slits, and is detected with a photomultiplier tube (PMT). Accordingly, when the more wavelengths to be measured, the longer measurement time is, but the sequential type does offer high wavelength resolution. On the other hand, with the multichannel type, the echelle diffraction grating is used in conjunction with a prism to form the spectrometer, and the emission spectrum is developed in two dimensions using a charge coupled device (CCD) or the like as the detector. The advantage of this type is the ability to analyze multiple elements at the same time. The structure of a multichannel type instrument is shown in Figure 4.

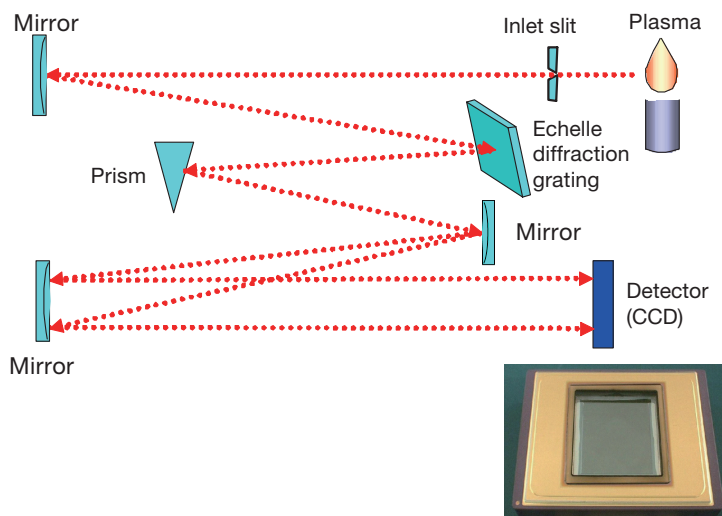


Figure 4: Structure of a Multichannel Spectrometer (ICPE-9000) Optical System

2-3 The Shimadzu ICP-AES

Shimadzu's ICP-AES instruments include both the sequential and multichannel types, but for the analysis of residual catalysts and the like in pharmaceutical products, the multichannel ICPE-9000 is most effective due to the rapidity with which it can measure multiple elements. Following are descriptions of the ICPE-9000's most salient features.

(1) Wavelength Measurement

Since a large number of spectra are generated by the elements in emission spectrometry when multiple elements exist, there is a tendency for the spectral peaks to overlap (called spectral interference). Thus, it is necessary to confirm the multiple wavelengths in order to improve measurement reliability. The ICPE-9000 uses the latest CCD system, a 1 megapixel unit, as its detector. In addition to the high resolution of this CCD system, all of the wavelength information is constantly stored in memory, making it possible to obtain a great deal of information with just one measurement. The principal characteristics will be noted below.

1. Wavelengths can be added even after the measurement. (Figure 5)
Since wavelengths can be added for evaluation even after the measurement, there is no need to determine the optimal wavelength in advance.
2. Elements can be added even after the measurement. (Figure 5)
When standard solutions containing multiple elements are being measured, if an element is forgotten or is later found to be necessary, it is possible to obtain the quantitative data on the required element after the measurement.
3. Qualitative data can be obtained even after the measurement. (Figure 5)
Since the data for all of the elements and their wavelengths is stored in memory it is possible to read out all of the qualitative data for the total number of elements (71 elements) from only the quantitative analysis data.
4. Automatic confirmation of the measurement data using the diagnostic assistant (Figure 6)
An example of the diagnostic assistant function is introduced in Figure 6. Using it when there are samples of different compositions, and where there is spectral interference among the measured wavelengths, allows the automatic selection of the optimal wavelength.

