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The determination of palladium in fosinopril sodium (monopril) by ICP-MS

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Abstract

A rapid, sensitive ICP-MS method was developed to determine palladium in fosinopril sodium. The assay could not be carried out in a purely aqueous solvent owing to the instability of the palladium species in this media. It was found that the most appropriate vehcile for solubilization of this material was a solution of 25% (v/v) 2-butoxyethanol and water. A minimum quantifiable limit of 0.1 $\mu m\, g^{-1}$ for Pd in the sample (corresponding to 1 ng Pd mL^{-1} in the analyte solution) was obtained.

Keywords: Fosinopril sodium; ICP-MS; Monopril; Palladium

1. Introduction

Fosinopril sodium is an angiotensin converting enzyme (ACE) inhibitor, and is prescribed for the treatment of hypertension. The compound has the structure shown in Fig. 1.

One of the steps in the synthetic pathway for the manufacture of fosinopril sodium makes use of a palladium catalyst to effect a reduction process. To demonstrate the safety profile of this drug substance, it was required that all potential impurities in the material be identified and quantified. Palladium was therefore considered as a potential impurity, requiring its monitoring in the drug substance. To satisfy questions from certain regulatory agencies, a method was developed to determine palladium in the drug substance at concentrations anticipated to be at least as low as 1 $\mu g\, g^{-1}$.

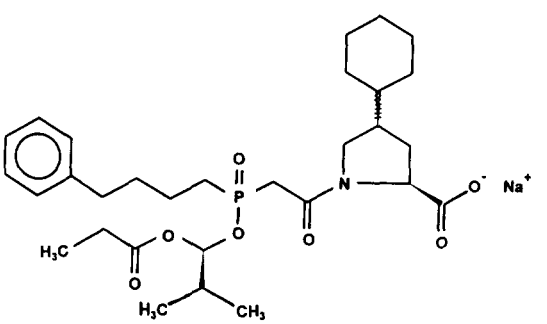

Fig. 1. Structure of fosinopril sodium.

All regulatory requirements were satisfied with the development of a rapid, sensitive ICP-MS method for palladium in fosinopril sodium. A purely aqueous system could not be used to solubilize the analyte owing to the instability of the palladium species in this medium, necessitating that work be carried out in a mixed solvent system. It was found that fosinopril

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sodium could be adequately solubilized in a system consisting of 25% (v/v) of 2-butoxyethanol in water, and that samples prepared in this manner could be directly introduced into the spectrometer system.

The method of sample introduction into the ICP-MS system often yields a variety of sample interferences, which can greatly complicate the analysis procedure [1]. In our laboratory, we have sought to develop methods of sample processing which avoid the usual pitfalls associated with acid digestion in the hope of avoiding substantial matrix effects. The use of organic cosolvents to solubilize analytes serves to eliminate the time-consuming step of digestion, thus yielding an enhancement in the productivity of the system by permitting the analysis of more samples within a given timeframe.

2. Experimental

2.1. Instrumentation

A PlasmaQuad PQII Turbo Plus ICP-MS (Fisons Instruments), with the DOS software suite, was used to measure the palladium concentration in fosinopril sodium. The operating parameters used in the present methodology are given in Table 1. A jacketed Scott-type spray chamber was cooled to 5 °C, and all other operating parameters were default parameters or were set while tuning the instrument. The instrument was tuned with a solution of 50 ng In ml^{-1} in 2% (v/v) nitric acid. Because of the organic content of the solutions, it was necessary to use solvent-resistant peristaltic pump tubing. It was also necessary to use a platinum sampling cone (rather than a nickel cone), as nickel cones were rapidly degraded by the solvent solution and did not even survive calibration of the instrument. Three replicates were taken for each solution analyzed.

