



Application of LA-ICP-MS as a rapid tool for analysis of elemental impurities in active pharmaceutical ingredients



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ABSTRACT

The control of inorganic contaminants in active pharmaceutical ingredients has a significant role in the quality control of drug products. The concentration limits for metal residues in drug products have been defined by various regulatory guidelines. Laser ablation inductively coupled plasma mass spectrometry (LA-ICP-MS) is a powerful and fast analytical technique for multi-elemental analysis. A disadvantage in using LA-ICP-MS method is the lack of matrix reference materials for validation and calibration purposes. This article focuses on the handling strategy of laboratory-made matrix calibration standards for the quantification of elemental impurities in an active pharmaceutical ingredient by LA-ICP-MS.

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1. Introduction

The monitoring of elemental impurities in active pharmaceutical ingredients or drug products is vitally important as some of these impurities may present hazards to human health. Metals and metal compounds originate from the synthesis of active pharmaceutical ingredients (due to impurities in raw materials, reagents or solvents, use of catalysts, corrosion of reaction vessels and other equipment) as well as from degradation of pharmaceutical packaging materials during storage (e.g. oxidation, hydrolysis products) [1].

Compounds of Cr, Cu, Mn, Mo, V, Ni, Os, Rh, Ru, Ir, Pd, Pt may contaminate active pharmaceutical ingredients in salt or reduced metal form as a consequence of certain manufacturing processes. While some elements (such as Al, As, Bi, Cu, Fe, Mn, Mg, Se) may be introduced in drug products for therapeutic purposes, other elements (Cd, Pb, Hg) must be controlled due to extremely high toxicity to humans [2].

The control of elemental contaminants in drug products is crucial for release of pharmaceutical products by manufacturers. European Medicines Agency (EMA) [1], United States Pharmacopoeia (USP) [3] and European Pharmacopoeia (Eur.Ph.) [4] regularly update their guidelines on specification limits for metal residues in pharmaceuticals. The inclusion of elements such as Cd,

Pb, As, Hg, Ir, Os, Pd, Pt, Rh, Ru, Cr, Mo, Ni, V, Cu, Mn, Fe and Zn in pharmaceutical product specifications depends on the possibility of contamination during the manufacturing process, while the concentration limit for each element is assigned according to the potential toxicity to humans.

Complex and sometimes hazardous matrices of pharmaceutical samples can cause problems during the sample preparation stage prior to instrumental analysis. A variety of sample preparation procedures for active pharmaceutical ingredients have been used such as dry ashing, wet digestion (microwave assisted or on a hot plate) and direct dissolution [5–12]. Selection of mineralization method frequently depends on the identity of analyzed elements (e.g., for volatile elements it is better to use a microwave system), recovery of elements, matrix interferences, consumed volumes of reagents and contamination risk due to the working environment. The quantification of elements can be successfully done by AAS (atomic absorption spectrometry), ICP-OES (inductively coupled plasma atomic emission spectrometry) and ICP-MS (inductively coupled plasma mass spectrometry) techniques. All mentioned are wet chemistry techniques [5–15].

For direct solid state analysis LA-ICP-MS (laser ablation inductively coupled plasma mass spectrometry) and LIBS (laser induced breakdown spectroscopy) can be used [6,16]. LA-ICP-MS method is rarely used for pharmaceutical material analysis. Widely known problems for quantification of elements are: the requirement for sample matrix similarity to the matrix of standard reference material (SRM) (which is often not available for elemental analysis); the effect of organic matrices; sample homogeneity. In order to

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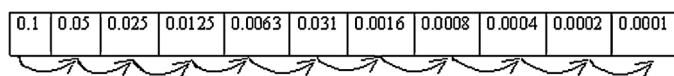


Fig. 1. Scheme for the cascade of the concentration dilution of the calibration standards (the concentration of each element in substance is given in %).

solve the problem of standard reference material inaccessibility, manufactory produced pellets containing elements with different concentration were suggested by, e.g., Rebecca and Salin [16] for calibration curve construction. In other reports elemental quantification in samples was performed using samples matrix powder doped with standard solutions for the calibration of the LA-ICP-MS [17,18]. Similar sample preparation technique was used in this study.

