Short communication

High-efficiency sample preparation with dimethylformamide for multi-element determination in pharmaceutical materials by ICP-AES

Qiang Tu*, Tiebang Wang, Vincent Antonucci

Merck Research Laboratories, Merck & Co., Inc., RY818-C102, P.O. Box 2000, 126 E. Lincoln Ave., Rahway, NJ 07065, United States

ABSTRACT

The pressure to reduce cycle times of sample analysis has made it increasingly important to improve sample throughput during pharmaceutical process development. For ICP-based analyses, sample preparation is often the bottleneck of the entire analytical scheme due to the tedious digestion procedure and lacking a universal diluent for organic compounds. In this work, N,N-dimethylformamide (DMF) was used as a "universal" organic diluent so that the sample preparation can be simplified as a "dilute-and-shoot" procedure. An optimized interface with a commercial membrane desolvation unit was implemented, which enabled the introduction of organic solvents into an ICP-AES without organic loading. Mixed standard solutions of 15 elements (Al, Co, Cr, Cu, Fe, Mn, Mo, Ni, Pd, Pt, Rh, Ru, W, Zn, and Zr), which covered the majority of processing metals routinely monitored in pharmaceutical development, were prepared for the study and stability of each element in a multi-element DMF solution was investigated. It was found that the addition of a stabilizing agent (EDTA) was necessary to ensure that all the elements at concentrations of 0.10–0.50 μg/mL remained physically stable in solution (recovery better than 95%) for 2 weeks. It was also important to use an internal standard (yttrium) in order to compensate for signal drift and matrix effects from different sample matrices. A 2–10-fold increase of sensitivity (due to enhanced analyte transport efficiency) and acceptable levels of precision (RSD < 3%) and recoveries (91–111%) were achieved. The LOQs of all 15 elements were less than 10 μg/L in the solution, which translates to less than 5 μg/g or μg/mL in pharmaceutical samples tested. This technique would minimize the effort required for sample preparation, thus reducing the cycle time by approximately 60–90% in the entire analytical scheme for samples that are difficult to be dissolved in nitric acid. This will provide opportunities for a new level of sample handling and automation for metal analysis in pharmaceutical process development.

© 2010 Elsevier B.V. All rights reserved.

1. Introduction

Trace impurity control in pharmaceutical processing is of critical importance to reproducibly achieve the desired product quality, which in turn assures patient safety is being safeguarded. One important category of impurities in pharmaceutical compounds is inorganics, including residual metals, which may be introduced in many ways. As inorganic impurities may influence the efficacy and safety of the pharmaceutical products [1], identification and monitoring of metals is essential for rapid quality control to better meet regulatory requirements [2–8]. The increasing pace of pharmaceutical development has brought about a need for faster and more efficient means for carrying out metals analysis. Therefore a high-efficiency approach can be a valuable tool for monitoring residual

metals in process intermediates and for verifying the effectiveness of purification procedures, thus directing some important synthetic purification decisions.

The United States Pharmacopoeia (USP) *Heavy Metals* <231> and other similar compendial methods have been used for many years to control selected metal impurities (Pb, Hg, Bi, As, Sb, Sn, Cd, Ag, Cu, and Mo). However, it is now widely accepted that these wet chemistry-based procedures lack the sensitivity, specificity, and recovery to monitor properly the levels of these metals [2–4,9,10]. A proposed new USP General Chapter recommends procedures that rely on more modern analytical technology and introduces a performance-based approach for the selection of the appropriate technology [9,10].

Atomic spectroscopy is playing an increasingly significant role as a quantitative analysis, characterization, and quality control tool in pharmaceutical industry [2–11]. Especially, inductively coupled plasma (ICP) is widely used as a radiation source in atomic emission spectrometry (AES) or as an ionization source in mass spectrometry (MS). Both techniques offer distinct advantages such as multi-

element analyses, wide dynamic range, excellent sensitivity and specificity. However, for ICP-based analysis, the tedious sample preparation process is often the bottleneck of the entire analytical scheme. This is especially true when large numbers of samples are to be analyzed. Although techniques such as microwave-assisted or ultrasound-assisted digestion may help to accelerate the digestion process, the sample handling is still cumbersome for large numbers of samples. In addition, the optimization of a variety of operating parameters for samples of different kinds of matrices may become a very time-consuming step [12]. Thus a simplified procedure with minimized sample preparation will greatly increase the sample throughput for metals analysis in pharmaceutical process development.

