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Article

Determination of Osmium and other Platinum Group Elements in Active Pharmaceutical Ingredients by ICP-MS

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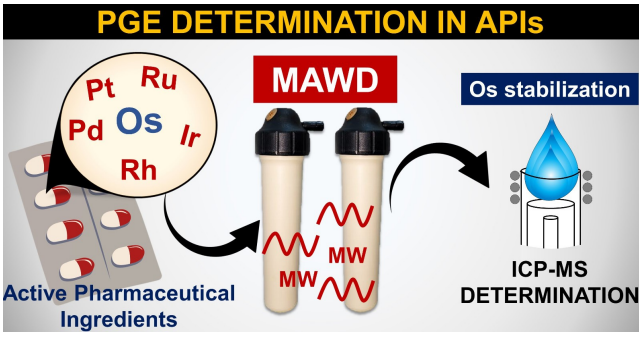
ABSTRACT: Accurate determination of platinum group elements (PGEs) in active pharmaceutical ingredients (APIs) is critical due to stringent regulatory requirements and the potential toxicological effects of these elements. In this study, a microwave-assisted wet digestion (MAWD) method was developed to allow interference-free determination of PGEs, including Os, in APIs by inductively coupled plasma mass spectrometry (ICP-MS). Five widely used API samples were selected and a study of interferences was performed. The evaluated conditions included the composition of the digestion solution, and sample mass. The calibration and washing solution mediums were also evaluated: 5% HCl solution or a stabilizing solution (composed of acetic acid, thiourea and ascorbic acid). Furthermore, carbon interference (up to 2000 mg L^{-1} of C), which is critical for PGE determination by ICP-MS, was evaluated, and it was observed that C concentrations higher than 800 mg L^{-1} caused interferences for PGE determination, with the exception of Os. The method was validated according to the United States Pharmacopeia (USP). The optimized conditions for the proposed MAWD method were 500 mg of sample and a mixture of HNO_3+HCl (1+1, 6 mL) as digestion solution. The 5% HCl solution was suitable for the determination of all PGEs, except for Os. In the case of Os, the stabilizing solution, added to samples, blanks, standards, and as washing solution, was necessary for its quantitative determination. The proposed procedure allowed quantitative PGE recoveries, including Os, using an efficient and relatively simple sample preparation method based on MAWD. Furthermore, the limits of quantification were suitable for PGE determination according to USP requirements.



INTRODUCTION

Contamination by elemental impurities in active pharmaceutical ingredients (APIs) is an ever present concern regarding consumer safety, as these impurities provide no therapeutic benefit and can lead to adverse effects ranging from mild reactions to acute toxicity.[1, 2] These contaminants can be introduced from the raw materials or during fabrication, by the use of catalysts or contact with other materials.[1-3] Hence, it is of extreme importance to identify the presence and monitor the concentration of these elements in drug components during the whole production and storage processes. In this sense, the ICH Q3D guideline was implemented in 2019 establishing the maximum limits for elemental impurities in pharmaceutical formulations, which were followed by several institutions globally.[4-7]

Among the elemental impurities included in the ICH Q3D guideline, class 2B, which is composed by elements generally used as catalysts (Ag, Au, Ir, Os, Pd, Pt, Rh, Ru, Se, and Tl), is worthy of mention.[1] Among these impurities, platinum group elements (PGEs) can pose significant challenges in pharmaceutical products due to their potential toxicity and the difficulties involved in controlling their presence during the

manufacturing process.[1] Platinum group elements may compromise the safety and efficacy of pharmaceuticals, so strict quality control measures are necessary to ensure compliance with regulatory standards.[8] It is also important to mention that the ICH Q3D guideline established that not enough toxicological data was available to calculate the exact permitted daily exposure (PDE) values for most PGEs, with their limits being based on data of Pt and Pd (100, 10, and 1 μg day^{-1} for oral, parenteral and inhalation routes, respectively).[1] Hence, new limits could be established in the future, which should be taken into consideration during the development of quality control methods for these elements. For the PGEs, close attention should be given to Os. This element is most commonly used in pharmaceutical synthesis in the form of OsO_4 as a catalyst in dihydroxylation reactions.[1, 9, 10] Although osmium tetroxide is not highly soluble in water,[11] it can cause damage to several tissues in the gaseous form.[1, 11]