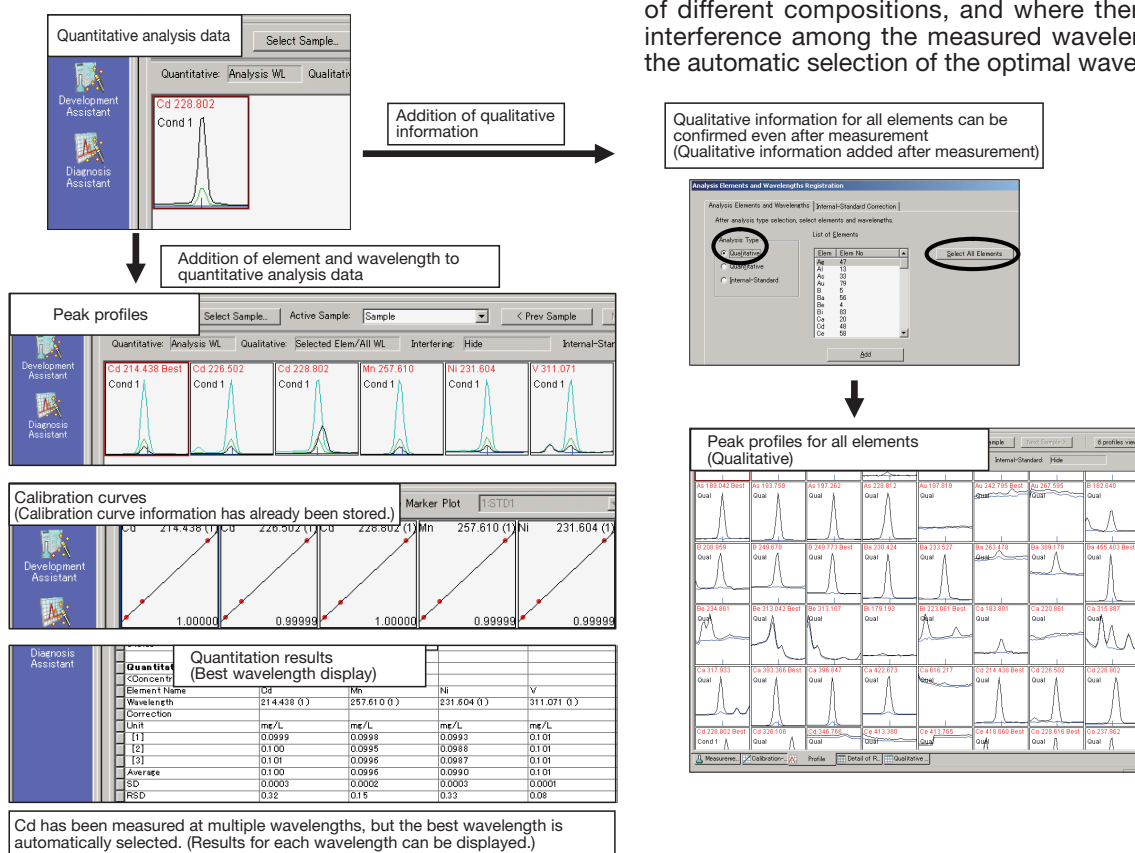


Figure 5: Example of Data Processing (After the measurement of the data for quantitative analysis, elements/wavelengths can be added, and qualitative data for all elements can be added).