Several years ago, a procedure using 80% nitric acid solution [2,3] for sample dissolution for metals analysis was applied in our laboratory to various raw materials, active pharmaceutical ingredients (APIs) and intermediates, and drug products to improve analysis time cycles. While this is a very efficient method for most of our samples, careful handling of the acid solutions is necessary. With the increasing industry trend of less water soluble pharmaceutical compounds and more complicated sample matrices entering into development, we have noticed that a growing number of samples need to be heated up to complete their solubilization, which adds extra time for sample preparation. Other workers have proposed use of 2-butoxyethanol:water (25:75) as a dissolution solvent for a wide variety of pharmaceutical matrices [4]. Unfortunately, we have found that only a limited number of our samples can be dissolved in this solvent. In addition, depending on the instrument used, direct introduction of organics-containing solutions is usually hampered by a number of problems such as plasma loading and carbon deposits on the sampler/skimmer cones [13]. Despite these observations, we were convinced that there is still a real need for a "universal" organic diluent for sample preparation and a more effective methodology for direct analysis of the resultant organic solution by an ICP-based technique; hence, we evaluated other potential solvents.

In this work, a high-efficiency sample preparation procedure is described for multi-element detection by ICP-AES. N,N-dimethylformamide (DMF) was used as a "universal" organic diluent so that the sample preparation can be simplified as a "dilute-and-shoot" procedure, which significantly reduced the amount of time and labor spent on sample preparation. The coupling of a membrane desolvation unit with ICP-AES was investigated for direct introduction and analysis of the DMF solutions.

2. Experimental

2.1. Reagents and materials

A DMF solution (CHROMOSOLV® PLUS for HPLC ≥ 99.9%) used to prepare the samples and standards was purchased from Sigma–Aldrich (St. Louis, MO, USA). Mixed stock standard solutions of 15 elements with a concentration of 1000 μg/mL for each individual element (Al, Co, Cr, Cu, Fe, Mn, Mo, Ni, Pd, Pt, Rh, Ru, W, Zn, and Zr) were purchased from High-Purity Standards (Charleston, SC, USA). These elements covered the majority of analytes in our routine analysis. Internal standardization was performed with yttrium (Y), which was not present in significant concentrations in any pharmaceutical samples we tested. A 1000 μg/mL stock solution of yttrium was also purchased from High-Purity Standards. Ethylenediamine tetraacetic acid (EDTA), disodium salt dehydrate, which was used as a stabilizing agent, was purchased from Fisher Scientific (Fair Lawn, NJ, USA).

To conduct comparison studies, concentrated nitric acid (70%, v/v, trace metal grade) was purchased from Fischer Scientific (Fair Lawn, NJ, USA). The deionized water used in the experiments was prepared by passing water through a Hydro Ultrapure water system (Hydro Service and Supplies, Garfield, NJ, USA).

Sample matrices referenced in this paper refer to investigational small molecule APIs and intermediates under development or drug substances, and were all obtained from Merck Research Laboratories. The solid or liquid samples selected included a variety of matrices such as neutral, free acid/free base and salt compounds. Most of the samples had elevated levels of different metals, and were generated from various sources such as synthetic process and waste stream.

2.2. Preparation of standard and sample solutions

A universal solvent used for the study was prepared by adding an extra amount of EDTA to DMF (~2 g/100 mL) and heating the solution at 120 °C for 30 min. After cooling down, transfer the supernatant to another bottle and add the Y stock solution to make the final Y concentration in DMF 1.0 μg/mL. This solution was used for the preparation of all standard and samples, and also used as the calibration blank. Multi-element working standards (normally at 0.10, 0.25 and 0.50 μg/mL) were prepared by diluting the mixed stock solutions with 15 elements using this solvent. The stability of each element in a multi-element DMF solution was investigated.