The most popular technique for PGE determination in pharmaceutical drugs is inductively coupled plasma mass spectrometry (ICP-MS),[12-20] a multi-elemental technique with relatively wide linear range and low limits of detection (LODs, in the range of ng L^{-1}).[21, 22] However, only a few studies have been successful in quantifying Os in pharmaceuticals, considering the acceptable recovery of 70 to 150% established in USP chapter 233[6], as can be seen in Table S1 (Supporting Information). Although still lacking concrete evidence, unsuccessful attempts were associated with possible memory effects caused by the presence of OsO_4 species, which is relatively volatile (boiling temperature of 160 °C)[15, 23]. On the other hand, studies in which Os recoveries were closer to 100% all used a stabilizing agent during the determination step.[12-14, 18, 19]

Another important aspect to be considered for PGEs, but especially for Os determination in pharmaceuticals by ICP-MS, is the sample preparation method.[15, 19, 24] For this, microwave-assisted wet digestion (MAWD) has been extensively used in pharmaceuticals decomposition aiming at elemental impurities determination, including Os (Table S1).[21] Among these methods, the use of MAWD allows for faster heating and shorter digestion times. Furthermore, other advantages include a lower risk of volatile analyte losses and contamination, as well as increased digestion efficiency.[25]

Taking into account the drawbacks involved in PGE determination to attend the ICH Q3D guidelines, this study aimed at developing a simple sample preparation method based on MAWD for further PGE determination, including Os, in APIs by ICP-MS. Furthermore, a study of interferences caused by carbon was performed and the use of different stabilizing and/or calibration solutions was evaluated in order to develop a method for quantitative determination of all PGEs.

EXPERIMENTAL

Instrumentation. A Synthos 3000 microwave was used for MAWD procedures (Anton Paar, Austria). The HF100 rotor was used in this system, containing 16 modified polytetrafluorethylene (PTFE-TFM) vessels (100 mL internal volume, Anton Paar). The maximum temperature, pressure and microwave power of the system for this rotor were 220 °C, 40 bar and 1400 W, respectively.

The determination of PGEs was performed by ICP-MS (Elan DRC II, Perkin Elmer, Canada). Carbon, an important parameter affecting plasma conditions and an indicative of the digestion efficiency, was determined in digests by ICP-OES (Optima 4300 DV, Perkin Elmer, Canada). Instrumental parameters for PGEs (Ir, Os, Pd, Pt, Rh and Ru) determination by ICP-MS, and C determination by ICP-OES,[26] are described on Table S2. Samples were dried prior to experiments (hot air oven, 400/2ND, Nova Ética, Brazil). Residual acidity was determined according to a previous study.[26]

Reagents and samples. The reagents used were of analytical grade unless stated otherwise. The water used in the study was purified using a Milli-Q system (18 MΩ cm, Millipore, USA). Distilled nitric and hydrochloric acids were obtained (sub-boiling system, Duopor, Milestone, Italy) from the PA reagents (65% HNO_3 and 37% HCl, Sigma Aldrich, USA). Acetic acid (99.7%, Sigma Aldrich), ascorbic acid (Merck, Germany) and thiourea (Merck) were used to prepare the Os stabilizing solution.

A multi-element stock standard solution of Ir, Pt, Pd, Rh, and Ru (10 mg L^{-1} in 10% HCl, IMS-103, Agilent, USA) and a mono-element standard solution of Os (1000 mg L^{-1}, $(NH_4)_2OsCl_6$ in 5% HCl, Inorganic Ventures, USA) were used in recovery experiments and calibration curves. The calibration curves for PGE determination by ICP-MS were prepared either in the stabilizing solution, or in 5% HCl. For the C calibration curve (in 5% HNO_3), citric acid (Dinâmica, Brazil) was dissolved to obtain a stock solution containing 1000 mg L^{-1} of carbon (1 mg L^{-1} Y, SpexCertPrep, USA, was used as internal standard). Argon 4.0 (99.996%, Air Products, Brazil) was employed for ICP-MS and ICP-OES analyses as well as purging of samples at 0.1 L min^{-1} for 2 min prior to C determination.

