

# Special Feature: Pharmaceutical Analysis (5)

## Analysis of trace impurities in pharmaceutical products using polarized EDXRF spectrometer NEX CG

Takao Moriyama\*

### 1. Introduction

The analysis of metal impurities for pharmaceutical products such as harmful elements contained in the raw materials and residual catalysts in the manufacturing process is important for the risk assessment in actual large scale production.

Various guidelines and criteria of harmful elements in pharmaceutical products have been established. According to USP<232> of the United States Pharmacopoeia (USP), pharmaceutical products are classified based on toxicity levels<sup>(1)</sup>. The European medicines agency (EMA) has set guidelines for the limit of residual metal elements<sup>(2)</sup>. Recently, the international conference on harmonization of technical requirements for registration of pharmaceuticals for human use (ICH) has proposed safety standard guidelines for metal impurities (Q3D) for the purpose of quality assurance of pharmaceutical products<sup>(3)</sup>.

ICP-MS and ICP-OES have been typically used for the elemental analysis of impurities, but XRF analysis has been increasingly attracting attention due to the ease of sample preparation.

In this article, trace element analysis in pharmaceutical samples using an EDXRF (Energy-Dispersive X-ray fluorescence) spectrometer NEX CG that has superior sensitivity compared to conventional EDX spectrometers is introduced.

### 2. Features of XRF analysis

XRF spectrometry is an analytical technique which irradiates a sample with excitation X-rays and measures the element-specific fluorescence X-ray energies emitted from the sample.

The followings are general features of XRF analysis. (1) Any sample form such as solid, powder and liquid can be analyzed. (2) Since it is a non-contact analysis, the instrument will not be easily contaminated. (3) It is possible to reuse the sample after measurement. (4) Running cost is low.

On the other hand, ICP-MS and ICP-OES require extensive sample preparation such as acid decomposition. In addition, ICP-MS with high sensitivity can analyze low concentration ppb levels, but if the sample contains elements with high concentration levels, the measurement device may be contaminated and therefore may require screening of the sample for all

elements in advance.

In comparison to these methods, XRF analysis can analyze various sample forms with sample recovery after measurement, and is able to yield elemental information in a short time. Therefore it can also be used for preventing contamination and determining sample preparation methods for ICP-MS and ICP-OES.

### 3. High sensitivity analysis of trace elements using NEX CG

The Rigaku EDXRF spectrometer NEX CG and its specifications are shown in Fig. 1 and Table 1. It does not require special utilities such as liquid nitrogen or water since it is equipped with a thermoelectrically cooled semiconductor detector and X-ray tube cooled by air.

Secondary targets and the polarized optics as shown in Fig. 2 provide a high P/B ratio spectrum compared to direct excitation optics for a wide energy range. Blue and red curves in Fig. 2 show typical spectra of a multi-element oil sample obtained by spectrometers with polarized optics and direct excitation optics. Polarized optics give greatly improved performance compared to the direct excitation optics for trace element analysis.

Furthermore, it is possible to analyze highly reactive pharmaceutical samples susceptible to heat and damage caused by the X-ray tube since the sample is not irradiated directly. The NEX CG has a wide



Fig. 1. Rigaku EDXRF spectrometer NEX CG.

Table 1. The specifications of NEX CG.

X-ray tube	Pd target, air cooled
Tube power	50W : 50 kV-2 mA (max)
Secondary targets	5 targets (max)
Detector	High performance SDD (Silicon Drift Detector)
Atmosphere	Vacuum, Air, He

\* SBU-WDX, X-ray Instrument Division, Rigaku Corporation.

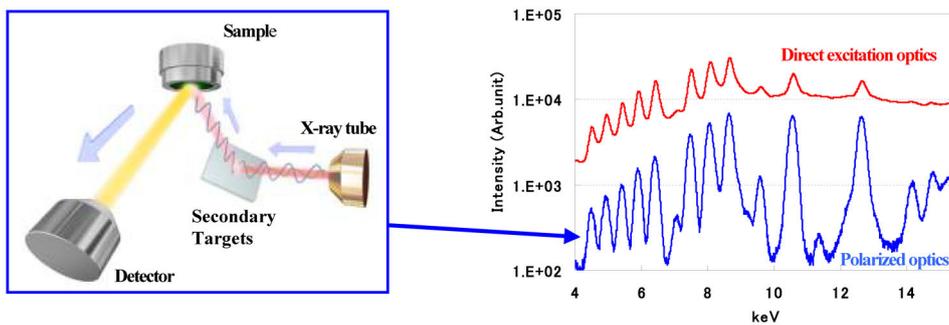


Fig. 2. Polarized optics and comparison spectra with direct excitation optics of an oil sample. (Spectra are rescaled to adjust the intensities at Mo-K $\alpha$  Compton scattered X-rays.)

