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Application News

No. X278

Shimadzu EDX-7000 Energy Dispersive X-ray Fluorescence Spectrometer

Elemental Analysis in Active Pharmaceutical Ingredients (APIs) Development Using EDX: Residual Catalysts, Drug Salts, Contaminants

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User Benefits

- Chemical pretreatment of APIs is not necessary and measurement of samples as little as 0.1 g is possible.
- Unlike ICP-MS which requires complicated sample preparation, EDX requires minimal sample preparation.
- Various applications such as analysis of residual catalysts, drug salts, and contaminants are possible using EDX.

■ Introduction

Elemental analyses are carried out for various reasons during API development and manufacturing processes. For example, in the development stage, quick and simple analysis of target elements in drug salts and elements regulated in ICH Q3D [(1)] and Japanese Pharmacopoeia [(2)] is required. During acceptance and pre-shipment testing, there is also a need to check for contamination that may have occurred during the manufacturing process. Analysis by EDX is simple, does not require special sample preparation skills, and can easily be analyzed by anyone. Startup of the instrument is fast, and analysis can be carried out by just placing the sample as-is into a dedicated container. EDX can non-destructively analyze a small amount of sample with sufficient sensitivity. Hence it is especially useful for API development where samples are little and valuable.

As examples of analysis during API development, this article introduces the following examples of EDX analysis:

1. Residual metal catalysts

It is shown that quantitative analysis of Ir, Pt, Ru, Rh, Pd, and Os is possible with only 0.1 g of sample.

2. Drug Salts

Cl, Br, and S were quantified by assuming the presence of counter ions.

3. Contamination

Contaminants that could enter during the manufacturing process were analyzed using the EDXIR- Analysis™ software for EDX and FTIR.

1. Residual Catalysts

■ Elements

Under the ICH Q3D guidelines, the following Class 2B elements must be measured if they are intentionally added into pharmaceutical products. These elements were evaluated by the calibration curve method.

$_{77}$Ir, $_{78}$Pt, $_{44}$Ru, $_{45}$Rh, $_{46}$Pd, $_{76}$Os

■ Samples

The following two commercially available API powders and cellulose powder were used. Considering the possibility of reaction with the APIs, cellulose was used for the analysis of Os, as it has a composition similar to the drug material.

① Benazepril hydrochloride [(3)]
② Captopril [(3)]
③ Cellulose powder

■ Standard Samples for Calibration

Sample solutions with 6 concentration levels were prepared using the following two commercially available reagents. Table 1 shows the concentrations.

(A) USP-TXM4 (SPEX CertiPrep): Ir, Pt, Ru, Rh, Pd
(B) Os 1000 (Osmium standard stock solution) (Kanto Chemical Co.,Inc.): Os

Table 1 Concentrations of Standard Samples [µg/g]

	Ultrapure water	STD1	STD2	STD3	STD4	STD5
Ir, Pt, Ru, Rh, Pd	0	5	10	20	50	100
Os	0	5	10	20	50	100

■ Verification Samples

The verification samples were prepared by adding standard reagent (A) to samples ① and ② and adding standard reagent (B) to sample ③, and mixing the solutions until uniform [(3)]. Verification samples with the following three concentration levels were prepared.

10, 5, 0 (blank; no addition) [µg/g]

■ Sample Preparation

A constant volume of the samples, as shown below, was introduced into a sample container lined with polypropylene film and measured as-is. Fig. 1 shows the appearance of the samples.

Standard samples: 8 mL
Verification samples: 2.0 g (sufficient to assume bulk thickness)
0.5, 0.3, 0.1 g (small amounts)

Verification sample (2.0 g) Standard sample

Fig. 1 Samples

■ Calibration Curve

Fig. 2 shows the calibration curves.

Linearity was satisfactorily obtained for all six elements, as the correlation coefficient R = 0.999 or higher.

