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Development of a rapid multi-element method of analysis of antitussive syrups by inductively coupled plasma atomic emission spectrometry and direct sample introduction

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Abstract

A new rapid method was developed and optimized for routine multi-element determination of traces of metals in antitussive syrups using direct introduction of diluted syrup into the nebulization system of inductively coupled plasma atomic emission spectrometer (ICP-AES). Using a Scott-type double-pass spray chamber combined with a cross-flow nebulizer, the optimum ICP conditions, like RF incident power, argon gas flow rate and nebulizer sample uptake flow rate were found. A critical objective of the study was to evaluate the matrix effect on the intensity and consequently on the sensitivity of the developed method. Thus, the maximum syrup concentration which could be introduced into the argon plasma, was estimated. The sensitivity variation was calculated as compared to the corresponding sensitivity obtained from aqueous solutions for each analyte. The performance characteristics of the proposed method were evaluated for quantitative and semi-quantitative determination and finally, the method was applied to the analysis of various commercial antitussives.

Keywords: Trace elements; Antitussives; Inductively coupled plasma; Atomic spectrometry

1. Introduction

The determination of various trace elements in pharmaceutical preparations is of increasing importance because of the toxic effect of some of them and, on the other hand, the extended consumption of pharmaceuticals. The problem becomes more complicated because of the possibility of various elements to form stable complexes with various pharmaceutical substances, as it is extensively investigated in last decades [1–3]. Although it is less likely to detect residues of metals in the synthetic bulk pharmaceutical substance [4], it is more likely to detect the presence of metal traces in the final product or formulation which contain various excipients, diluting agents, natural flavors, etc.

International pharmacopoeias like the European Pharmacopoeia have already specified certain limits of heavy metals concentration in pharmaceutical products. Also they recommend specific analytical methods [5] for the detection or quantitative determination of heavy metals in various pharmaceutical formulations, which are usually based on time-consuming procedures like complete wet-acid sample digestion or dry ashing or other sample preparation technique and subsequent determination of the analytes by an atomic or a molecular spectroscopic technique [6,7]. Alternatively, a visual qualitative test after formation of metal sulfides with thioacetamide, for estimation of the total heavy metals can be employed.

For this reason, a number of methods is reported recently concerning the multi-element analysis of various pharmaceutical powder formulations, like antibiotic, anti-inflammatory, painkillers, etc., based on the use of powerful multi-element techniques like inductively coupled plasma atomic emission spectrometry [8,9] or mass spectrometry [10–12]. As far as we know, no methods have been reported in the literature for multi-element analysis of antitussives by inductively coupled plasma atomic emission spectrometry, although this technique offers a number of significant advantages over others. Less costly instrumentation is needed in comparison to other multi-element techniques and the sensitivity is in the low μg/l level for the majority of the analytes. In addition, the spectral interferences are easily countered by using alternative spectral lines for each element.

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Antitussive and anticough syrups are extensively used to symptomatic treatment of acute bronchitis and cough which is the most commonly observed symptom [13,14]. The extended consumption of these syrups defines the need for routine analysis methods for the determination of traces of contaminants. They are aqueous or semi-aqueous solutions containing the active substance and organic content in the form of various excipients. The most common approach to analyze pharmaceutical samples by atomic spectrometric techniques is the preliminary wet or dry digestion of the sample and nebulization of the resulting solution. This is a time-consuming step in the whole procedure, causes contamination and analyte losses and may result to poor reproducibility. An alternative procedure is the direct introduction of the sample to the nebulizer. In this category belong the slurry formation technique, which has been applied successfully to various types of solid samples and the direct introduction of diluted samples. In both cases a careful optimization of the operating parameters is needed in order to assure maximum analytical performance.

Consequently, the objective of this work was to develop and optimize an inductively coupled plasma atomic emission spectrometric method for the determination of trace elements in antitussive or anticough syrups using the direct aspiration of the diluted syrup into the nebulization system. In order to keep plasma stability and nebulizing ability in presence of high organic matrix solutions, the optimum conditions of the plasma were found, such as power of RF generator, nebulizer argon gas flow rate and sample uptake flow rate. The optimum aspirated syrup concentration, which could be introduced into the argon plasma, without plasma extinguishing, was also estimated. The performance characteristics of the method were evaluated and the proposed method was applied to the analysis of common pharmaceutical formulations.

2. Experimental

2.1. Instrumentation

All ICP-AES measurements were made using a Perkin-Elmer Optima 3100 XL axial viewing spectrometer, according to the operating conditions described in Table 1. The analytical wavelengths were set at the first and second sensitivity order spectral atomic (I) or ionic (II) lines of the analytes, and they are listed in Table 2. A two-point background estimation procedure was applied in order to minimize any possible spectral interference between analytes.

