

MINIPAL 4 PHARMA

Trace element analysis of heavy metals in pharmaceutical materials



Introduction

The word pharmaceutical defines an industry, study or a material (commonly referred to as medicine), that is meant as remedy for a disease or illness in either animals or humans. Throughout the globe there are many definitions of medicine and regionally-based regulatory-bodies define which materials may be sold over-the-counter or require prescription.

The pharmaceutical industry is heavily regulated beyond all other industries. This is for a good reason because many of the materials produced are potentially dangerous and can be severely toxic if not manufactured with proper care. Regulation has led to the mandatory examination of all substances from starting materials to finished products. Generally this includes the proof of product stability, drug-release profiles, Active-Pharmaceutical-Ingredient (API) form, API quantification, and product safety including sterility (for non-biological materials) and foreign materials including heavy-metals.

One of the most common product safety-related analytical tests (often referred to as a Limit Test) is the quantification of heavy metals or inorganics in all materials within a pharmaceutical product. This normally includes the toxic heavy metals such as As, Hg and Pb. Most of the elements identified for heavy metal Limit Testing have been well documented as significant health risks with numerous effects from organ failure to blindness and even death.

It is also common practice to measure catalysts, such as Pd and Pt, which are also well classified toxic elements. Throughout the manufacturing processes there are many potential sources of contamination. Therefore, in addition to measuring the starting materials it is essential to measure all finished products and in some cases intermediates, to demonstrate the compliancy with the various regulations.

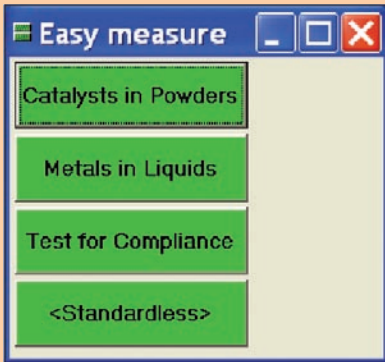
The MiniPal 4 Pharma is an EDXRF benchtop instrument that is designed for the analysis of a wide variety elements from Na to U. To demonstrate the performance of the MiniPal 4 Pharma, seven heavy metals representing contaminants, stainless steel residuals and catalysts that are commonly analyzed were tested in pharmaceutical materials. This rapid analysis was conducted with minimal sample preparation.

MiniPal 4 Pharma
EDXRF bench-top spectrometer
PANalytical's MiniPal 4 Pharma energy-dispersive XRF bench-top spectrometer performs non-destructive analysis of elements from sodium to uranium, in concentrations from 100 % down to $\mu\text{g/g}$ levels. MiniPal 4 Pharma offers high levels of sensitivity and versatility. Featuring a new Silicon Drift Detector, with currently the best resolution in this market segment, it demonstrates high maximum count rates and an excellent resolution, improving accuracy, precision and lower limits of detection. MiniPal 4 Pharma is one of the smallest full-function spectrometers currently available. With a mass of only 28 kg, it is configured with a 12-position sample changer, a helium gas attachment for light element analysis and a Mo anode X-ray tube. Installation and application set-up are further simplified by a Quick Start Guide that is supplied as part of the package.

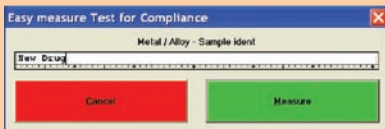
Easy measure mode

- Operator friendly
- 21 CFR Part 11 - ready

1. Choose method



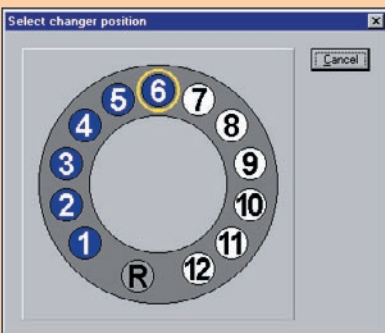
2. Identify sample



3. Sign for analysis



4. Identify sample location



Preparation of standards

A common excipient material (pharmaceutical grade cellulose) was chosen as a base material. In-house standards were prepared using ultra-pure commercially available organo-metallic standards comprising 7 heavy-metals. The materials were chosen to

represent a large area of the periodic table ranging from medium to heavy transition metals (Cr to Pt). Standard chemical techniques were employed to dope the cellulose and produce a set of multiple concentration standards. Standard concentrations were confirmed by ICP-MS.