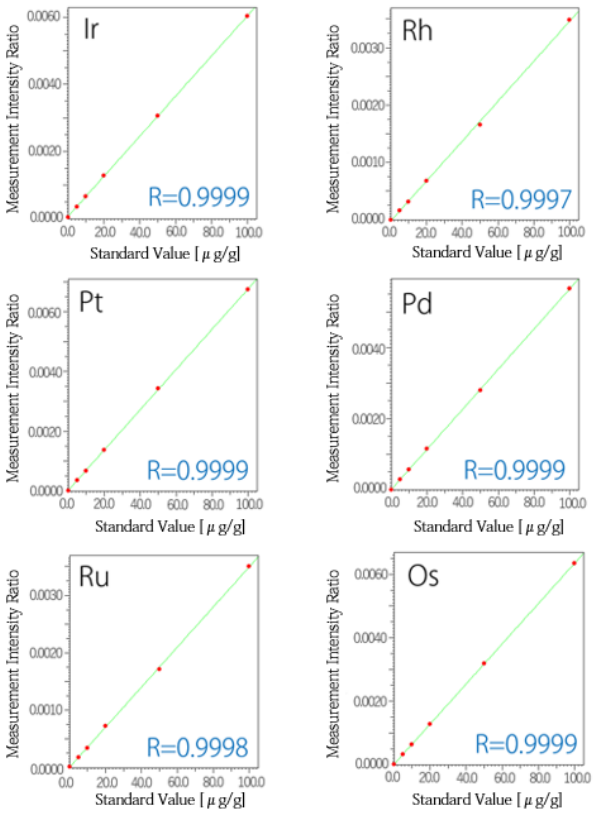


Fig. 2 Calibration Curves and Correlation Coefficient R

■ Analysis Line Profile

Fig. 3 shows the profile of the Os Lα line. A peak is clearly detected even with only 0.1 g of sample. (The other 5 elements are omitted [3])

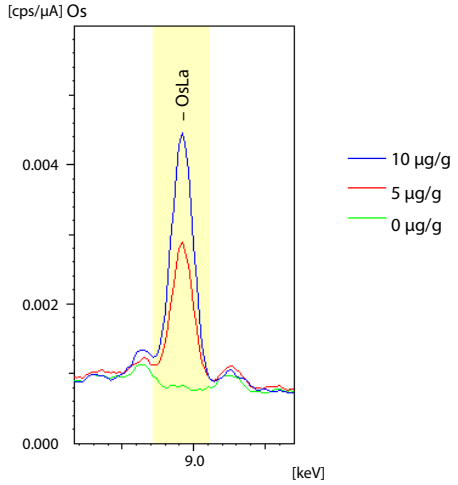


Fig. 3 Os Analysis Line Profile: 0.1 g Verification Sample

■ Analysis Results

Table 2 and Table 3 show the results of the quantitative analyses of the verification samples by the calibration curve method. The quantitation values are simply the average values of 3 repeated measurements.

(1) 2.0 g verification sample (bulk sample)

The maximum error with respect to the added concentration was approximately 8 % for all elements.

(2) 0.1, 0.3, 0.5 g verification samples (small amounts)

Values similar to those of the 2.0 g sample were obtained for all elements.

■ Discussion

Quantitative analysis with error at the order of 10 % is possible even with small amounts of samples.

Table 2 Results of Quantitative Analysis of Verification Samples (1) ① Benazepril Hydrochloride ② Captopril

[μg/g]

