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Green approaches with amino acids-based deep eutectic solvents (AADES) for determining as in medicinal herbs by ICP-MS

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ABSTRACT

In this work, an innovative ultrasound-assisted matrix solid-phase dispersion (UA-MSPD) method and microwave-assisted extraction (MAE) were applied with amino acids-based deep eutectic solvents (AADES) for the extraction of arsenic (As) from medicinal herbs. Multivariate optimization by Doehlert design (DD) was performed to determine the optimal experimental conditions. The effects of temperature (TP), time (TM), and sample-solvent ratio (SSR) were evaluated, and the optimized conditions were 50 °C, 60 min, and 10:1 mg mL^{-1} for UA-MSPD and 100 °C, 40 min, and 40:1 mg mL^{-1} for MAE, employing AADES 2 (β-alanine, citric acid, and water), where the hydroxyl and carboxyl groups of the citric acid structure favored formation of a chelate complex with the analyte. AADES 3 (β-alanine, xylitol, and water) was effective for MAE, while AADES 1 (β-alanine, malic acid, and water) proved to be inefficient for As extraction. The parameters of the analytical methods were evaluated using certified reference materials. The accuracy, based on percentage recovery, was in the range 77–101 %, while the limits of detection and quantification were in the ranges 0.010–0.039 mg kg^{-1} and 0.011–0.130 mg kg^{-1}, respectively. The analytical curves presented $R^2 > 0.99$. The proposed methods were shown to be environmentally friendly, based on the Analytical Eco-Scale and RGB 12 procedures. Both optimized methods were applied for the determination of As in commercial medicinal herbs (0.059–0.101 mg kg^{-1}), with the values obtained being within the maximum daily intake limit established by the World Health Organization (WHO). It should be noted that there are no previous reports in the literature concerning the application of a sample preparation method using AADES, employing their solid precursors, with no requirement for prior solvent synthesis, as proposed here in the case of the UA-MSPD method.

1. Introduction

The increasing consumption of medicinal herbs in recent years has raised concerns about the need for quality control to ensure the safety of the consumer population [1]. Medicinal herbs are used in some of the most commonly consumed beverages worldwide, due to suggested health benefits related to their chemical composition, since they may be rich in amino acids, vitamins, minerals, and phenolic compounds with antioxidant activity that can inhibit or prevent diseases such as cancer, heart disease, diabetes, and asthma [2,3].

Arsenic (As) is a toxic, mutagenic, and carcinogenic element that is regulated by public health guidelines and agencies worldwide, with maximum permitted values established for daily intake by humans [1]. Previous studies have reported the presence of As in samples of medicinal herbs, at concentrations in the range 0.015–1.078 mg kg^{-1} [5–8], sometimes above the maximum limit established by Brazilian [9] and MERCOSUL [10] regulations (0.60 mg kg^{-1} in teas, yerba mate, and plants used for infusions), or very close to that established by the World Health Organization (WHO) (1 mg kg^{-1} in medicinal herbs) [11]. Therefore, it is important to monitor the As levels in medicinal herbs, requiring quality control strategies to ensure safe consumption [1,12].

The low permissible limits for As in medicinal herbs represents a challenge in the development of analytical methods for the quantification of this element. The availability of more accurate and reliable methods is essential for ensuring quality control and safe consumption, assisting public health policies [1]. The increasing interest in simplified, low-cost, and sustainable analytical methods has led to advances in different research areas [13]. Sample preparation is essential for ob-

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taining quantitative data, although it is often the most complex and time-consuming step before elemental determination [14]. In addition, there is a growing demand for alternative methods that comply with the principles of green analytical chemistry (GAC) [15]. The application of alternative or diluted solvents in methods that are more efficient and low-cost is promising [16]. However, low-toxicity reagent availability and high-risk procedures are still limiting factors [16].

The use of deep eutectic solvents (DES) in sample preparation has shown promising results in different applications, with the aim of combining the benefits of eco-friendly solvents and high-efficiency methods [15–17]. A DES is formed by the combination of a hydrogen bond donor (HBD) component and a hydrogen bond acceptor (HBA) component [18], in a specific proportion that reduces the melting temperature of the mixture [19,20]. The advantages of DES include low cost and low volatility [18,20]. In addition, the physicochemical properties of DES can be modulated based on variation of the precursors and their molar ratios, which makes it possible to synthesize them targeting specific applications [21].

