Macedonian Journal of Chemistry and Chemical Engineering, Vol. **40**, No. 1, pp. 43–50 (2021)

MJCCA9 – 817

ISSN 1857-5552
e-ISSN 1857-5625

Received: July 20, 2020
Accepted: December 13, 2020

DOI: 10.20450/mjcce.2021.2100
Original scientific paper

ICP-OES ELEMENTAL IMPURITIES STUDY ON DIFFERENT PHARMACEUTICAL DOSAGE FORMS OF IBUPROFEN USING A MICROWAVE-ASSISTED DIGESTION PROCEDURE

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A fast and simple closed-vessel microwave-assisted digestion procedure was developed for decomposition of three pharmaceutical dosage forms of ibuprofen, including tablets, suspension and gel, prior to elemental impurity analysis by one robust and precise ICP-OES method. Samples were digested by a four-step microwave program consisting of a 10 min temperature gradient to 180 °C, maintaining at 180 °C for 10 min, followed by 5 min ramping time to 210 °C with a holding time of 10 min at 210 °C. Subsequently, an ICP-OES method was developed and validated for simultaneous determination of selected elemental impurities. Results of recovery studies ranged between 77 % and 105 % for each element in all analyzed formulations. Coefficients of determination of the regression equations were higher than 0.999 for all analyzed elements. Validation results reveal that the proposed method is specific, accurate, and precise and could be applied for simultaneous quantitative analysis of multi-element solutions in different pharmaceutical dosage forms of ibuprofen.

Keywords: ibuprofen; pharmaceutical; elemental impurities; inductively coupled plasma-optical emission spectroscopy; microwave-assisted digestion

ОПРЕДЕЛУВАЊЕ НА ЗАГАДЕНОСТ СО ЕЛЕМЕНТИ НА РАЗЛИЧНИ ФАРМАЦЕВТСКИ ФОРМИ НА ИБУПРОФЕН СО ПРИМЕНА НА ICP-OES И МИКРОБРАНОВА ДИГЕСТИЈА

Развиена е брза и едноставна постапка за разложување со микробранови на три фармацевтски форми ибупрофен: таблети, суспензија и гел, за понатамошно определување на загаденоста со елементи во траги, користејќи го методот на оптичка емисиона спектроскопија со индуктивно спрегната плазма (ICP-OES). Применета е четиристепена температурна програма на микробранова дигестија, која се состои од покачување на температурата од собна температура до 180 °C во времетраење од 10 минути, проследено со 10 минутно задржување на 180 °C, повторно покачување на температурата од 180 °C до 210 °C во времетраење од 5 минути, проследено со 10-минутно задржување на 210 °C. Следствено, ICP-OES е оптимизиран и валидиран методот за определување селектирани загадувања со елементи. Добиени се задоволителни резултати за аналитичкиот принос на методот кој се движи од 77 % до 105 % за анализираните елементи во сите испитувани формулации. Добиени се коефициенти на корелација поголеми од 0,999 за сите испитувани елементи. Резултатите од валидацијата потврдуваат дека оптимизираниот метод е селективен, точен и сигурен и може да се применува за определување на загадувања со елементи на различно дозирани форми на ибупрофен.

Клучни зборови: ибупрофен; фармацевтски производи; загадувања со елементи; индуктивно спрегната плазма – оптичка емисиона спектроскопија; микробранова дигестија

1. INTRODUCTION

Nowadays, the control of elemental impurities (EI) is one part of the overall control strategy in the manufacture of drug products. Driven by the requirements established by the Guideline for Elemental Impurities-Q3D of the International Conference on Harmonization (ICH), as well as respecting Pharmacopeias, the pharmaceutical industry confronts the vast challenge of developing fast and precise procedures for sample preparation, as well as developing methods for accurate determination of EI using modern analytical methods. The ICH Q3D guideline evaluates the toxicity data of EI, establishing Permitted Daily Exposure (PDE) for each element of toxicological concern and provides a platform for application of a risk-based approach to control EI in drug products [1–5].