Concentration		10					5					0				
Element		Ir	Pt	Ru	Rh	Pd	Ir	Pt	Ru	Rh	Pd	Ir	Pt	Ru	Rh	Pd
① Benazepril Hydrochloride	2.0 g	10.2	10.2	10.3	10.0	10.7	4.8	4.9	5.1	5.3	5.3	<0.5	<0.4	<0.4	<0.7	<0.7
	0.5 g	10.2	10.2	10.3	10.0	10.6	4.9	4.8	5.3	5.3	5.1	<0.4	<0.4	<0.5	<0.7	<0.9
	0.3 g	10.5	10.7	10.3	10.0	10.8	5.0	4.9	5.4	5.4	4.9	<0.4	<0.4	<0.5	<0.7	<0.9
	0.1 g	11.0	10.9	10.3	10.0	10.6	5.0	5.0	5.3	5.2	4.8	<0.3	<0.3	<0.6	<0.8	<1.1
② Captopril	2.0 g	9.3	9.2	10.0	10.1	10.4	4.4	4.5	5.2	5.4	5.2	<0.6	<0.6	<0.4	<0.7	<0.7
	0.5 g	9.3	9.5	9.9	10.0	10.4	4.4	4.6	5.3	5.4	5.1	<0.5	<0.4	<0.5	<0.7	<0.9
	0.3 g	9.5	9.4	9.9	9.9	10.2	4.4	4.5	5.2	5.5	5.1	<0.5	<0.4	<0.5	<0.7	<0.9
	0.1 g	9.6	9.5	9.9	9.8	10.1	4.5	4.6	5.3	5.2	4.8	<0.4	<0.4	<0.6	<0.7	<1.2

Table 3 Results of Quantitative Analysis of Verification Samples (2) ③ Cellulose Powder

[μg/g]

Element		Os		
Concentration		10	5	0
③ Cellulose Powder	2.0 g	10.4	5.0	<0.4
	0.5 g	9.9	4.9	<0.3
	0.3 g	9.8	4.9	<0.3
	0.1 g	9.8	4.9	<0.3

Measurement Conditions (Residual Catalyst)

Instrument	: EDX-7000, turret unit
Elements	: Ir, Pt, Ru, Rh, Pd, Os
Analysis group	: Quantitative analysis
Detector	: SDD
X-ray tube	: Rh target
Tube voltage-current	: 50 [kV]-Auto [μA]
Collimator	: 10 [mm φ]
Primary filter	: #1 [Ru, Rh, Pd], #2 [BG], #4 [Ir, Pt, Os]
Atmosphere	: Air
Integration time	: 1800 [s] x 3 Ch (#1, #2, #4)
Dead time	: Max. 30 [%]

2. Drug Salts

The number of API molecules in a sample can be determined through a quantitative analysis of the elements that are found in the counter ions of drug salts. A quantitative analysis of Cl, Br, and S, which are constituent elements of representative counter ions, was carried out by EDX using FP method.

■ Elements

$_{13}$Al – $_{92}$U

$_{16}$S, $_{17}$Cl, $_{35}$Br : Target elements

■ Samples

The following six commercially available API powders were analyzed. For Br and S, drug salts containing these elements in the free base API or free base part were used.

① Benazepril hydrochloride
② Cetirizine dihydrochloride
③ Propranolol hydrochloride
④ 1-(4-Chlorophenylsulfonyl)-3-propylurea
⑤ Bromhexine hydrochloride
⑥ Nalidixic acid

■ Sample Preparation

0.2 g of the sample was placed in a small sample container lined with polypropylene film and measured. Fig. 4 shows an example of sample in a small sample container and a sample observation camera image.

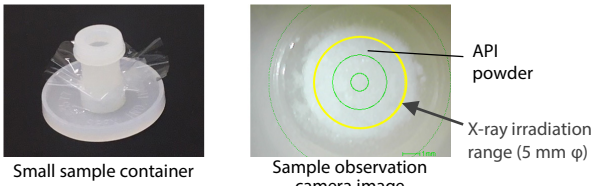


Fig. 4 Samples

■ Analysis Results

Table 4 shows the quantitative analysis results obtained by the FP method, together with the compositional formula, molecular weight, and theoretical value of the content of each sample. Analysis results with an error in the order of only ±1 % with respect to the theoretical values were obtained for all three elements Cl, Br, and S.

Fig. 5 shows profiles of the qualitative analysis results of drug salts.

