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Advancing impurity analysis: **X-ray fluorescence** for small molecule drug purity validation

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This paper explores the requirements for elemental analysis in pharmaceutical intermediates and final dosage forms, highlighting X-ray Fluorescence Spectroscopy (XRF) as a simple, robust alternative to traditional techniques like ICP-MS, ICP-OES, and AAS. In line with ICH Q3D guidance.

We examine the detection of elemental impurities - whether introduced through raw materials, processing, or intentionally added catalysts. We also demonstrate how energy-dispersive XRF spectrometers can be effectively used for rapid characterization across various pharmaceutical matrices.

Introduction

X-ray fluorescence (XRF) novel analytical procedure for the screening of elemental impurities in drug substances and products in compliance with compendial standards. Its ease-of-use and cost-effectiveness make it stand out compared to common methodologies (ICP-MS or ICP-OES), particularly due to low sample preparation effort, non-destructive nature of the measurements, as well as accessibility to less experienced individuals.

What is XRF spectroscopy?

XRF can be used to determine chemical composition of a wide variety of sample types including solids, liquids, slurries and loose powders.

The basic concept of all spectrometers is a radiation source, a sample and a detection system. In energy dispersive (ED) XRF spectrometers, the X-ray tube acting as a source irradiates a sample directly, and the fluorescence coming from the sample is measured with an ED detector.

This detector is able to measure the different energies of the characteristic radiation coming directly from the sample.

The detector can separate the radiation from the sample into the radiation from the different elements present in the sample.

This separation is called dispersion of XRF spectrum. The intensity of the lines in the spectrum is proportional to the concentration of the corresponding elements in the sample.

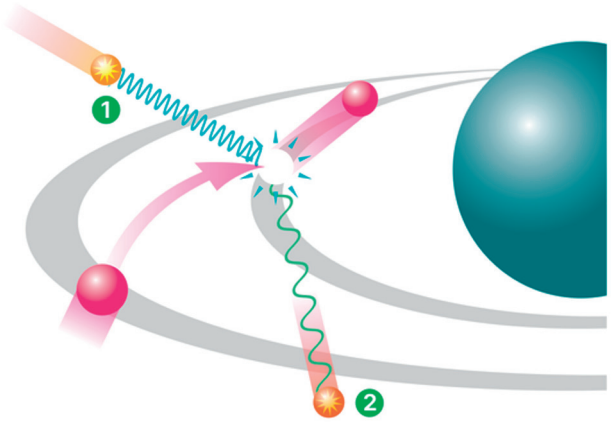

Figure 1. XRF process:
1) Incoming photon
2) Characteristic photon.

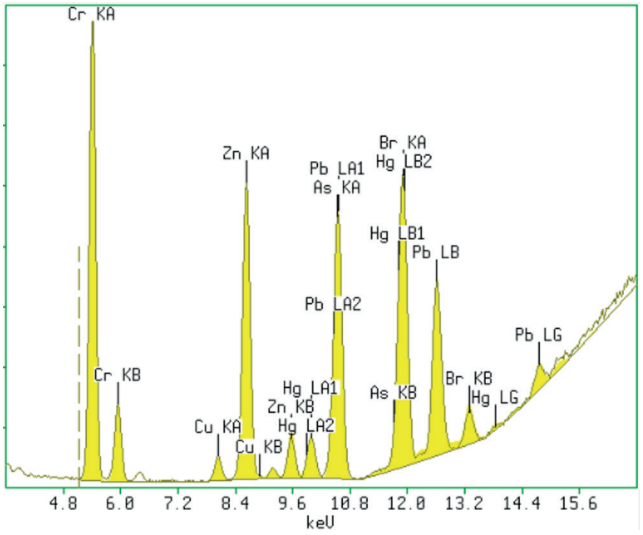

Figure 2. Typical XRF spectrum.

Advantages of XRF compared to ICP:

Introducing ED XRF into your workflow will allow you to accelerate your drug development process and shorten route to market significantly.

It's fast and non-destructive, making it a robust screening solution for the elemental purity of drug substances, pharmaceutical intermediates, and final drug products.

Figure 3. Comparison of typical ICP and XRF workflows.

Experimental

The method scope for use of ED XRF for elemental impurities screening is set as quantitative evaluation of elements in class 1, 2A, 2B and 3 (limit test). In general, the intent is for the method to distinguish between elemental impurities concentrations above or below the defined concentration limits for verifying product compliance with the guideline, such as ICH Q3D.

Revontium – High Performance Compact ED XRF spectrometer

Measurements were carried out on a Malvern Panalytical Revontium, compact ED XRF spectrometer, equipped with:

- Close-coupling patented 50 W
- 60 kV silver anode X-ray tube
- Four simultaneous high-resolution silicon drift detectors
- Sample spinner and a 32-position sample changer

Introducing Revontium into your workflow will allow you to accelerate your drug development process and shorten route to market significantly. It's fast and non-destructive, making it a robust screening solution for the elemental purity of the final product. Its versatility and ease of use make it suitable for a wide range of pharmaceutical research applications.