For the optimization of the instrument's performance, variable radio frequency (RF) incident power levels and nebulizer flow rates were investigated. The torch inner tube was consisted from alumina, which is sufficiently resistant to acidified solutions. A peristaltic pump was employed to introduce the sample solutions into the ICP–AES at a flow rate of 1 ml/min and to discard the wastes at higher flow rate. The diluted syrup samples were transported through the peristaltic pump using Tygon PVC tubing (i.d. 0.030 in.).

A Perkin-Elmer 5100 PC atomic absorption spectrometer working either as flame AAS and as graphite furnace AAS with Zeeman background correction, was employed for the analysis of syrups and cross-validation of the proposed method.

Table 1
Operating conditions and instrumentation of the ICP-AES instrument

RF generator	40 MHz, free-running
RF incident power	Optimized (1300–1500 W)
Torch, inner tube, id	Fassel type, Alumina, 2.0 mm
Auxiliary argon flow rate	0.5 l/min
Nebulizer argon flow rate	Optimized (0.60–1.15 l/min)
Plasma gas flow rate	15 l/min
Air flow rate	18 l/min
Sample uptake flow rate	1 ml/min
Spray chamber	Scott double-pass
Nebulizer	Gem tip cross-flow
Sample propulsion	Peristaltic pump, three channel
Polychromator	Echelle grating
Resolution	0.006 nm at 200 nm
Signal Correction	Interelement correction algorithm (IEC, optional)
Detector	Segmented-array charge-coupled (SCD)

2.2. Reagents and solutions

All chemicals were of analytical reagent grade (pro analysi) and were provided by Merck (Darmstadt, Germany). Chemical reagents used for preparation of multi-element standards were of analytical grade, provided by Merck. Ultra pure water of Milli-Q quality (Millipore, Bedford, USA) with 18.2 MΩ cm resistivity (25 °C) was used throughout. A mixed working standard solution containing 10 mg/l of all the above listed analytes was prepared by mixing suitable aliquots of a multi-element stock solution (Merck) (containing 1000 mg/l of each of the following: Ag, Al, Ba, Bi, Ca, Cd, Co, Cr, Cu, Fe, Ga, In, Mg, Mn, Ni, Pb, Zn) with four single-element stock standard solutions (containing 1000 mg/l of each of the following As, Be, Pd, Se,

Table 2
Analytical spectral wavelengths used for the determination of analytes in antitussive syrups by ICP-AES

Analyte	Spectral lines (atomic (I) and ionic (II))
Ag	Ag I: 328.068 nm, Ag I: 338.289 nm
Al	Al I: 308.215 nm, Al I: 237.313 nm
As	As I: 188.979 nm, As I: 193.696 nm
Ba	Ba II: 233.527 nm, Ba II: 230.424 nm
Be	Be I: 313.107 nm, Be I: 234.861 nm
Bi	Bi I: 223.061 nm, Bi II: 190.171 nm
Ca	Ca II 317.933 nm, Ca II 396.847 nm
Cd	Cd II: 214.440 nm, Cd II: 226.502 nm
Co	Co II 228.616 nm, Co II 238.892 nm
Cr	Cr II: 283.563 nm, Cr II: 284.325 nm
Cu	Cu I: 324.752 nm, Cu II: 224.700 nm
Fe	Fe II: 238.204 nm, Fe II: 239.562 nm
Ga	Ga I: 294.364 nm, Ga II: 209.134 nm
In	In II: 230.606 nm, In I: 325.609 nm
Mg	Mg II: 279.077 nm, Mg II: 280.271 nm
Mn	Mn II: 257.610 nm, Mn II: 259.372 nm
Ni	Ni II: 221.648 nm, Ni II: 232.003 nm
Pb	Pb II: 220.353 nm, Pb I: 217.000 nm
Pd	Pd I: 340.548 nm, Pd I: 363.470 nm
Se	Se I: 196.026 nm, Se I: 203.186 nm
Zn	Zn I: 213.857 nm, Zn II: 202.548 nm

respectively) in 0.5 mol/l HNO_3 (Merck) and appropriate dilution. From this, a series of lower concentration standards was prepared daily by stepwise dilution using a 0.5 mol/l HNO_3 diluent solution. Since this multi-element standard was prepared to contain 21 elements, the compatibility among all the included elements should be confirmed. No precipitation or turbidity was observed by visual inspection of the stored standard (in refrigerator) during a period of 1 month. In addition, a calibration test of the multi-element standard against a freshly prepared one showed no significant differences for all analytes. Thus, the multi-element standard can be used during a month-period without causing any bias in the calibration procedure.