Quantitative analytical techniques such as plasma-based spectrochemical instrumental techniques are required to determine accurately and rapidly a variety of EI with sufficient sensitivity [6–10]. Optical emission spectroscopy using inductively coupled plasma (ICP-OES) as the excitation source is widely recognized as an extremely robust and rapid technique for multielement analyses in various sample matrices. It can obtain multi-element information in a fraction of the time needed to prepare the samples [11–13]. Sample preparation is the crucial predetermination step in accurate detection of EI. Analysis by ICP-OES is prone to interferences and requires an efficient sample preparation, especially with complex matrixes such as pharmaceuticals. This implies the use of specific and powerful equipment for sample digestion such as microwave-assisted digestion in closed vessels, which is considered the state of the art in sample preparation for organic matrices [14]. In order to avoid interferences in sample introduction (e.g. aspiration rate, aerosol generation and aerosol transport) and plasma characteristics, the acidity of solutions after their digestion was evaluated [15]. Residual carbon content (RCC) was also monitored and controlled in order to estimate the efficacy of the digestion procedure [16–20].

In this study, three different dosage forms of ibuprofen were evaluated. Ibuprofen is a well-known drug that belongs to a class of therapeutic agents known as non-steroidal anti-inflammatory drugs. These drugs have multiple actions in different inflammatory pathways that are involved in acute and chronic inflammation [21, 22]. As a widely used medication, ibuprofen is available in different dosage forms such as tablets, gels and suspensions. Comprising complex and different formulations, the ibuprofen drug products need to be efficiently decomposed to ensure breakdown of the organic matrix and release of the elements and transformed to a liquid form that is compatible for ICP-OES analysis. Three drug products, Ibuprofen 200 mg/5ml oral suspension, Ibuprofen 400 mg film coated tablets, and Ibuprofen 50 mg/g gel were submitted for closed-vessel microwave decomposition prior EI determination by ICP-OES. Since the ICH Q3D guideline does not provide PDE for topical products, the PDE for Ibuprofen gel was considered to be the same as that of the oral drug products. Developing one simple and fast sample decomposition procedure for all dosage forms is preferable because EI testing has become a routine test in the pharmaceutical industry.

Hereby, we present a fast and precise procedure for sample preparation of three drug products of ibuprofen in different dosage forms, as well as an in-house ICP-OES method for accurate determination of selected EI. The ICP-OES method was validated according to USP Pharmacopeia, chapters <232> and <233>, and European Pharmacopeia, Chapter 2.4.20 *Determination of elemental impurities*, which is considered to be a reference when designing validation studies [2–4, 23].

2. MATERIALS AND METHODS

2.1. *Reagents and materials*

Concentrated nitric acid (70 %, v/v, trace metal grade) and concentrated hydrochloric acid (37 % v/v, trace metal grade) used for sample decomposition were purchased from Sigma-Aldrich (St. Louis, MO, USA). Sodium hydroxide solution (1 mol/l, Titripur) used for acid–base titrations (acidity of digests) was purchased from Merck KGaA (Darmstadt, Germany). Ultrapure water with a resistivity of 15 MΩ was used in the experiments. It was prepared by passing water through a Milli-Q Type 1 Ultra-pure water system (EMD Millipore, Billerica, MA, USA). Filter discs, grade 391 (blue) with 84 g/m^3 and 125 mm diameter were purchased from Boeco, Germany. Standard solutions for calibration and spike solutions for recovery assessments were prepared by diluting commercially available, NIST traceable, single element stock solutions (1000 mg/l) purchased from Merck. Test samples employed for this study consisted of standard production batches of the oral drug products Ibuprofen 200 mg/5ml oral suspension, Ibuprofen 400 mg film coated tablets and Ibuprofen 50 mg/g gel manufactured by Alkaloid, Skopje, North Macedonia.

2.2. *Sample preparation*

Ibuprofen 200 mg/5ml oral suspension contains fifteen constituents with the following functions: dispersing agent, viscosity-building agents, wetting agent, sequestering agent (preservative synergistic agent), sweetening agent, buffering agents, preservative, flavor, taste masking agents, antifoaming agent and solvent. Ibuprofen 400 mg film coated tablets contain fillers, disintegrants, glidant, lubricant and a film coating. Whereas, Ibuprofen 50 mg/g gel contains cooling agent (skin penetration enhancer), gelling agent, pH balancer and gel-forming agent (penetration enhancer), solubilizer, solvent, and vehicle.