Table 1
Instrumental parameters for the ICP-MS method

Parameter	Setting
Starting mass	102.90 u
Ending mass	117.04 u
Number of channels	1024
Number of sweeps	50
Peak jump dwell (μs)	10240
Points per peak	9
DAC steps between points	9
Collector type	Pulse counting
Measurement mode	Peak jumping
Palladium masses	104, 105, 106, 108, 110 u
Indium mass	115 u
Auxiliary gas flow rate	0.5 $dm^3 min^{-1}$
Nebulizer pressure	24 psi
Nebulizer gas flow rate	0.776 $dm^3 min^{-1}$
Nebulizer type	Meinhard
Cooling gas flow rate	14 $dm^3 min^{-1}$

2.2. Reagents and working standards

Primary standard solutions containing palladium and indium were prepared from 1000 μg ml^{-1} single-element stock standard solutions (Inorganic Ventures, Inc., Lakewood, NJ, USA). A stock solution consisting of 25% (v/v) 2-butoxyethanol–water solution and 50 ng ml^{-1} in indium was prepared, and used to prepare all dilutions. When diluted in this fashion, all standard and sample solutions contained indium at a concentration of 50 ng ml^{-1}. This element served as the internal standard for quantitative work.

Working standard solutions containing palladium in concentration of 10.0, 25.0, and 50.0 ng ml^{-1} were freshly prepared by serial dilution of the primary standard solutions with the 25% (v/v) 2-butoxyethanol–water solution (which contained 50 ng ml^{-1} indium). Secondary standard solutions of these were obtained through serial dilution of the primary standards.

2.3. Sample preparation

Approximately 100 mg of fosinopril sodium was weighed into a 10 ml, acid-washed volumetric flask. Approximately 5 ml of a previously prepared solution of 25% (v/v) 2-butoxyethanol–water and 50 ng ml^{-1} with respect to indium was added, and the sample was sonicated until completely dissolved. Once dissolution was complete, the flask was diluted to volume with the 25% (v/v) 2-butoxyethanol–water solution (containing also 50 ng ml^{-1} of indium).

3. Results and discussion

ICP-MS was essentially the only method judged to be sufficiently rapid to meet all analytical requirements, and yet sensitive enough to satisfy all regulatory requirements, no mat-

ter how excessive. Once solubilized, the sample was introduced into the system via an axial argon plasma, whose temperature of 7000–10 000 K was sufficient to ionize the sample. The ionized sample was then guided through a set of two sample orifices (a platinum sampling cone and a smaller diameter skimmer cone), through a photon stop, and then to a lens stack. Once inside the quadrupole mass spectrometer, the mass/charge ratios of the species within the sample were determined. The intensity of the signal at the electron multiplier was related directly to the concentration of a given element in the sample. The technique afforded excellent sensitivity, because only small fragments of limited possibilities actually reached the mass spectrometer. With traditional ICP-OES, there are thousands of potential wavelengths, which can yield many possible interferences.

3.1. Selection of solvent

Although fosinopril sodium is highly soluble in water, it was not possible to quantify palladium in aqueous solutions owing to the known instability of aqueous solutions of palladium. In particular, it is well established that Pd(II) species will readily hydrolyze in aqueous media, and that the endpoint product of these hydrolysis reactions is insoluble $Pd(OH)_2$. Hydrochloric acid, aqua regia, and/or combinations of these, have been widely used in digestion procedures to solubilize palladium species for analysis [2–5]. This approach was tried in the present work by using hydrochloric acid solutions to ensure that all palladium species remained soluble. Unfortunately, the insoluble free acid of fosinopril formed and was immediately precipitated as an intractable gel.

Other researchers have found success with fire assay techniques [6], and some have used resin pretreatment or separation [6,7], or chromatographic preconcentration [8,9]. These methods are usually quite time-consuming, and not readily adaptable to the analysis of large numbers of samples. We sought to apply alternative methods of sample solubilization, with the ultimate goal of and attempting to develop "dilute-and-shoot" techniques as alternatives to acid solubilization or acid digestion.

A variety of solubilization conditions and organic cosolvents were investigated as to their ability to yield stable solutions of fosinopril sodium and spiked palladium. It was ultimately found that both the drug compound and palladium were soluble in a solution of 25% (v/v) 2-butoxyethanol and water, and that both species were equivalently stable in this dissolution medium. Because the 2-butoxyethanol–water system allowed rapid sample preparation, it was selected over all other possibilities as the means to solubilize fosinopril sodium.