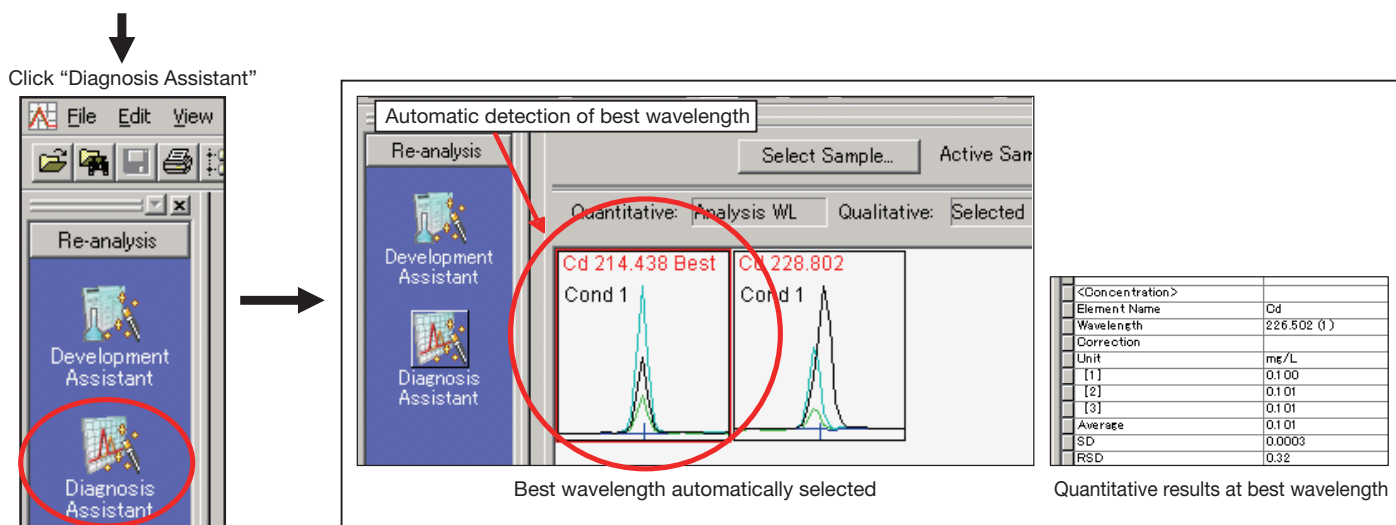
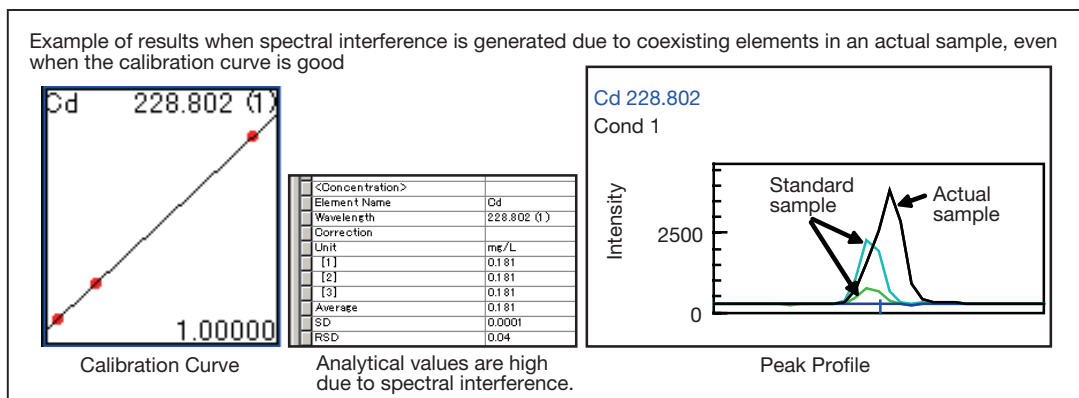


Figure 6: Example of Reanalysis of the Data Using the Diagnostic Assistant.

(2) Organic Solvent Measurement

In most ICP instruments, when measuring samples that include organic solvents, oxygen must be introduced into the plasma torch to prevent carbon deposits from forming on the tip of the plasma torch. Shimadzu, however, has adopted a type of torch for its ICP Emission Spectrometer that is not prone to the formation of carbon deposits. Furthermore, the vertical orientation of the torch in the Shimadzu ICPE-9000 makes it difficult for sample residuals to remain inside the torch. For these reasons, the introduction of oxygen is not required for measurements of samples containing organic solvents such as dimethyl sulfoxide (DMSO), methanol, ethanol, etc.

(3) Measurement for the Vacuum Ultraviolet Range with a Vacuum Spectrometer

It is possible to measure elements such as P and S that have high sensitivity or low spectral interference at wavelengths in the 190 nm or shorter wavelength range using ICP emission spectrometry. However, if there is air present within the spectrometer at this wavelength range, the emission spectrum is absorbed by the oxygen contained therein and these elements cannot be detected. Because of this, analysis at this wavelength range requires a gas-purge type

spectrometer, which allows a highly pure gas to flow into it, or a vacuum spectrometer, into which a vacuum can be introduced. In the case of a gas purge, a highly pure gas, normally 99.999% pure or higher, must be used to meet the objectives of eliminating the oxygen and preventing degradation to the optical system. Further, to assure the stability of the instrument, not only is a purge gas used during measurement, but the flow must be continued after the measurement as well, which increases operating costs. The Shimadzu ICPE-9000 uses a vacuum spectrometer to remove the air, thus eliminating the need for gas flow inside the spectrometer. This brings excellent stability and keeps operating costs down.

(4) Radial/Axial Direction Light Measurements

Axial direction plasma observations are used as a high sensitivity method for ICP emission spectrometry. Observing the plasma light from the axial direction makes it possible to observe the emission for a longer period of time than from the radial position. As the observation time increases, there is a corresponding increase in sensitivity because the emission is observed for a longer time period than in radial view mode. The Shimadzu ICPE-9000 can automatically switch between axial and radial view measurements within the same run.

