Semiquantitative Screening of Pharmaceutical Antiviral Drugs using the Agilent 7500ce ICP-MS in Helium Collision Mode

Application Note

Pharmaceutical

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Abstract

Rapid semiquantitative elemental screening of pharmaceutical samples is described using the Agilent 7500ce ICP-MS with helium as collision gas. Polyatomic interferences are eliminated in the He pressurized cell, enabling rapid elemental profiling of pharmaceutical tablets for screening purposes. Elements which normally suffer from polyatomic interferences have been included in the semiquantitative analysis and trace metal profiles obtained for the pharmaceutical tablets from three different batches agreed with those obtained by fully quantitative analysis. The method has potential therefore as a fast analytical tool in the pharmaceutical manufacture chain.

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Introduction

The control of pharmaceutical impurities is currently a critical issue to the pharmaceutical industry [1]. Most pharmaceutical products are specified to be essentially free of inorganic impurities. 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; therefore, fast screening methods for the detection of inorganic contaminant impurities is required.

The presence of contaminants in pharmaceutical products may be related to the active ingredient, excipient materials, or colorant. Contamination can also result from the manufacturing process; examples include detergents and lubricant oils and catalyst residues [1]. The production chain involves, in many cases, the use of mixing/reaction tanks, water, filters, or other equipment. Failure of any of those to be sufficiently clean might lead to inorganic contamination of the end product. Thus, trace elemental composition of a substance is commonly used to fingerprint unknown samples and can also give information regarding the manufacturing process. It has also been shown that in some pharmaceutical products, traces of inorganic impurities can clearly reduce drug stability and shelf life [1]. Methods for the rapid assessment of inorganic impurities are therefore of high interest to the pharmaceutical industry for rapid quality control and trace elemental profiling of a large number of samples of unknown composition. Thus the presence of inorganic contaminants can be quickly detected and further action can be taken.

In this work, the potential of semiquantitative elemental screening by inductively coupled plasma mass spectrometry (ICP-MS) with collision/reaction cell technology (CRC) using helium gas is demonstrated. Semiquantitative analysis has proved useful in situations where either calibration standards are not available or a rapid screening of a large number of unknown samples is required [2–4]; however, little has been published about its applicability to real-world samples. Recent advances in reaction cell technology have shown the ability of the Octopole Reaction System (ORS) to eliminate polyatomic interferences using controlled kinetic energy discrimination (KED) in helium collision mode, enabling relatively accurate semiquantification in unknown matrices [5].

Semiquantitative elemental screening has been performed for a suite of 29 elements, and quantitative measurements have been performed for comparison.

Experimental

Sample Preparation

Six pharmaceutical tablets from different production batches of an antiviral drug were used in the study. The tablets were crushed with a pestle and mortar. Approximately 0.06 g of sample was accurately weighed and microwave digested with 4 mL of high-purity nitric acid (Romil, Cambridge, UK) and 2 mL of high-purity hydrogen peroxide (Romil, Cambridge, UK). The microwave program consisted of heating the samples to 180 °C over 10 minutes and holding for a further 20 minutes. Once cool, digests were made up to 30 g using deionized water, and the solutions were subjected to element determination by ICP-MS.

Blanks and quality control materials were included in each digestion run. Aquacheck solutions used in the Aquacheck proficiency testing scheme, with known concentrations of the analytes (ranging from 2 ng/g [ppb] of Cd to 11 µg/g [ppm] of Ca), were analyzed as independent quality checks (QC) on the accuracy and precision of each ICP-MS run.

Instrumentation

Sample digestion was performed in a Multiwave 3000 microwave (Perkin Elmer, Beaconsfield, UK). Measurements were performed using an Agilent 7500ce collision/reaction cell inductively coupled plasma mass spectrometer (CRC-ICP-MS) operating in helium semiquantitative mode for the elemental screening. Tuning conditions are given in Table 1. The Integrated Sample Introduction System (ISIS) was used with the nebulizer pump speed set at 0.1 rps during the analysis and washout in order to minimize overloading of the sample introduction system and the plasma with matrix components.

The torch was equipped with a 2.5 mm diameter injector. A 30 second stabilization time was used for each cell gas mode when performing quantitative measurements in different gas modes. Measurements were performed in triplicate and a QC sample was included in each run.

Table 1. Tune Conditions Used for SemiQuant Analysis in Helium Collision Mode.