Two grams of Ibuprofen 200 mg/5 ml oral suspension and Ibuprofen 50 mg/g gel and 0.5 g of Ibuprofen 400 mg film coated tablets were weighed into a microwave digestion vessel, separately. Following addition of 2 ml of ultrapure water, 5 ml of concentrated nitric acid and 1 ml of concentrated hydrochloric acid, the samples were subjected to closed vessel microwave digestion, allowing sample decomposition under high temperature and pressure. A microwave digestion program was used. It employed a four-step microwave program that consisted of a 10 min ramping time to 180 °C with a holding time of 10 min at 180 °C and 1800 W power. This was followed by a 5 min ramping time to 210 °C with a holding time of 10 min at 210 °C and 1800 W power. Samples were allowed to cool for 20 min prior to venting and opening the digestion vessels. Digested samples were quantitatively transferred into 25 ml volumetric flasks, then diluted to the final volume of 25 ml with ultrapure water. Prior to analysis by ICP-OES, the samples were filtered through filter disks (blue) into vials.

The same sample preparation was employed for the preparation of blank solutions for limit of detection and limit of quantification studies.

2.3. *Preparation of standards*

Calibration standards were prepared from stock solution consisting of the elements of interest by serial dilution with a mixture of concentrated nitric and hydrochloric acids diluted in ultrapure water. In order to be applicable for the three different pharmaceutical dosage form products with different maximum permitted daily exposures, the calibration standards were prepared to encompass the range of level 30 % to level 200 % of the maximum permitted concentration for each element. Element concentrations in mg/l are presented in Table 1.

T a b l e 1

Concentration levels (mg/l) of the calibration standards for the studied EI

Element	Level 30 %	Level 50 %	Level 100 %	Level 200 %
Cd	0.006	0.010	0.020	0.040
Pb	0.006	0.010	0.020	0.040
Hg	0.038	0.061	0.122	0.243
As	0.019	0.030	0.061	0.122
Co	0.063	0.101	0.203	0.405
V	0.127	0.203	0.405	0.810
Ni	0.253	0.405	0.810	1.619

2.4. *Methods*

An EthosUP microwave digestion system employing SK-15 digestion vessels (Milestone, Sheldon, CT USA) was used for sample digestion.

T a b l e 2

Instrument parameters for Agilent 5100 ICP-OES

Parameter	**Setting**	**Parameter**	**Setting**
RF power	1.40 kW	Pump speed	12 rpm
Plasma Ar flow rate	14 l/min	Stabilization time	30 s
Auxiliary Ar flow rate	1.0 l/min	Rinse time	40 s
Pneumatic Nebulizer Ar flow rate	0.70 l/min	Sample uptake	30 s
Rinse time fast pump	On	Sample uptake fast pump	On
Background correction	Fitted	Number of replicates	5
Read time	30 s	Viewing mode	Axial
Wavelengths (nm)			
Pb(II) ionic line	220.353	Co(II) ionic line	238.892
As(I) atomic line	188.980	V(II) ionic line	292.401
Hg(I) atomic line	184.887	Ni(II) ionic line	216.555
Cd(II) ionic line	226.502		

The SK-15 teflon vessels have a volume of 100 ml, a maximum pressure of 100 bar, and a maximum temperature of 300 °C. A total Organic Carbon Analyzer TOC-VCPH/CPN (Shimadzu, Kyoto, Japan) was employed for residual carbon content measurements, and a potentiometer, 888 Titrando (Metrohm, Herisau, Switzerland), was used to measure the acidity of digests. An Agilent 5100 ICP-OES VDV system coupled with an Agilent SPS-4 autosampler was employed for the experiments. The instrumental parameters for ICP-OES are listed in Table 2.