A DES prepared with at least one amino acid in its composition is defined as an amino acid-based deep eutectic solvent (AADES) [22]. Although studies of DES toxicity are still limited, Marchel et al. [23], in a review of possible microbial toxicities of different DES compositions, concluded that more harmful solvents are formed by precursors that present charge delocalization (e.g., choline chloride) and that have a higher proportion of acid or organic acid. Therefore, using an AADES with composition including a high proportion of amino acid, as well as high addition of water, is advantageous due to its low toxicity.

Analytical methods based on AADES have many applications that comply with the GAC principles, with attractive analytical and environmental features. Extraction techniques considered green, combined with DES, can be applied in the determination of As, highlighting microwave-assisted extraction (MAE) and ultrasound-assisted extraction (UAE). These techniques can provide accurate results, in addition to benefits such as short extraction time, low consumption of reagents and energy, and improved safety for the operator [24].

Matrix solid-phase dispersion (MSPD) is a versatile, low-cost, and rapid method applied for the extraction and cleaning of solid or semi-solid samples [25]. It involves three simple steps: (1) manual mixing of the sample and the dispersant sorbent material, for shearing the sample into small pieces that disperse, retaining components of the interfering matrix on the surface of the sorbent, resulting in a homogeneous mixture; (2) compaction of this mixture into a syringe or solid phase extraction (SPE) cartridge; and (3) elution of the analyte using a suitable organic solvent [26–30]. The association of the MSPD technique with DES as the elution solvent, replacing toxic organic solvents, has been explored recently, but is normally applied in the extraction of organic compounds [31–36]. Applications for As extraction are still limited to certain matrices, typically liquid phase samples, where the extraction occurs due to miscibility differences between the matrix and the DES [37–42].

The use of AADES as extracting solvent in MAE and in MSPD associated with UAE, in a single-step procedure, offers the potential for the development of efficient and eco-friendly applications. The evaluation of different experimental conditions using response surface methodology (RSM) can enable the establishment of optimal conditions that provide versatility, rapidity, and fewer experimental steps [43,44].

In order to simplify the analytical process, the present study proposes an innovative approach based on the application of AADES in ultrasound-assisted matrix solid-phase dispersion (UA-MSPD), in addition to the optimization of a microwave-assisted extraction (MAE) procedure. The RSM technique was used to optimize the extraction conditions in the sample preparation methods for the determination of As. The applicability of the methods and the performance parameters were evaluated. As far as is known, the application of the UA-MSPD/AADES combination is a pioneering approach for the extraction and determination of As in medicinal herbs, since it does not require the prior synthesis of these solvents before starting the extraction procedure. In addition, compared to other works found in the literature [31–36], there is no need to use dispersing sorbents in the MSPD, since the sample undergoes abrasion together with the solid precursors of the AADES, followed by the addition of water, constituting a highly GAC-compliant method.

2. Experimental procedures

2.1. Reagents, solutions, apparatus and samples

Nitric acid (HNO_3, 65 % v v^{-1}), obtained using a sub-boiling system (subCLEAN, Milestone, Italy), and hydrogen peroxide (H_2O_2, 30 % v v^{-1}, Sigma-Aldrich, USA) were used in the microwave-assisted acid digestion (MW-AD). The equipment used in this work was decontaminated in an HNO_3 (10 % v v^{-1}) bath for 48 h. Ultrapure water (18.2 MΩ cm) obtained from a Milli-Q system (ICW-3000, Merck, Darmstadt, Germany) was used in the experimental procedures.

The AADES used for the extraction procedures were prepared using β-alanine (ALA), DL-malic acid (MA), citric acid (CA), and xylitol (XY), all obtained at 99 % purity (Sigma-Aldrich, Missouri, USA). Optimization of the proposed sample preparation methods and evaluation of the accuracy of the results employed a certified reference material (CRM) of forage grass (*Brachiaria brizantha* cv Marandu, E1001a), supplied by the Brazilian Agricultural Research Corporation (EMBRAPA, São Paulo, Brazil). A peach leaves CRM (NIST 1547) supplied by the National Institute of Standards and Technology (NIST, Maryland, USA) was used to assess the applicability of the methods.