The aim of this research was to develop an LA-ICP-MS method for fast direct elemental analysis of active pharmaceutical substances using laboratory-made standards.

2. Materials and methods

2.1. Physical characteristics of an active pharmaceutical ingredient

The active pharmaceutical ingredient arbidol was supplied by one of the leading pharmaceutical companies in Latvia. The largest market for this product is Russian Federation. The molecular formula of this white, crystalline powder selected for our study is $C_{22}H_{25}BrN_2O_3S$, with the melting range of 133–137 °C, and it is practically insoluble in water in the form of free base [19]. Therefore, in order to increase its solubility, this drug product is manufactured in the form of arbidol hydrochloride. The therapeutic area of arbidol and its salts is antiviral treatment of influenza and hepatitis C infections [20–22]. Internal use of 200 mg active ingredient is mandatory 4 times a day for successful treatment of illnesses mentioned above [23].

2.2. Preparation of samples

All inorganic salts ($MnCl_2 \cdot 4H_2O$, $Co(NO_3)_2 \cdot 6H_2O$, $NiCl_2 \cdot 6H_2O$, $Cu(NO_3)_2 \cdot 3H_2O$, $Cd(NO_3)_2 \cdot 4H_2O$, $Pb(NO_3)_2$) used at certain concentrations as additives to active pharmaceutical ingredient were purchased as analytical grade reagents from Lachema. The exact amount of inorganic salts (Table 1) was weighed and added to non-spiked pharmaceutical ingredient (the concentration of each element was approximately 0.1 wt.% in substance). The spiked pharmaceutical ingredient was homogenized manually using an agate pestle. In order to prepare the laboratory standards the serial concentration reduction method by using non-spiked pharmaceutical ingredient was adopted. In every next laboratory standard the spikes were reduced two times: 0.2 g of non-spiked substance was added to 0.2 g of spiked substance etc., in total this procedure was repeated 10 times until the final concentration of spikes was reduced to ~0.0001% for each element (Fig. 1.).

For analysis a set of 8 powder samples with various inorganic salt content were used. Each sample was divided into 2 parts: one for elemental analysis by LA-ICP-MS and the other for ICP-MS as reference method.

One 0.1 g portion of the homogenized sample powder was pressed into a pellet of 12 mm diameter with 1 mm thickness using a manual press (Noshok) at 4000 psi pressure for 1 min (LA-ICP-MS measurements). The pressed pellets were stored in desiccator in a dark place.

The other portion (for ICP-MS measurements) of each sample was digested in oxidizing acidic medium. The following digestion procedure was used: approximately 0.1 g of a homogenized

powder sample was weighed with the 0.0001 g accuracy into a 100 ml PTFE vessel, then 6 ml of 65% nitric acid (Suprapur, Merck) and 2 ml 30% hydrogen peroxide (Suprapur, Merck) were added. For the homogenization of sample an ultrasonic bath (Sonorex RK100) was used. Then a closed vessel microwave digestion system (Anton Paar 300) was used for the mineralization of active pharmaceutical ingredient. During the acid digestion process the temperature was controlled by infrared sensor. The temperature of microwave heating program was adjusted at 125 °C for half an hour. Deionised water (Millipore, $0.056 \mu S cm^{-1}$) was used for the dilution of solutions.

The performance of mineralization procedure was verified by spike recovery experiment. The samples of active pharmaceutical ingredients were spiked with $1 \mu g g^{-1}$ of each analyte element to the solid substance. Spiked samples were prepared in similar procedure as described above using microwave digestion system.