Element	Class[2]	Oral PDE µg/day	Parenteral PDE, µg/day	Inhalation PDE, µg/day
Cd	1	5	2	3
Pb	1	5	5	5
As	1	15	15	2
Hg	1	30	3	1
Co	2A	50	5	3
V	2A	100	10	1
Ni	2A	200	20	6
Tl	2B	8	8	8
Au	2B	300	300	3
Pd	2B	100	10	1
Ir	2B	100	10	1
Os	2B	100	10	1
Rh	2B	100	10	1
Ru	2B	100	10	1
Se	2B	150	80	130
Ag	2B	150	15	7
Pt	2B	100	10	1
Li	3	550	250	25
Sb	3	1200	90	20
Ba	3	1400	700	300
Mo	3	3000	1500	10
Cu	3	3000	300	30
Sn	3	6000	600	60
Cr	3	11000	1100	3

Table 1. Permitted daily exposures for elemental impurities (from ICH Q3D guideline).

Set-up samples for calibration of Revontium

Three sets of Malvern Panalytical cellulose-based setup samples were used for determining acceptable limits of elemental impurities and permitted daily exposure.

The sets cover twenty elements mandated in USP <232> and ICH Q3D (Cd, Pb, As, Hg, Co, V, Ni, Tl, Pd, Ir Rh, Ru, Se, Pt, Sb, Ba, Mo, Cu, Sn, and Cr) in concentrations ranging from 0 to 200 mg/kg (ppm).

USP <232/233> and ICH Q3D

USP <232/233> and ICH Q3D are new chapters/guidelines requiring testing and controlling of elemental impurities in drug products. These norms cover the following:

Stipulate Permitted Daily Exposures (PDEs) for 24 potential elemental impurities across three administration routes (oral, parenteral, and inhalation).
Describes analytical procedures for testing and includes options for alternative techniques including XRF.

Results and discussion

Three sets of cellulose-based setup samples were measured to determine acceptable limits of elemental impurities and permitted daily exposure of 10g daily dose. The limit of quantification (LoQ) was calculated based on the relative standard deviation (RSD) of repeated measurements of 1 mg/kg spiked samples. Investigated samples contain twenty elements mandated in USP <232> and ICH Q3D (see Table 1).

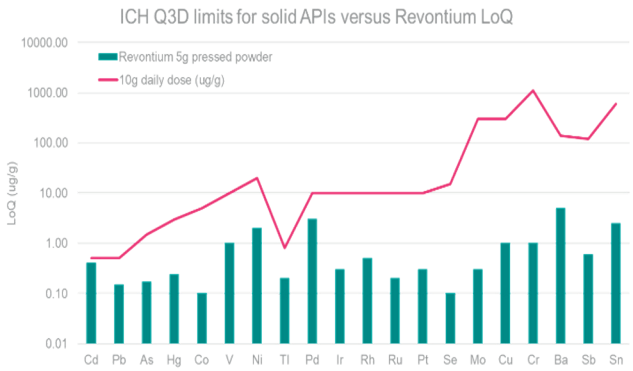

Figure 4: Limits of quantification (LoQ) in clean cellulose set-up sample (petrol bars) presented next to the limits set in the ICH Q3D guideline (magenta line).

The results presented in Figure 4 show that the developed method can be used as a limit test for most of class 1, 2A, 2B and 3 elements at the defined specification limits, even at 10g daily dose, and is fully compliant with method validation requirements.

Benefits of XRF over ICP

- Measure substances as they are (solids, liquids, slurries)
- No need to dissolve the powders: saves operator time, avoids sample preparation errors, and reduces ecological footprint by avoiding the use of hazardous reagents
- Non-destructive analysis: after the measurement, the exact same sample can be analyzed further using other techniques
- Up to 50% lower operational costs than ICP
- No need for expensive and aggressive acids, nor for gases
- Easy operation: no need for extensive training or complex data analysis
- At-line analysis: analysis closer to the production line
- XRF has been approved as an alternative method for metal impurity testing (USP <735>)

Figure 5. Drug substance development: where can XRF help?

Summary

This study demonstrates the capability of energy dispersive XRF, specifically compact XRF Revontium, for elemental impurities screening.

ED XRF, and Revontium in particular, can address analytical questions around elemental purity throughout the whole drug development process for both innovator and generic type of small molecule pharmaceuticals (Figure 5 above).

The developed method can be used as a limit test for class 1, 2A, 2B and 3 elements as per ICH Q3D guideline. Revontium achieves compliance with the guidelines from US Pharmacopeia (232, 233, 735) and European Pharmacopoeia (2.2.37), in less than 30 minutes per sample,.

This study proves that EDXRF is an approved alternative method for testing metal impurities in line with USP <735>. As initially proposed, EDXRF represents an economic alternative for elemental impurities screening within the pharmaceutical industry.

References

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