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ARTICLE

Multi-Techniques for Iodine Determination and Dose Uniformity Assays in Iodized Mineral Dietary Supplements

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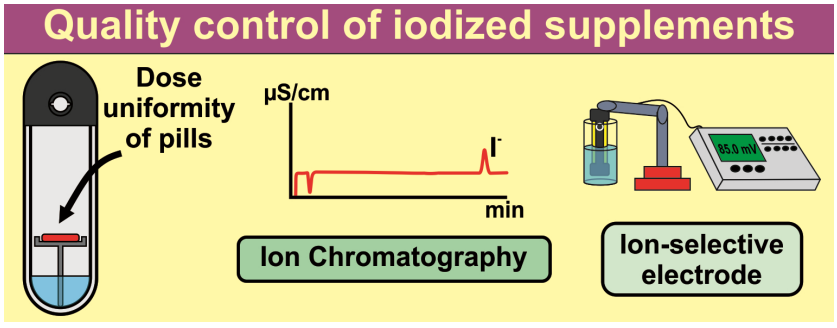

The determination of iodine in iodized mineral dietary supplements is considered a challenge, especially in view of the variety in the sample composition and the analyte concentration. Thus, in this work, microwave-induced combustion (MIC) was combined with ion chromatography (IC) and ion-selective electrode potentiometry (ISE) for iodine determination and dose uniformity assays in mineral dietary supplements. Sample masses up to 800 mg were efficiently digested and only a diluted alkaline solution (200 mmol L^{-1} NH_4OH) was necessary to absorb the analyte for further determination step. The final digest was fully compatible with multi-technique detection usually available in routine analysis laboratories. Recoveries ranging from 94% to 106% was achieved and relative standard deviations for repeatability and intermediate precision were always lower than 8%. Limits of quantification were 4 µg g^{-1} and 10 µg g^{-1}, respectively, by using IC and ISE. The analytical method was applied for iodine determination in mineral dietary supplements from four brands with different iodine dosages (from 100 to 1250 µg g^{-1}, according to the manufacturers) and for uniformity assay evaluation using individual tablets/capsules of mineral dietary supplements. Non-compliance regarding label information for some samples was reported, drawing the attention of supervisory institutions. The analytical strategies presented in the present study can be successfully used in routine analysis of the quality control of mineral dietary supplements.

Keywords: dietary supplements, iodine determination, microwave-induced combustion, ion chromatography, ion-selective electrode

INTRODUCTION

Iodine is an indispensable nutrient for human health and an essential substrate for thyroid hormone syntheses - triiodothyronine (T_3) and thyroxine (T_4).[1] These hormones are involved in several important

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biological roles as the development of the central nervous system, skeletal growth, and multiple organ regulation.[2] However, iodine can cause several disorders in unsuitable concentrations as hypothyroidism and hyperthyroidism.[2] Iodine absence is more common than excess in humans, in addition to hypothyroidism, causing damage to brain development, endemic cretinism, delayed physical development, spastic diplegia, and infant mortality.[3] To overcome the iodine absence growing public, institutions such as United Nations Children's Fund (UNICEF), International Council for Control of Iodine Deficiency Disorders (ICCIDD), and World Health Organization (WHO) have recommended iodine addition in cooking salt ranging from 15 to 45 μg g^{-1}.[4] Even so, other iodine sources have been recommended as mineral dietary supplements.