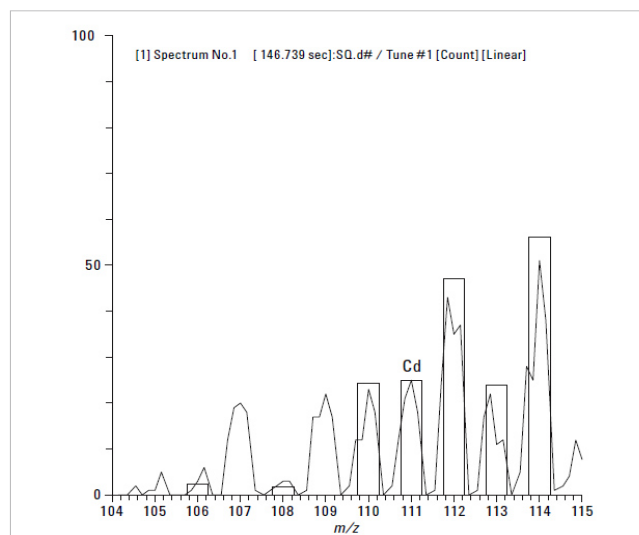| Parameter	Value
RF power	1520 W
Sample depth	8.0 mm
Carrier gas	0.88 L/min
Make-up gas	0.27 L/min
Sample flow rate	0.5 mL/min
Nebulizer	Glass concentric, MicroMist
Spray chamber	Quartz cooled to 2 °C
Interface cones	Ni
Cell gas	He
Cell gas flow rate	4.6 mL/min
KED voltage	+2 V

Semiquantitative Measurements in He Mode

For the most accurate semiquantitative determination, it is essential that all elements are acquired under the same conditions, so the consistent relationship between the responses of adjoining elements is maintained. The unique ability of the Agilent 7500 ORS to eliminate polyatomic interferences using carefully controlled kinetic energy discrimination (KED) in helium collision mode allows accurate semiquantification of a range of elements in the unknown samples. Helium is a non-reactive gas and thus no new interferences are formed in the cell, there are no analyte losses by reaction, and the interferences formed in the plasma are eliminated through a physical "molecular filtering" process [2].

Polyatomic interferences are eliminated in helium collision mode simply due to their size [6]. Regardless of the sample matrix, only a single set of ORS parameters is used. This approach is simple, fast, accurate, and interference free for all analytes (note that interference-free isotopes of elements suffering from isobaric interferences must be used).

The instrument was therefore tuned for typical robust plasma conditions as indicated in Table 1. A single calibration standard containing 100 ppb of Al, Ce, Cd, Co, Li, Tl, U, and Y made up in 10 percent HNO_3 (w/w) was used to update the semiquantitative response factors for a set of elements across the mass range. This means that noncalibrated elements are updated by interpolating between calibrated isotopes. The ICP-MS ChemStation software does this automatically. Though any number of elements can be used for the semiquantitative calibration, increasing the number of elements reduces the mass range over which the factors are interpolated between measured reference elements and thus improves semiquantitative accuracy. Internal standardization was applied using a typical suite of internal standard elements across the mass range.

Sensitivity in helium semiquant mode is essentially the same as in full quant mode when similar integration times are used. While method detection limits were not specifically calculated in semiquant mode in this work, they can be estimated from the measured semiquant response factors and the response in low-level samples. For example, Figure 1 shows the response for Cd isotopes in one of the samples. The calibrated semiquant response factor for [111]Cd was 9,960 cps/ppb and the response for [111]Cd in this sample was 41 cps (with excellent isotopic fit), resulting in an estimated concentration of 4.1 ppt (pg/g) in solution. Based on this, a very conservative 100 ppt (50 ppb in original sample) was used as the limit of detection for all elements measured in semiquant mode. Semiquantitative acquisition parameters are listed in Table 2.

Figure 1. Cd isotopes in an antiviral drug measured in helium semiquant mode at approximately 5 ppt. Overlay shows expected isotope ratios normalized to m/z 111.

Table 2. Semiquantitative ICP-MS Acquisition Parameters.

Parameter	Value
Total acquisition time	150 seconds
Acquisition mode	Spectrum- peak hopping
Number of masses m/z	250
Integration time	0.6 seconds
Number of points per mass	6
Repetition	1
Uptake time	50 seconds
Stabilization time	20 seconds
Post-acquisition rinse	30 seconds

Fully Quantitative Measurements for Comparison Purposes

Fully quantitative analyses in standard (no gas), helium, and hydrogen modes were performed for comparison purposes. Multielemental standards were prepared and a five-point calibration curve was obtained. Calibration standards containing the following elements: Al, As, Au, Ba, Be, Bi, Ca, Cd, Cr, Co, Cu, Fe, Ge, Li, Mg, Mo, Nd, Ni, Pb, Pd, Pt, Rh, Ru, Se, Si, Sb, Sn, Sr, Te, Ti, Tl, V, Zn, and Zr from 1 ppb to 2,000 ppb were prepared in HNO_3 1 percent (w/w).

Results and discussion

Six tablets of the antiviral drug from three different production batches were analyzed. Results are shown for each batch: B1, B2, and B3. Figure 2 shows the trace metal profile obtained from the semiquantitative analysis in He mode and that obtained from the full quantitative analysis results. In each case, the two profiles show very good agreement.