For the development of this study, 5 commercial APIs present in several widespread pharmaceutical drugs were used, namely methyldopa, acetylsalicylic acid, sulfamethoxazole, acetaminophen, and bupivacaine hydrochloride. Sulfamethoxazole was arbitrarily selected for MAWD optimization, and the remaining samples were used in the application of the optimized method. The samples were dried for 2 h at 105 °C and stored in polypropylene vessels prior to experiments.

Microwave-assisted wet digestion. A 10 mg L^{-1} PGE standard was pipetted onto the samples in the PTFE-TFM vessels, followed by addition of the digestion solution (6 mL). After closing and securing the vessels in the rotor and placing it in the microwave, the samples were decomposed. The irradiation program was based on a previous study[15] and had three steps: *i)* 10 min ramp to 1400 W; *ii)* 30 min stay at 1400 W; and *iii)* 20 min at 0 W (cooling step). Digests were made up to 20 mL with water after the digestion step. For Os determination, this solution was diluted 20-fold in a stabilizing solution in a separate vessel to a final volume of 20 mL.[19, 24] The stabilizing solution contained a mixture of 85 mmol L^{-1} acetic acid, 10 mmol L^{-1} thiourea and 0.6 mmol L^{-1} ascorbic acid, which was based on previous studies.[19, 24] All samples and standards were diluted in this stabilizing solution, which was also used as washing solution for Os determination by ICP-MS.

Sample mass (100, 250 or 500 mg) and digestion solution (14.4 mol L^{-1} HNO_3, or 14.4 mol L^{-1} HNO_3 and 12 mol L^{-1} HCl mixed in the ratios of 3+1, 1+1, and 1+3) were evaluated. Additionally, the calibration and dilution solutions were evaluated. For this, 5% HCl or stabilizing solution were evaluated for the determination of both Os and the other PGEs. The best conditions were selected based on analyte recovery and signal stability. Digestion efficiency was determined taking into consideration the residual carbon content (RCC) and acidity in digests. The RCC was calculated taking into account the carbon content of the API molecules as 100%.

Evaluation of carbon interferences. It is known that high C concentrations in digests can lead to rather severe interferences in plasma-based techniques.[27] In this study, the relative signal intensity of standard 1 µg L^{-1} solutions of the analytes containing C concentrations from 50 to 2000 mg L^{-1} was monitored. Solutions were prepared in 5% HCl, and citric acid was used as carbon source for the interference evaluation.

Method validation. The optimized MAWD method was validated according to USP chapter 233[6] by evaluating the following parameters: limit of quantification (LOQ), accuracy, working range, linearity, precision (repeatability and intermediate precision), and specificity. Since no certified reference materials (CRMs) were available for the specific elements analyzed in this study (PGEs) or for the matrix type (API), accuracy was evaluated by standard addition experiments using standard solutions (10 mg L^{-1}), which were added to the samples prior to MAWD at 100% of the J level for each analyte.[6] Analyte recovery tests at two more concentration levels (50 and 150% of J) were performed using the optimized method conditions.[6] All spiked samples were prepared in triplicate (n=3).

As Os can be considered as highly unstable depending on the conditions, a stability evaluation was also performed after digestion. This experiment was performed for final digests using the optimized method conditions. For this, digests were 20-fold diluted in the stabilizing solution immediately after the MAWD procedure and Os measurement was performed by ICP-MS in 1 h intervals during 12 h and every 24 h until 72 h. Samples were stored under refrigeration (at 2 °C) between measurements.