Mineral dietary supplements have also been commonly used to supply iodine deficiency in human organisms. These products are relatively inexpensive and easily purchased in several markets without prescription from healthcare professionals. The quality control of capsules/tablets used for supplementation has been established in official compendiums such as British and United States Pharmacopoeia.[5,6] However, the use of wet digestion with concentrated acids or fusion methods can lead iodine to losses by volatilization. Classical volumetric techniques have been recommended for iodine quantification, and even an important classical method, these techniques are extremely dependent on analyst visual acuity and are not very sensitive, making difficult quantification at low concentrations.[5-10] Nowadays, sensitive and selective instrumental analytical techniques have been included in some Pharmacopoeias given the disadvantages of classical methods. Atomic absorption spectrometry (AAS),[11] high-resolution continuum source molecular absorption spectrometry (HR-CS-MAS),[12] ion-selective electrode potentiometry (ISE),[13] neutron activation analysis (NAA),[14] inductively coupled plasma-mass spectrometry (ICP-MS),[15,16] and ion chromatography (IC)[17,18] have been proposed for iodine determination in several matrices including raw materials and pharmaceutical products.

Among sensitive and selective instrumental analytical techniques, IC and ISE stand out because they present several advantages for routine analyses as suitable sensitivity, selectivity, and lower acquisition and maintenance costs than others.[13,18] These techniques are interesting alternatives for iodine quantification in mineral dietary supplements in routine analysis. However, they require the sample in a solution form to be analyzed. Thus, a suitable sample preparation method is fundamental to the success of the analysis. The sample preparation step can be considered a challenge for further iodine determination in solid samples. Digestion methods using concentrated acids during the sample preparation, to convert the solid sample in an aqueous solution, are not suitable for further iodine determination considering the formation of volatile compounds – HI or I_2 – and non-quantitative recoveries are consequences of this carelessness.[13] Concentrated acids in the final solution are not adequate for using analytical techniques such as IC and ISE.

Thus, microwave-induced combustion (MIC) can be an excellent alternative as a sample preparation method for mineral dietary supplements for further iodine determination by IC and ISE.[19,20] Microwave-induced combustion is performed in closed vessels, minimizing losses by volatilization, presenting high sample throughput compared to other combustion methods in closed vessels, and allowing to choose a suitable absorbing solution for the analyte and the determination technique. This method still allows a reflux step to wash the vessel wall and ensure a quantitative recovery of the analyte. Microwave-induced combustion has been employed for the digestion of different matrices such as foods, biological materials, polymers, and drugs, aiming for the subsequent iodine determination by several analytical techniques.[21-27] Recently, MIC was reported as a suitable sample preparation method for subsequent halogen determination in Brazilian Pharmacopeia,[28] but still not optimized for subsequent determination of iodine in mineral dietary supplements.

Thus, considering the relevance of iodine determination in mineral dietary supplements, the main objective of this study was to propose two analytical alternatives for iodine determination in mineral dietary supplements using MIC as a sample preparation method and IC or ISE as a determination technique. Accuracy was evaluated by recovery tests in two levels using standard solutions and by comparison of the results. Precision was evaluated by repeatability and intermediate precision. Proposed analytical methods

were applied for iodine determination in mineral dietary supplements from four brands with different iodine dosages (from 100 to 1250 μg g^{-1}, according to the manufacturers). Moreover, proposed analytical methods were applied for iodine dose uniformity assays considering each tablet/capsule of mineral dietary supplements.

MATERIALS AND METHODS

Instrumentation

A microwave oven (Multiwave 3000™, Anton Paar, Austria), equipped with eight high-pressure quartz vessels with an internal volume of 80 mL (maximum pressure and temperature of 80 bar and 280 °C, respectively), was used for the sample preparation method by MIC. Quartz holders were used to supporting the samples and the filter paper inside the vessels. An ion chromatograph (861 Advanced Compact IC, Metrohm, Switzerland), equipped with a chemical suppression system, a conductivity detector, an anion-exchange column (250 mm x 4 mm i. d.) based on polyvinylalcohol with quaternary amine groups (Metrosep A Supp5, Metrohm), and a 20 μL sampling loop were used for iodine determination by IC. A potentiometer (HI 3221 pH/ORP/ISE meter, HANNA Instruments, USA) equipped with an electrode of iodide (HI 4111, HANNA Instruments, USA) was used for iodine determination by ISE. A hot plate with agitation (RH Basic, IKA, USA) was used for sample homogenization.