Instrumentation and measurement conditions

The measurements were performed using a MiniPal 4 Pharma EDXRF spectrometer, equipped with a molybdenum anode X-ray tube, 5 tube filters, a helium purge facility and a high-resolution silicon drift detector.

The measurement conditions for the various heavy-metals in a cellulose matrix are listed in Table 1.

Multiple elements can be measured with a single condition set. This degree of simultaneous data collection led to a total counting time of 15 minutes per sample.

Loose powder samples, weighing approximately 2500 mg were placed directly into disposable P1 sample cups with an X-ray transparent polypropylene foil (6 µm). All samples were tapped lightly to remove air voids and measured directly. All analyses were performed in an air atmosphere.

Where ever possible the intensities of the all elements are measured using K α lines. However due to power limitations of benchtop XRF technology some elements such as Pt are restricted to using L α lines.

Element	Voltage (kV)	Current (µA)	Medium	Tube filter	Counting time per sample (s)
Cr	20	400	Air	Al	300
As, Ni, Pt, Se	30	300	Air	Ag	300
Pd, Ru	30	300	Air	Cu	300

Table 1. Measurement conditions

An example of a the typical spectrum collected for this application is illustrated in Figure 1.

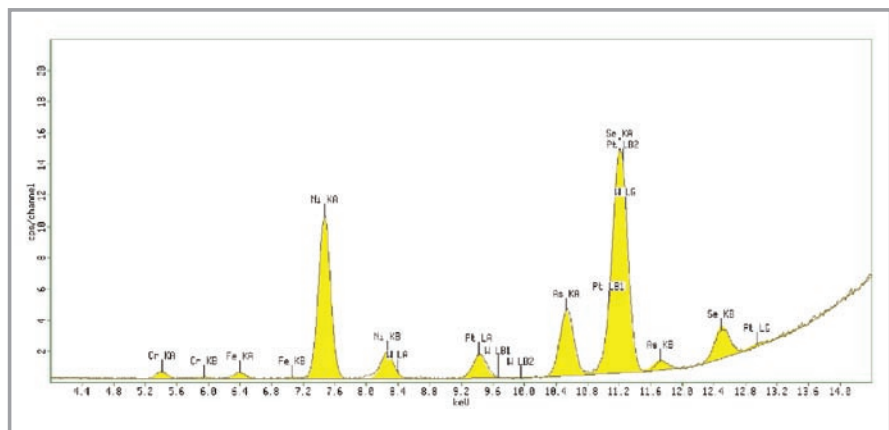


Figure 1. Typical spectrum of cellulose excipient materials using 20 kV, 400 µA and Al filter)

Calibration results

Calibration graphs were set up using the regression model of the MiniPal software. Figures 2 through 4 show calibration plots for Pt, As and Ni using multiple in-house standards of cellulose doped excipient materials.

The plots demonstrate a good correlation between the expected concentration and the measured intensities. The calibration results for all analyzed elements are shown in Table 2. The root mean square (RMS) error listed in Table 2 is a measure

of the difference between the calculated concentration and the chemical concentration and is therefore a measure of the accuracy of the method. However, the magnitude of the calibration RMS value is dependent on the range of concentrations in the calibration. A weighted error estimate, the K-value, is independent of the concentrations and gives a more reliable indication of accuracy. The lower K-value the more accurate the calibration.