A microwave digestion system (Multiwave GO, Anton Paar, Graz, Austria) was employed in the MAE and MW-AD procedures. An ultrasonic bath (Model Q3.0/40A, Eco-Sonics, São Paulo, Brazil) was employed in the UA-MSPD procedure. A centrifuge (Model K 14–4000, KASVI, São Paulo, Brazil) and quantitative filter paper (25 μm/ 80 g m^{-2}, J. Prolab, São Paulo, Brazil) were used for phase separation whenever necessary.

Commercial samples of fennel (*Foeniculum vulgare* Mill.), yerba mate (*Ilex paraguariensis*), lemongrass (*Cymbopogon citratus* Stapf.), and chamomile (*Matricaria recutita* L.) were purchased at a local market in the city of São José do Rio Preto (São Paulo, Brazil).

2.2. AADES preparation

The AADES were prepared using ALA (HBA) combined with the HBDs MA (AADES 1), CA (AADES 2), and XY (AADES 3), in a 1:2:17 M ratio (HBA:HBD:water) [45]. The preparation was carried out on a heating plate, at 50 °C, with constant agitation (220 rpm) for 2 h [46].

2.3. Experimental design

Doehlert design (DD) was applied to optimize the experimental conditions in MAE and UA-MSPD using AADES 1, 2, and 3. The factors evaluated were temperature (TP, °C), time (TM, min), and sample-solvent ratio (SSR, mg mL^{-1}). The experiments and the levels of the factors are shown in **Tables* S1 and S2** (Supplementary Material). Fifteen experiments were performed, including repetitions of the central points to evaluate the experimental error. Statistical analysis of the data (95 % confidence level) employed Statistica v. 12 software (StatSoft, USA).

2.4. Sample preparation methods

2.4.1. MAE

Sample masses of 200, 300, and 400 mg were used with 5 mL of the previously prepared AADES, giving SSR of 40:1, 60:1, and 80:1 mg mL^{-1}, respectively, according to the DD (**Table S1**). The mixtures were subjected to microwave irradiation, using the following temperature

program: (i) heating during 2 min to the temperature established in the DD (**Table S1**), (ii) maintaining the temperature for the predetermined time (**Table S1**), and (iii) cooling to 50 °C. The extracts and blanks were made up to 10 mL with ultrapure water, followed by separation of the supernatants from the solid phase using quantitative filter paper.

2.4.2. UA-MSPD

Sample masses of 50, 100, and 150 mg, giving SSR of 10:1, 30:1, and 50:1 mg mL^{-1}, respectively, according to the DD (**Table S2**), were macerated in a mortar for 3 min, together with the powdered AADES (1, 2, or 3) precursors, used in this case as an abrasive solid support. The mixtures were then transferred to 50 mL conical tubes and ultrapure water was weighed and added, followed by ultrasonication in a bath at 40 kHz, for each time determined by the DD (**Table S2**). The TM and TP were set according to the DD. The blanks and extracts were then made up to 10 mL and centrifuged at 4000 rpm for 10 min. The supernatants were separated from the solid phase using quantitative filter paper.

2.4.3. Microwave-assisted acid digestion (MW-AD)

MW-AD was used as a reference method for determining the total As concentration in the samples, and as a comparative method for the proposed extraction procedures employing AADES. The sample (100 mg, n = 3) was digested in a closed vessel, using 6 mL of HNO_3 (7 mol/L) and 2 mL of H_2O_2 (30 % v v^{-1}) [47], with the following temperature program: (i) ramp to 190 °C during 10 min, (ii) hold at 190 °C during 40 min, and (iii) cooling to 50 °C. The digests were diluted to 25 mL.

2.5. ICP-MS analysis

The determination of As employed a NexION 300X ICP-MS instrument (PerkinElmer, Shelton, USA). Conventional nebulization was used, with the gas flow and torch alignment adjusted as recommended by the manufacturer. Table 1 shows the ICP-MS operating conditions. Calibration curves were prepared using a 1000 mg/L stock standard solution (Sigma-Aldrich, Missouri, USA). The calibration curves for analysis of the extracts/digests were prepared using the standards in AADES medium (1 % v v^{-1}) or HNO_3 medium (1 % v v^{-1}).

2.6. Quality assurance (QA) and quality control (QC)

The use of QA and QC procedures is a requirement for ensuring reliable results. The accuracy (% recovery) and precision (relative standard deviation, RSD%) were evaluated using the CRMs. The linearity of the calibration curves (R^2) was determined and the limits of detection (LOD) and quantification (LOQ) were calculated using the formulas 3 s/a and 10 s/a, respectively, where "s" is the standard deviation of the responses for ten analytical blanks and "a" is the slope of the analytical curve [48]. Comparison was made of the proposed sample preparation methods and the conventional method (Student's *t*-test, α = 0.05).