3. Analytical Examples

3-1 EMEA Guidelines

Table 1 shows the permissible amounts and concentrations according to the Guidelines issued by the European Medicines Agency (EMA) on February 21, 2008. From the perspective of risk to human health, these guidelines classified 14 types of metals into three classes, Class 1 – 3. Class 1 (concerns over metals having the possibility of being carcinogenic or posing other serious toxicity issues in humans) was further divided into three subcategories. The permissible limits were set forth further for the three administration pathways of oral, parenteral or inhalation

exposure for each of the classes. Here, the values for the permissible levels were based on the Guideline for Residual Solvents (ICH Q3C)⁴. As the maximum permitted value for pharmaceuticals, the Permitted Daily Exposure (PDE, units $\mu\text{g/day}$) was used. The permissible concentration values were based on computing the PDE assuming a 10 g dosage of the pharmaceutical/day. In cases where the daily dosage exceeds 10 g, the permissible value was computed based upon the content of the active ingredients in the pharmaceutical.

Table 1: EMEA Guideline Classification and Permissible Levels for the Various Elements

		Oral Exposure		Parenteral Exposure		Inhalation Exposure
		($\mu\text{g/day}$)	(ppm)	($\mu\text{g/day}$)	(ppm)	(ng/day)
Class 1A	Pt, Pd	100	10	10	1	Pt : 70
Class 1B	Ir, Rh, Ru, Os	100	10	10	1	
Class 1C	Mo, Ni, Cr, V	250	25	25	2.5	Ni : 100 Cr(VI) : 10
Class 2	Cu, Mn	2500	250	250	25	
Class 3	Fe, Zn	13000	1300	1300	130	

Guideline on the Specification Limits for Residues of Metal Catalysts or Metal Reagents (EMA/CHMP/SWP/4446/2000)

3-2 Analysis of Pharmaceutical Substances

The 14 elements under the EMA Guidelines were measured as residual metal catalysts in the pharmaceutical substances. Reagents commercially available for research purposes were used as the samples. In these tests an organic solvent containing little contamination was selected for pretreatment of the test samples for convenience, rather than resorting to acid digestion, in this case the choice being DMSO due to its high solubility. 0.5 g each of the test samples was weighed and dissolved in DMSO to bring the volume to 5 mL (a 10-fold dilution). At this time yttrium (Y) was added as an internal standard element to produce a Y concentration of 0.1 $\mu\text{g/mL}$, and further, a standard sample of tosylloxacin tosylate was added to a dilution solution (to obtain a tosylloxacin tosylate concentration of 1 $\mu\text{g/mL}$), and this was used for addition and recovery testing. The solutions used to make the calibration curves were standard single-element solutions diluted with DMSO solvent. In preparing these calibration solutions, Y was also added as an internal standard element to produce a Y concentration of 0.1 $\mu\text{g/mL}$.

Table 2 shows the analytical conditions. Table 3 shows the analytical results, while Table 4 shows the addition and recovery test results when the tosylloxacin tosylate was used. A good recovery rate was achieved in the addition

and recovery tests. Based on computations from the measurement results on the calibration solutions, the lower limit for detection (3σ) was confirmed to be a value that was 1/10 or lower than the permissible exposure values for oral exposure to all of the elements (Table 5).

Next, 1.0 $\mu\text{g/mL}$ concentration solutions were used to prepare calibration curves and changes over time were measured during the course of two hours of continuous measurement. Good results were obtained; the RSD (relative standard deviation) over the two hours of measurement was less than 1% for all of the elements. The results are shown in Table 7. Further, the addition and recovery samples to which the tosylloxacin tosylate was added were subjected to repeated testing over a three-day period in a reproducibility test. The results are shown in Table 6. In these reproducibility tests, a calibration curve was prepared each time in performing the quantitative analysis. Very good reproducibility was obtained with each element, with the 3-day RSD being about 1%.

At last, spectral curve profile for each element (Calibration solution (0, 0.1, 1.0 $\mu\text{g/mL}$), Pharmaceutical substance, Standard sample addition (pharmaceutical substance + standard sample 1.0 $\mu\text{g/mL}$)) is shown in Figure 8.