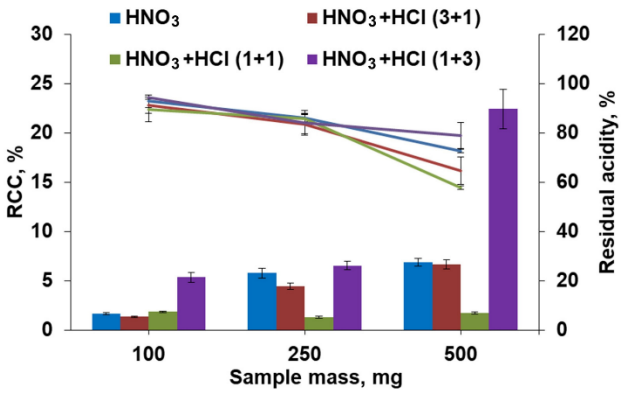


Fig. 1 Evaluation of sample mass and digestion solution. Bars represent RCC and lines represent residual acidity in MAWD digests. Standard deviations are represented by error bars (n=3).

RESULTS AND DISCUSSION

Evaluation of sample mass and digestion solution. Different digestion solutions (14.4 mol L^{-1} HNO_3, and 3+1, 1+1, and 1+3 mixtures of 14.4 mol L^{-1} HNO_3 and 12 mol L^{-1} HCl) were evaluated for each sample mass (100, 250 or 500 mg). For these evaluations, the calibration and washing medium for PGE determination was 5% HCl. The RCC and residual acidity of the evaluated conditions are shown in Fig. 1.

Regarding sample mass, the condition using 500 mg of sample was selected due to the higher detectability associated with better LODs. When comparing the digestion solutions for this mass, the lowest RCC and acidity were obtained when a mixture of HNO_3+HCl in the proportion of 1+1 was used (Fig. 1). Furthermore, the dissolved carbon concentration for this condition (205 ± 12 mg L^{-1}) was relatively low. Moreover, it is important to highlight that under none of the tested conditions was residual material or particulate matter observed, indicating complete dissolution of the samples. In this sense, the condition using 500 mg of sample and HNO_3+HCl 1+1 (6 mL) as digestion solution was selected for further experiments.

When analyte recoveries were evaluated, it could be observed that Ir, Pd, Pt, Rh, and Ru recoveries were within the acceptable range established by USP (70 to 150%)[6] for all evaluated conditions (Table 1). For Os, however, the recoveries were far from

Table 1. Recovery of PGEs determined by ICP-MS after MAWD of spiked samples, using different digestion solutions and sample masses. Results expressed in triplicate (mean ± standard deviation).

Sample mass	Digestion solution	Analyte recovery, %					
		^{191}Ir	^{192}Os	^{105}Pd	^{194}Pt	^{103}Rh	^{99}Ru
100 mg	HNO_3	102 ± 1	160 ± 26	102 ± 2	103 ± 2	105 ± 1	105 ± 1
	HNO_3+HCl 3+1	106 ± 5	176 ± 49	101 ± 4	101 ± 3	102 ± 2	104 ± 4
	HNO_3+HCl 1+1	105 ± 2	200 ± 31	103 ± 2	105 ± 2	105 ± 1	106 ± 1
	HNO_3+HCl 1+3	103 ± 2	155 ± 27	101 ± 1	106 ± 1	103 ± 2	104 ± 1
250 mg	HNO_3	106 ± 2	184 ± 24	102 ± 3	100 ± 2	106 ± 3	106 ± 4
	HNO_3+HCl 3+1	106 ± 3	196 ± 41	103 ± 2	100 ± 4	105 ± 3	104 ± 5
	HNO_3+HCl 1+1	103 ± 0	259 ± 10	101 ± 1	99.4 ± 0.5	103 ± 1	104 ± 2
	HNO_3+HCl 1+3	104 ± 2	153 ± 11	104 ± 3	104 ± 2	106 ± 2	105 ± 4
500 mg	HNO_3	105 ± 3	177 ± 32	104 ± 2	102 ± 3	101 ± 3	102 ± 3
	HNO_3+HCl 3+1	104 ± 2	165 ± 10	105 ± 3	105 ± 1	103 ± 1	102 ± 1
	HNO_3+HCl 1+1	102 ± 3	241 ± 17	101 ± 5	105 ± 4	103 ± 3	100 ± 5
	HNO_3+HCl 1+3	107 ± 2	174 ± 15	103 ± 3	101 ± 2	100 ± 2	105 ± 4