Six-point calibration curves were obtained using aqueous multi-element standards. Also, the standard addition procedure was applied by using the above aqueous standards as diluents in the formation of slurries. The final mixed working standard solutions had the following concentrations: 0, 10, 50, 100, 200 and 500 μg/l for each metal. In order to check the overall repeatability of the ICP-AES detector two different calibration procedures were made at two different time periods. The slope of the calibration curves was used to estimate the sensitivity of the method.

2.3. Procedure for direct syrup dilution and analysis by ICP-AES

The density of each type of syrup was calculated through mass measurement of defined volumes. The optimization of the concentration of the syrup in the aspirated solution was made off-line by using suitable volumes of syrup and of 0.5 mol/l HNO_3 diluent. The syrup samples were then diluted to contain 30% (v/v), with 0.5 mol/l HNO_3 using a peristaltic pump and Tygon tubes. The inner tube of the plasma torch must be carefully cleaned because traces of carbon deposits appear after some decades of regular samples, which may cause problem to the nebulization process and decrease the precision of the analysis. Commercially available rinsing solutions could be periodically aspirated for cleaning the nebulizer, otherwise frequent aspiration of the diluent solution is recommended.

2.4. Procedure for wet digestion of samples and analysis by ICP-AES

Due to the absence of any commercially available certified reference material of the same nature as the antitussive syrups and with a multi-element certification, the samples were completely decomposed by wet-acid digestion, in order to use the results of this analysis as reference values and evaluate the accuracy of the direct sample introduction method. In addition, spiked samples were used to obtain the recovery of the method.

The most common approach involves the acid attack of the sample by a mixture of oxidative acids, in closed polytetrafluoro-ethylene (PTFE) vessels, thus it was also applied to this research. The drawbacks of this and other similar procedures, as it was mentioned above, are that they need several hours to finish the digestion, contamination is possible and dilution is unavoidable. To avoid contamination all glassware and Teflon digestion vessels were soaked in freshly prepared 10% (v/v) HNO_3 for 24 h, and finally washed three times with Milli-Q grade water.

Aliquots of ca. 2 or 3 ml of each sample were accurately weighed into PTFE vessels, with subsequent addition of 5 ml concentrated HNO_3 (65%, m/m). The vessels were closed, placed into a steel pressurized bomb and heated on a hot plate up to 130 °C. The final digest was quantitatively transferred to 25 ml volumetric flask and diluted with 0.5 mol/l HNO_3. Blanks of the whole method were prepared following exactly the same acid digestion procedure in Milli-Q water. Also, multi-element standard solutions were similarly digested in order to monitor any losses during the digestion procedure.

3. Results and discussion

3.1. Optimization of operating conditions

One of the most critical parameters in direct sample introduction is the matrix concentration. Preliminary experiments with direct introduction of not diluted syrup proved that although the plasma is not extinguished, the stability of plasma is not sufficient for all types of syrups. In addition, clogging of the inner tube by carbon deposits is very frequent and introduction of the sample through the peristaltic pump is not precise.

Consequently, the effect of syrup concentration of the aspirated solution on the emission intensity of a 200 μg/l spiked sample of an ambroxol containing syrup was studied in the range 5–60% (v/v), using 1300 W incident power, 1 ml/min sample uptake flow rate and 0.80 ml/min nebulizer gas flow rate. In Fig. 1 the results of this study are given for the two spectral lines of Ag, Ba, Cd, Mn, Pb and Zn. In these charts, the intensity is the net signal calculated after the subtraction: net signal = signal of 200 μg/l spiked sample − signal of not spiked sample.

The results for all other analytes are similar, and in all cases there is a monotonously decline of the signal when increasing the concentration of the syrup in the aspirated solution. This is caused mainly by the presence of the bulk organic content in the plasma, which decreases its nebulization efficiency. However, the loss in sensitivity due to matrix interference (ranging between 5 and 40%) is compensated by the increase of the sensitivity due to higher sample intake (ranging between 100 and 1200%) thus the overall result is a significant increase of the sensitivity. Finally, a 30% (v/v) concentration was selected for the rest of the optimization as a compromise between medium sample consumption and high sensitivity.

In some commercial antitussives, this effect was less significant due to lower viscosity of them. According to these observations, it is recommended to test each type of syrup before starting routine analysis, in order to check the possibility of using higher concentrations and achieve further gain in sensitivity.