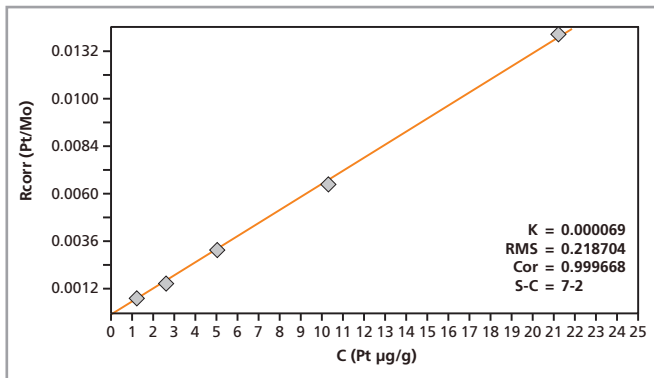


Figure 2. Calibration plot for Pt in cellulose excipient material

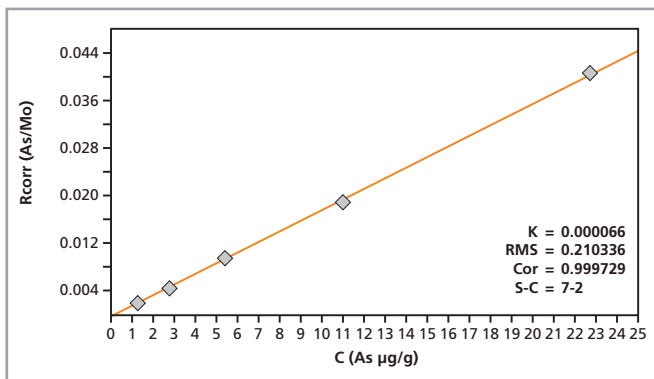


Figure 3. Calibration plot for As in cellulose excipient material

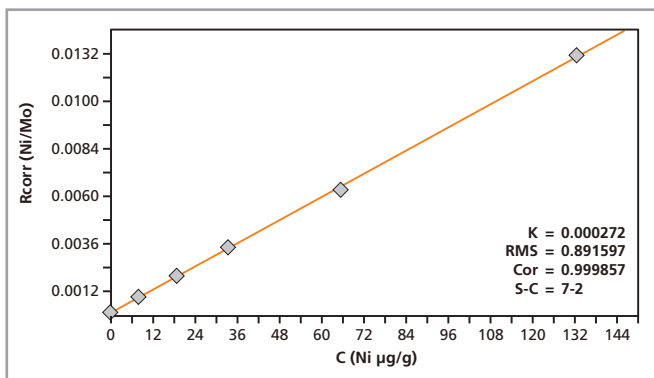


Figure 4. Calibration plot for Ni in cellulose excipient material

Element	Concentration range (µg/g)	RMS (µg/g)	K-value	Correlation
As	0 – 22.7	0.2	0.0001	0.9997
Cr	0 – 20.7	0.1	0.0001	0.9998
Ni	0 – 132.6	0.9	0.0003	0.9999
Pd	0 – 300	3.8	0.0011	0.9995
Pt	0 – 21.3	0.2	0.0001	0.9997
Ru	0 – 21.1	2.5	0.0008	0.9558
Se	0 – 84.7	2.3	0.0007	0.9975

Table 2. Calibration results for heavy metals in a cellulose excipient

Sample changer and spinner

The MiniPal 4 Pharma is equipped with a 12-position removable sample changer enabling unattended batch analysis. It is possible that pharmaceutical samples may show heterogeneity affecting the precision and accuracy of the analysis. Fortunately, rotating or spinning the sample in the X-ray beam can average out these heterogeneities. For this reason, a robust sample spinner is included in the MiniPal 4 Pharma system.