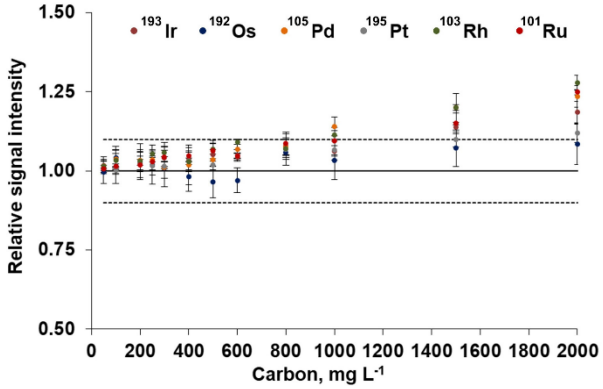


Fig. 2 Influence of carbon concentration on relative signal intensity of a standard solution containing 1 µg L^{-1} PGEs in 5% HCl medium. The standard deviations are represented by error bars (n=3). The continuous line represents the relative signal intensity of a 1 µg L^{-1} PGEs solution without C and dashed lines represent a 10% variation for this signal. Relative intensities within the dashed lines were considered interference-free.

the acceptable range. As Os recoveries were not quantitative in any of the evaluated conditions, a more detailed study was performed for this element in order to identify and correct this drawback. The high RSDs and poor recoveries could be derived from matrix interferences or from an instability during the determination step. Hence, two experiments were performed: a study on carbon interferences on PGE determination, and an evaluation of the use of a stabilizing solution for Os determination.

Evaluation of carbon interferences. It is well known that depending on digestion conditions and sample composition, especially for APIs, the residual carbon in digests can be relatively high.[28] Therefore, in this study, the occurrence of carbon interference on the determination of PGEs (up to 2000 mg L^{-1} of carbon, present in the form of citric acid) was evaluated to assess the most suitable conditions for all analytes. For this experiment, the signal intensities of 1 µg L^{-1} PGEs standard solutions in mediums of known C concentration (ranging from 50 to 2000 mg L^{-1}) were monitored. The solutions were prepared in 5% HCl. The relative signal intensity was calculated as the ratio of the analyte signal intensity in a solution containing C to that in a solution without C. The results of the effect of C concentration on PGE signals are shown in Fig. 2. Relative signal intensities with a deviation of more than 10% (represented by the dashed line in Fig. 2) from 1.00 were considered signal suppression (< 0.90) or enhancement (> 1.10).

In a previous study, it was suggested that interferences related to charge transfer reactions could occur for Os, Pd, Ir and Pt, which are considered hard-to-ionize elements.[27] However, the results were not conclusive, depending on the instrumental conditions. Furthermore, the influence of carbon on the signal of other PGEs, which are not typically considered hard-to-ionize, was not evaluated in that study.[27]

In the present study, the effect of C was evaluated for all PGEs in a different C concentration range from what was previously reported.[27] As can be seen in Fig. 2, it was observed that increasing C concentration led to signal increase, with 800 mg L^{-1} being the critical C concentration in which signal enhancement was observed for all PGEs, except for Os. However, a tendency for signal enhancement can also be observed for this element and higher C concentrations (> 1500 mg L^{-1}) could possibly lead to a significant interference on Os determination. Hence, these results corroborate with the previously reported observations for Os, Pd, Ir, and Pt.[27] Furthermore, the signal enhancement effect was more pronounced for Pd, Rh, and Ru, although Rh and Ru are not usually considered hard-to-ionize elements.

Table 2. Analyte recovery in different calibration solutions (5% HCl or stabilizing solution). Results in triplicate (mean ± standard deviation).

Calibration solution	Analyte recovery, %					
	^{193}Ir	^{192}Os	^{105}Pd	^{195}Pt	^{103}Rh	^{101}Ru
5% HCl	102 ± 3	241 ± 17	101 ± 5	105 ± 4	103 ± 3	100 ± 5
Stabilizing solution [a]	116 ± 1	103 ± 3	79.9 ± 8.9	46.6 ± 8.1	108 ± 6	131 ± 12

[a] 85 mmol L^{-1} acetic acid, 10 mmol L^{-1} thiourea and 0.6 mmol L^{-1} ascorbic acid.