Table 2: ICP-AES Analytical Conditions

Analytical instrument	ICPE-9000
High frequency power	1.3 kW
Plasma gas flow rate (Ar)	18 L./min
Auxiliary gas flow rate (Ar)	1.4 L./min
Carrier gas flow rate (Ar)	0.70 L./min
Sample introduction	Coaxial nebulizer
Spray chamber	Double tube (Scott type)
Observation direction	Axial

Table 3: Analytical Results for Pharmaceutical Substances (3 types) (concentrations in reagent powders: µg/g)

Element Name	Cr	Cu	Fe	Ir	Mn	Mo	Ni	Os	Pd	Pt	Rh	Ru	V	Zn
tosufloxacin tosilate	0.11	0.05	4.37	<	0.03	<	<	<	<	<	<	<	<	0.06
benazepril hydrochloride	0.36	0.52	5.17	<	0.07	<	<	<	<	<	<	<	<	1.12
captopril	0.37	0.26	0.52	<	0.10	<	<	<	<	<	<	<	<	14.4

< ; Less than lower limit of detection

Table 4: Addition and Recovery Results for Tosufloxacin Tosilate (concentrations in solution: µg/mL)

Element Name	Cr	Cu	Fe	Ir	Mn	Mo	Ni	Os	Pd	Pt	Rh	Ru	V	Zn
Pre-addition	0.011	0.005	0.437	<	0.003	<	<	<	<	<	<	<	<	0.006
Post-addition	0.997	0.994	1.423	0.978	0.987	1.010	0.991	1.003	0.981	0.996	0.978	0.977	1.000	0.989
Recovery (%)	99	99	99	98	98	101	99	100	98	100	98	98	100	98

< ; Less than lower limit of detection

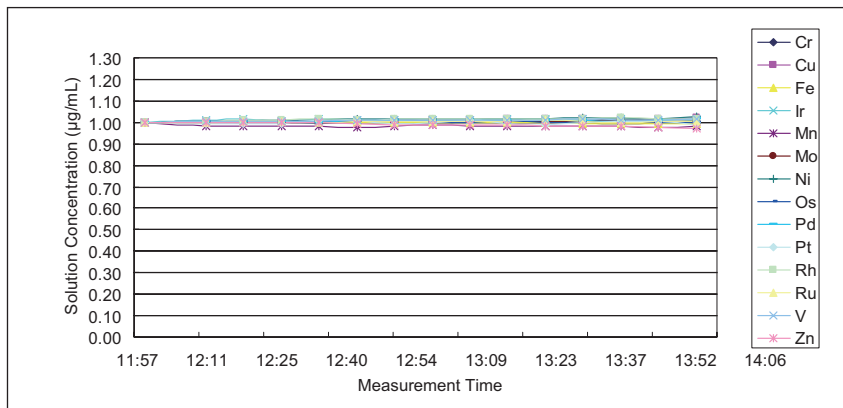
Table 5: Lower Limit for Detection (3σ) in Pharmaceutical Substance Analysis

(top row: concentrations (µg/g) in reagent powders, lower row: concentrations (µg/mL) in solution)

Element Name	Cr	Cu	Fe	Ir	Mn	Mo	Ni	Os	Pd	Pt	Rh	Ru	V	Zn
Lower Limit of Detection	0.03	0.04	0.007	0.07	0.007	0.03	0.07	0.08	0.02	0.3	0.1	0.04	0.007	0.04
	0.003	0.004	0.0007	0.007	0.0007	0.003	0.007	0.008	0.002	0.03	0.01	0.004	0.0007	0.004

Table 6: Reproducibility Results over 3 Days (units µg/mL)

Element	1 ST Day	2 ND Day	3 RD Day	RSD(%)
Cr	1.00	1.00	1.02	1.18
Cu	0.99	1.00	0.99	0.46
Fe	1.42	1.43	1.43	0.19
Ir	0.98	0.98	0.97	0.60
Mn	0.99	0.99	1.00	0.89
Mo	1.01	1.01	1.01	0.26
Ni	0.99	0.99	0.99	0.24
Os	1.00	1.00	1.01	0.66
Pd	0.98	0.98	0.99	0.85
Pt	1.00	1.00	1.02	0.96
Rh	0.98	0.97	0.97	0.55
Ru	0.98	0.98	1.00	1.35
V	1.00	1.00	1.00	0.23
Zn	0.99	0.98	0.97	0.87