Table 1
ICP-MS operating conditions for As determination.

Parameter	Operating condition
Radiofrequency power (kW)	1.6
Plasma gas flow (L min^{-1})	18
Auxiliary gas flow (L min^{-1})	1.2
Nebulizer gas flow (L min^{-1})	1.0
Sample uptake rate (mL min^{-1})	0.7
Number of replicates	3
Nebulizer	Concentric
Spray chamber	Cyclonic
Isotope (*m*/*z*)	$^{75}As^+$

3. Results and discussion

3.1. Multivariate optimization of extraction procedures by Doehlert design

The 1:2:17 M ratio of β-alanine, HBD component, and water was determined as ideal in our previous work, where a restricted mixture design was applied, based on the lower density and viscosity values obtained (1.25 ± 0.01 g mL^{-1} and 7.332 ± 0.005 mPa.s for AADES 1, 1.26 ± 0.01 g mL^{-1} and 9.56 ± 0.01 mPa.s for AADES 2, and 1.21 ± 0.01 g mL^{-1} and 9.02 ± 0.29 mPa.s for AADES 3) [45]. Less viscous solvents are ideal for application in extraction procedures, because they allow greater mass transfer [49]. Furthermore, considering ICP-MS analysis, less viscous solvents are preferable as they favor the sample spray formation process in the nebulizer and, consequently, transport of the sample to the plasma [49]. In this same work, Fourier transform infrared (FTIR) spectra confirmed the formation of the AADES, since the characteristic bands of the precursor materials were maintained, with small shifts to lower wavenumbers for the AADES [45]. The FTIR spectra of AADES 1 and AADES 2 showed peak shifts from 1675 to 1629 cm^{-1}, and from 1683 to 1635 cm^{-1}, respectively, due to the increase in electron density at the carbonyl oxygen atom (C═O) of the HBDs, indicating the occurrence of hydrogen bond formation [45,50]. For AADES 3, wavenumber shifts were observed from 1431 to 1411 cm^{-1}, and from 743 to 700 cm^{-1}, related to in-plane and out-of-plane bending bands, respectively, of – OH present in the xylitol molecule [45].

The efficiency of the mass transfer process and the interaction of the analyte with the solvent is determined by the composition and physicochemical properties of the AADES, and by the sample preparation conditions, including the extraction time, temperature, and sample-solvent ratio [50]. The DD was employed to identify the optimal conditions for the MAE and UA-MSPD methods.

For optimization of the experimental conditions, recovery (%) values in the range 80–110 % (for mg kg^{-1} levels) were considered to be indicative of a satisfactory method [48,51]. AADES 1 did not show satisfactory As extraction capacity (Fig. 1**a**) for either of the proposed sample preparation methods, due to strong interaction between the HBA and HBD components, which decreased the proton donating capacity, preventing interaction between the HBD and the analyte [52]. A noteworthy point is the selectivity that these solvents present for the extraction of organic or inorganic analytes [53–55]. AADES are highly selective and modulable solvents, suggesting that the sample matrix and the characteristics of the analyte must be previously considered in determining the ideal synthesis procedure and the proportions of precursors used, in order to avoid the occurrence of unwanted effects [56,57].

AADES 2 showed acceptable accuracy (Fig. 1**b**) using both sample preparation methods (MAE and UA-MSPD), while AADES 3 showed promise when employing MAE (Fig. 1**c**). The applicability of AADES as extraction solvents is related to their ability to form hydrogen bonds between their functional groups and the analyte, by acting as Lewis acids in the presence of electron-donating groups [58,59]. Furthermore, carboxylic acid-based AADES are capable of forming a chelate complex with the analyte in its multi-charged cation form, which is more intense for AADES containing an HBD component rich in carboxyl and hydroxyl groups [59,60]. This provides an explanation for the high mass transfer and good recoveries observed for AADES 2. Given the results obtained, statistical evaluation was applied to the MAE/AADES 2, MAE/AADES 3, and UA-MSPD/AADES 2 methods.