When injected into the ICP-MS system, the mixed solvent system was not found to yield experimental artifacts, and did not interfere with the observation of either palladium or indium. As shown in Fig. 2, the mass spectrum of the palladium response consists of lines observed at mass/charge ratios of 104, 105, 106, 108, and 110. The observed intensity pattern is consistent with the known isotope ratios of 11.0%, 22.2%, 27.3%, 26.7%, and 11.8%, respectively [10]. The indium standard yields a single ion at a mass/charge ratio of 115, since this species accounts for 95.8% of the isotope ratio [10].

3.2. Validation

Precision

The precision of the assay method was determined through the analysis of multiple samples, and was evaluated by considering the degree of reproducibility among the assay results. As the lower limit of the regulatory concern was approximately 5 ng ml^{-1} of palladium in fosinopril sodium, a standard solution containing 5.5 ng ml^{-1} of palladium was repeat-

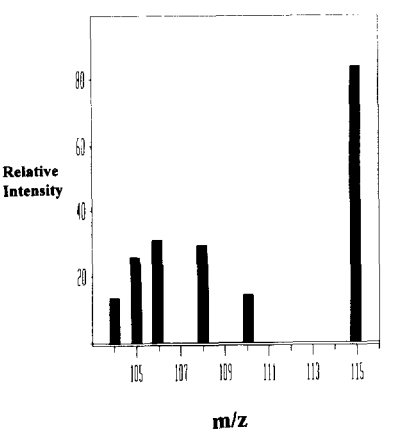

Fig. 2. ICP-MS spectrum of a standard solution containing palladium (25 ng ml^{-1}) and indium (50 ng ml^{-1}). The responses at m/z 104, 105, 106, 108, and 110 u correspond to palladium, while the response at m/z 115 u is due to indium.

Table 2
Results of the precision study

Replicate	Measured Pd concentration ($ng\ ml^{-1}$)
1	5.66
2	5.52
3	5.59
Mean	5.59
SD	0.07
RSD(%)	1.25

edly assayed by the ICP-MS method. The results of this study are shown in Table 2. As shown by the low RSD value, the method exhibits acceptable precision.

Linearity

The linearity of the assay method was studied through the analysis of a series of samples prepared at concentrations of 2.5, 5.0, 10.0, 25.0, and 50.0 $ng\ ml^{-1}$ in palladium. The data shown in Table 3 clearly illustrate the linearity in system response as a function of palladium concentration over the concentration interval studied. In addition, recoveries of palladium from each standard solution were calculated, and an average recovery of 99% was obtained. This latter finding demonstrates that the method is accurate, in addition to being both linear and precise.

Accuracy

The accuracy of the method was further studied by evaluating the recoveries of palladium from a matrix consisting of fosinopril sodium dissolved in the 25% (v/v) 2-butoxyethanol–water system. A series of samples was prepared at palladium concentrations of 1.25, 2.5, 5.0, 10.0, 20.0, and 40.0 $ng\ ml^{-1}$, and the corresponding results are found in Table 4. For this particular data set, an average recovery of 100% with an RSD of approximately 5% was obtained, and the results were also demonstrated to be totally linear over this concentration range. These findings demonstrate that the presence of fosinopril sodium in the analysis system provides no matrix effect, which might bias the final calculated results for palladium.