A default amount of 10 mg solid or 10 μL liquid sample was dissolved in 5 mL of DMF/EDTA. Further dilution was required for samples with high expected metal concentrations (e.g., >1000 μg/g or μg/mL). Analysis was carried out shortly after the samples were prepared.

Selected samples were also digested/diluted with 80% nitric acid and analyzed by the same ICP-AES using the conventional sample introduction method [2]. Yttrium was also added to the nitric acid solutions as an internal standard (1.0 μg/mL in all solutions). In cases where a sample could not be easily dissolved in the acid solution, the solid/liquid mixtures were heated on a hot plate at 120 °C until dissolved. The obtained results were compared with those prepared in DMF/EDTA.

Two spiked API samples were prepared to contain 150 μg/g of each element by directly spiking the solid sample with an appropriate volume of the mixed stock standard solutions prior to dissolution in DMF/EDTA.

2.3. Instrumentation

An iCAP 6500 ICP Spectrometer (Thermo Electron, England) equipped with an ASX-260 autosampler (CETAC Technologies, Omaha, NE, USA) was used throughout this study. As a DMF solution was not amenable to plasma conditions, a membrane desolvation unit (Aridus I Desolvating Nebulizer System, CETAC) was used for sample introduction. The outlet of the Aridus was connected to the ICP-AES through Tygon tubing (3/16 in. I.D., 5/16 in. O.D.) and a quartz adapter. Through self-aspiration, a solution was nebulized into a heated PFA spray chamber using a PFA micro-concentric nebulizer, and transported to a heated micro-porous PTFE tubular membrane. The membrane can be heated up to 160 °C so that any solvent with a boiling point of less than 160 °C will be vaporized. The solvent vapor passed through the membrane and was removed by a stream of argon gas, while the analyte particles passed through the center of the membrane tube owing to low permeation and were conveyed to the plasma. Through this mechanism the desolvating unit enabled the handling of organic solutions without plasma loading.

The analytical wavelengths were selected based on the minimum potential spectral interferences and maximum analytical performance. Three analytical wavelengths were selected for Fe, Pd and Ru since they were among the elements analyzed most fre-

Table 1
Operating conditions of the Aridus I and Thermo Electron iCAP 6500 ICP-AES using different sample preparation and introduction methods.

Aridus I conditions		
Sweep gas flow (mL/min)	72	
N$_2$ gas flow (mL/min)	None	
Spray chamber temperature (°C)	110	
Desolvator temperature (°C)	160	
ICP-AES conditions		
Sample solution	DMF	80% HNO$_3$
Interface	Aridus I Desolvating Nebulizer System	Conventional nebulization
Sample introduction	Self-aspiration	Pumped
RF power (W)	1350	1150
Plasma gas flow (L/min)	15	12
Auxillary gas flow (L/min)	0.2	0.5
Nebulizer gas flow (L/min)	0.75	0.75
Plasma view	Axial	Axial

Table 2
Recoveries of elements (%) in a multi-element standard (0.50 µg/mL of individual element) in different solutions.

Elements	DMF only, 3 days	DMF/0.1% HCl, 7 days	DMF/EDTA, 14 days
Al	99	97	105
Co	101	99	100
Cr	102	99	102
Cu	100	96	102
Fe	75	76	103
Mn	102	99	101
Mo	101	95	100
Ni	100	98	101
Pd	82	95	97
Pt	90	98	95
Rh	93	95	96
Ru	94	97	97
W	98	98	96
Zn	99	99	101
Zr	101	98	103

quently in our lab. Two wavelengths were selected for each of the other elements. The instrument settings were checked regularly and optimized when necessary. The operating conditions for all instrumentation are summarized in Table 1.