When taking into account the C concentration in the digests obtained using the optimized MAWD conditions, the dissolved C concentration (205 ± 12 mg L^{-1}) was approximately four times lower than the carbon concentration for which matrix effects started to be observed for the analytes (800 mg L^{-1}). In this sense, C did not interfere in the determination step for any PGE when in concentrations up to 800 mg L^{-1}.

It is worth mentioning that the unsuitable Os recoveries (> 150%) were not caused by C interferences, since, in the evaluated C concentration range, no signal suppressions or enhancements were detected, and RSDs were lower than 10%. For this reason, in order to further investigate the problems regarding Os determination by ICP-MS, the calibration and washing solution mediums were evaluated, based on promising results reported by a previous study.[24]

Calibration medium evaluation for determination of Os and other PGEs by ICP-MS. It is well known in literature that Os determination using ICP-MS is challenging due to memory effects, leading to overestimated signals. Several authors have reported overestimated recoveries for Os (up to 500%) obtained by ICP-MS after sample decomposition by wet digestion methods.[15, 16, 18, 29, 30] Thus, in order to avoid those effects and obtain accurate results, several stabilizing solutions have been proposed.[12-14, 19, 24] In the present study, a stabilizing solution containing 85 mmol L^{-1} acetic acid, 10 mmol L^{-1} thiourea and 0.6 mmol L^{-1} ascorbic acid was evaluated.[19, 24] Each component of this solution plays a crucial role in mitigating the volatility and potential oxidation of Os during storage and analysis: acetic acid helps maintain an appropriate pH level, which may potentially reduce Os oxidation; thiourea acts as a reducing agent, preventing the formation of OsO_4 and helping to maintain the integrity of Os during storage; and ascorbic acid further minimizes oxidation, thereby preserving the stability of Os in solution. Thus, an aliquot of the digests was diluted 20-fold in the stabilizing solution after the MAWD procedure using the optimized conditions. This solution was also evaluated for the determination of the other PGEs. Lower dilution factors were evaluated, but overestimated values (> 150% recovery) were observed for Os. Additionally, the ICP-MS equipment was calibrated using an analytical curve prepared in the same stabilizing solution, which was also used as washing solution for the sample introduction system.

All PGEs were determined using analytical curves and washing solutions prepared either in the stabilizing solution, or in 5% HCl. For this test, 500 mg of sample, spiked with 100% of the J level for each analyte, were used, and the digestion solution was composed of 6 mL of a mixture of HNO_3+HCl (1+1). The digests were diluted, separately, in both calibration solutions prior to the determination step. The data on calibration medium evaluation are shown in Table 2.

As can be seen in Table 2, analyte recoveries varied greatly in the different calibration solutions. As expected, for Os, acceptable recovery was only obtained when the stabilizing solution was used, with the concentration being severely underestimated (41%) when 5% HCl was used as the calibration medium. For this reason, the stabilizing solution (85 mmol L^{-1} acetic acid, 10 mmol L^{-1} thiourea and 0.6 mmol L^{-1} ascorbic acid) was selected as the calibration medium for further Os determination. It should be noted that the carbon content in the stabilizing solution was approximately 2000 mg L^{-1}. However, all samples and calibration solutions used for Os determination contained this same amount of carbon, as they were all prepared with the same stabilizing solution. Consequently, no carbon interference was observed during Os measurements, allowing for accurate quantification of this analyte. On the other hand, for the determination of the other PGEs, recoveries were within the acceptable range established by USP (70 to 150%)[6] for all analytes in both calibration mediums, with the exception of Pt in the stabilizing solution (which was about 47%). However, as recoveries for Ir, Pd, Pt, Rh, and Ru presented lower standard deviations and were closer to 100% when 5% HCl was used as the calibration medium, this solution was selected for further experiments involving these analytes.