Analysis of variance (ANOVA) was applied for the assessment of statistical significance. The use of a quadratic model resulted in satisfactory R^2 values of 0.6 (MAE/AADES 3), 0.78 (MAE/AADES 2), and 0.97 (UA-MSPD/AADES 2). The influence of the variables on the experimental response (% recovery) was assessed using the standardized effect (SE), shown in Fig. 2. No significant variable was observed for MAE/AADES 2 (Fig. 2**a**), while for MAE/AADES 3 (Fig. 2**b**), the variables TP

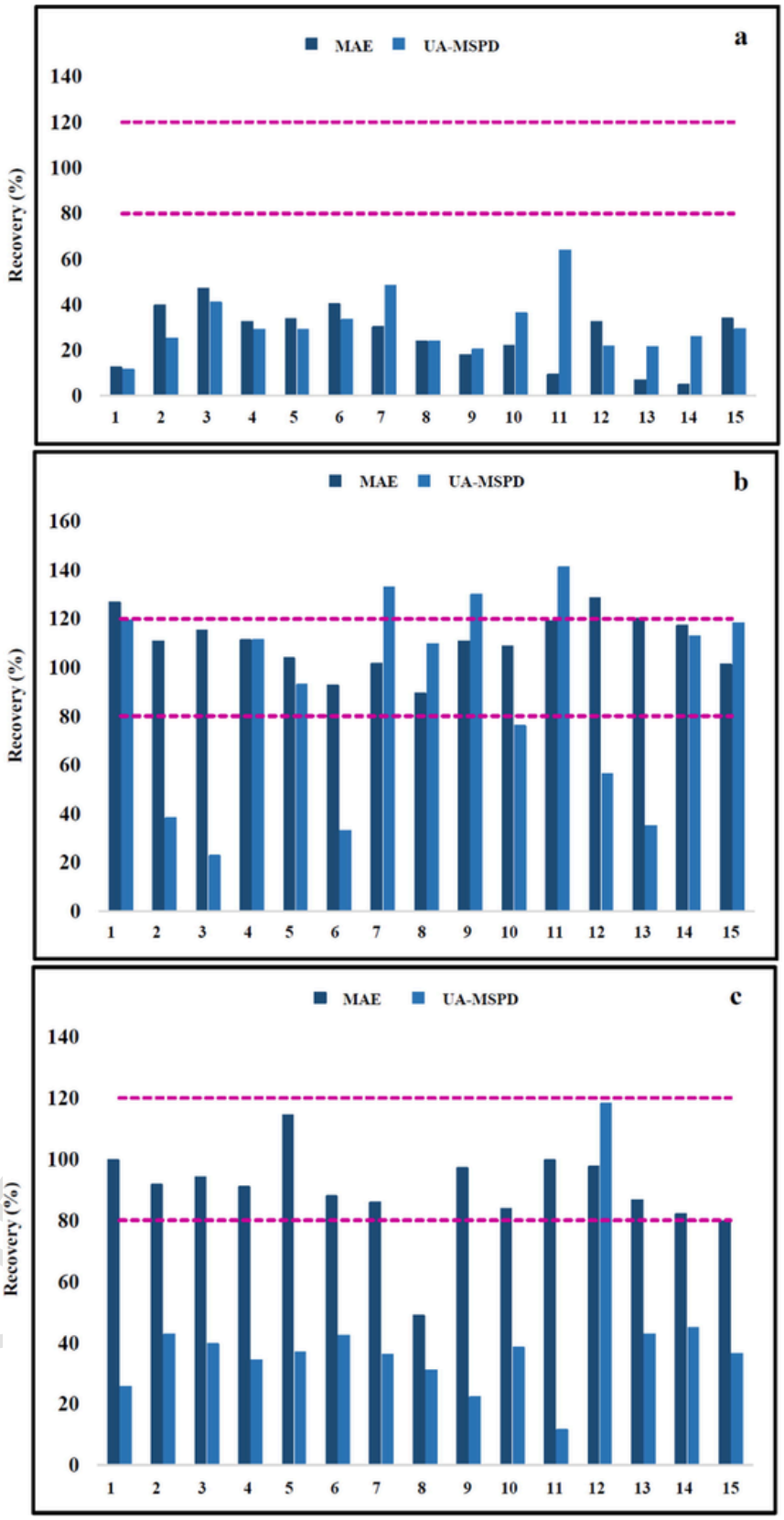

Fig. 1. Arsenic recovery (%) values after application of Doehlert design for MAE and UA-MSPD, using the extractant solvents AADES 1 (**a**), AADES 2 (**b**), and AADES 3 (**c**).

