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Application News

No. X265

X-Ray Analysis

X-Ray Fluorescence Analysis of Residual Catalysts

Many familiar industrial products are made of organic compounds and their manufacturing processes involve various synthesis reactions and metal catalysts. Catalysts are mainly divided into two categories: homogeneous catalysts and heterogeneous catalysts. In general, homogeneous catalysts are used for manufacturing pharmaceuticals and chemicals. While the reactions of homogeneous catalysts can be controlled rigorously, separation of reaction products is difficult.
Meanwhile, there is a need to control the amount of residual catalysts in terms of the safety of the products and the re-use of expensive catalysts. For example, the Guideline for Elemental Impurities (ICH Q3D) enforced in April 2017 requires a risk assessment for substances, such as catalysts, that are purposely added during the manufacturing process.
This article introduces an example analysis of the amount of residual homogeneous catalyst following a synthesis reaction using the Pharmaceuticals Impurities Screening Method Package; in this example we used palladium (Pd), a substance widely used as a catalyst, for a cross-coupling reaction which is widely used for the synthesis of organic compounds.

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Sample

(1) Measurement Samples

1. Suzuki-Miyaura Cross Coupling Reaction Experiment Kit 2: sold by Wako Pure Chemical Industries
2. Silia*MetS*™ DMT metal scavenger: made by SiliCycle

We used a scientific experiment kit consisting of reagents and a catalyst, palladium acetate, for synthesizing two types of fluorophores (fluorophore 1 and 2) by employing the Suzuki-Miyaura cross-coupling reaction. A metal scavenger for palladium (Pd) was used to remove the catalyst.

(2) Calibration curve standard solution

USP-TXM 4 (standard solution made by SPEX, U.S.A.)

Solutions with six different concentration levels were prepared: blank (pure water), 1 mg/kg, 10 mg/kg, 20 mg/kg, 50 mg/kg, and 100 mg/kg.

Elements

Pd

Pretreatment and Sample Setting

Without any pretreatment, each solution was poured into a sample container, which was covered with 5 µm thick polypropylene film, until the liquid depth was 5 mm or more. The container was then directly set on the instrument stage as shown in Fig. 1.

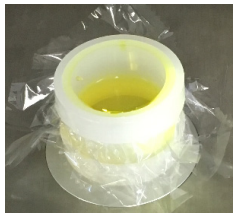

Fig. 1 Sample Set in Instrument

Calibration Curve

The calibration curve is shown in Fig. 2 and the correlation coefficient and accuracy are shown in Table 1.

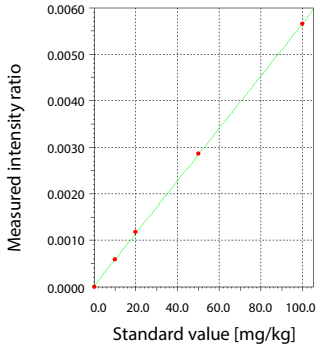

Fig. 2 Calibration Curve

Table 1 Calibration Curve Data

Correlation coefficient	0.9996
Accuracy [mg/kg]	0.36

Quantitative Analysis Results

The amount of Pd was quantitatively analyzed by the calibration curve method at three stages: ① prior to adding the catalyst, ② after adding the catalyst (adjusted value: 60 mg/kg), and ③ after separating and removing the catalyst. The results are shown in Table 2. It was found that by using the pharmaceuticals impurities screening method package, it is possible to perform an analysis in the order of mg/kg even when the integration time is substantially shortened to 300 s from the standard condition of 1,800 s.

Table 2 Quantitative Analysis Results [mg/kg]

Sample	Fluorophore 1	Fluorophore 2
①	Below the lower quantitation limit	Below the lower quantitation limit
②	64.4	70.0
③	Below the lower quantitation limit	Below the lower quantitation limit
Post-filtration powder (for reference)	(426)	(430)
Lower quantitation limit	2.3*1	

*1 Calculated from the repeatability from six measurements of the mg/kg solutions.

Measurement Conditions

Table 3 Measurement Conditions

Instrument	:	EDX-7000
Analysis Method	:	Calibration curve method
Detector/X-Ray Tube	:	SDD/Rh target
Tube Voltage - Current	:	50 [kV] - Auto [µA]
Collimator/Primary Filter	:	10 [mmϕ] / #1, #2
Measurement Atmosphere	:	Air
Integration Time/Dead Time	:	300 [sec.]/Max. 30[%] (sample)
Integration Time/Dead Time	:	1,800 [sec.]/Max. 30[%] (calibration curve)

Analysis Flow

The analysis process flow, images of the samples at each stage in analysis, and the X-ray fluorescence (XRF) spectra are shown in Fig. 3.