3. Results and discussion

3.1. System optimization

The majority of samples analyzed in support of pharmaceutical process development (e.g., raw materials, process intermediates, and drug substances) are soluble in organic solvents, so it follows the logic that there would be an advantage if organic solutions could also be directly introduced into the ICP for residual metals analyses in these compounds. Spectral interferences due to the presence of organic solvents in the plasma are usually not a limiting consideration for trace elements analysis by ICP-AES, since there are a relatively low number of analytical lines that suffer from potential spectral interferences [13]. However, this practice will often lead to increased solvent loading in the plasma, which will result in a number of problems including unstable or even extinguished plasma, decreased sensitivity, carbide polyatomic ion interferences and carbon deposits in the ICP sample introduction area. Various approaches have been reported in order to avoid, or at least to reduce, these problems. Examples of these include the use of low-flow sample introduction systems [14,15], addition of oxygen to the nebulizer and outer gas flows [14,15], cooled spray chambers [16], and use of desolvation systems [17–19]. However, no publication can be found regarding a technique for direct analysis of DMF solutions by ICP-AES.

In this work, an interface between the Aridus I Desolvating Nebulizer System and ICP-AES was developed in our laboratory as a significant modification of the previously reported interfaces for HPLC–ICP-MS [8] and FI–ICP-MS [11] applications. The Aridus I was primarily designed for ICP-MS. For this application, the optimized parameters were largely different from those used in conventional ICP-AES determinations, as well as quite different from those applied when the desolvation unit was interfaced with ICP-MS. Most interestingly, in contrary to ICP-MS with which the addition of a small amount of nitrogen to the carrier gas would result in significant enhancement in sensitivity, the introduction of a nitrogen gas reduced the sensitivity in ICP-AES detection. The mechanism of this effect warrants further investigation. After optimization, better sensitivities for almost all the studied elements were achieved, apparently due to enhanced analyte transport efficiency and reduced plasma loading with the desolvating process.

The degree of sensitivity enhancement is dependent on the element analyzed and the wavelength selected.

It should be pointed out that the amount of organic solvent load into the Aridus should be limited. Exceeding the limit could result in overload of the membrane desolvator, leading to plasma instability. An optimum sample uptake rate for DMF was utilized using a self-aspiration mode with a nebulizer gas flow rate of 0.75 L/min which led to the best sensitivity. Without use of the peristaltic pump, signal variation was decreased. Another advantage of using the self-aspiration mode was the reduced sample consumption (<0.4 mL per analysis). For best performance, both the spray chamber and desolvator temperatures were set at their maximum operating values (110 and 160 °C, respectively) and the sweep gas flow was also set to its maximum value. This can be attributed to the low volatility of DMF due to its relatively high boiling point (153 °C). Nonetheless, it was observed that the use of high desolvation temperatures and high sweep gas flow resulted in the efficient removal of DMF vapors. Residual DMF vapors did not have any detrimental effect on the plasma integrity. The addition of oxygen, though recommended by CETAC for ICP-MS, did not seem to be needed under these conditions. No visible carbon built-up in the torch or the sampler cone was observed after prolonged use. Running without oxygen addition was advantageous because problems such as accelerated degradation of the sampler and skimmer cones could be avoided.

The proposed method has been successfully applied to hundreds of samples with no major issues identified, indicating that this configuration is an easy and robust setup of metal analysis. The interface can also be easily modified to switch between conventional sample introduction and membrane desolvation.

3.2. Stability of the elements in standard solutions

An ideal "universal" diluent is projected to be a polar solvent that dissolves both polar and nonpolar compounds and is miscible in a wide range of organic solvents as well as water. Dimethyl sulfoxide (DMSO) and DMF were considered for this application. However, the high boiling point of DMSO (189 °C) will limit its potential utility as the maximum temperature of the membrane in the Aridus is 160 °C. Therefore DMF was selected as a candidate for this application.

As commercially available stock solutions (1000 µg/mL for each element tested in this work) were normally prepared in dilute acid, the physical stability of a multi-element DMF solution was unknown. The physical stability of the 15-element standard solution vs. a freshly prepared solution was determined as a function of time. Initial experiments revealed that several elements (Fe, Pd, Pt,

Table 3
Comparison of LODs and LOQs of different procedures in ICP-AES determination.