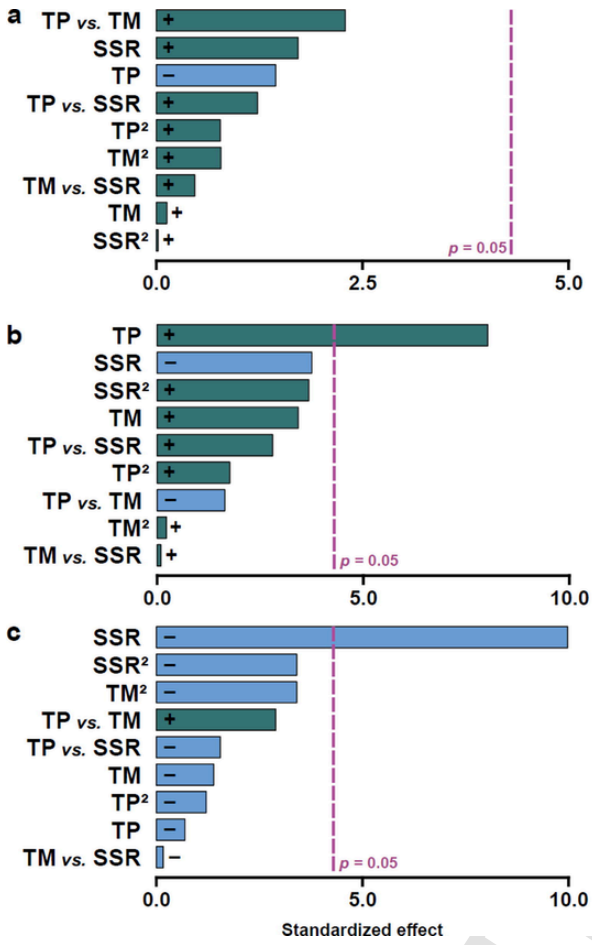

Fig. 2. Standardized effects obtained by Doehlert design in the quadratic models for MAE/AADES 2 (**a**), MAE/AADES 3 (**b**), and UA-MSPD/AADES 2 (**c**). Variables: temperature (TP), time (TM), and sample-solvent ratio (SSR).

(SE = 9.21) and SSR (SE = –4.66) were significant, with higher recoveries (%) predicted using higher TP (150 °C) and lower SSR (40:1 mg mL^{-1}). For UA-MSPD/AADES 2 (Fig. 2**c**), SSR (SE = –9.98) was significant, with the best results obtained using SSR of 10:1 mg mL^{-1}.

The contour plots confirmed the results obtained previously and delimited the optimum conditions for the application of MAE and UA-MSPD. For MAE/AADES 2 (Fig. 3**a**) and MAE/AADES 3 (Fig. 3**b**), acceptable accuracies were obtained using higher levels for TP and TM, and lower SSR. For UA-MSPD/AADES 2 (Fig. 3**c**), acceptable accuracies were obtained using lower SSR, TP of 50 °C, and TM of 60 min. Hence, the variables TP, TM, and SSR were optimized at 100 °C, 40 min, and 40:1 mg mL^{-1} for MAE/AADES 2 and MAE/AADES 3, and at 50 °C, 60 min, and 10:1 mg mL^{-1} for UA-MSPD/AADES 2.

The use of temperatures above 100 °C would be inconsistent with the ninth principle of GAC, which aims at greater energy efficiency [15]. It would also approach the degradation temperatures of the AADES, which have previously been found to be near 150 °C for AADES 2 and AADES 3 [45]. Given the complexity and high silica content of the plant tissue employed, use of a lower mass would reduce the amount of interfering matrix in the solution [61]. Furthermore, the volume of extracting solvent must be sufficient to wet all the plant material, ensuring optimal absorption and high mass transfer [62]. A higher temperature increases kinetic energy between the molecules and, consequently, reduces the viscosity and surface tension of the AADES, resulting in increased permeation of the solvent in the sample and improved solubilization of the solute [63–66]. Longer heating periods result in higher accuracy of the method, due to increased exposure of the solute to the solvent [64–66]. However, excessive exposure times at high temperatures can result in analyte degradation or loss by volatilization (in the case of volatile analytes), reducing the extraction efficiency [64].