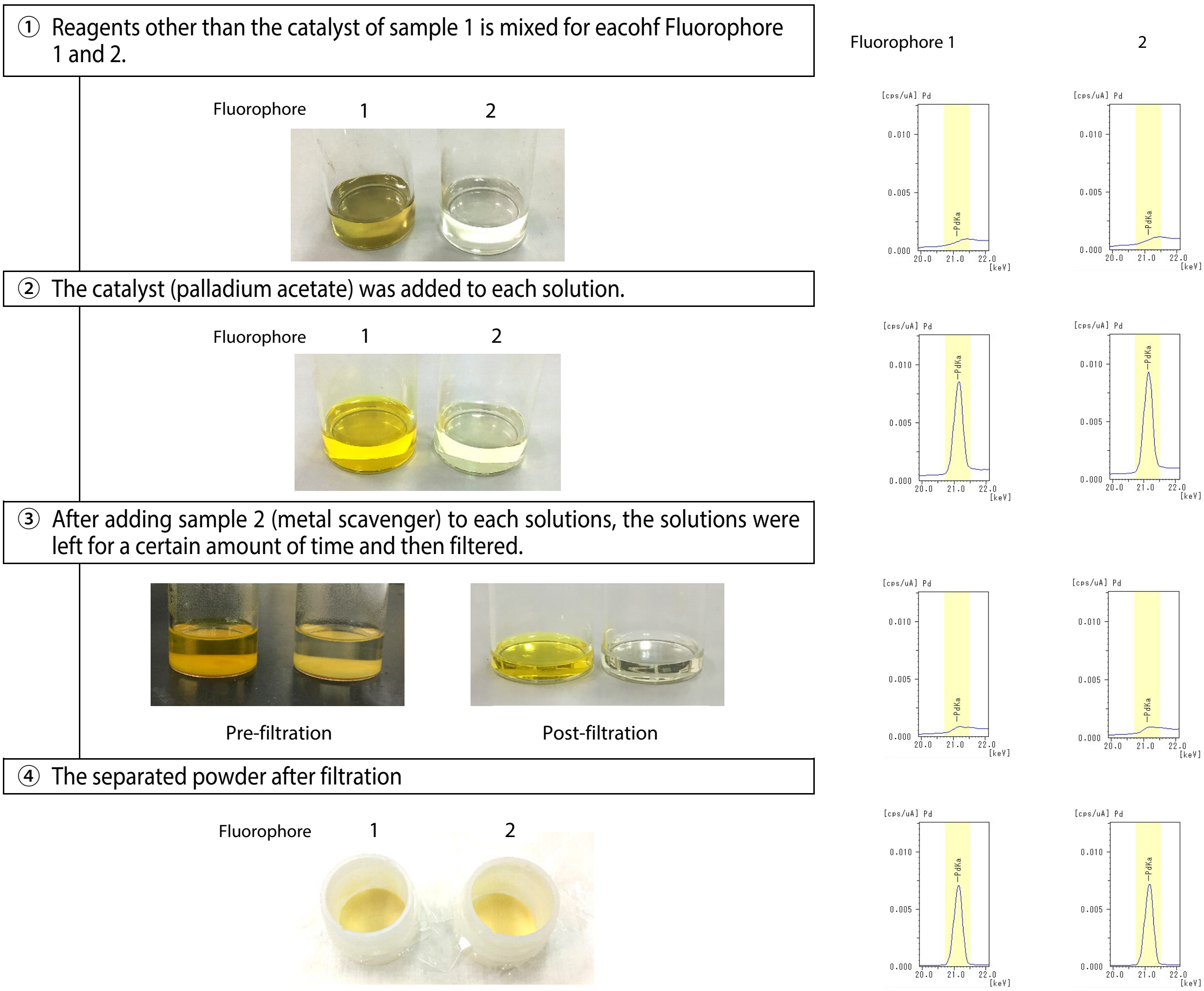

Fig. 3 Analysis Flow, Sample Images, and Analysis Results

Pharmaceuticals Impurities Screening Method Package

Elements that can be analyzed with the pharmaceuticals impurities screening method package for XRF spectrometry are shown in Table 4. Among the 24 elements listed in the ICH Q3D, a total of 12 elements can be analyzed.

Table 4 Elements That Can Be Analyzed with the Method Package

Classification	Elements
Class 1	: Cd, Pb, As, Hg
Class 2A	: V, Co, Ni
Class 2B	: Ir, Pt, Ru, Rh, Pd

Silia*MetS* is a trademark of SiliCycle Inc.

Conclusion

Methods commonly used for analyzing inorganic impurities such as atomic absorption spectrophotometry, inductively coupled plasma (ICP) atomic emission spectroscopy, and ICP mass spectrometry require the wet digestion of solid and powder samples as pretreatment. However, by using XRF spectrometry, samples of all forms can be analyzed in their original form, such as a solution or powder, without pretreatment as long as the element to be analyzed is evenly dispersed in the sample.
This study shows that by using the pharmaceuticals impurities screening method package, an analysis in the order of mg/kg can be performed even when the integration time is substantially shortened to 300 s from the standard condition of 1,800 s. The package is effective in controlling the residual amount of catalysts in accordance with control standards and target accuracy levels.

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