The incident power was optimized in the range 1300–1500 W and the results proved that for all the examined analytes at both spectral lines the highest sensitivity was obtained at 1500 W incident power, except for In, Ni, and Zn for which the sensitivity at 1400 W was a little better. The results of this study are presented in Fig. 2, for Al, Ba, Cd, Cr, Fe and Ni. According to

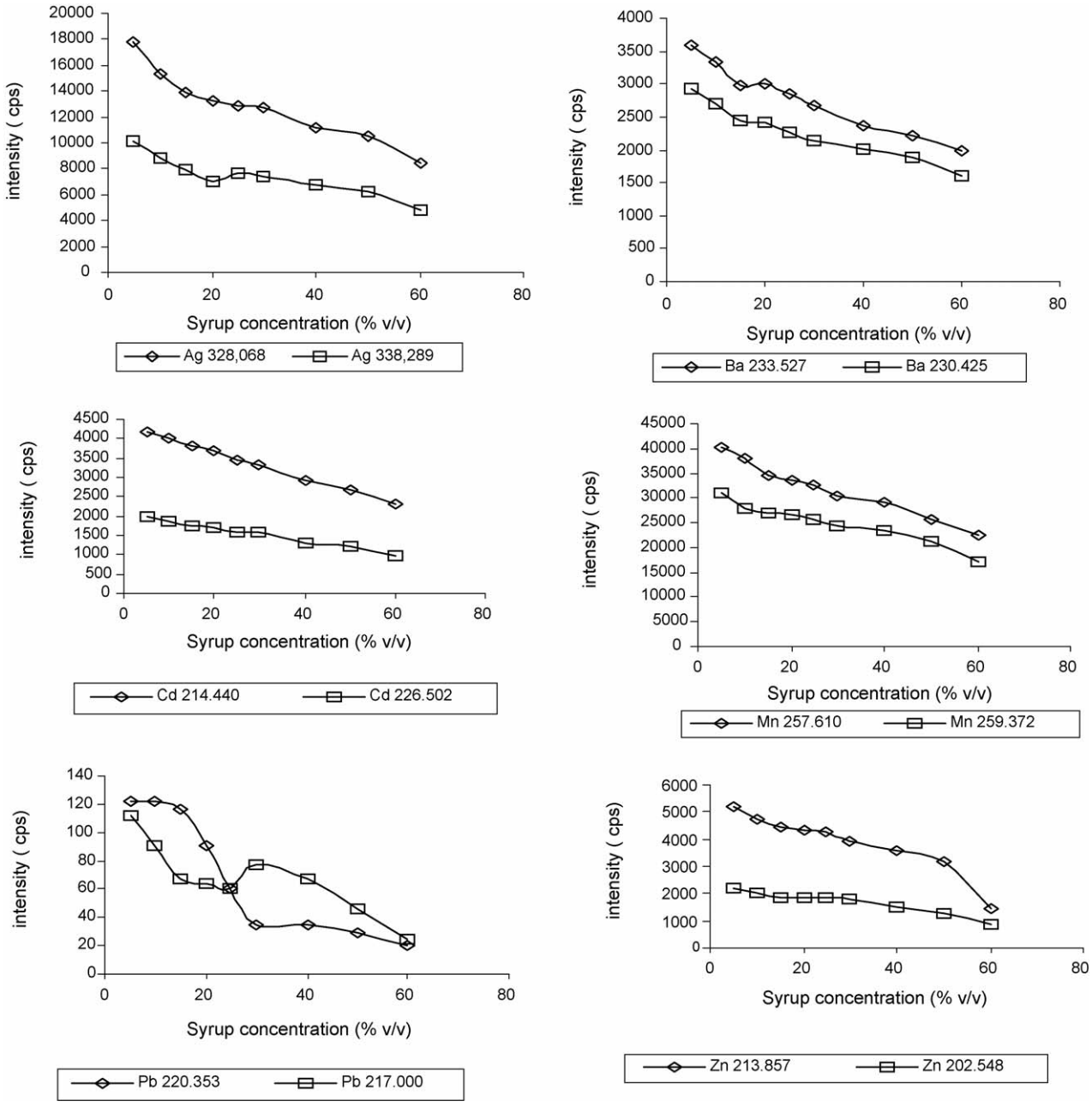

Fig. 1. Matrix effect from increased syrup concentration of the aspirated solution on the emission intensity of several analytes.

these observations, the incident power was fixed at 1500 W for all analytes for multi-element determination.

The nebulizer gas flow rate was then optimized in the range 0.65–1.15 ml/min, for introduction of 30% (v/v) syrup concentrations and 1 ml/min sample uptake gas flow rate. The optimum flow rate was found at 0.80 ml/min for the majority of the analytes. Finally, the optimum spectral line for each analyte was selected according to sensitivity checks, as it is described below.