3.2. Analytical performance

For validation of the proposed MAE and UA-MSPD methods using AADES, as well as for comparison with MW-AD, the parameters accuracy (% recovery – considering CRMs analysis), precision (RSD%), linearity (R^2), and sensitivity (slope) were determined. The conventional method (MW-AD) presented acceptable recoveries in the range from 80 to 83 % (Table 2), in agreement with other studies using closed vessels in MW-AD procedures for the preparation of plant samples, due to minimization of analyte loss by volatilization and the reduction of possible contamination [67,68]. The optimized sample preparation methods were satisfactory, with recovery values between 77 and 101 % (Table 2).

The accuracies obtained for CRMs analysis employing MAE and UA-MSPD were compared with the values for the conventional method (MW-AD). No significant differences were observed (Student's *t*-test), indicating the potential applicability of the proposed sample preparation methods, in combination with ICP-MS analysis, for the determination of As in plant tissues.

The precision (RSD%) of the method was evaluated in terms of repeatability and intermediate precision, by calculation of the ratio between the standard deviation of the responses for ten measurements of samples and the average concentration for ten measurements of blanks [51]. Lower RSD values of 15 % were obtained for MW-AD and MAE, while UA-MSPD showed RSD of 24 %.

The LOD values were 0.017, 0.015, 0.030, and 0.039 mg kg^{-1} for MW-AD, MAE/AADES 2, MAE/AADES 3, and UA-MSPD/AADES 2, respectively, while the corresponding LOQ values were 0.058, 0.0048, 0.011, and 0.13 mg kg^{-1}, respectively. In general, the LOD and LOQ values obtained for the methods using AADES as extraction solvents were lower than the values found for MW-AD, with statistically significant differences shown using ANOVA. It is known that increase of the plasma carbon content results in an increase of the analytical signal for analytes that have ionization potential between 9 and 11 eV (As = 9.79 eV), due to the occurrence of a charge transfer reaction between As and C^+, as well as other carbon species including CO^+, CO^{2+}, C^{2+}, and ArC^+ [72,84]. Hence, there is an increase of the ionization rate, due to the increased number of atoms and ions of the analyte in the excited state, resulting in an increase of the analytical signal that contributes to improved performance parameters [57,69,70].

Evaluation of the linear dynamic ranges employed As concentrations from 0.10 to 15.0 μg/L, with coefficient of determination (R^2) values above 0.999 obtained in all cases.

3.3. Comparison of DES-based sample preparation methods

The application of DES in analytical chemistry is fairly recent and poorly explored [71]. A comparison of the methods proposed here and those reported in the literature is provided in Table 3. As far as is known, there have been no previous works investigating the application of AADES in a method based on MSPD with AADES precursors as solid abrasive support, for elemental analysis of plant matrices.

The proposed MAE and UA-MSPD methods showed acceptable analytical characteristics and, unlike some of the other methods, the procedures optimized here do not require any previous steps involving prolonged heating under high temperatures [72,73], subsequent digestion by MW-AD or conventional digester block [73,74], or the addition of HNO_3 volumes greater than the DES volumes [72,74,75]. The proposed procedures are simple to perform for direct analysis by ICP-MS. Furthermore, the UA-MSPD method can be considered especially advanta-