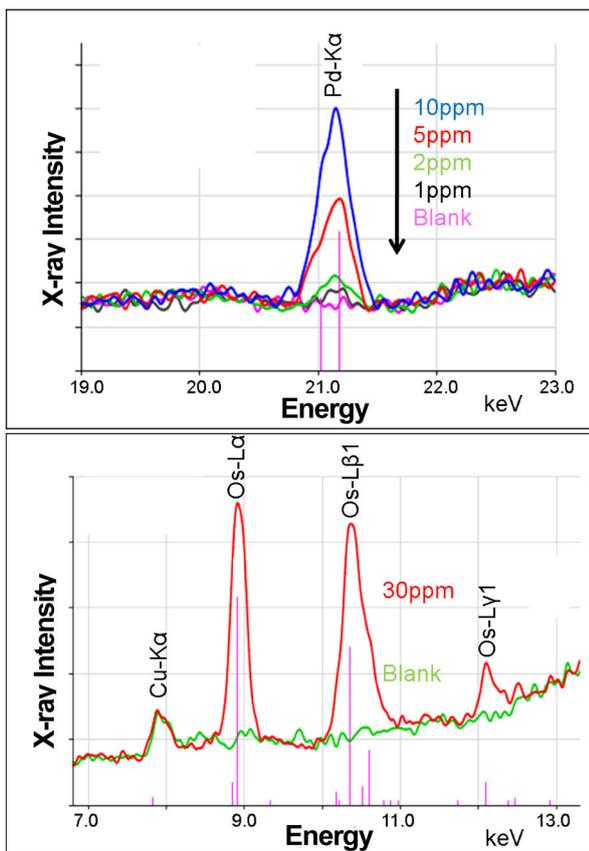


Fig. 3. (a) Pd qualitative spectra of gastrointestinal medicine and nutritional supplies. (b) Qualitative spectrum of Os.

measurement range from Na to U with high sensitivity, and especially the monochromatic excitation of the Pd-L $\alpha$  allows ppm level analysis of halogen Cl whose analysis is difficult by ICP.

**4. Analysis Example**

Figure 3 (a) shows an example of Pd catalyst residue analysis in gastrointestinal medicine and nutritional supply samples. Pd reagent was added to the sample in varying concentrations. Figure 3 (b) shows the spectrum of highly toxic Os, which is sometimes used as catalyst. The figures show that ppm level analysis is possible with easy sample preparation—the powder sample is

Table 2. The guidelines of criteria of residual metal catalysts and metal reagent (concentrations excerpted) and LLDs of NEX CG.

Unit: ppm

Classification	Elements	Oral Exposure		Parenteral Exposure	
		concentration limit	LLD <sup>a)</sup>	concentration limit	LLD <sup>b)</sup>
Class 1A	Pt	10	1.0	1	0.1
	Pd		0.9		0.6
Class 1B	Ir	10	1.0	1	0.1
	Rh		0.9		0.6
	Ru		0.8		0.6
	Os		1.0		0.1
Class 1C	Mo	25	5.0	2.5	1.5
	Ni		0.7		0.05
	Cr		0.5		0.07
	V		0.8		0.07
Class 2	Cu	250	0.8	25	0.05
	Mn		0.8		0.06
Class 3	Fe	1300	0.8	130	0.06
	Zn		0.5		0.04

a) LLDs were estimated from powdered health food products, b) LLDs when using Ultracarry light.

These LLDs are representative values. Matrix of sample can influence values.

Counting time: a) Cu target: 300sec, Mo target: 300sec, Al target: 600sec.

b) Cu target: 600sec, Mo target: 600sec, Al target: 900sec.

simply poured into a sample cup.

NEX CG can perform accurate quantitative analysis by the calibration method as well as the scattering FP (fundamental parameter) method<sup>(4),(5)</sup>. The scattering FP method is a newly developed technique that obtains accurate analysis results by automatically estimating the non-measurable organic elements using the scattering lines. This cannot be achieved with the conventional FP method.

Table 2 compares the lower limit of detection (LLD) of the NEX CG to the limitations of residue metal catalyst and metal reagents established by the EMA<sup>(6)</sup>. For oral exposure such as solid medications and supplements, NEX CG meets the concentration limits readily. Pharmaceuticals by parenteral exposure have stricter limitations than for oral exposure medications. NEX CG can meet these limitations as well by

increasing the measurement time. By using the filter paper method “Ultra carry<sup>®</sup>”, the LLD of some elements can be improved by an order of magnitude.

## 5. Conclusion

Impurity analysis in pharmaceuticals using NEX CG has been presented. The NEX CG can measure samples in various forms such as liquids and solids. Since the spectrometer’s LLDs meet most criteria established by the EMA, it can be used for quality control analysis in the manufacturing process. In addition, since the measurement causes little damage to the sample, it is possible to reuse the sample after measurement. Therefore it can also be used to determine sample preparation method and for contamination prevention for ICP-MS and ICP-OES. The high sensitivity energy

dispersive XRF NEX CG can have broad applications for the pharmaceutical industry.

## References

- (1) USP website: <http://www.usp.org/>
- (2) EMA website: <http://www.ema.europa.eu/ema/>
- (3) ICH website: <http://www.ich.org/>
- (4) T. Moriyama: *Rigaku Journal* (Japanese version), **39** (2008), No. 2, 22–25.
- (5) T. Moriyama and M. Doui: *JAPAN FOOD SCIENCE* (in Japanese) **49**, March, 2010, 51–57.
- (6) *GUIDELINE ON THE SPECIFICATION LIMITS FOR RESIDUES OF METAL CATALYSTS OR METAL REAGENTS*, European Medicines Agency, London, (2008).
- (7) T. Moriyama, Y. Yamada and H. Kohno: *Adv. X-Ray. Chem. Anal., Japan*, **36** (2005), 201–212.