The determination of the palladium content in valacyclovir hydrochloride using an Agilent 720 ICP-OES according to USP 35

Application note

Pharmaceutical

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Introduction

The control of impurities from catalysts or raw materials (e.g. plants, animal proteins, rDNA) and excipients (stabilizers, fillers, binders, release agents, flavors, colors and coatings) has always been a critical issue to the pharmaceutical industry. Traces of inorganic impurities can not only be toxic, but can also have less immediate effects such as reducing the stability and shelf life of pharmaceutical products. The U.S. Food and Drug Administration (FDA) and the British Pharmacopeia (BP) strongly advise that contamination problems be fully investigated in a timely fashion.

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For testing of pharmaceutical samples, laboratories require instruments that have the flexibility to handle a wide range of sample matrices, while also meeting ever decreasing detection limit requirements. The instrumentation must also be capable of delivering accurate and precise results while meeting the strict requirements of the regulations specified by the U.S. Pharmacopeia (USP).

In this work, the active pharmaceutical ingredient (API) valacyclovir hydrochloride was analyzed. Valacyclovir hydrochloride is an anti-viral drug used in the treatment of the herpes virus. Samples were analyzed for the presence of the impurity palladium (Pd), which is a required analysis in the official monographs in USP 35.

Experimental

Instrumentation

An Agilent 720 ICP-OES with axially viewed plasma was used for the analysis. The Agilent 720 ICP-OES features a custom designed Charge-Coupled Detector (CCD) which provides true simultaneous measurement, full wavelength coverage from 167 to 785 nm and fast read-out enabling short sample analysis times. The optical system is housed within a thermally stabilized environment at 35 °C and contains no moving parts, ensuring excellent long-term stability. The polychromator can be purged with either argon or nitrogen gas for improved performance when measuring at low UV wavelengths. The robust RF system of the 720 ICP-OES is capable of handling a wide range of samples, including challenging organic samples, such as dimethyl sulfoxide (DMSO).

An Auxiliary Gas Module (AGM 1) was used to inject oxygen into the plasma to prevent the buildup of carbon on the torch injector from the incomplete combustion of the carbon present in the organic sample matrix.

Method conditions used in the analysis are shown in Table 1.

Table 1. Method conditions used in the analysis of Pd using the Agilent 720 axial ICP-OES

Parameter	Setting
RF power	1.35 kW
Plasma flow	15.0 L/min
Auxiliary flow	2.25 L/min
Nebulizer flow	0.60 L/min
Replicate read time	3 sec
Replicates	3
Sample uptake delay	20 sec
Stabilization delay	15 sec
Rinse time	20 sec
Wavelength	Pd 340.458 nm
Oxygen flow (via AGM 1)	7 units (200 - 300 mL/min)
Torch	1.4 mm ID injector
Nebulizer	Conikal

Sample preparation

A 98:2 mixture of dimethyl sulfoxide (DMSO) and hydrochloric acid (HCl) was used as the blank and diluent (as defined in the official monograph relating to the analysis of valacyclovir hydrochloride). Standards were prepared from single element Pd standards and diluted with the diluent.

Three samples of the API were taken at random and 0.10 g of the sample was weighed into a 10 mL standard flask, followed by the addition of the diluent up to 10 mL. These samples were labeled Sample A, Sample B and Sample C. Pd was added to Sample C at concentrations of 0.05 ppm, 0.10 ppm and 0.20 ppm to test spike recoveries.

Results

Detection limits

The Instrument Detection Limit (IDL) is expressed as three times the standard deviation of nine replicate measurements of the blank. The Instrument Quantitation Limit (IQL) is expressed as ten times the standard deviation of nine replicate measurements of the blank. The IDL and IQL for Pd in the DMSO:HCl matrix blank are shown in Table 2.

Table 2. Instrument Detection Limit and Instrument Quantification Limits for Pd in the DMSO:HCl matrix, reported in ppb

Element	IDL (ppb)	IQL (ppb)
Pd	1.0	3.5

Calibration linearity

The USP official monograph requires that the correlation coefficient to be not less than (NLT) 0.999. To test this requirement, a calibration was performed using a diluent blank and six Pd standards, spanning the concentration range from 0.01 ppm to 0.50 ppm. The resulting calibration curve is shown below in Figure 1 and shows excellent linearity over the calibration range. The correlation coefficient obtained in the experiment was 0.999743, easily meeting the requirement of NLT 0.999.