Reagents

All solutions were prepared using ultrapure water (18 MΩ cm) obtained from a purification system (Mega Up, MegaPurity, South Korea). Reagents were of analytical grade or higher purity. Water, $(NH_4)_2CO_3$ (concentrations of 25, 50, and 100 mmol L^{-1}), and NH_4OH (concentrations of 25, 50, and 200 mmol L^{-1}) were evaluated as absorbing solutions in the MIC method. The solution of 27% NH_4OH (Synth, Brazil) and $(NH_4)_2CO_3$ solid reagent (Merck) were used to prepare the evaluated absorbing solutions. Ammonium nitrate (6 mol L^{-1}) was used as a combustion igniter, which was prepared by the dissolution of the solid reagent (Merck) in water.

Small discs (12 mg, 15 mm in diameter) of filter paper (Qualy, J Prolab, Brazil) were used as a combustion aid, and polyethylene (PE) films were used to wrap the samples for digestion by MIC. Before combustion, the discs of filter paper and PE films were cleaned by immersion in 10% (v v^{-1}) HNO_3 (Vetec, Brazil) for 20 min in an ultrasonic bath (USC-1800 A, Unique, 40 kHz, 155 W, Brazil), subsequently rinsed with ethanol (Synth, Brazil) and ultrapure water, and dried in a class – 100 laminar bench (CSLH-12, Veco, Brazil). Oxygen (99.5%, Linde, Brazil) was used for the pressurization of the vessels in the MIC method. Quartz vessels and holders were cleaned with 6 mL of 14.4 mol L^{-1} HNO_3 (Vetec) using a microwave heating program set at 1000 W for 10 min (heating step) and 0 W for 20 min (cooling step). After that, the same procedure was repeated using 6 mL of water to decrease the blank values and eliminate the traces of acid.

The standard solutions used for the iodine determination by IC and by ISE were prepared by the dilution of a stock standard solution (100 μg mL^{-1}) obtained by the dissolution of KI salt (Merck) in water. Mixtures containing Na_2CO_3 and $NaHCO_3$ solutions were evaluated as eluent in IC analysis, prepared by dissolution of the respective salts (Merck) (recommended by the manufacturer). HPLC-grade acetonitrile (JT Baker, Phillipsburg, USA) was evaluated as an organic modifier in the mobile phase. Ionic strength adjusters (ISA, HI 4000-00, HANNA Instruments, USA) were used in iodine determination by ISE.

Samples of mineral dietary supplements

Samples of mineral dietary supplements, composed mostly of organic excipients, containing different dosages of iodine (according to the manufacturers – 100 μg g^{-1}, 260 μg g^{-1}, 870 μg g^{-1}, and 1250 μg g^{-1}, respectively) were labeled as A, B, C, and D. Around 100 g of each sample, regardless of their presentation, were homogenized and dried in an oven (400/2ND, DeLeo, Brazil) for about 4 h at 60 ± 5 ºC before the start of the experiments. Dietary supplements in tablet form were homogenized in porcelain mortar and pestle until obtaining a fine powder (less than 80 mesh or 180 μm) and subjected to a sieving step to guarantee

the homogeneity of all samples. Dietary supplements in capsule form had their contents removed. The samples (30 capsules/tablets of each one) were also digested individually, according to the United States Pharmacopoeia, to evaluate the test uniformity of dosage units.[6]

Proposed mineral dietary supplement sample preparation by microwave-induced combustion