Method Validation. After the development of the method and selection of the best conditions for API sample digestion and PGE recovery, the optimized MAWD procedure was validated in accordance with USP specifications.[6, 31] The working range of PGE determination by ICP-MS was 0.5 to 10 µg L^{-1}. Moreover, the coefficient of determination (R^2) was better than 0.99 for all analytes in the calibration curve. Analyte recovery experiments at three levels (50, 100, and 150% of the J level for the analytes) on a test sample were used to evaluate accuracy.[6] These evaluations were performed using 500 mg of sulfamethoxazole and HNO_3+HCl 1+1 (6 mL) as digestion solution. The analyte recoveries for these experiments are shown in Table 3. Analyte recoveries were all within the acceptable range established by USP chapter 233, and varied from around 93 to 110%. From these recovery experiments, it was also possible to assure the specificity of the proposed method, since it was possible determine each analyte

Table 3. Analyte recoveries (in %) after analyte addition experiments at 50, 100, and 150% of the J level (mean value ± standard deviation, n=3).

Calibration solution	Analyte recovery, %					
	^{193}Ir [a]	^{192}Os [b]	^{105}Pd [a]	^{195}Pt [a]	^{103}Rh [a]	^{101}Ru [a]
Sulfamethoxazole (50% J)	104 ± 2	105 ± 10	99.1 ± 0.9	95.7 ± 1.6	100 ± 4	99.6 ± 0.6
Sulfamethoxazole (100% J)	102 ± 3	103 ± 3	101 ± 5	105 ± 4	103 ± 3	100 ± 5
Sulfamethoxazole (150% J)	104 ± 1	97.7 ± 0.7	104 ± 2	96.7 ± 1.4	101 ± 1	101 ± 1

[a] Calibration in 5% HCl; [b] Calibration in stabilizing solution

Table 4. Analyte recoveries (%) obtained by ICP-MS and dissolved C concentration (mg L^{-1}) obtained by ICP-OES after decomposition of API samples by the proposed MAWD method (mean value ± standard deviation, n=3).

Sample	Analyte recovery, %						C, mg L^{-1}
	^{193}Ir [a]	^{192}Os [b]	^{105}Pd [a]	^{195}Pt [a]	^{103}Rh [a]	^{101}Ru [a]	
Methyldopa	95.6 ± 2.4	100 ± 1	95.1 ± 4.8	98.4 ± 1.7	96.8 ± 1.5	95.3 ± 3.7	559 ± 47
Acetylsalicylic acid	105 ± 2	103 ± 2	102 ± 8	97.5 ± 2.2	104 ± 6	104 ± 3	406 ± 38
Acetaminophen	100 ± 1	96.1 ± 4.7	96.9 ± 2.5	99.1 ± 3.3	96.5 ± 1.2	98.1 ± 4.8	106 ± 14
Bupivacaine hydrochloride	106 ± 6	103 ± 2	104 ± 8	99.7 ± 6.2	101 ± 5	102 ± 6	690 ± 77

[a] Calibration in 5% HCl; [b] Calibration in stabilizing solution

in the presence of matrix components and other target elements.

Repeatability and intermediate precision experiments were used to assess the precision. For this, six sulfamethoxazole samples spiked at 100% of J level before the MAWD procedure were analyzed in the same day (repeatability), and in three different days (intermediate precision). The repeatability RSD value was approximately 13%, being within the USP specifications (RSD should be lower than 20%). The obtained intermediate precision RSD was lower than 15%, also being within USP specifications (RSD should be lower than 25%).

Limits of quantification of the proposed method were calculated as the addition of the mean value to 10 times the standard deviation of 10 procedural blank measurements (500 mg of sample mass and a volume of 20 mL were considered).[32] The LOQs obtained after MAWD were 0.003, 0.013, 0.007, 0.001, 0.001 and 0.001 μg g^{-1} for Ir, Os, Pd, Pt, Rh, and Ru, respectively. Even the highest obtained LOQ (Os) was at least 7.5 times lower than the maximum concentration limit established by USP for inhalation drugs, 75 times lower than the limit for parenteral drugs, and 750 times lower than the limit for oral drugs.[7] These values allow PGE determination at very low concentrations in API samples. It is important to highlight that the procedural blank values were below the LOQ for all analytes, indicating negligible contributions from other elements and ensuring that no significant interference affected the determination of PGEs. Furthermore, the evaluation of Os stability after digestion and dilution into the stabilizing solution was performed. It was possible to observe that Os remained stable in digests for up to 72 h, making it possible to store samples prior to analysis.