A multi-element stock standard solution (ICP-MS-68 Solution A, HIGH-PURITY STANDARDS) was used for the preparation of 4 external working calibration standard solutions with concentrations 5, 50, 100, 150 $\mu g l^{-1}$ respectively.

2.3. Instrumentation

Measurements were performed with a New Wave Research laser ablation system coupled with a PerkinElmer ELAN DRC-e ICP-MS. Laboratory-made PTFE interface was used to connect the laser ablation system to the injector tube of the ICP-MS torch assembly.

The laser ablation system was supplied with ultraviolet radiation of Nd:YAG laser (213 nm wavelength). Standard reference material (NIST 612) was used only for tuning the ablation system.

The carrier gas to the ICP-MS instrument was He ($600 ml min^{-1}$). The He gas flow was optimized using glass standard reference material (NIST 612) for measuring isotope signal intensities and calculation the precision. After increasing the flow rate of He carrier gas above $600 ml min^{-1}$ – the measured intensities of elements did not change, while decreasing the flow rate – the measured intensities of elements diminished and the relative standard deviation increased.

Ablation for laboratory-made standard pellets was achieved in the line-continuous scanning mode using a pulse rate of 20 Hz with ~1.6 mJ pulse energy and 200 μm spot diameter. These parameters were optimized using pellet where the concentration of each element was approximately 0.0036 wt.% in substance (mid-level concentration of calibration curve).

PerkinElmer ELAN DRC-e ICP-MS instrumental conditions were adjusted and checked using Daily Performance (PurePlus, Elan 6100 Setup, PerkinElmer) utility. The ICP-MS operating conditions were following: RF power – 1500 W, nebulizer argon flow $0.91 l min^{-1}$, coolant argon flow $15.0 l min^{-1}$, auxiliary argon flow $1.0 l min^{-1}$, sample introduction system – pneumatic nebulizer, Ni sampling and skimmer cones.

3. Results and discussion

As it is known from manufacturer, catalysts are not used for the synthesis of arbidol. It means that the possible sources of metallic contamination in this substance can be reagents, solvents, reaction vessels or other sources.

Six elements (Mn, Co, Ni, Cu, Pb, Cd) were selected for the method development. According to Pharmacopeia requirements the elemental content in active pharmaceutical ingredient should not exceed the values given in Table 2. The mass concentration of elemental trace additives in the pharmaceutical ingredient for laboratory-made matrix standards was adjusted according to accepted concentration limit values.

Table 1
Schematic illustration of laboratory standards preparation for the calibration of LA-ICP-MS.

Inorganic salt	MnCl ₂ ·4H ₂ O	Co(NO ₃) ₂ ·6H ₂ O	NiCl ₂ ·6H ₂ O	Cu(NO ₃) ₂ ·3H ₂ O	Cd(NO ₃) ₂ ·4H ₂ O	Pb(NO ₃) ₂
Mass, g	0.0180	0.0247	0.0248	0.0190	0.0137	0.0080
Initial spiked standard	\sum (inorganic salts), g + 4.8918 g non-spiked pharmaceutical ingredient. Initial spikes amounts in substance (~0.1%)					

Table 2
Elemental concentration limits for oral drug substances ($\mu\text{g g}^{-1}$) [3,24].

Element	USP ^a	ICH ^a
Ni	50	60
Co		5.0
Cu	100	130
Cd	2.5	0.5
Pb	0.5	0.5

^a Given concentration values correspond to the daily dose of drug product not exceeding 10 g per day.

Table 3
The recovery of spiked elements by ICP-MS.

Element	Spike found ($\mu\text{g g}^{-1}$)	Recovery (%)	Precision RSD (%)
Mn	0.96	96	1.1
Ni	0.94	94	1.5
Co	0.99	99	2.2
Cu	0.99	99	1.5
Cd	0.91	91	2.0
Pb	1.04	104	1.9

The selected preparation procedure for active pharmaceutical ingredient mineralization in concentrated nitric acid using closed vessel microwave digestion system was verified by recovery test at $1 \mu\text{g g}^{-1}$ spike level. The multi-element quantification was done by ICP-MS. The results of recovery test are given in Table 3.