Element	Wavelengths (nm)	DMF		80% HNO$_3$	
		LOD (µg/L)	LOQ (µg/L)	LOD (µg/L)	LOQ (µg/L)
Al	167.0	0.3	1.0	–	–
	309.2	0.4	1.3	5.0	16.7
Co	228.6	0.2	0.8	0.4	1.5
	238.8	0.4	1.4	0.8	2.8
Cr	283.5	0.2	0.5	0.5	1.5
	284.3	0.2	0.8	0.9	3.0
Cu	224.7	0.4	1.2	0.6	2.1
	324.7	0.6	2.1	1.7	5.7
Fe	238.2	1.1	3.5	1.7	5.6
	239.5	2.2	7.4	1.0	3.3
	259.9	1.0	3.3	0.7	2.4
Mn	257.6	0.2	0.5	0.4	1.4
	259.3	0.2	0.6	0.6	1.8
Mo	202.0	0.3	0.9	2.6	8.5
	281.6	0.3	0.9	7.5	24.8
Ni	231.6	0.5	1.7	2.1	6.9
	341.4	0.7	2.3	3.3	11.0
Pd	324.2	1.9	6.4	9.0	29.9
	340.4	0.5	1.6	3.4	11.4
	360.9	1.3	4.5	8.2	27.3
Pt	214.4	0.7	2.2	2.1	7.1
	265.9	1.9	6.4	15.1	50.4
Rh	343.4	0.9	2.9	2.4	7.9
	369.2	0.7	2.2	5.8	19.3
Ru	240.2	0.9	3.0	3.0	9.9
	266.1	1.9	6.4	5.9	19.5
	267.8	0.5	1.7	1.9	6.3
W	207.9	0.5	1.5	3.3	10.9
	224.8	0.5	1.8	2.2	7.3
Zn	202.5	0.7	2.5	–	–
	213.8	0.4	1.2	–	–
Zr	339.1	0.2	0.6	0.5	1.5
	343.8	0.2	0.6	0.4	1.5

Table 4
Spike recoveries (%)[a] of two API samples using DMF/EDTA for sample preparation.

Elements	Sample A		Sample B	
	Mean	RSD (%)	Mean	RSD (%)
Al	91	0.4	95	1.4
Co	95	0.4	96	1.0
Cr	94	1.2	95	0.4
Cu	92	0.8	94	0.8
Fe	95	1.5	97	1.5
Mn	99	0.6	99	0.6
Mo	96	0.7	97	1.2
Ni	105[b]	0.8	111[c]	1.7
Pd	91	1.2	97	1.3
Pt	96	1.3	96	2.4
Rh	92	0.8	96	1.2
Ru	96	1.7	97	1.2
W	97	0.8	100	1.3
Zn	91	0.3	95	1.1
Zr	95	0.9	96	0.5

[a] Spike amount: 150 µg/g of each element in both samples.
[b] Ni = 6 µg/g in the original sample A.
[c] Ni = 3 µg/g in the original sample B.

and Rh) were physically unstable in DMF within 3 days at a concentration of 0.50 µg/mL as determined by low recoveries (see Table 2). Therefore hydrochloric acid and EDTA, well-known for their chelating characteristics, were evaluated as potential stabilizing agents for the multi-element DMF solutions. Results of this study are also listed in Table 2.

Addition of 0.1% of hydrochloric acid enhanced the physical stability of the solution with respect to Pd and Pt and to a lesser extent Rh, but did not improve the Fe recovery. By comparison, a DMF solution saturated with EDTA ensured that all the elements at concentrations of 0.10–0.50 µg/mL remained physically stable in solution (recovery better than 95%) for at least 2 weeks and was therefore selected for this application.

3.3. Analytical figures of merit

Method performance was tested on three multi-element standard solutions (0.10, 0.25 and 0.50 µg/mL with respect to each element) in DMF/EDTA diluent. Linearity of calibration was routinely achieved with correlation coefficients of >0.999 for all selected wavelengths, showing good correlations by this procedure. Relative standard deviations (RSDs) of the signal were normally less than 3%.

Limits of detection (LOD) and limits of quantitation (LOQ) in DMF/EDTA or 80% HNO$_3$ were estimated by analyzing 11 replicate aliquots of the spiked calibration blanks as 11 samples (with rinsing between samples) at concentrations of 0.01 and 0.02 µg/mL, respectively. The LOD and LOQ are defined as three and ten times of the standard deviation of the 11 measurements, respectively. The results are given in Table 3.