**Figure 7: Variation with Time over 2 Hours**

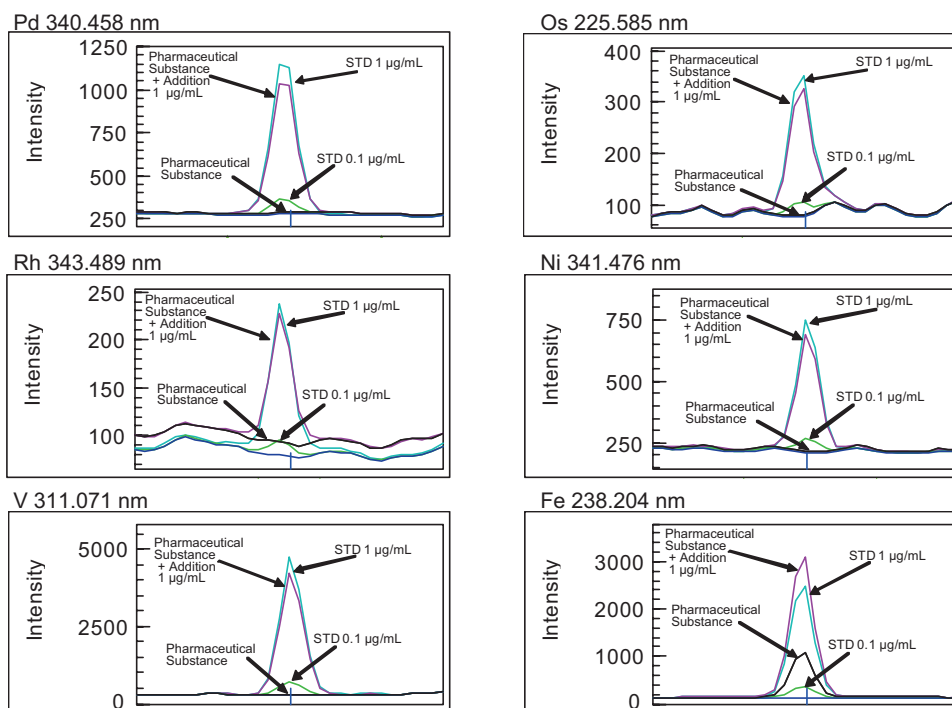


Figure 8: Spectral Curve Profile for Each Element (Calibration solution (0, 0.1, 1.0 µg/mL), Pharmaceutical substance, Standard sample addition (pharmaceutical substance + standard sample 1.0 µg/mL))

4. Summary

In this paper, an overview of the ICP emission spectrometry instrument was introduced and examples were presented for using the ICP emission spectrometry method to quantify 14 elements in pharmaceutical substances identified under the EMEA guidelines, as a method for the analysis of residual catalysts in pharmaceuticals. Currently, the Japanese Pharmacopoeia (15th Revision) lists only the colorimetric method, a test method for heavy metals, and atomic absorption spectrometry as analytical methods for metals in pharmaceuticals, and no other metal analysis methods have been adopted. However, in reviewing

the testing for metals in pharmaceuticals that has been conducted abroad over the past few years, it is certain that the ICP analytical method will be essential for the analysis of pharmaceuticals. As demonstrated in this introduction, the ICP emission spectrometry method is one of the optimal analytical methods for analyzing multiple elements, and Shimadzu's ICP-AES, which does not require the selection of a pretreatment method, offers the highest level of performance. We promise that Shimadzu's ICP-AES will be of absolute service to your business.

References

- ¹ Director of the Evaluation and Licensing Division, the Pharmaceutical and Food Safety Bureau (Iyaku Shokuhinkyoku Shinsa Kanrikan), the Ministry of Health, Labour and Welfare: Revised Guidelines on Impurities in New Drug Substances, No. 1216001, issued by the Evaluation and Licensing Division, the Pharmaceutical and Food Safety Bureau (Iyaku Shokuhinkyoku Shinsa Kanrikan) (December 16, 2002).
- ² Committee for Medical Products for Human Use (CHMP): Guideline on the Specification Limits for Residues of Metal Catalysts or Metal Reagent (Doc. Ref. EMEA/CHMP/SWP/4446/2000). London (February 21, 2008)
- ³ USP Ad Hoc Advisory Panel on Inorganic Impurities and Heavy Metals and USP Staff: "General Chapter on Inorganic Impurities: Heavy Metals," stimuli to the revision process, Pharmacopoeial Forum 34 (5), 1345-1348 (Sept.-Oct. 2008)
- ⁴ International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: ICH Harmonised Tripartite Guideline, Impurities: Guideline for Residual Solvents Q3C(R3). Step 4 version

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