Initial studies were performed using an arbitrarily selected sample of mineral dietary supplement labeled as sample "DS-A". Initially, sample masses (400 to 1000 mg) were weighed and wrapped in PE films (8 x 8 cm), and the PE films were sealed by heating, resulting in small wraps. The wrap of PE containing the sample was placed under a small disc of filter paper, moistened with an NH_4NO_3 solution (50 µL, 6 mol L^{-1}), on the base of a quartz holder. The quartz holders were transferred into quartz vessels, previously charged with 6 mL of absorbing solution (water, 25, 50, and 100 mmol L^{-1} $(NH_4)_2CO_3$ or 25, 50, 100, and 200 mmol L^{-1} NH_4OH). After closing, the vessels were positioned in the rotor, pressurized with 20 bar of oxygen, and the combustion process was carried out. The heating program used for combustion was as follows: *i)* 50 s at 1400 W (ignition step); *ii)* 1 min at 0 W (combustion step); *iii)* 5 min at 1400 W (reflux step) and *iv)* 20 min at 0 W (cooling step). After digestion, the pressure of each vessel was released, and the digests were transferred to volumetric flasks and diluted with ultrapure water up to 25 mL for subsequent iodine determination by IC and ISE.

The accuracy of the proposed method was evaluated by analyte recovery tests. A reference solution containing 2000 µg mL^{-1} of iodine was added at two concentration levels (50% and 75% of the concentration in the solution present in the sample before digestion by MIC). All iodine species (organic and other inorganic species) are converted to iodide after combustion step.[13,27] The precision was evaluated using the relative standard deviations (RSDs) of the measurements at repeatability (intra-day precision) and intermediate precision (inter-day precision) according to Eurachem guidelines.[29] The maximum variation in conditions between the runs was performed by the analysis of mineral dietary supplements on different days and by different analysts. All results were statistically evaluated using GraphPad InStat version 3.00 computer software package (GraphPad, San Diego, USA). The limit of detection (LOD) and limit of quantification (LOQ) were calculated from the mean of the blank values plus three times (for LOD) or ten times (for LOQ) the standard deviation obtained for ten replicates of blank, according to the instructions described in the protocols of the Instituto Nacional de Metrologia, Qualidade e Tecnologia (INMETRO).[30]

RESULTS AND DISCUSSION

Evaluation of the eluent for iodine determination by ion chromatography

During the sample preparation by MIC, the total iodine concentration present in the sample (bonded to organic compounds or in iodate form) is converted to iodide.[13] Thus, total iodine is determined as iodide by IC. Initially, a relatively high time of analysis is required for iodine determination (retention time of iodide is around 45 min because of its high interaction with anion-exchange column based on polyvinylalcohol with quaternary amine groups) using the eluent recommended by the manufacturer (a mixture containing 3.2 mmol L^{-1} Na_2CO_3 and 1.0 mmol L^{-1} $NaHCO_3$) and the peak resolution for iodide was considered insufficient ($R < 1.5$).[29] Thus, a mixture of 9 mmol L^{-1} Na_2CO_3 and 3 mmol L^{-1} $NaHCO_3$ was evaluated to reduce the IC analysis time and to improve the peak resolution. Although the retention time for iodide has been reduced to approximately 25 min, noise and drift in baseline, considered unsuitable for analysis, were observed, probably related to the high concentration of the eluent. Thus, a mixture containing 6 mmol L^{-1} Na_2CO_3 and 2 mmol L^{-1} $NaHCO_3$ was evaluated, and the retention time for iodide was approximately 30 min. Using this solution as an eluent, the noise was reduced, the drift was eliminated, and the peak resolution was considered suitable ($R \geq 1.5$).

Organic solvents can change the retention characteristics of the column packing toward the analyte and alter retention order, peak efficiency, and resolution to optimize the separation.[31,32] Thus, the eluent of 6 mmol L^{-1} Na_2CO_3 and 2 mmol L^{-1} $NaHCO_3$ in 10% (v v^{-1}) acetonitrile medium was studied. Acetonitrile

was used as an organic modifier in the mobile phase to facilitate the elution of analytes in a strong interaction with the ion exchange sites of the chromatographic column.[33] Retention time of iodide was decreased to approximately 24 min, which represents a reduction time of around 50% compared to the eluent recommended by the manufacturer. A larger amount of acetonitrile was not evaluated to avoid excessive system pressure increase. Thus, the mixture of 6 mmol L^{-1} Na_2CO_3 and 2 mmol L^{-1} $NaHCO_3$ in 10% (v v^{-1}) acetonitrile medium was selected as the eluent, and the final chromatograms with the established conditions are shown in Figure 1.