3. RESULTS AND DISCUSSION

The goal of this study was to develop a common microwave digestion program for sample preparation and an analytical method for the determination of selected elemental impurities in different pharmaceutical dosage forms with ibuprofen as the active pharmaceutical ingredient. The drug product Ibuprofen 200 mg/5 ml oral suspension was selected as the referent product for development and optimization of the microwave program for sample decomposition. It is comprised of fifteen excipients, and it is the most complex formulation. The permitted daily amount of this product is about 31.59 g/day which leads to the lowest permitted concentrations of the elements of interest. This is in comparison with Ibuprofen 50 mg/g gel and Ibuprofen 400 mg film coated tablets which have permitted daily amounts of 20 g/day and 4.8 g/day, respectively. Table 3 depicts the maximum permitted concentrations of selected elements for ibuprofen drug products.

In order to simultaneously analyze the selected elemental impurities in all three drug products using one ICP-OES analytical method, one calibration curve was created to encompass the various concentration levels, in line with the maximum daily amount of the drug products.

Concentrated nitric acid and concentrated hydrochloric acid were the acids of choice for closed vessel digestion. The temperature program for decomposition was optimized and established by measuring the content of total organic carbon in the digests after their dilution to the final volume. Low residual carbon content (RCC below 0.1% *m/V*) confirmed the quality of digests. Residual acidity was also monitored in terms of an acid base titration of the digests to confirm the suitability of the sample preparation prior ICP-OES measurement.

The rapid and precise ICP-OES method for determination of the selected elemental impurities in all digests was optimized and validated according to the manufacturer's specifications, as well as the requirements given in USP Pharmacopeia Chapter <233>, and European Pharmacopeia, Chapter 2.4.20, *Determination of elemental impurities*. The validation of the developed quantitative method was performed using the drug product Ibuprofen 200 mg/5 ml oral suspension which is the most complex formulation with the highest daily intake. Analytical figures of merit–linearity and range, accuracy, method precision, system precision, limit of detection and limit of quantification were defined. All of the samples analyzed as part of the method validation were prepared in triplicate.

As part of the validation procedure, an accuracy study was conducted on all pharmaceutical dosage forms to confirm the suitability of the sample preparation. Before decomposition, the samples were spiked with a known quantity of a reference standard comprising the elements of interest at three concentration levels. Method precision was verified by determining the relative standard deviation of the measurements from the accuracy study.

T a b l e 3

Maximum permitted concentration limits for selected EI

ICHQ3D classification	Element	Oral PDE	Ibuprofen 200 mg/5ml oral suspension	Ibuprofen 50 mg/g gel	Ibuprofen 400 mg film coated tablets
		µg/day	Max permitted concentration, µg/g	Max permitted concentration, µg/g	Max permitted concentration, µg/g
Class I	**Cd**	5	0.158	0.250	1.042
	Pb	5	0.158	0.250	1.042
	Hg	30	0.950	1.500	6.250
	As	15	0.475	0.750	3.125
Class 2a	**Co**	50	1.583	2.500	10.42
	V	100	3.166	5.000	20.83
	Ni	200	6.331	10.00	41.67

3.1. *Validation of the analytical method for determination of elemental impurities*

Coefficients of determination from a linear regression curve using peak intensity count and the concentration of the standards were set to be $R^2 > 0.990$ for the elements of interest evaluated by ICP-OES. System precision was evaluated by analyzing six consecutive measurements (aliquots) from one sample spiked with a 100 % standard solution containing the elements of interest before the digestion procedure. The results obtained from the linearity and precision study are presented In Table 4. They indicate that the ICP-OES method is suitable in terms of linearity and precision for determination of the selected elements.

T a b l e 4

Linearity and system precision results

	Linearity	System precision		
Element	Coefficients of determination	Average mg/l	Stdev	RSD %
As	0.9994	0.039	0.001	2.17
Pb	0.9998	0.013	0.001	4.08
Cd	0.9993	0.013	0.00002	0.13
Hg	0.9999	0.077	0.0004	0.53
Co	0.9999	0.129	0.0001	0.09
V	0.9999	0.259	0.001	0.21
Ni	0.9999	0.512	0.001	0.15

The limit of detection (LOD) and limit of quantification (LOQ) were determined by measuring 10 blank solutions. The LOD is defined as the lowest analyte concentration that yields a signal equal to three times the standard deviation of the signal derived from the blank, whereas LOQ is defined as ten times the standard deviation of the signal derived from the blank [24–26]. The LOD and LOQ values expressed as μg/g are presented in Table 5.