3.2. Analytical performance of the method

The above described optimum conditions were applied in order to prepare (i) calibration curves using aqueous multi-element standard solutions and (ii) standard addition curves using spiked syrup solutions. Regression analysis was applied and the results are given in Table 3. The slopes of the obtained regression line in each case were compared, and the sensitivity change for each analyte could be estimated. The results are illustrated in Fig. 3. It was proved that for the majority of the analytes, except Zn, there is a decrease in the slope of the standard addition curve, which varied in the range 0 to −45%. This sensitivity loss is mainly caused to the presence of high carbon concentration in the nebulizer, which absorbs part of the induced plasma energy. Thus, the use of the standard addition curve is recommended, in order to compensate with this sensitivity variation.

The most efficient spectral line of each analyte was selected and used for further study and in application of the method in var-

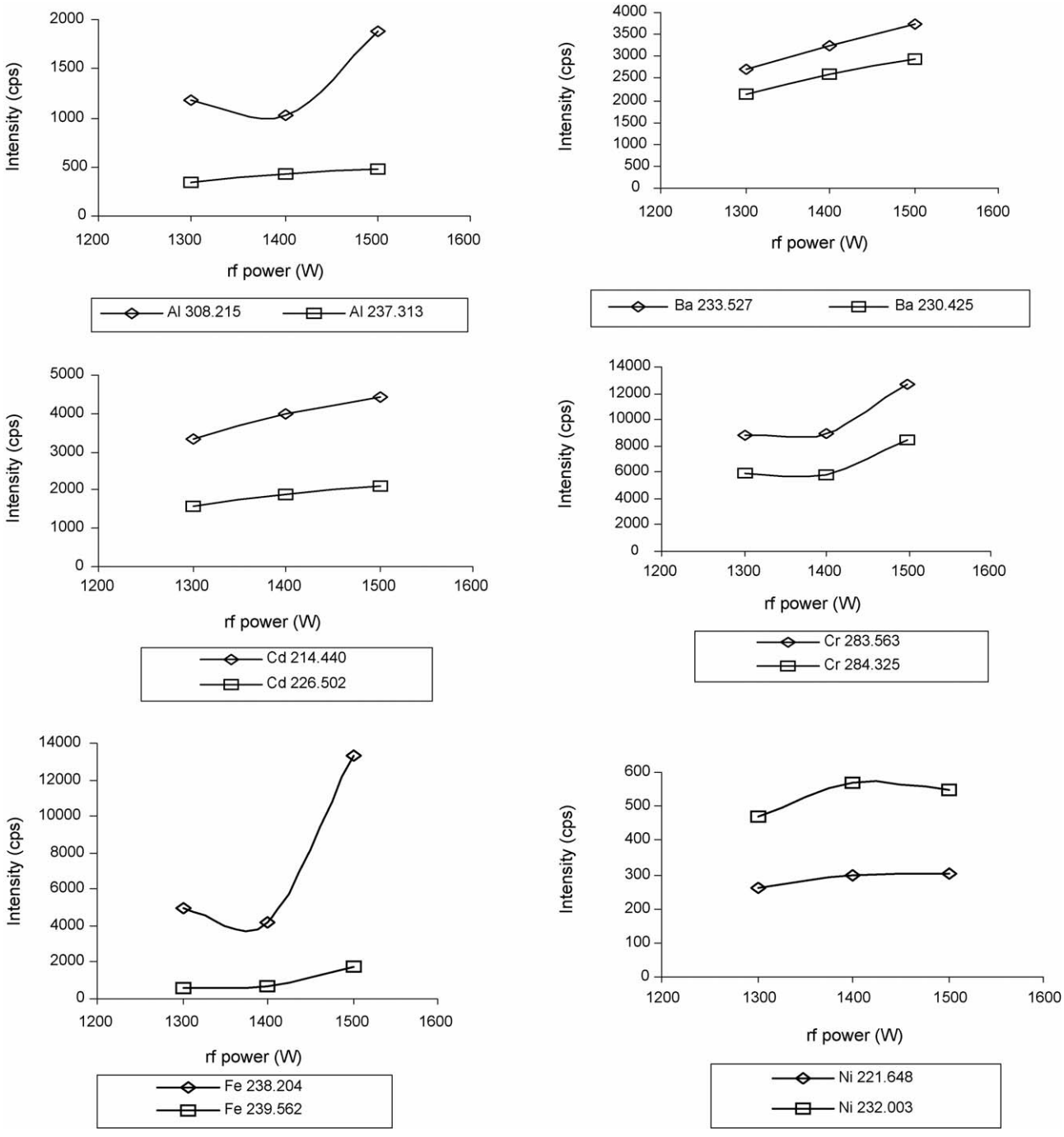

Fig. 2. Effect of incident power on the emission intensity of several analytes.

ious commercial antitussives. The optimum spectral line for each analyte is listed in bold type letters in Table 3. The selected lines are in all cases the most sensitive (higher slopes) and with better correlation coefficient ($r > 0.99$). Analytes with low sensitivity in both lines like As, Bi, Pb and Se can be determined only at higher concentration levels. Since, Se and As showed lower correlation coefficients and higher standard errors in both lines, these two elements could be determined only semi-quantitatively.