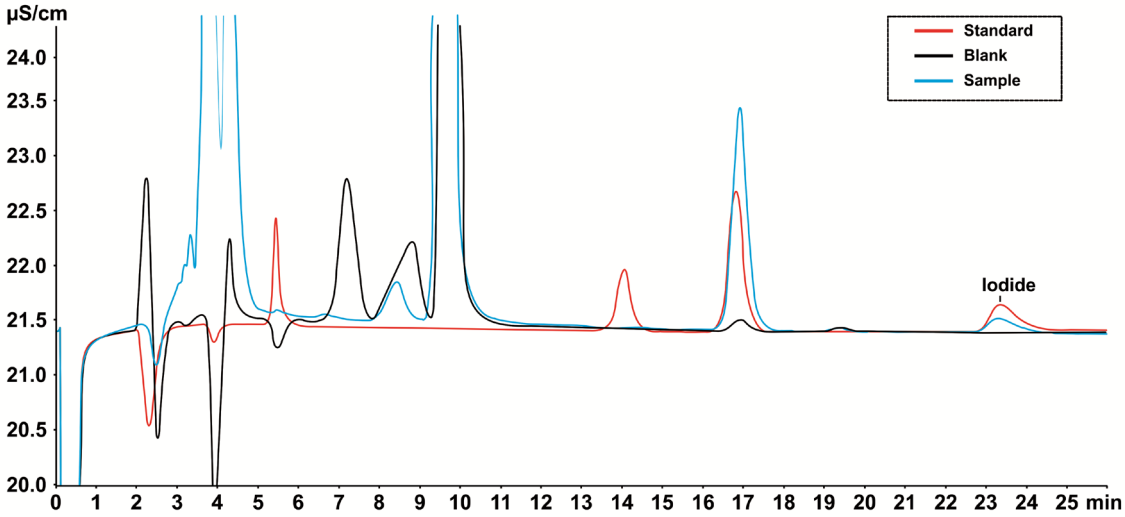

Figure 1. Chromatograms for iodine determination by IC for (—) standard containing 1 µg mL^{-1}, (—) blank after MIC method, and (—) mineral dietary supplements after MIC method.

Evaluation of microwave-induced combustion on the sample preparation of mineral dietary supplements for subsequent iodine determination

Sample mass and absorbing solution during sample preparation by MIC were carefully evaluated for further iodine determination in mineral dietary supplements by IC and ISE. Initially, sample mass was evaluated considering the pressure reached in the quartz vessel and the final aspects of the digests at the end of the combustion process. The aspects of the resulting solutions from the combustion of sample masses, ranging from 400 to 1000 mg, are shown in Figure 2. As can be observed, from 400 mg to 800 mg (Figures 2A to 2E), the aspect of the solutions was clear, suggesting a complete combustion reaction. Combustion of 900 mg (Figure 2F) and 1000 mg (Figure 2G) lead to yellowish color with particulate residues final solution. However, sample masses up to 800 mg (Figure 2E) resulted in a colorless solution without residue presence. Thus, 800 mg of sample mass was chosen for further evaluation. The maximum pressure of the system reached about 50% of the maximum pressure (80 bar) recommended as safe by the manufacturer.