■ Discussion

Although ion chromatography is generally used in analysis of counter ions, EDX is effective as a simple analysis technique.

Measurement Conditions (Drug Salts)

Instrument	: EDX-7000
Elements	: Na-U
Analysis group	: Qualitative/Quantitative analysis
Detector	: SDD
X-ray tube	: Rh target
Tube voltage	: 15 [kV] (Al-Sc), 50 [kV] (Ti-U, Br)
Tube current	: Auto [μA]
Collimator	: 5 [mm φ]
Primary filter, channel	: Non [Al-U], #2 [S-K]
Atmosphere	: Air
Integration time	: 100 [s] x 4 Ch
Dead time	: Max. 30 [%]

Table 4 Results of Quantitative Analysis and Compositional Formula, Molecular Weight, and Theoretical Value of Content of Samples [wt%]

No.	Sample	Compositional formula	Molecular weight	Theoretical value / Quantitative value	$_{17}$Cl content	$_{16}$S content	$_{35}$Br content	Balance (compositional formula)
①	Benazepril Hydrochloride	$C_{24}H_{28}N_2O_5 \cdot HCl$	460.95	Theoretical value	7.69	–	–	$C_{24}H_{29}N_2O_5$
				Quantitative value	7.51	–	–	92.49
②	Cetirizine Dihydrochloride	$C_{21}H_{25}ClN_2O_3 \cdot 2HCl$	461.81	Theoretical value	23.03	–	–	$C_{21}H_{27}N_2O_3$
				Quantitative value	23.00	–	0.002	77.00
③	Propranolol Hydrochloride	$C_{16}H_{21}NO_2 \cdot HCl$	295.80	Theoretical value	11.99	–	–	$C_{16}H_{22}NO_2$
				Quantitative value	12.90	–	–	87.10
④	1-(4-Chlorophenylsulfonyl)-3-propylurea	$C_{10}H_{13}ClN_2O_3S$	276.74	Theoretical value	12.81	11.59	–	$C_{10}H_{13}N_2O_3$
				Quantitative value	12.35	11.58	0.004	76.07
⑤	Bromhexine Hydrochloride	$C_{14}H_{20}Br_2N_2 \cdot HCl$	412.59	Theoretical value	8.59	–	38.73	$C_{14}H_{21}N_2$
				Quantitative value	8.86	–	38.81	52.33
⑥	Nalidixic Acid (Blank)	$C_{12}H_{12}N_2O_3$	232.24	Theoretical value	0	–	–	$C_{12}H_{12}N_2O_3$
				Quantitative value	0.015	–	–	99.99