Table 3
Results of the linearity study

Prepared Pd concentration ($ng\ ml^{-1}$)	Measured Pd concentration ($ng\ ml^{-1}$)	Recovery (%)
2.5	2.4	96
5.0	5.9	110
10.0	9.5	95
25.0	24.5	101
50.0	49.1	98
Slope	0.979	
Intercept	0.089	
Correlation coefficient	0.99985	
Mean		99.4
SD		6.1
RSD(%)		6.1

Table 4
Results of the accuracy study

Prepared Pd concentration ($ng\ ml^{-1}$)	Measured Pd concentration ($ng\ ml^{-1}$)	Recovery (%)
1.25	1.2	96
2.5	2.4	96
5.0	5.3	106
10.0	10.1	101
20.0	21.1	106
40.0	38.8	97
Slope	0.977	
Intercept	0.341	
Correlation coefficient	0.9989	
Mean		100.3
SD		4.8
RSD(%)		4.7

Range

The range of the ICP-MS method was established as the span of concentration values for which the computed results were demonstrated to be accurate, precise, and within the linear response region. The data contained in Tables 3 and 4 permit the conclusion that the range of the current method spans palladium concentrations of 1–50 $ng\ ml^{-1}$. This range corresponds to 0.1–5.0 $\mu g\ g^{-1}$ of palladium in the fosinopril sodium drug substance.

Limits of quantification

As the regulatory requirement was that a method be developed for the determination of palladium concentrations above 1 $\mu g\ g^{-1}$ of palladium in fosinopril sodium, the limit of quantification was taken as the lower limit of the acceptable range of the method. The actual limit of quantification may have actually been lower than this, but the present study was concluded at a limit of 1 $ng\ ml^{-1}$ palladium or 0.1 $\mu g\ g^{-1}$ of palladium in fosinopril sodium.

Analysis of real samples

Fourteen batches of fosinopril sodium were analyzed for their palladium content, but no palladium was found in any of the samples. Because the quantification limit of the method far exceeded the regulatory concern, it was concluded that even though palladium was used as a reduction catalyst in the production of fosinopril sodium, it did not leave any detectable residue in the product.

4. Conclusions

Palladium concentrations in fosinopril sodium were easily and accurately determined by ICP-MS using a system of 25% (v/v) 2-butoxyethanol and water to solubilize the analyte. When using this medium to solubilize samples, only a few precautions were necessary in order to perform the analysis with an organic solvent. Other than the need to use a platinum sampling cone, a cooled spray chamber, and solvent-resistant tubing, no other variations on normal aqueous operating parameters were required. A method range for palladium of 1–50 ng ml^{-1} was established, which corresponds to a range of 0.1–5.0 μg g^{-1} of palladium in the fosinopril sodium drug substance. The minimum quantifiable limit for the method was taken as the lower limit of the range, or a palladium concentration of 1 ng ml^{-1}, corresponding to 0.1 μg g^{-1} of palladium in fosinopril sodium drug substance.

References

[1] E.H. Evans and J.J. Giglio, Anal. At. Spectrom., 8 (1993). 1–18.
[2] M. Baucells, G. Lacort and R.J. Montserrat, Anal. At. Spectrom., 2 (1987) 645–647.
[3] J.B. Tillery and D.E. Johnson, Environ. Health Perspect., 12 (1975) 19.
[4] H. Niskavaara and E. Kontas, Anal. Chim. Acta, 231 (1990) 273.
[5] M.E. Farago and P.J. Parsons, Analyst, 107 (1982) 1218.
[6] U.V. Rao, M. Triska, P. Bridger and R.L. Deming, in T.P. Mohide (Ed.), Precious Met., Proc. 8th Int. Precious Met. Inst. Conf., 1984, Int. Precious Met. Inst., Allentown, PA, 1985 pp. 217–225.
[7] Y.S. Chung and R.M.J. Barnes, Anal. At. Spectrom. 3 (1988) 1079.
[8] R.M. Barnes and A. Diallo, in L.R.P. Butler (Ed.), Anal. Chem. Explor., Min. Process. Mater., Invited Lect. 2nd Int. Symp., 1985, Blackwell, Oxford, 1986, pp. 3–13.
[9] S. Usami, T. Fukami, E. Kinoshita, B.K. Puri and M. Satake, Anal Chim, Acta, 230 (1990) 17–22.
[10] J.A. Dean (Ed.), Lange's Handbook of Chemistry, 11th ed., McGraw-Hill, New York, 1973, pp. 3-41 to 3-47.