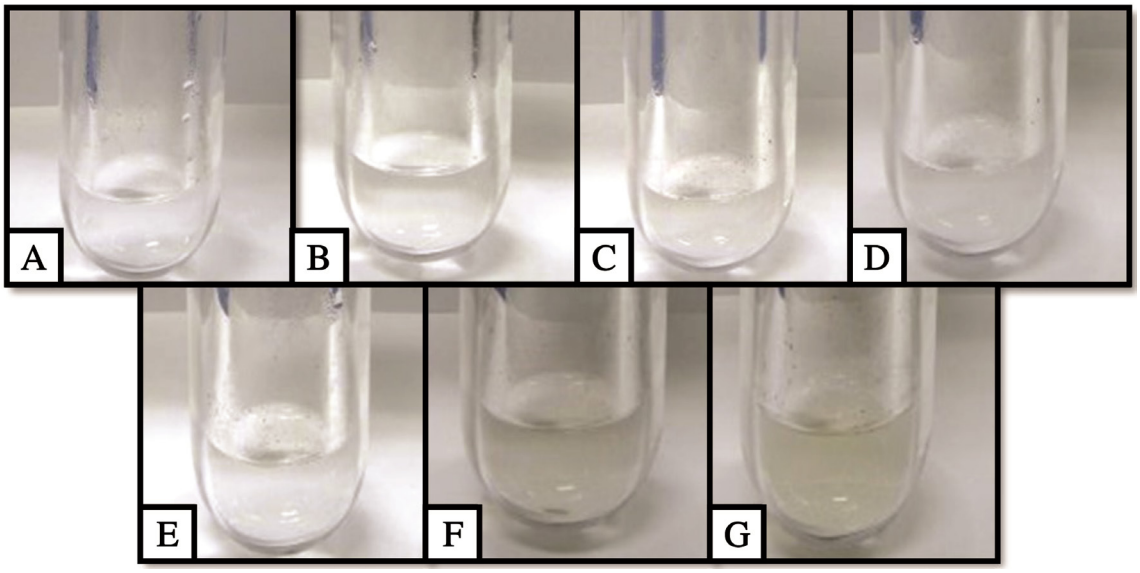

Figure 2. Aspects of solutions obtained after digestion by MIC using (A) 400 mg; (B) 500 mg; (C) 600 mg; (D) 700 mg; (E) 800 mg; (F) 900 mg and (G) 1000 mg of mineral dietary supplement.

The most suitable solution for iodine absorption after mineral dietary supplement combustion was also optimized. Water, $(NH_4)_2CO_3$ (25, 50, and 100 mmol L^{-1}), and NH_4OH (25, 50, and 100 mmol L^{-1}) were initially evaluated according to previous studies presented in the literature.[34,35] Iodine concentrations after combustion of 800 mg of mineral dietary supplement using different absorbing solutions are shown in Figure 3. Ion chromatography was used as a determination technique. As shown in Figure 3, iodine concentration using water as the absorbing solution was always lower than those using alkaline absorbing solutions, which is probably related to its instability in the final solution at low pH (around 3).[13] This pH value may be related to iodine volatile species.[36] Additionally, the precision of the measurements for the repeatability using water as the absorbing solution was considerably high (RSD ≤ 19%). No statistical differences were observed for iodine concentration using $(NH_4)_2CO_3$ or NH_4OH as absorbing solutions. Thus, 100 mmol L^{-1} NH_4OH was chosen as the absorbing solution considering better results for repeatability (RSD < 6%).

