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Analytical performance of a fast multi-element method for titanium and trace elements determination in cosmetics and pharmaceuticals by ICP-AES

Short Communication

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Abstract: A multi-element analytical method based on inductively coupled plasma atomic emission spectrometry (ICP-AES) was developed for trace elements in pharmaceutical tablets and cosmetics. Titanium was also included in the analytes since it is widely used in pharmaceuticals. Critical ICP conditions, like RF incident power, argon gas flow rate and nebulizer sample uptake flow rate were optimized. The most sensitive spectral line of each analyte was selected as optimum for further study. Detection limits in the low $\mu g\ g^{-1}$ range were obtained. Prior to chemical analysis, the samples were decomposed by acid digestion, using various mixtures of HCl, HNO_3 and HF. Yttrium was used as a suitable internal standard in order to correct for possible matrix effects. The method was applied to the analysis of six different pharmaceutical products (anti-biotic, anti-inflammatory, anti-hypertensive) in the form of tablets with film coating and also three cosmetic products like hair and face masks.

Keywords: *Titanium • Elemental analysis • Cosmetics • Pharmaceuticals • Inductively coupled plasma emission spectrometry*

1. Introduction

The vast increase of the production of pharmaceuticals and their wide consumption requires the development of rapid and sensitive methods for the determination of heavy metals and other contaminants which can be used in quality control and routine analysis. Pharmaceutical tablets are usually produced from a powder blend comprising the active pharmaceutical ingredients (APIs) and an inactive organic matrix [1-3]. Film coating of capsules and tablets can also provide physiological advantages by reducing irritation associated with the exposure of the stomach to high concentrations of medications [4]. Most of the components are plasticizers, pigments or cellulosic and acrylic polymers since they have good film coating properties [5].

Titanium dioxide and iron oxides are widely used for film coatings [3]. Therefore, the determination of impurities of various metals in pharmaceutical drugs is important because some of these trace elements are toxic while some others even in ultra trace concentrations could decrease the stability of active ingredients. Some of the impurities could be indicators of non-adequate handling and storage or could be used as fingerprints for the source of drug crude material. Thus, international pharmacopoeias have already specified certain limits of heavy metals concentration in pharmaceutical products.

In this context, heavy metal tests are included in all pharmacopoeias [6-7]. Several analytical methods are reported in literature suitable for heavy metals determination in pharmaceutical formulations, which are based on wet-acid sample digestion or dry ashing or other sample preparation technique. There is a trend to replace the simple heavy metal tests with modern instrumental analytical techniques [8-9]. Analytical techniques like inductively coupled plasma optical emission (ICP-AES) or mass spectrometry (ICP-MS) and electrothermal atomic absorption spectrometry usually require sample digestion. The frequently used multi-element methods for the analysis of drugs and film coatings are based on ICP atomization and measurement of the metals [3].

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A rapid and reliable ICP-AES method was developed by Wang *et al.* and validated for its precision and specificity [9]. ICP-MS was successfully applied by Lewen *et al*. [10] for the determination of heavy metals and by Lasztity *et al*. for trace metal analysis of pharmaceuticals [11]. It was also used by Kauffman *et al*. to determine lead concentrations in a variety of widely used pharmaceutical products, and assess the risk of lead exposure from the use of these products [12]. Plasma-based techniques offer the advantages of screening capability, smaller required sample size, element-specific information, quantitation and rapid sample throughput [10]. Jürgens *et al*. employed spectrophotometric and flame atomic absorption spectrometric techniques for iron determination in a pharmaceutical product [13] while direct coupled plasma atomic emission spectrometry and atomic absorption spectrometry can be used for indirect determination of non-metal analytes also [14].

The aim of this study was to develop a generally applicable method of inductively coupled plasma atomic emission spectrometry for simultaneous determination of trace elements in pharmaceutical and cosmetic formulations after acid digestion by a mixture of HCl, HNO_3 and HF. In our recent work on sunscreens analysis [15], it was showed that the presence of titanium in moderate concentrations has not any significant effect on the determination of other analytes. Therefore, titanium was included in the analytical procedure, while yttrium was used as internal standard (IS) in order to correct for any matrix effect, since this element is unlikely to be found in regular samples [16].