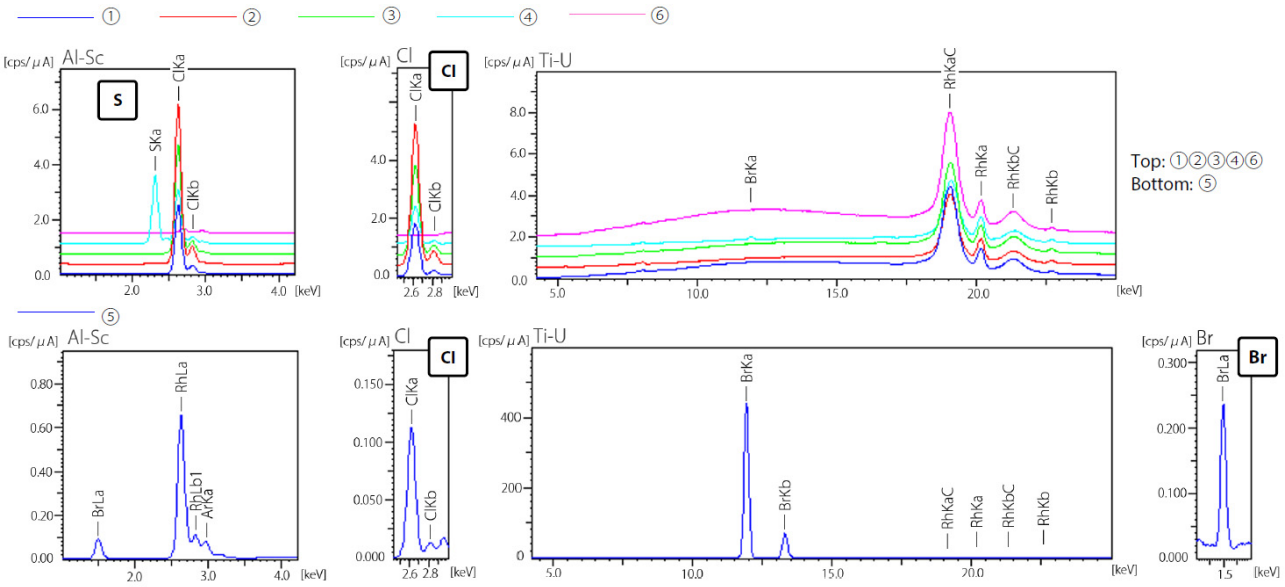


Fig. 5 Results of Qualitative Analysis of Drug Salts

3. Contaminant Analysis

Contaminant analyses such as acceptance testing of APIs are carried out during manufacturing processes. EDX is capable of measuring contaminants with sizes from several 10 µm and is particularly well-suited for detecting metals, glass, and other inorganic materials.

■ Samples

Two samples: Contaminants A and B

■ Elements

$_{11}$Na-$_{92}$U

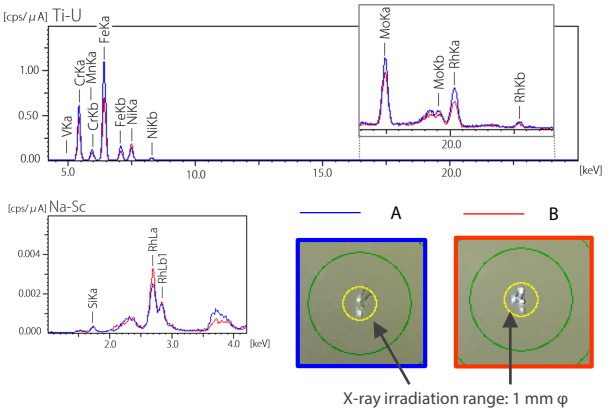
■ Sample Preparation

The samples were placed between two polypropylene films and measured.

■ Analysis Results

Fig. 6 shows the quantitative analysis results and profiles obtained by the FP method.

Because the main components were Fe, Cr, and Ni, the samples were assumed to be some kind of stainless steel.



[wt%]

Contaminant	Fe	Cr	Ni	Mn	Si	Mo	V
A	61.834	22.637	12.990	1.657	0.543	0.240	0.100
B	52.192	24.278	21.173	1.195	0.847	0.267	0.048

Fig. 6 Results of Qualitative/Quantitative Analysis of Contaminants A and B by FP Method

■ Integrated Data Analysis

Fig. 7 shows the results of an EDX analysis using the EDXIR-Analysis software. The top items of the hit lists are shown below.

A: SUH309 (heat-resistant steel)

B: SUH310 (heat-resistant steel)

In addition to conventional stainless steels, these heat-resistant steels are also registered as private library items.

Using EDXIR-Analysis software, metals and other inorganic contaminants can be identified by a single EDX analysis, and composites with organic compounds can be identified by use of EDX data in combination with FTIR data. Other examples of analysis using EDXIR-Analysis software may be found in the following Application News articles.