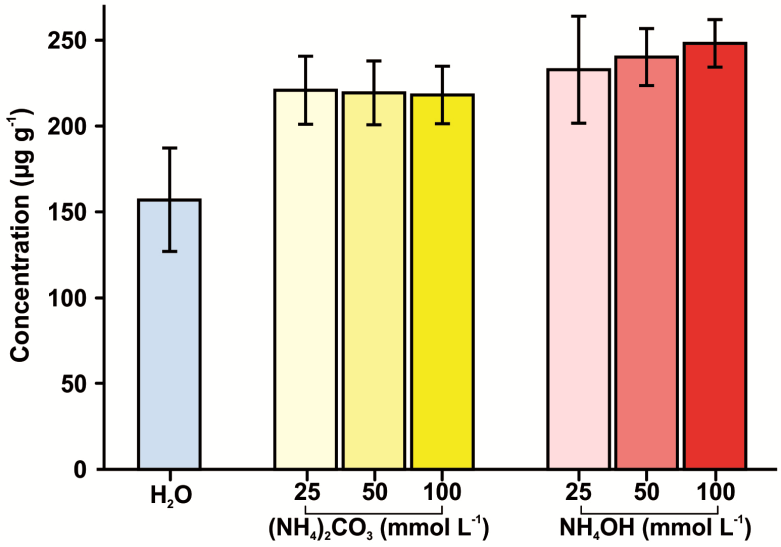

Figure 3. Iodine concentration obtained after digestion of 800 mg of the mineral dietary supplement "DS-A" by MIC using water or different concentrations of $(NH_4)_2CO_3$ or NH_4OH solutions, and iodine determination by IC (n = 5).

Feasibility of the proposed MIC method for iodine determination by ion chromatography and potentiometric ion-selective electrode

The feasibility of the proposed MIC method for further iodine determination by IC and ISE was evaluated by comparison of the results obtained for the sample DS-A. Iodine determination was performed indirectly through the determination of iodide by IC and ISE. The results for iodine in the sample DS-A after the MIC method obtained by IC (244 ± 20 μg g^{-1}) did not present a statistical difference from those obtained by ISE (250 ± 23 μg g^{-1}). Calibration curves of both determination techniques were performed ranging from 0.1 to 1.0 μg mL^{-1}. Limits of detection and quantification using IC (2 μg g^{-1} and 4 μg g^{-1}, respectively) were quite similar to those using ISE (4 μg g^{-1} and 10 μg g^{-1}, respectively). Thus, both determination techniques can be considered suitable for routine analysis. The high digestion efficiency of the MIC method provides a suitable solution for an accurate and precise total iodine determination using IC and ISE.

Analytical figure of merit

For accuracy evaluation of the proposed MIC method and further iodine determination by IC and ISE, spikes in two levels of concentration (corresponding to 50% and 75% of the iodine concentration in solution after sample preparation of DS-A sample by MIC using the selected conditions) were carried out. For the first level of the spike (50%), iodine recoveries ranged from 95 to 103%; however, for the second level of the spike (75%), recoveries for iodine were always less than 70%. Thus, considering the high iodine concentration in the mineral dietary supplement, 200 mmol L^{-1} NH_4OH was also evaluated as the absorbing solution, and thus, recoveries ranging from 94 to 106% were obtained. Additionally, the RSDs for repeatability were always lower than 2%, and 200 mmol L^{-1} NH_4OH was chosen as the absorbing solution of the method. Intermediate precision was also evaluated, and the RSD was always lower than 8%. Therefore, the proposed MIC sample preparation method using 800 mg of sample mass and 200 mmol L^{-1} NH_4OH as absorbing solution presents suitable accuracy and precision for iodine determination by IC and ISE in a wide range of concentrations, which is essential for the quality control of mineral dietary supplements.

Determination of iodine in mineral dietary supplements and dose uniformity assays

The proposed analytical strategies were applied for iodine determination in iodized mineral dietary supplements from four manufacturers containing different dosages of iodine. Results obtained from homogenized tablets/capsules of each sample are shown in Table I.

Table I. Iodine concentration in iodized mineral dietary supplements after sample preparation by MIC and determination by IC and ISE (mean ± standard deviation, n = 5)

Samples	Reported concentration (μg g^{-1})	Obtained concentration (μg g^{-1})	
		IC	ISE
DS-A	260	244 ± 20	250 ± 23
DS-B	100	773 ± 54	750 ± 30
DS-C	870	741 ± 20	761 ± 32
DS-D	1250	1209 ± 44	1218 ± 48

