ELEMENTAL IMPURITY ANALYSIS IN PHARMACEUTICALS

ICP-OES

Addressing the new ICH and USP methods for measuring elemental impurities in pharmaceutical materials

New methods for determining elemental impurities must be implemented by the pharmaceutical industry

Control of impurities, including elemental (inorganic) contaminants, has always been a critical issue in the development and production of pharmaceutical products. However, the previous US Pharmacopeia (USP) method for trace metals, USP<231> (heavy metals limit test), though widely used, did not give adequate information regarding the potential toxicity of these contaminants. USP <231> was not specific or quantitative, had limited scope, and often gave poor recoveries for volatile analytes, which were lost during the high temperature ashing step.

To address these limitations, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and USP have released new, harmonized, performance-based methods: ICH Q3D, USP<232> (limits), and USP<233> (procedures) for determining elemental impurities in pharmaceutical products and raw materials. A related method, USP<2232>, applies to dietary supplements.

ICH Q3D and USP<232> define the target analytes and permitted daily exposure (PDE) limits based on toxicological data rather than method capability, and require the quantitative determination of individual metal concentrations, in place of the previous sulfide precipitate test in USP<231>.

The twenty-four target analytes in ICH Q3D and USP<232> include the "Big Four" Class 1 elements: arsenic (As), cadmium (Cd), mercury (Hg) and lead (Pb) which are controlled at the lowest levels and must be assessed in all drug products. Additional regulated elements should be limited in drug products and must be measured if they may have been introduced during the formulation process (e.g. in raw materials, metal catalysts, Pt, Pd, etc), or as a result of production processes.

The reference analytical techniques suggested in the new methods are ICP-MS and ICP-OES, replacing the colorimetric test used in the earlier methods.

Both ICP-OES and ICP-MS can determine all the regulated elemental impurities at the "J" value levels required for direct analysis of oral drug products. The "J" value is the maximum level for each element and is calculated from the target PDE limit in the test sample, corrected for the sample preparation dilution; i.e. "J" is the PDE equivalent concentration in the sample solution as analyzed.

ICP-OES has benefits of sensitivity in the presence of high matrix loads, simplicity of operation and high throughput speed.

Agilent Technologies

Measure tough samples

Agilent's 5110 ICP-OES is an ideal instrument for pharma labs focused on oral dosage raw material and drug products requiring little to no sample dilution. Its vertical torch allows the analysis of a wide range of samples, including those with total dissolved solids content around 25%. The vertical torch gives long term analytical stability on the toughest samples and can easily handle a variety of sample matrices – such as aqueous and organic solvents.

Figure 1 demonstrates the resolution and sensitivity capabilities of the 5110 ICP-OES for an organic matrix for pharmaceutical analysis – an oil sample dissolved in solvent. The sample was diluted 10 times and aspirated directly into the instrument. The instrument can easily measure the USP's target limit (J value) of 50 µg/L for Cd at this dilution.

Get accurate results, quickly

The Vista Chip II detector in the 5110 ICP-OES has very wide wavelength coverage and has a high clocking speed. It is able to measure all wavelengths, from 167—785 nm in a single measurement. This easily allows the selection of wavelengths that are free from interferences and its fast processing speed reduces analysis time.

This capability allows multiple wavelengths to be used as an unequivocal confirmation of concentration accuracy. This is done by verifying the calculated concentration from primary emission wavelengths against the calculated concentration at alternate emission wavelengths for the same element. Table 1 shows the results of an "in method" verification of Cd concentration, performed by simultaneously measuring two separate Cd emission wavelengths three times, giving the analyst confidence of accurate results, unaffected by interferences.

The 5110 ICP-OES has both Fitted background correction and FACT (Fast Automated Curve fitting Technique) which is a spectral deconvolution algorithm used to correct for spectral overlap. The analyst can use the unique default Fitted background correction, which is an algorithm that automatically selects the best background points. Fitted background correction reduces method development time and reduces complexity for the analyst. Figure 1 also shows the dotted line under the spectrum which illustrates the automated placement of the Fitted background correction.

FACT is able to be quickly developed to subtract spectral overlaps. FACT is a simple, but powerful tool that does not require special software settings or changes in optics configurations in order to subtract spectral interference.

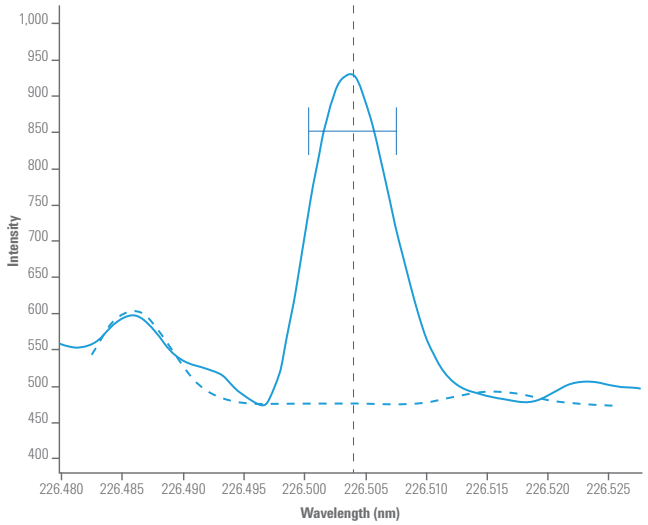

Figure 1. The emission signal of 35 µg/L Cd at 226.502 nm, in an oil sample, dissolved in kerosene. The Cd spectrum is clearly resolved, despite the presence of 21 elements in the sample.

The Agilent 5110 ICP-OES revolutionizes ICP-OES analysis. It is designed to run your samples faster, use less gas, without compromising performance on your toughest samples. A range of hardware and software facilitates elemental impurity analysis on pharmaceuticals. The Vista Chip II detector and ICP Expert software creates simple, fast analysis that is reproducible from analyst to analyst, lab to lab.

Table 1. Measured concentration of 35 ppb Cd in an oil sample at two different emission wavelengths. The correlating results give in-method confirmation of the Cd results with no time penalty for the analysis.

Measurement	Measured Concentration (µg/L)of Cd at 214.439 nm	Measured Concentration (µg/L)of Cd at 226.502 nm)
1	37.4	35.4
2	39.3	34.5
3	36.1	34.8

For more information:
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