- X261: Contaminant Analysis in Food Manufacturing Process by EDX and FTIR
- A522A: Contaminant Analysis Using EDXIR-Analysis Software for Combined EDX-FTIR Analysis
- A535: Taking Advantage of the Contaminant Library
- A567: Combined Analysis of a Contaminant Using a Compact FTIR and EDX

Contaminant A

Rank	Similarity	ID	Sample Name	Comment
1	0.9971	0016	Contaminants (Metal) 016_SUH309	SUH309, Major elements;Fe, Cr, Ni, Mn, Mo Color;Silver Shape;Plate Hardness;Hard
2	0.9779	0456	Contaminants 456_Stainless steel_2	Stainless steel_2 Materials;Unidentified(Adsorbate on metal surface) Major elements;Fe,Cr,Ni,Mo,Mn
3	0.9779	0457	Contaminants 457_Stainless steel_2_D	Stainless steel_2 Materials;Metal Major elements;Fe,Cr,Ni,Mo,Mn Color;Silver Shape;Fragment
4	0.9717	0003	Contaminants (Metal) 003_SUS316	SUS316, Main Components;Fe, Cr, Ni, Mo, Mn Color;Silver Shape;Plate Hardness; Hard
5	0.9716	0454	Contaminants 454_Stainless steel_1	Stainless steel_1 Materials;Metal Major elements;Fe,Cr,Ni,Mn Color;Silver Shape;Metal

Contaminant B

Rank	Similarity	ID	Sample Name	Comment
1	0.9968	0017	Contaminants (Metal) 017_SUH310	SUH310, Major elements;Fe, Cr, Ni, Mn, Mo Color;Silver Shape;Plate Hardness;Hard Metallic luster;Yes
2	0.9523	0016	Contaminants (Metal) 016_SUH309	SUH309, Main Components;Fe, Cr, Ni, Mn, Mo Color;Silver Shape;Plate Hardness;Hard Metallic luster;Yes
3	0.9422	0456	Contaminants 456_Stainless steel_2	Stainless steel_2 Materials;Unidentified(Adsorbate on metal surface) Major elements;Fe,Cr,Ni,Mo,Mn
4	0.9422	0457	Contaminants 457_Stainless steel_2_D	Stainless steel_2 Materials;Metal Major elements;Fe,Cr,Ni,Mo,Mn Color;Silver Shape;Fragment
5	0.9307	0001	Contaminants (Metal) 001_SUS303	SUS303, Major elements;Fe, Cr, Ni Color;Silver Shape;Fragment Hardness;Hard

Fig. 7 Results of EDX Single Analysis by EDXIR-Analysis

Measurement Conditions (Contaminants Analysis)

Instrument	: EDX-7000
Elements	: Na-U
Analysis group	: Qualitative/Quantitative Analysis
Detector	: SDD
X-ray tube	: Rh target
Tube voltage	: 15 [kV] (Al-Sc), 50 [kV] (Ti-U)
Tube current	: Auto [µA]
Collimator	: 1 [mm φ]
Primary filter, channel	: Non [Al-U], #2 [S-K]
Atmosphere	: Vacuum
Integration time	: 100 [s] x 2 Ch
Dead time	: Max. 30 [%]

■ Conclusion

It was found that elemental analysis by EDX is effective in the development of Active Pharmaceutical Ingredients (APIs). The advantages of this technique are summarized below.

1. Simplicity

   Chemical sample preparation is not required, and measurement is possible by simply setting the drug material in the sample container.

2. Safety

   When analyzing osmium (Os) by ICP-MS, Osmium Tetroxide, which is highly volatile and toxic, may be formed in the sample preparation procedure. This is not a concern in analysis by EDX because sample preparation is not necessary.

3. Convenience

   Various applications, including analysis of residual catalysts, drug salts, and contaminants, are possible with a single instrument.

<References>
(1) Concerning Guideline for Elemental Impurities in Pharmaceutical Products (Notification of the Director of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, September 30, 2015)
(2) Supplement II to the Japanese Pharmacopoeia Seventeenth Edition (Notification No. 49 of the Ministry of Health, Labour and Welfare, June 28, 2019)
(3) Application News No. X271
ICH Q3D Elemental Impurities Analysis of Drug Substances by EDX

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