As shown in Table I, iodine concentration in DS-A, DS-C, and DS-D did not present significant differences (Student's *t*-test, confidence level of 90%, $p > 0.10$) when compared with the values informed on the labels. On the other hand, iodine concentration in DS-B presents a significant difference (Student's *t*-test, confidence level of 90%, $p > 0.10$) when compared with the value informed on the label. This is indicative

of the unreliability of the value reported on the label and the importance of quality control of these products using accurate and precise analytical tools. An additional study was performed based on the uniformity dosage units assessment of the United States Pharmacopeia.[6] This test has been also a demand by the pharmaceutical industry for routine analysis. Considering an official demand recommended by Pharmacopoeias, new analytical strategies are being proposed,[13,37-39] presenting results in agreement and disagreement with the limits established by Pharmacopoeias. United States Pharmacopeia establishes that each tablet must contain between 90% and 110% of the amount of active substance declared by the manufacturer. The individual tablets/capsules of mineral dietary supplements were digested using the proposed MIC method and iodine was determined by IC and ISE. The results are presented in Table II.

Table II. Iodine concentration in mineral dietary supplements obtained by IC and ISE after digestion of samples in commercial form (30 tablets or capsules) by MIC (mean ± standard deviation, n = 5)

Sample	Reported value (μg g^{-1})	Obtained concentration (μg g^{-1})	
		IC	ISE
DS-A	260	251 ± 32	231 ± 24
DS-B	100	596 ± 460	571 ± 510
DS-C	870	631 ± 132	651 ± 122
DS-D	1250	1206 ± 56	1226 ± 44

Similarly, iodine concentration in DS-A, DS-B, and DS-D did not present significant differences (Student's *t*-test, confidence level of 90%, $p > 0.10$) when compared with the values informed on the labels. On the other hand, the concentration of iodine in the DS-C sample units presented significant differences (Student's *t*-test, confidence level of 90%, $p > 0.10$) when compared with the values informed on the labels. In addition, iodine concentration in samples DS-B and DS-C presented a high RSD (77% and 21%, respectively), which demonstrates problems in the uniformity of doses and reinforces the importance of effective quality control of dietary supplements. The iodine concentration obtained for sample DS-B in the uniformity of dosage units test and homogenized sample (Table I) was higher than the values reported by the manufacturer, while the iodine concentration obtained for sample DS-C in the uniformity of dosage units test and homogenized sample (Table I) were lower than values reported by the manufacturer.

The determination of uniformity was performed using the recommendations of the United States Pharmacopoeia. This uniformity results in disagreement with United States Pharmacopoeia can be associated with several factors during medication production. Inspection of regulatory agencies that supervise the production of the supplements is quite flawed and there is a significant demand presented through analytical studies. While the consumption of a product with concentrations above those reported on the label may cause health problems due to continued exposure, such as hyperthyroidism, the products with concentrations below those described on labels may be ineffective for suitable supplementation. These results indicate a need for a suitable analytical method for the quality control of this kind of product and the proposed method is an excellent alternative for the quality control of mineral dietary supplements.

CONCLUSIONS

The proposed MIC sample preparation method was feasible and suitable for the digestion of mineral dietary supplements for the subsequent iodine determination by IC or ISE. The use of the proposed analytical strategies allows efficient sample digestion using a suitable absorbing solution according to green chemistry for the iodine, in addition to being compatible with IC and ISE. Moreover, the proposed analytical tools presented high throughput, suitable sensitivity and selectivity, and accuracy and precision. The high

digestion efficiency of the proposed MIC method also allowed accurate and precise iodine determination by IC and ISE, which are interesting alternatives for routine analysis because they present low acquisition and maintenance costs when compared to other determination techniques. The proposed method was also suitable for uniformity of dosage units test – a requested test from the pharmaceutical industry for routine analysis - and it can be also an excellent tool for this purpose. In this sense, the proposed analytical methods may be promising alternatives for mineral dietary supplement quality control, considering the importance of controlling the concentration of iodine in this type of sample.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

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