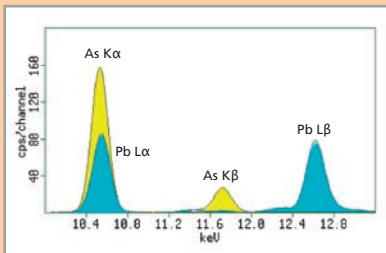


High resolution Silicon Drift Detector

Because of the high resolution of the Silicon Drift Detector in the MiniPal 4 Pharma (typically 145 eV for Mn-K α), deconvolution of the spectra can be carried out more accurately leading to better results.

Powerful MiniPal software

Even with the best detector resolution, some elements cannot be separated in the XRF spectrum. These line overlaps seriously affect the quality of trace element data and accurate line overlap correction in the software is important. In the MiniPal software, line overlap problems are taken care of by spectrum deconvolution based on the AXIL algorithm developed by the University of Antwerp (Belgium). An example of the line overlap handled by this deconvolution is the overlap of Pb L α line on As K α line in the analysis of arsenic.



Analytical precision

To demonstrate the long-term analytical precision of the MiniPal 4 Pharma spectrometer, one excipient sample was measured seven hundred times without any recalibration.

Standard #5	As	Cr	Ni	Pd	Pt	Ru	Se
Average conc. (µg/g)	22.3	20.9	137.5	18.7	22.2	19.2	75.9
RMS (µg/g)	0.2	0.4	0.8	3.2	0.3	1.4	0.97

Table 3. Results of the precision test (700 measurements)

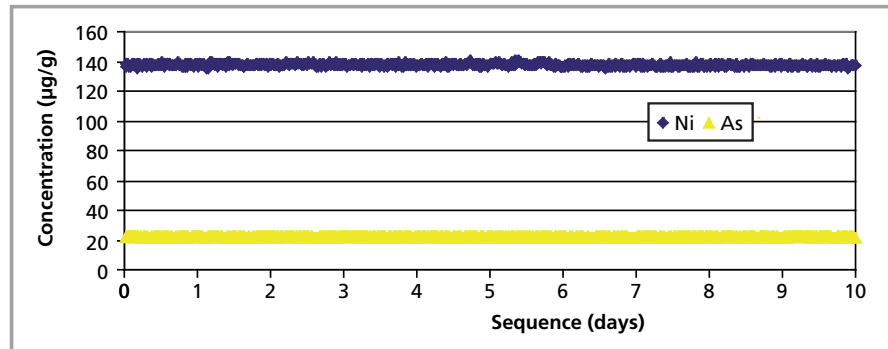


Figure 5. Precision results (approximately 700 measurements over 10 days) for nickel and arsenic in cellulose excipient without recalibration

Detection limits

The detection limits (using the application measurement times) for the metals studied are presented in Table 4. Here two commonly used excipient materials are compared representing the range of limits that can be expected with most organic pharmaceutical products.

Detection limits (µg/g)	As	Cr	Ni	Pd	Pt	Ru	Se
Cellulose (LLD)	0.2	0.4	0.3	9.0	0.6	4.5	0.3
Lactose (LLD)	0.2	0.4	0.5	7.2	0.4	4.2	0.2

Table 4. Excipient detection limits using application method settings

The average concentration and RMS error are presented in Table 3. The precision for Ni and As are illustrated graphically in Figure 5.

The lower limit of detection is calculated from:

$$LLD = \frac{3}{s} \sqrt{\frac{r_b}{t_b}}$$

Where:

s = sensitivity (cps/µg/g)

r_b = background countrate (cps)

t_b = counting time background (s)

Conclusion

The results from this study clearly demonstrate that the MiniPal 4 Pharma EDXRF spectrometer is well suited for the analyses of pharmaceutical materials including excipients, API's and finished products. The repeatability results demonstrate the long-term stability and robustness of the MiniPal 4 Pharma. Good results are demonstrated for the regressions and lower limits of detection. High detector resolution and powerful software correction models contribute to this result. Furthermore, the compact size and low weight of the spectrometer makes it an ideal system for investigations and limit testing of heavy metals in pharmaceuticals.

Global and near



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