With nitric acid treatment, the LOQ values ranged between 1.4 and 50.4 µg/L. With DMF treatment, the LOQ values ranged between 0.5 and 7.4 µg/L. While there was a large difference in LOQ from different analytical wavelengths used, the new procedure generally achieved a 2–10-fold lower LOQ compared with the conventional sample introduction. These results demonstrated that the membrane desolvation offered not only the convenience of direct analysis of organic solvent but also improved sensitivity.

With DMF, the LOQs of all 15 elements were less than 10 µg/L in the solution. This translates into LOQs of lower than 5 µg/g or µg/mL for each element in a sample, on the basis of a 10 mg solid or 10 µL liquid sample dissolved in 5 mL of DMF. If necessary, a lower LOQ can be easily achieved by preparing a more concentrated sample solution, as long as the resulting matrix effect can be effectively compensated for by internal standardization.

To further assess the influence of the pharmaceutical matrix on the analytical results obtained in the DMF/EDTA diluent system, two API samples were spiked to a concentration of 150 µg/g of each element, and the recoveries of the elements were determined. The results summarized in Table 4 revealed that recoveries of all the elements were in the acceptable range of 91–111%. It should be pointed out that there were small amounts (3 and 6 µg/g, respectively) of Ni present in both samples prior to spiking. Although these amounts had been corrected for in calculation, slightly higher recoveries of Ni were still obtained in both samples.

3.4. Comparison of results using different methods for sample preparation

Our experiences with hundreds of pharmaceutical samples (APIs, intermediates and drug products) indicate that at least 95% of the samples can be easily dissolved in DMF, proving that it is an ideal "universal" diluent with which the sample preparation can be largely simplified. In addition, the potential of cross-contamination with some traditional sample digestion procedures can be avoided.

However, initial attempts to apply the DMF/EDTA diluent to real-world pharmaceutical samples generally produced lower results than those generated in 80% nitric acid. This is most likely a result of a more severe matrix effect from the undigested samples which leads to signal suppression. This effect is strongly dependent on the sample matrix and the dilution factor used, and is also dependent on some other factors such as the element measured, the energy of the plasma and the sample uptake rate. No interference was observed from the sodium introduced from EDTA disodium salt.

Table 5
Comparison of analytical results (in μg/g or μg/mL) from different sample preparation methods.

Sample	Element	Prepared with HNO₃	Prepared with DMF
A	Pd	69	70
	Cu	30	34
	Fe	31	28
B	Pd	124	123
C	Pd	47	47
D	Cr	84	88
	Ni	38	37
	Fe	23	15
E	Fe	1240	1000
	Cr	304	302
	Ni	180	150
	Cu	11	9
F	Ru	7	8
G	Pd	154	156
H	Pd	122	117
I	Pd	9	9
J	Pd	880	890
K	Pd	130	136
L	Pd	11	8
	Ni	49	38
M	Pd	9	6
	Ni	39	33
N	Fe	87	83
	Cr	28	35
	Ni	5	6

Internal standardization has been widely employed to mitigate matrix effects and the instrumental noise, leading to the improvement on both accuracy and precision. For example, it was reported that real-time internal standardization using the yttrium ion line at 371.030 nm provided significant improvements in precision with an axially viewed ICP-AES [20]. In this work, yttrium was added to the DMF/EDTA diluent at a concentration of 0.5 μg/mL and sample dilution factors of more than 500-fold were employed.

Fourteen different pharmaceutical samples were analyzed using both the internally standardized DMF/EDTA and 80% nitric acid sample preparation procedures, and the comparison results are summarized in Table 5. There is generally good agreement in results across both sample preparation methods for all elements of interest except for samples E and L, where slightly higher differences (20–30%) were observed for Fe and Ni. This may be due to the discrepancy between the corrections of matrix effects in different sample solutions.

Overall, the results proved that the use of a single internal standard was effective in compensating for matrix effects from different sample matrices in the DMF/EDTA solution. The similarity of the results from a wide variety of pharmaceutical matrices using both methods indicates that the two procedures could be used interchangeably for routine analyses.