T a b l e 5

LODs and LOQs of the studied EI

ICP-OES		
Element	**LOD, μg/g**	**LOQ, μg/g**
As	0.033	0.111
Pb	0.045	0.150
Cd	0.001	0.004
Hg	0.007	0.024
Co	0.003	0.009
V	0.002	0.008
Ni	0.007	0.025

In order to evaluate the suitability of sample preparation as well as any matrix effect, an accuracy study was performed on all dosage forms of ibuprofen. The samples were spiked with known amounts of the elements of interest at three different concentration levels before submitting to decomposition, and the tests were run in triplicate. The results from the accuracy and method precision studies are presented in Table 6 and given as the average values from the measurements of the triplicates. The spike recoveries ranged between 77 % and 105 % with relative standard deviations below 20 % for each element in all analyzed drug products. From the results presented in Table 6, it is evident that the applied method is accurate and precise.

Selected ibuprofen products were submitted for decomposition prior their analysis using the validated in-house ICP-OES method for determination of the selected EI. In line with the recommendation from the ICH Q3D guideline, a control threshold of 30 % of the specification level is defined for each element. If the total EI level in the drug product is found to be below 30 % of the specification level for each element, additional measures are not required [1]. The levels obtained from the EI testing on all ibuprofen drug products were found to be below the control threshold of 30 % for each element, as shown in Table 7.

T a b l e 6

Accuracy study for the studied elemental impurities

Element	50 % spike solution		100 % spike solution		150 % spike solution	
	Recovery, %	RSD, %	Recovery, %	RSD, %	Recovery, %	RSD, %
Spike recoveries from analysis of the drug product Ibuprofen 200 mg/5ml oral suspension						
As	100.8	0.8	100.9	5.4	105.6	2.5
Pb	95.0	9.1	89.7	5.0	96.5	3.2
Cd	100.4	0.3	94.9	4.7	100.1	0.1
Hg	94.7	1.6	97.8	4.7	100.6	2.5
Co	92.6	2.0	91.9	4.3	94.2	1.1
V	97.9	0.9	91.1	4.1	100.0	1.0
Ni	94.6	0.2	93.7	3.3	96.1	1.1
Spike recoveries from analysis of the drug product Ibuprofen 50 mg/g gel						
Element	50 % spike solution		100 % spike solution		200 % spike solution	
	Recovery, %	RSD, %	Recovery, %	RSD, %	Recovery, %	RSD, %
As	95.6	6.0	96.2	4.5	98.9	0.8
Pb	77.0	2.6	76.8	0.4	84.3	0.9
Cd	86.7	6.7	88.3	3.3	89.2	1.6
Hg	85.3	3.0	86.1	1.5	87.8	1.1
Co	84.8	2.4	85.1	1.2	86.3	1.3
V	87.0	2.3	88.2	1.6	89.8	1.3
Ni	89.6	2.4	89.9	1.5	91.7	1.3
Spike recoveries from analysis of the drug product Ibuprofen 400 mg film coated tablets						
Element	50 % spike solution		100 % spike solution		200 % spike solution	
	Recovery, %	RSD, %	Recovery, %	RSD, %	Recovery, %	RSD, %
As	105.6	4.8	103.3	1.6	101.9	0.2
Pb	100.0	5.8	101.7	5.7	97.1	0.4
Cd	98.9	2.1	99.3	3.1	93.2	0.5
Hg	100.0	1.6	99.5	1.7	100.9	0.9
Co	101.3	1.5	101.3	1.6	102.8	0.1
V	101.2	2.0	98.4	1.9	98.0	0.2
Ni	99.1	1.1	97.4	1.5	98.1	0.3