Taking into account the 30% dilution of the sample and the measured mean density of the commercial syrup (ca. 1.08 g/ml), the resulting detection limits (μg/g) for the optimum spectral lines were calculated using the three sigma criterion (concentration giving a signal equivalent to the mean of 10 blank measurements plus three times the standard deviation of these measurements). For the majority of the analytes, they varied in the range between 0.01 and 0.04 μg/g, except for Ga and In, for which the LODs were 0.05 and 0.06 μg/g, respectively. The precision was assessed by means of relative standard deviation of 10 replicates of a spiked sample at 200 μg/l concentration level. The R.S.D. ranged between 2 and 9% for almost all analytes. Finally, the recovery from spiked samples was sufficient and ranged between 92 and 106%.

Table 3
Comparative regression data between aqueous calibration and standard addition curve in syrup matrix for all the examined spectral lines

Analyte	Spectral line[a] (nm)	Aqueous			Syrup (30%, v/v)			Level[c]
		Slope	S.E.[b]	r	Slope	S.E.[b]	r	
Ag	**328.068**	101	0.7	0.9999	70.5	2.8	0.9970	Q
	338.289	60.4	0.4	0.9999	39.8	1.5	0.9971	
Al	**308.215**	15.1	0.6	0.9973	10.4	0.8	0.9992	Q
	237.313	3.02	0.03	0.9999	2.26	0.14	0.9919	
As	**193.696**	0.55	0.02	0.9987	0.50	0.13	0.9408	S-Q
	188.979	0.50	0.03	0.9971	0.42	0.11	0.9356	
Ba	**233.527**	19.4	0.1	0.9999	18.1	0.2	0.9996	Q
	230.425	15.4	0.0	0.9999	15.0	0.2	0.9997	
Be	**313.107**	1366	6	0.9999	1319	16	0.9995	Q
	234.861	599	3	0.9997	487	8	0.9989	
Bi	**223.061**	2.00	0.09	0.9967	1.79	0.10	0.9941	S-Q
	190.171	0.14	0.04	0.9770	0.12	0.05	0.9668	
Ca	**396.847**	2581	62	0.9991	2363	117	0.9951	Q
	317.933	28.3	2.3	0.9988	28.0	3.1	0.9774	
Cd	**214.440**	24.6	0.1	0.9999	22.7	0.6	0.9987	Q
	226.502	10.7	0.1	0.9999	10.9	0.2	0.9996	
Co	**228.616**	9.80	0.1	0.9999	8.71	0.23	0.9986	Q
	238.892	11.0	0.2	0.9990	8.85	0.39	0.9982	
Cr	**283.563**	64.7	0.9	0.9997	56.3	1.6	0.9983	Q
	284.325	45.6	0.7	0.9996	41.3	0.9	0.9990	
Cu	**324.752**	151	0.9	0.9999	113	2.0	0.9994	Q
	224.700	7.20	0.1	0.9998	5.59	0.12	0.9991	
Fe	**238.204**	35.8	0.1	0.9999	29.7	1.1	0.9975	Q
	239.562	3.44	0.23	0.9936	3.46	0.23	0.9394	
Ga	**294.364**	9.69	0.10	0.9999	7.37	0.20	0.9985	Q
	209.134	0.03	0.02	0.8602	0.03	0.02	0.8737	
In	**325.609**	7.81	0.28	0.9981	4.86	0.21	0.9962	Q
	230.606	1.33	0.03	0.9991	1.15	0.07	0.9936	
Mg	**280.271**	631	2	0.9999	641	30	0.9956	Q
	279.077	5.06	0.07	0.9997	4.01	0.36	0.9845	
Mn	**257.610**	224	1	0.9999	201	4	0.9994	Q
	259.372	166	1	0.9999	147	3	0.9993	
Ni	**232.003**	3.45	0.07	0.9994	2.78	0.09	0.9979	Q
	221.648	1.64	0.01	0.9999	1.70	0.05	0.9981	
Pb	**220.353**	0.60	0.02	0.9989	0.62	0.05	0.9968	S-Q
	217.000	0.57	0.03	0.9849	0.43	0.05	0.9766	
Pd	**340.458**	21.7	0.3	0.9993	17.0	0.4	0.9850	Q
	363.470	14.1	0.3	0.9999	7.48	0.66	0.9970	
Se	**196.026**	0.66	0.02	0.9983	0.63	0.10	0.9753	S-Q
	203.186	0.41	0.03	0.9964	0.36	0.06	0.9720	
Zn	**213.857**	28.5	0.1	0.9999	32.3	2.0	0.9944	Q
	202.548	12.0	0.1	0.9999	13.3	1.0	0.9994	