Platinum group element determination in APIs. After validation of the method, four additional API samples (methyldopa, acetylsalicylic acid, acetaminophen, and bupivacaine hydrochloride) were digested and PGE determination was performed by ICP-MS. These samples were chosen based on their widespread use and relevance in the pharmaceutical industry. However, PGE concentrations in all evaluated API samples were below the LOQs of the optimized MAWD and ICP-MS method. In this sense, standard addition at 100% of the J level was performed in the API samples prior to decomposition. Analyte recoveries (%) obtained after digestion of the API samples are expressed in Table 4. Additionally, dissolved C content in digests was also quantified to evaluate the efficiency of the optimized method for different API samples (Table 4).

As can be observed in Table 4, analyte recoveries were quantitative for all analytes in all samples, varying from 95.1 to 106%. Furthermore, dissolved C concentrations in digests were lower than the critical concentration (800 mg L^{-1}) in which matrix effects were observed. Regarding digestion efficiency, the RCC of digests was lower than 5% for all samples (3.93 ± 0.33% for methyldopa, 2.71 ± 0.25% for acetylsalicylic acid, 0.665 ± 0.091% for acetaminophen, and 4.15 ± 0.46% for bupivacaine hydrochloride). In this sense, the optimized MAWD procedure was considered efficient and suitable for all samples used in this study, and the determination step could be carried out without interferences being observed.

The proposed method presents several advantages over existing methods. Firstly, the use of a higher sample mass (500 mg) significantly improves the LOQs, enhancing the detectability power of the proposed method. Furthermore, results obtained in this study demonstrate high accuracy, with recoveries for Os around 100%, in contrast to other studies that have reported poor or overestimated recoveries for this element (Table S1, Supplementary Material). Recoveries for other PGEs were also

satisfactory, ranging from 95 to 104%, which highlights the reliability of the method. Moreover, the MAWD method allows for the simultaneous recovery of Os and other PGEs using the same sample preparation procedure, resulting in a more efficient analytical process. Additionally, the method is characterized by low residual carbon content and acidity in the digests, further contributing to the stability and reliability of the measurements.

CONCLUSION

In this study, a relatively simple digestion method was optimized for PGE determination in several commercial APIs used in the production of widespread pharmaceutical drugs. The proposed method was efficient and accurate, and no matrix interferences were observed in the determination step. Furthermore, it is important to notice that Os is an especially difficult analyte, given the tendency for overestimated recoveries during determination by ICP-MS. With the use of a stabilizing solution as the calibration and dilution mediums, this issue was avoided and Os recoveries were within the acceptable range established by USP in all tested conditions. This stabilizing solution could also potentially be used for determination of Ir, Pd, Rh, and Ru in APIs (recovery within the USP range). However, contrarily to Os, recoveries for these elements, as well as for Pt, were better (closer to 100%) when 5% HCl was used as calibration medium, so 5% HCl was considered the most adequate for determination of Ir, Pd, Pt, Rh, and Ru in APIs. Additionally, the proposed MAWD method enabled decomposition of a considerable sample mass (500 mg), which helped improve detectability via lower LOQ values. Finally, using the optimized conditions, analyte recoveries were quantitative at all standard addition levels and for all samples, and determination of all PGEs, including Os, could be achieved using a relatively simple sample preparation method based on MAWD.

AUTHOR INFORMATION

Erico Marlon Moraes Flores is a Titular Professor in Federal University of Santa Maria (UFSM-Brazil). He was the Director of Analytical Chemistry Division of the Brazilian Chemical Society and Scientific Director of Rio Grande do Sul State Research and is currently the vice-president of Analytical Chemistry Division of IUPAC. He has been working as member of editorial board for *Atomic Spectroscopy*. He has experience in the development of methods for sample preparation for element determination using atomic spectrometry and chromatography, speciation analysis and the use of microwaves and ultrasound for process intensification and control of industrial process. He has published more than 400 papers, one book, many book chapters, and patents.

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Notes

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