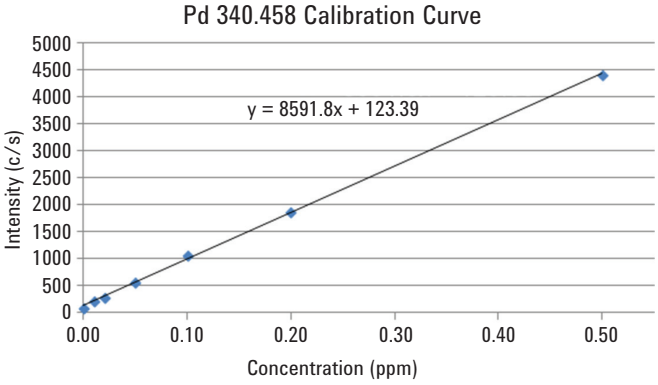

Figure 1. Calibration curve for Pd obtained on the 720 ICP-OES

Sample analysis

Each API sample was measured in triplicate. The concentration results for Pd are corrected for the dilution factor applied during sample preparation (Table 3). The results show the excellent precision and stability that can be obtained on the 720 ICP-OES when analyzing this challenging matrix.

Table 3. Results for the triplicate analysis of three samples of the API. Results are shown as the concentration in the sample.

Label	Number of determinations	Pd 340.458 nm Concentration µg/g (ppm)
Sample A	Measurement-1 (0.10039 g/10 mL)	3.59
	Measurement-2 (0.10014 g/10 mL)	3.56
	Measurement-3 (0.10009 g/10 mL)	3.65
	Average, µg/g (ppm)	3.60
	Stdev	0.04
	RSD %	1.25
Sample B	Measurement-1 (0.10065 g/10 mL)	3.33
	Measurement-2 (0.10063 g/10 mL)	3.25
	Measurement-3 (0.10001 g/10 mL)	3.30
	Average, µg/g (ppm)	3.29
	Stdev	0.04
	RSD %	1.27
Sample C	Measurement-1 (0.09800 g/10 mL)	0.43
	Measurement-2 (0.10025 g/10 mL)	0.44
	Measurement-3 (0.1005 g/10 mL)	0.43
	Average, µg/g (ppm)	0.43
	Stdev	0.01
	RSD %	1.53

Spike recoveries

Recoveries of the Pd spikes in Sample C are shown in Table 4. Recoveries for the three spikes of increasing Pd concentration were within 100% to 108%, which is well within the 80% to 120% limits required in the USP monograph.

Table 4. Recoveries for Pd spikes in Sample C. Results are shown as the concentration in the solution

	Sample ID	Pd 340.458 nm Result µg/mL (ppm)
Spike-1: 0.05 ppm	Sample C	0.0043
	Sample C-Spike-1: 0.05 ppm	0.0547
	Spike amount	0.050
	Spike sample	0.050
	Recovery (%)	100.9
Spike-2: 0.1 ppm	Sample C-Spike-2: 0.10 ppm	0.1070
	Spike amount	0.100
	Spike sample	0.103
	Recovery (%)	102.7
Spike-3: 0.2 ppm	Sample C-Spike-3: 0.20 ppm	0.2207
	Spike amount	0.200
	Spike sample	0.216
	Recovery (%)	108.2

Conclusion

This work has demonstrated the ability of the Agilent 720 ICP-OES with axially viewed plasma to accurately measure Pd in a tough organic matrix to the requirements of the USP 35 monograph relating to the analysis of the API valacyclovir hydrochloride. This includes:

- Excellent sensitivity with an IDL of 1.0 ppb and IQL 3.5 ppb
- A linear calibration curve for Pd with a correlation coefficient of 0.999743, meeting the analytical requirement of NLT 0.999
- Spike recoveries ranging from 100% to 108%, well within the limits of 80% to 120%

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