Concentration (μg/l) vs. intensity (cps).
[a] The selected optimum response lines are listed in bold type.
[b] Standard error of the slope.
[c] Q, quantitative; S-Q, semi-quantitative.

As it was mentioned above, no certified reference material of similar matrix is commercially available so the accuracy of the proposed method was evaluated versus complete acid digestion of spiked commercial antitussive syrup containing ambroxol hydrochloride and the standard addition technique. Additional analysis of the digests was performed by single-element atomic absorption spectrometry using flame and electrothermal atomization for comparative purposes. The results are

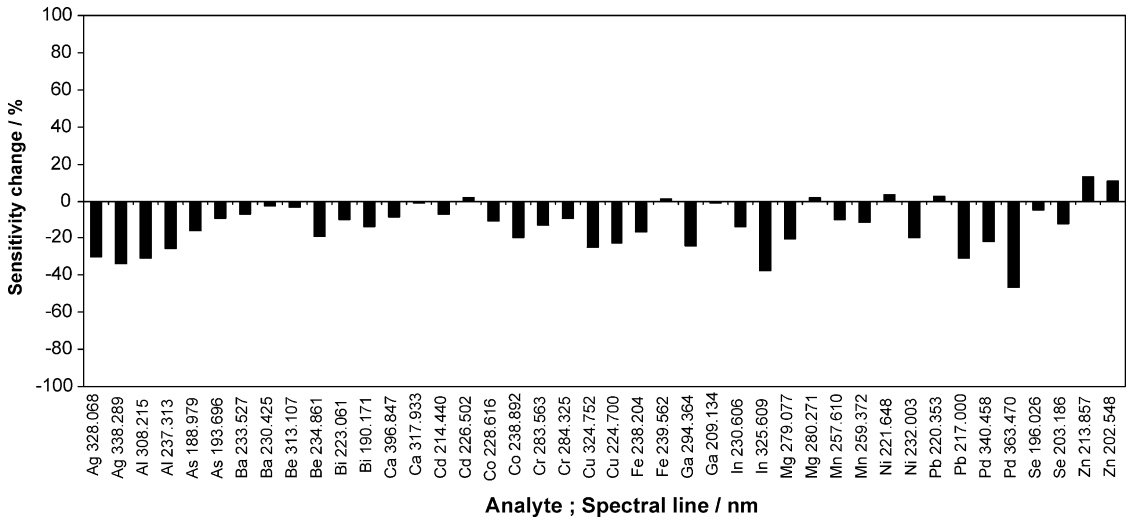

Fig. 3. Percentage sensitivity variation using standard solutions containing 30% (v/v) antitussive as compared to aqueous solutions, at the optimum conditions (RF 1500 W, 30% (v/v) syrup concentration, sample introduction flow rate 3 ml/min).

given in Table 4. Concerning the analytes, which were found in measurable levels, it is seen that sufficient agreement is achieved between the digested samples and the proposed method of direct introduction of diluted sample. Since there is no sample pretreatment step, a sampling frequency of 20 samples per hour can be easily handled.

3.3. Application to commercial antitussives

The developed method was applied to the determination of trace elements in commercial antitussives, containing ambroxol hydrochloride (ATS-1: 3 mg/ml; ATS-2: 6 mg/ml), carbocisteine (ATS-3: 50 mg/ml) and butamyrate citrate (ATS-4: 1.5 mg/ml) as active substances, and various other excipients like glycerol, hydroxyethyl cellulose, sorbitol, saccharin, fruit essences, benzoic acid, propylene glycol, ethanol, menthol, etc. The results are presented in Table 5.