T a b l e 7

Results from ICP-OES analysis of EI from Class 1 and Class 2a

				Ibuprofen 200 mg/5ml oral suspension			**Ibuprofen 50 mg/g gel**			**Ibuprofen 400 mg film coated tablets**		
ICHQ3D classification	**Element**	**LOD, µg/g**	**LOQ, µg/g**	**Maximum permitted concentration, µg/g**	**30% (control threshold)**	**Results, µg/g**	**Maximum permitted concentration, µg/g**	**30% (control threshold)**	**Results, µg/g**	**Maximum permitted concentration, µg/g**	**30% (control threshold)**	**Results, µg/g**
Class I	**Cd**	0.001	0.004	0.158	0.047	*BLD	0.250	0.075	BLD	1.042	0.313	BLD
	Pb	0.045	0.150	0.158	0.047	BLD	0.250	0.075	BLD	1.042	0.313	BLQ
	Hg	0.007	0.024	0.950	0.285	BLD	1.500	0.450	BLD	6.250	1.875	0.16
	As	0.033	0.111	0.475	0.142	**BLQ	0.750	0.225	BLQ	3.125	0.938	0.24
Class 2A	**Co**	0.003	0.009	1.583	0.475	BLD	2.500	0.750	BLD	10.42	3.125	0.06
	V	0.002	0.008	3.166	0.950	BLD	5.000	1.500	0.01	20.83	6.250	0.09
	Ni	0.007	0.025	6.331	1.899	BLD	10.000	3.000	BLD	41.67	12.50	BLD

*BLD – below limit of detection
**BLQ – below limit of quantification

4. CONCLUSION

As part of quality control in the pharmaceutical industry, EI testing has become an everyday routine. Their presence is monitored throughout the entire process of manufacturing, starting from raw materials and API's through primary packaging materials to the finished drug products.

Digestion of the drug products with acids prior the analysis of EI is a critical step. It plays the important role of destroying the components in the matrix while retaining the EI in a stable form in the solution. In this sense, the use of closed vessel microwave assisted techniques is preferred. It combines high digestion efficiency and fast heating, and it is capable of producing a digest for analysis that is almost free from interferences. The procedure presented for sample preparation implements a closed vessel microwave program that has shown great efficiency in decomposing the different dosage forms of ibuprofen. It should be noted that Ibuprofen gel includes ethanol in its formulation, and greater precautions must be taken during the addition of the acids due to their fast reaction in the mixture. Also, attention must be paid to the components in the formulation of the drug products that can't be completely decomposed by using only nitric and hydrochloric acids, such as films containing titanium dioxide (TiO_2). Titanium dioxide has a wide variety applications because it is a low-cost and accessible compound with low toxicity [27]. Therefore, it is not evaluated (as Ti) in the guidelines, and it does not represent any real toxicological concern. In the case of Ibuprofen 400 mg film coated tablets, the film contains 6.2 % w/w TiO_2, which is about 2.5 % of the tablet. Thus, although TiO_2 is not of interest in this study, one should always be very cautious regarding the presence of undecomposed TiO_2 particles because they can cause clogging and harm the sample introduction system as well as the ICP-OES instrument. Therefore, as a protective measure, filtering the samples prior to analysis must be included in the sample preparation procedure.

The suitability of sample preparation with microwave-assisted closed-vessel digestion combined with ICP-OES analysis was successfully verified on three different dosage forms of ibuprofen. It can be seen from the validation study that excellent recovery rates between 77 % and 105 % combined with very low variation (RSD <10 %, n = 3) were achieved (Table 6). The respective limits stated in USP general chapter <233> (70–150 % for spike recovery and <20 % RSD for repeatability) are satisfied in this study. Coefficients of determination (R^2) of the regression equations were greater than 0.999 for all analyzed elements. The data obtained from the analysis of ibuprofen drug products is presented in Table 7. It can be concluded that the detected EIs are far below the control threshold of 30 % of the maximum permitted specification levels.

From the presented results, it is evident that the method has high sensitivity and precision, and it is appropriate for the determination of EI in all of the ibuprofen dosage forms analyzed.

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