For samples that are difficult to be dissolved in 80% nitric acid, a period of 2–12 h of sample heating is normally needed to complete the sample solubilization. This would constitute about 60–90% of the time cycle of the entire analytical scheme including sample preparation and measurement. An even longer sample preparation time is required with other conventional sample digestion procedures. The instant dissolution of these samples in DMF/EDTA has provided a means for significant productivity gains and cycle time savings. Therefore a new level of sample handling for metal analysis can be achieved, which potentially opens the door for development of more practical automated sample preparation solutions to be integrated with the ICP instrument.

4. Conclusion

DMF can be used as an "universal" organic diluent to replace the tedious conventional acid digestion procedure for multi-element analysis by ICP-AES. This "dilute-and-shoot" procedure will significantly reduce the amount of time and labor spent on sample preparation, thus largely increase the sample throughput. Improved sensitivity and acceptable levels of precision and recoveries have been demonstrated. The versatility of the proposed method has been illustrated by successfully applying it to a wide variety of sample matrices. This high-efficiency approach provides a simple and effective way to enhance ICP-AES performance for metals analysis in pharmaceutical process development.

References

[1] J. Roy, AAPS PharmSciTech. 3 (2002), article 6, http://www.aapspharmscitech.org.
[2] T. Wang, J. Wu, R. Hartman, X. Jia, R. Egan, J. Pharm. Biomed. Anal. 23 (2000) 867–890.
[3] T. Wang, J. Wu, X. Jia, X. Bu, I. Santos, R. Egan, Pharm. Forum 29 (2003) 1328–1336.
[4] N. Lewen, S. Mathew, M. Schenkenberger, T. Raglione, J. Pharm. Biomed. Anal. 35 (2004) 739–752.
[5] A. Lásztity, Á. Kelkó-Lévai, I. Varga, K. Zih-Perényi, É. Bertalan, Microchem. J. 73 (2002) 59–63.
[6] J. Huang, X. Hu, J. Zhang, K. Li, Y. Yan, X. Xu, J. Pharm. Biomed. Anal. 40 (2006) 227–234.
[7] R.N. Rao, M.V.N.K. Talluri, J. Pharm. Biomed. Anal. 43 (2007) 1–13.
[8] Q. Tu, T. Wang, C.J. Welch, P. Wang, X. Jia, C. Raab, X. Bu, D. Bykowski, B. Hohenstaufen, M.P. Doyle, Anal. Chem. 78 (2006) 1282–1289.
[9] USP Ad Hoc Advisory Panel on Inorganic Impurities and Heavy Metals and USP Staff, Pharm. Forum 34 (2008) 1345–1348.
[10] M. Rios, Pharm. Technol. 33 (2009) 36–42.
[11] Q. Tu, T. Wang, C.J. Welch, J. Pharm. Biomed. Anal. 51 (2010) 90–95.
[12] C.E. Domini, M. Hidalgo, F. Marken, A. Canals, Anal. Chim. Acta 561 (2006) 210–217.
[13] A.W. Boorn, R.F. Browner, Anal. Chem. 54 (1982) 1402–1410.
[14] K. Kahen, A. Strubinger, J. Chirinos, A. Montaser, Spectrochim. Acta, Part B 58 (2003) 397–413.
[15] J.L. Todolĭ, J.M. Mermet, J. Anal. Atom. Spectrom. 17 (2002) 211–218.
[16] H.P. Longerich, W. Diegor, J. Anal. Atom. Spectrom. 16 (2001) 1196–1201.
[17] J. Mora, J.L. Todolĭ, A. Canals, V. Hernandis, J. Anal. Atom. Spectrom. 12 (1997) 445–451.
[18] I.B. Brenner, A. Zander, M. Plantz, J. Zhu, J. Anal. Atom. Spectrom. 12 (1997) 273–279.
[19] G. Grindlay, S. Maestre, L. Gras, J. Mora, J. Anal. Atom. Spectrom. 21 (2006) 1403–1411.
[20] J.C. Ivaldi, J.F. Tyson, Spectrochim. Acta, Part B 51 (1996) 1443–1450.