As seen in Table 3, the calculated results of recovery experiment correspond to the acceptance criteria for recovery and thus the sample preparation procedure is suitable for active pharmaceutical ingredient mineralization. An acceptance criterion for recovery test was predefined from 70% to 150% according to USP chapter <233> [11].

The operating conditions of laser ablation system such as laser radiation energy level, pulse rate and a spot size were optimized before measuring elements in laboratory-made standard pellets for the calibration curves purposes. The selected ablation parameters such as laser radiation energy level, pulse rate and a spot size

were optimized using pellet where the concentration of each element was approximately 0.0036 wt.% in substance and these values are given in the Experimental part. When lower laser radiation energy (from 1.6 to 0.036 mJ) is applied to the prepared pellets, the regression coefficient of correlation curves is decreasing, e.g., R^2 decreased from 0.9998 to 0.995 for Mn, from 0.9997 to 0.995 for Cu, from 0.9990 to 0.996 for Cd, and from 0.99992 to 0.996 for Pb. Rebecca and Salin applied [16] lower laser energy intensity (approx. 0.5 mJ) thus decreasing precision. More intense laser energy would not be recommended due to pellet thickness. For correlation curve statistics the Linest function in Excel was used.

The use of the line-scanning mode is better as it generates more stable signal in the larger area ablated, however, larger particles can cause stronger matrix effects because of the potential elemental fractionation due to incomplete ionization [25–27]. Representative (with constant elemental ratios) signal intensities were selected for construction of calibration curves as the stability of the different element isotope ratios in time was evaluated (Table 4).

The homogeneity of elemental distribution in the prepared standards of active pharmaceutical ingredient was evaluated using three replicates from different areas of pressed pellets. The homogeneous distribution of elements was acceptable as the relative standard deviation for measurements varied between 2.0% and 7.9%. The variance and trends of the calculated relative standard deviation data for elemental distribution in the prepared standards were the same as it is shown in Table 4. More inhomogeneous distributions of elements were obtained in Ni and Pb cases.

As can be seen in Table 4, the mass concentrations for determination of various elements in laboratory-prepared standards vary approximately from 1 to $150 \mu\text{g g}^{-1}$. These mass concentration ranges of standards were selected according to guideline values for element concentration limits in oral drug substances given by USP and ICH (Table 2).

As seen above from regression coefficients of the calibration curves, the laboratory-made standards were suitable for the calibration of LA-ICP-MS. The limit of quantification (LOQ) was calculated as $10 \cdot s_{\text{blank}}/b$ (s_{blank} – standard deviation of blank

Table 4
Experimental data levels for construction and equations of calibration curves (m – the slope of line, c – the y-intercept, S_m and S_c – standard deviations for m and c coefficients, R^2 – regression coefficient, RSD – the relative standard deviation calculated from intensities measurements).