Figure 1 shows the calibration curves for each analyte in the clean seawater matrix. Corresponding internal DLs (3σ of the calibration blank) and external MDLs (from the 40 blank seawater measurements throughout the run) are shown in Table 2.

It is important to highlight that the suite of elements analyzed in the drugs includes Co, Cr, Cu, Fe, Ni, V, and Zn, all elements with isotopes that can suffer from polyatomic overlaps in complex matrices. Figure 3 is the full-scan mass spectrum obtained from a single semiquant run, including an expanded inset showing the region containing Ni, Cu, and Zn. The excellent fit with expected isotope ratios for all three elements confirms that no polyatomic interferences are present. Those elements that were found to be in the pharmaceutical tablets below the limit of detection are also included in the plots. Since this is important information for the screening of impurities of pharmaceutical products, it is also important to know which elements are not present above LOD levels.

Results for the internal QC certified for the elements being analyzed in the tablets were within ± 30% of the certified concentration, from as low as 2 ppb for Cd to over 11 ppm for Ca in the aqueous solutions
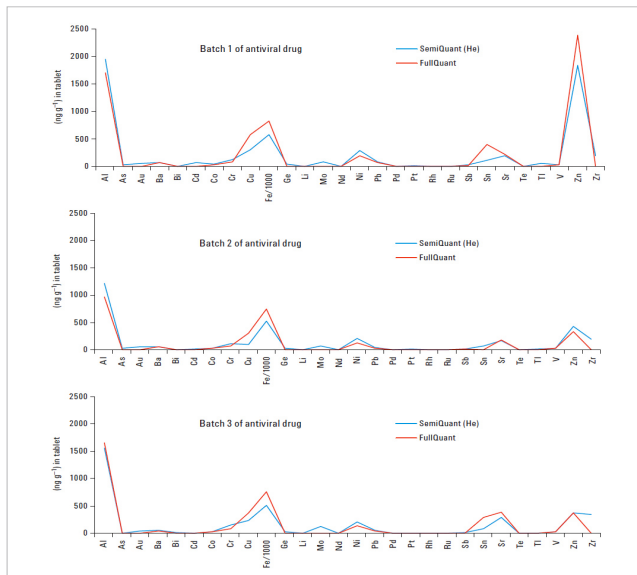
Figure 2. Trace metal profiling results for the pharmaceutical tablets from batches 1 to 3. Semiquantitative results are plotted with fully quantitative results for comparison. Fe concentrations have been divided by 1,000 and results are expressed in ng/g.

[1] Spectrum No.1   [146.739 sec]:SQ.d# / Tune #1 [Count] [Linear]
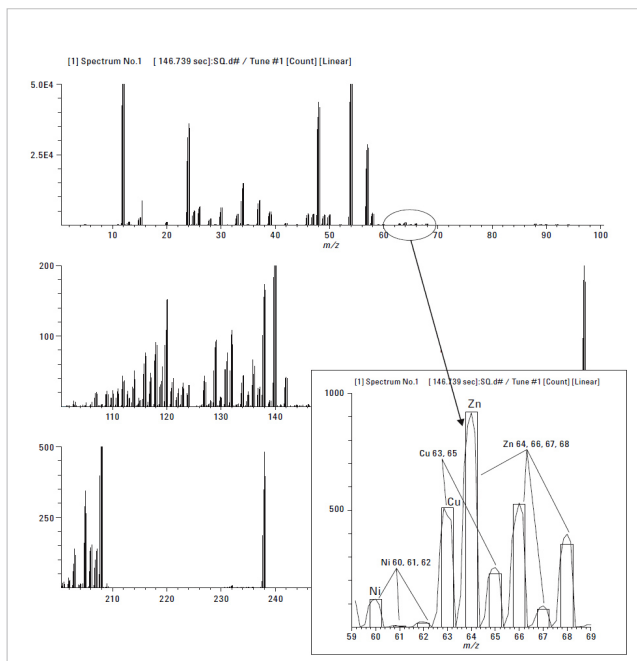
Figure 3. Full scan semiquant mass spectrum of antiviral drug representing entire elemental composition of sample. Inset shows expanded region between m/z 60 to 70, including all isotopes for Ni, Cu, and Zn with an overlay of theoretical isotope ratios.

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Conclusions

The control of inorganic impurities in pharmaceutical tablets is of high importance in the pharmaceutical manufactory chain and therefore rapid, elemental screening tools are needed.

In this work the potential of semiquantitative elemental screening by inductively coupled plasma mass spectrometry (ICP-MS) with collision/reaction cell technology (CRC) using ------- He gas has been shown. Elements which normally suffer from polyatomic interferences have been included in the semiquantitative analysis and trace metal profiles obtained for the pharmaceutical tablets from three different batches agreed with those obtained by fully quantitative analysis. Semiquantitative screening in He mode has proved to effectively remove polyatomic interferences, providing rapid screening of real pharmaceutical samples.

References

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