It is shown that the investigated syrups had not detectable concentrations of all toxic metals. Only Ca, Mg and Fe were found in measurable levels in all syrups, while Cu, Ni and Zn were detected in one case each. It is worth to mention that, although the first two samples contained the same active substance in different concentration levels, they do not differ proportionally to the observed concentration of the analytes. Consequently, it can be concluded that the presence of traces of a number of metals in syrups is

Table 4
Comparative results of the diluted sample introduction method vs. complete acid digestion method, using and the standard addition technique and antitussive sample (mean concentration ± standard deviation)

Analyte	Spectral line (nm)	ICP-AES				FAAS/ETAAS
		Diluted sample		Acid digestion		Digested sample
		LOD (μg/g)	Concentration (μg/g)	LOD (μg/g)	Concentration (μg/g)	Concentration (μg/g)
Ag	328.068	0.012	<0.012	0.015	<0.015	<0.004
Al	308.215	0.034	<0.034	0.042	<0.042	0.013 ± 0.004
Ba	233.527	0.024	<0.024	0.028	<0.028	0.011 ± 0.003
Be	313.107	0.006	<0.006	0.008	<0.008	<0.010
Ca	396.847	0.016	1.34 ± 0.04	0.024	1.19 ± 0.06	1.28 ± 0.07
Cd	214.440	0.024	<0.024	0.024	<0.024	<0.003
Co	228.616	0.040	<0.040	0.045	<0.045	<0.005
Cr	283.563	0.015	<0.015	0.018	<0.018	<0.003
Cu	324.752	0.010	0.012[a]	0.008	0.010[a]	0.008 ± 0.002
Fe	238.204	0.021	0.028[a]	0.020	0.023[a]	0.023 ± 0.003
Ga	294.364	0.054	<0.054	0.056	<0.056	<0.025
In	325.609	0.058	<0.058	0.060	<0.060	<0.033
Mg	280.271	0.010	0.270 ± 0.019	0.016	0.261 ± 0.025	0.268 ± 0.018
Mn	257.610	0.012	<0.012	0.010	<0.010	0.004
Ni	232.003	0.040	<0.040	0.030	<0.030	<0.010
Pd	340.458	0.038	<0.038	0.034	<0.034	<0.015
Zn	213.857	0.012	0.012[a]	0.012	0.014[a]	0.010 ± 0.003

[a] Results given just as estimation, because they are higher than LOD but lower than quantitation limit LOQ.

Table 5
Results of the analysis of commercial antitussive and anticough syrups (mean ± S.D., $n = 5$, μg/g)

Analyte	Spectral line (nm)	ATS-1	ATS-2	ATS-3	ATS-4
Ag	328.068	<0.012	<0.012	<0.012	<0.012
Al	308.215	<0.042	<0.042	<0.042	<0.042
Ba	233.527	<0.024	<0.024	<0.024	<0.024
Be	313.107	<0.006	<0.006	<0.006	<0.006
Ca	396.847	1.45 ± 0.05	1.11 ± 0.05	34.2 ± 2.4	1.79 ± 0.17
Cd	214.440	<0.024	<0.024	<0.024	<0.024
Co	228.616	<0.045	<0.045	<0.045	<0.045
Cr	283.563	<0.015	<0.015	<0.015	<0.015
Cu	324.752	<0.010	0.013[a]	<0.010	<0.010
Fe	238.204	0.025[a]	<0.021	0.554 ± 0.008	<0.021
Ga	294.364	<0.054	<0.054	<0.054	<0.054
In	325.609	<0.060	<0.060	<0.060	<0.060
Mg	280.271	0.188 ± 0.015	0.283 ± 0.012	0.144 ± 0.008	0.082 ± 0.008
Mn	257.610	<0.012	<0.012	<0.012	<0.012
Ni	232.003	<0.040	<0.040	0.074 ± 0.010	<0.040
Pd	340.458	<0.036	<0.036	<0.036	<0.036
Zn	213.857	<0.012	<0.012	0.015[a]	<0.012

[a] Results given just as estimation, because they are higher than LOD but lower than quantitation limit LOQ.

probably attributed to the excipients and not to the active compounds.

4. Conclusions

The direct nebulization technique of diluted sample in the plasma nebulizer of the ICP-AES was proved an efficient method for the analysis of commercial antitussive syrups independently of their other matrix constituents. The developed method can be used for quantitative determination of 17 elements and semi-quantitative determination of other 4 elements. Dilutions in the range up to 30% (v/v) can be easily employed and for certain syrups even the non-diluted sample can be aspirated without extinguishing the plasma, however with increased baseline instability and need for more frequent inner tube maintenance. By direct introduction of minimum diluted sample it is possible to achieve sufficient sensitivity, comparable to those of other more expensive multi-element techniques. As no sample pretreatment is needed and less costly instrumentation is needed than mass spectrometric techniques, the method is convenient as a screening method for routine analysis of such pharmaceutical formulations and possibly of other commercial products of similar matrix.

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