⁵⁵ Mn conc., $\mu\text{g g}^{-1}$	1.13	1.77	4.90	9.84	21.0	41.9	83.6	166
RSD, %	6.3	9.0	5.7	7.0	3.7	5.3	7.1	8.5
$y = m(S_m)x + c(S_c)$	10,680(60)x + 25,000(4000)				$R^2 = 0.9998$		LOQ = $0.93 \mu\text{g g}^{-1}$	
⁵⁹ Co conc., $\mu\text{g g}^{-1}$	0.82	1.40	3.84	8.12	18.9	37.7	74.9	150
RSD, %	6.2	7.0	5.8	4.8	3.9	3.7	5.2	6.1
$y = m(S_m)x + c(S_c)$	6950(70)x + 19,500(4000)				$R^2 = 0.9994$		LOQ = $0.25 \mu\text{g g}^{-1}$	
⁶³ Cu conc., $\mu\text{g g}^{-1}$	2.05	2.22	4.39	7.82	17.9	36.2	69.3	137
RSD, %	7.2	9.8	6.1	6.3	2.9	2.6	5.7	5.9
$y = m(S_m)x + c(S_c)$	4030(30)x + 13,900(1500)				$R^2 = 0.9997$		LOQ = $0.66 \mu\text{g g}^{-1}$	
⁶⁰ Ni conc., $\mu\text{g g}^{-1}$	1.10	1.62	4.25	8.61	19.7	38.7	76.9	153
RSD, %	9.9	8.9	5.7	5.6	6.5	7.0	9.9	8.8
$y = m(S_m)x + c(S_c)$	1335(24)x + 3800(1500)				$R^2 = 0.998$		LOQ = $0.37 \mu\text{g g}^{-1}$	
¹¹¹ Cd conc., $\mu\text{g g}^{-1}$	0.81	1.47	3.19	6.67	15.6	31.4	64.2	129
RSD, %	6.8	6.5	5.9	7.9	2.5	2.4	5.7	8.5
$y = m(S_m)x + c(S_c)$	1085(16)x + 2700(800)				$R^2 = 0.9990$		LOQ = $0.076 \mu\text{g g}^{-1}$	
¹⁰⁸ Pb conc., $\mu\text{g g}^{-1}$	1.22	2.22	5.27	10.3	18.2	38.0	70.5	140
RSD, %	10	9.8	9.6	9.7	5.8	7.0	7.7	9.1
$y = m(S_m)x$	12,100(40)x				$R^2 = 0.99992$		LOQ = $0.29 \mu\text{g g}^{-1}$	

Table 5
Values of regression coefficients for Mn, Ni, Cd, Co, Cu, and Pb in freshly prepared laboratory-made calibration standards and after 1 month (for 8 point calibration curve).

Element	R^2 (initial measurements)	R^2 (after month)	Element	R^2 (initial measurements)	R^2 (after month)
Mn	0.9998	0.9991	Co	0.9994	0.9991
Ni	0.9980	0.9970	Cu	0.9997	0.9991
Cd	0.9990	0.9980	Pb	0.99992	0.99991

(non-spiked pharmaceutical ingredient) and b – slope of the calibration curve).

For testing of the developed method 5 active pharmaceutical ingredient samples were obtained from our commercial partner and analyzed for elemental impurities. The measurements were performed using a calibration curve over a wide range of mass concentrations. As expected, the measured mass concentration level of elements in samples was lower, comparably to standards.

Although the calculated mass concentrations of elements in active pharmaceutical ingredient were below the limit of quantification, permitted concentration values of analyzed elements in drug product are not exceeded, what means that LA-ICP-MS method can be used for quality control of elemental impurities.

Good linearity of the calibration graphs with regression coefficients better than 0.997 was achieved for laboratory-made calibration standards measured after one month (Table 5). The long-term stability of prepared standards will be further evaluated.

The results of current studies show that laboratory-made standards for the calibration of LA-ICP-MS offer a great advantage in cases when commercial reference materials are not available.

4. Conclusions

Due to strict regulatory requirements in the field of pharmaceutical manufacturing, the importance of rapid quantitative analysis of pharmaceuticals is growing. The sensitive methods of LA-ICP-MS analysis meet Pharmacopeia requirements for analysis of elemental impurities in pharmaceutical goods. Our developed calibration strategy was found to be suitable for quantification of elements in active pharmaceutical ingredients.

The benefits of using laboratory-made standards for analysis of elemental impurities using LA-ICP-MS technique substantially are simplified sample preparation procedures, smaller sample size and amount requirements, minimized potential polyatomic interferences and diminished contamination problems compared to the widely used ICP-MS method.

To improve precision and accuracy of quantification method for lower concentrations of elements in active pharmaceutical ingredients, spiking with multi-element standard solutions can be done.

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