2. Experimental Procedure

2.1 Instrumentation

All ICP-AES measurements were carried out using a Perkin-Elmer Optima 3100 XL spectrometer by axially viewing of emission. The experimental conditions for measurements and method parameters are as previously reported [15]. Sample solutions were introduced into the ICP–AES at flow rates 1-3 mL min^{-1}. Tygon peristaltic pump tubes were used for sample delivery and a scott-type spray chamber was employed. The analytical wavelengths were set as Al 394.401 nm, B 249.772 nm, Cr 357.869 nm, Cu 327.393 nm, Fe 259.939 nm, Mg 279.553 nm, Mn 257.610 nm, Pb 283.306 nm, Ti 334.940 nm, and Zn 213.857 nm, respectively.

Table 1. Regression data and performance of the method for all analytes.

Element/Wavelength	Slope	r	LOD[a] (μg g^{-1})	RSD[b] (%)	Recovery[c] (%)
Ti 334.940 nm	397 ± 4.6	0.9994	0.1	5.1	95.0 ± 2.6
Al 394.401 nm	39.9 ± 1.3	0.9996	0.3	4.0	95.7 ± 3.9
Zn 213.857 nm	11.8 ± 0.4	0.9998	0.2	2.2	98.2 ± 2.0
Mg 279.553 nm	1476 ± 38	0.9987	0.4	6.2	97.8 ± 3.1
Fe 259.939 nm	46.5 ± 2.0	0.9999	0.3	8.1	101.3 ± 4.4
Cu 327.393 nm	71.2 ± 1.7	0.9990	0.8	6.0	100.2 ± 2.4
Mn 257.610 nm	253 ± 4.8	0.9998	0.2	2.6	95.9 ± 3.0
Cr 357.869 nm	116 ± 7.0	0.9994	0.5	4.4	94.6 ± 4.8
Pb 283.306 nm	4.79 ± 0.45	0.9993	2.8	2.5	97.1 ± 2.2
B 249.772 nm	87.3 ± 5.8	0.9994	0.9	3.0	102.8 ± 2.0

[a] *LOD was calculated beased on 3s criterion.*
[b] *RSD was calculated at 250 μg L^{-1} concentration level of each analyte.*
[c] *Mean recovery from n = 5 measurements.*

Table 2. Analysis of drugs and cosmetics by ICP-AES with and without yttrium correction. Mean concentrations in $\mu g\ g^{-1}$ (± standard deviation from 3 replicate analyses).

Analyte	Yttrium[a] correction	Analysed samples/ Concentrations in $\mu g\ g^{-1}$								
		D-MF	D-LC	D-OD	D-NC	D-ZN	D-ID	C-PR	C-VN	C-VD
Ti	-	0.854 (±0.033)	2.43 (±0.11)	1.53 (±0.02)	1.26 (±0.03)	n.d.[b]	1.81 (±0.07)	n.d.	n.d.	13.9 (±0.48)
	+	0.829 (±0.039)	2.03 (±0.04)	1.49 (±0.04)	1.04 (±0.02)	n.d.	1.56 (±0.05)	n.d.	n.d.	11.0 (±0.23)
Al	-	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	0.56 (±0.01)	41.9 (±3.3)	109 (± 4)
	+	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	0.52 (±0.01)	37.7 (±2.0)	99.8 (±4.1)
Zn	-	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	0.32 (±0.01)
	+	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	0.25 (±0.01)
Mg	-	n.d.	n.d.	n.d.	n.d.	n.d.	0.89	n.d.	6.19 (±0.33)	12.3 (±0.56)
	+	n.d.	n.d.	n.d.	n.d.	n.d.	0.78	n.d.	5.12 (±0.27)	10.6 (±0.39)
Fe	-	n.d.	0.63 (±0.04)	n.d.	n.d.	30.6 (±1.5)	n.d.	n.d.	60.2 (±2.6)	191 (±11)
	+	n.d.	0.60 (±0.05)	n.d.	n.d.	24.0 (±0.9)	n.d.	n.d.	42.3 (±3.7)	134 (±8)
Cu	-	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
	+	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Mn	-	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	2.07 (±0.11)	5.72 (±0.23)
	+	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	1.68 (±0.06)	4.49 (±0.20)
Cr	-	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	16.9 (±1.3)	47.7 (±3.9)
	+	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	14.0 (±0.5)	42.4 (±4.1)
Pb	-	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
	+	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
B	-	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	1.9 (±0.01)	n.d.	2.8 (±0.02)
	+	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	1.7 (±0.02)	n.d.	2.5 (±0.02)

[a] *With the use of yttrium as IS (+) and without its use (-).*
[b] *n.d. Not detected. Concentration lower than detection limit.*

2.2 Reagents and solutions

Concentrated HNO_3, HCl and HF used for acid digestion were of analytical grade (pro analysi) provided by Merck (Darmstadt, Germany). Special precautions should be taken when handling hydrofluoric acid and the digestions should be made in the hood. Ultra-pure quality water was used throughout the experiments (Milli-Q system 18.2 MΩ, Millipore, Bedford USA). The single-element standards used for preparation of multi-element standards were Merck traceable to NIST standards. An intermediate standard solution containing 10 mg L^{-1} of all the above mentioned analytes was prepared by mixing suitable aliquots of single-element stock solutions (Merck) containing Al, Ti, Zn, Mg, Fe, Cu, Mn, Cr, Pb, B, at 1000 mg L^{-1} each, and appropriate dilution. The above solution was further diluted in 0.5 mol L^{-1} HNO_3 to obtain a series of low-concentration working standards (0-1000 μg L^{-1}). Six-point calibration curves were prepared for all elements and their slope was used to estimate the sensitivity in presence of yttrium as IS.

2.3 Samples

Six different anti-biotic, anti-inflammatory drugs in tablet form with film coating were analyzed in triplicate and the code numbers given in this research were: D-MF 500 mg, D-NC 400 mg, D-OD 10 mg, (antibiotics), D-LC

20 mg, D-ZN 150 mg and D-ID 40 mg (anti-inflammatory). In addition, three cosmetic products in cream form were analyzed and their code numbers were: C-PR (hair mask), C-VN (anti-wrinkle face mask) and C-VD (face mask for cleaning). 0.1 – 0.3 g of all samples were acid digested by mixture of HNO_3, - HCl – HF [15] and to the in the final solution also 2.00 mg L^{-1} of yttrium as IS was added.

3. Results and Discussion

3.1 Calibration studies and performance of the method

The most sensitive spectral line (higher slopes and r > 0.09) of each analyte having the lower background signal was selected as optimum for further study. In Table 1 the selected lines together with the results of the regression and correlation analysis are given. The sensitivity of each calibration is expressed by the slope of the linear regression equation.

The detection limits (LOD, μg g^{-1}) were calculated using the 3*s* criterion (three times the standard deviation of 10 blanks). The detection limits for the most sensitive spectral lines ranged between 0.1-0.9 μg g^{-1} except for Pb for which higher LOD was obtained. The method accuracy was assessed through recovery tests, since there is no available CRM material.

3.2 Application to commercial drugs and cosmetics formulations

The developed method was applied to the determination of trace elements in two types of samples, *i.e.*, commercial cosmetics and drugs. The examined drugs contained cefadroxil, omeprazole, norfloxacin, ranitidine hydrochloride or propranolol hydrochloride as active substances, and other various excipients like magnesium stearate, titanium dioxide, microcrystalline cellulose, red iron oxide, gelatine, *etc*. The cosmetics contained propylparaben, methylparaben, zinc aspartate, copper aspartate, titanium dioxide, *etc.* The results are presented in Table 2 with or without yttrium correction, comparatively. The use of the IS correction resulted to lower concentrations than those obtained without its use. According to the results presented in Table 2, Cu and Pb were not detected in any of the samples, while B, Mn and Zn were found only in cosmetic creams. Al is possibly due to the presence of alumina or alumina stearate. Ti was present in almost all tablets as it was appeared on the product label, except in D-ZC, which does not include titanium dioxide in the ingredients. Fe was found in several samples, either containing Ti or not. Finally, Mg, Mn and Cr were found in the cosmetic creams.

4. Conclusions

The mixture of hydrochloric, nitric and hydrofluoric acids was proved suitable for the recovery of inorganic elements from various drugs and cosmetics which were analysed in this work. The ICP-AES technique was capable of detecting elements at trace levels and the detection limits are quite low for most analytes. Probably the critical advantage of the use of ICP atomization is the fact that simultaneous multi-elemental analysis can be accomplished rapidly to the determination of Ti, Al, Zn, Mg, Fe, Cu, Mn, Cr, Pb and B down to the μg g^{-1} level. Using yttrium as the internal standard in order to correct for possible matrix interferences during nebulization is critical, since for several analytes the obtained results are slightly different than without its use. In most of the examined samples, the determined analytes were related to metal-containing ingredients appeared on each product label. The method can be used efficiently in quality control and routine analysis.

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