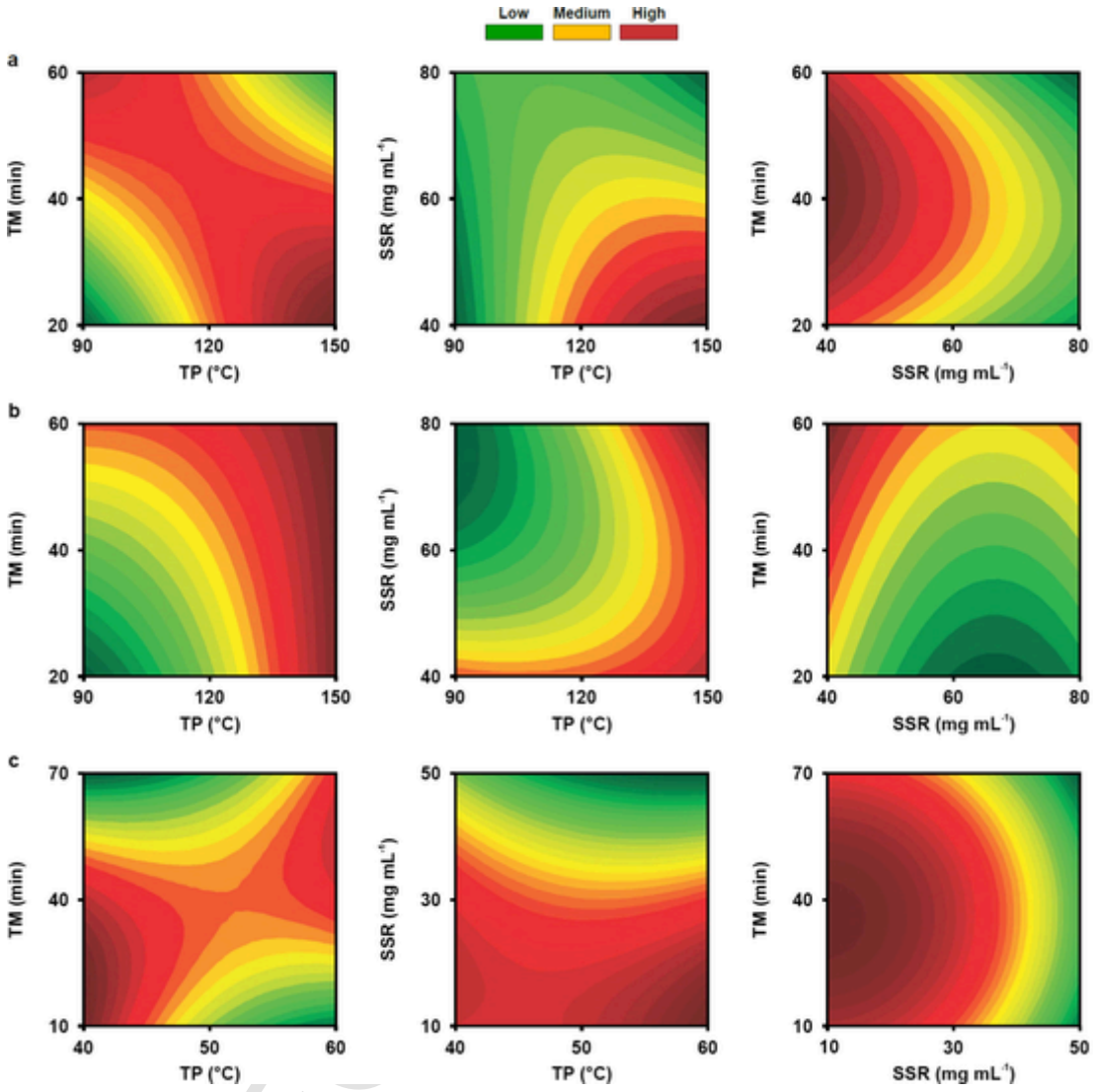

Fig. 3. Contour plots obtained by Doehlert design for the quadratic models applied to MAE/AADES 2 (**a**), MAE/AADES 3 (**b**), and UA-MSPD/AADES 2 (**c**). Variables: temperature (TP), time (TM), and sample-solvent ratio (SSR).

Table 2
Arsenic concentrations (mg kg^{-1}, mean ± standard deviation) and recoveries (%, mean ± standard deviation) using the conventional method (MW-AD) and the optimized methods (MAE and UA-MSPD) for the Marandu (EMBRAPA E1001a) and peach leaves (NIST 1474) CRMs and the commercial medicinal herb samples.

Samples		MW-AD Mean ± SD (% recovery [c])	MAE/AADES 2 [a] Mean ± SD (% recovery [c])	MAE/AADES 3 [b] Mean ± SD (% recovery [c])	UA-MSPD/AADES 2 [a] Mean ± SD (% recovery [c])
CRMs	Marandu (EMBRAPA E1001a) [d]	1.36 ± 0.056 (80 ± 1)	1.37 ± 0.023 (81 ± 1)	1.37 ± 0.032 (81 ± 2)	1.71 ± 0.284 (101 ± 16)
	Peach leaves (NIST 1474) [e]	0.050 ± 0.0016 (83 ± 3)	0.046 ± 0.0026 (77 ± 4)	0.051 ± 0.013 (85 ± 2)	0.057 ± 0.0014 (95 ± 2)
Medicinal herbs	Fennel	0.059 ± 0.0038	0.015 ± 0.0030	0.027 ± 0.0015	0.059 ± 0.0098
	Yerba mate	0.101 ± 0.0390	0.101 ± 0.0256	0.016 ± 0.0031	0.074 ± 0.026
	Lemongrass	0.043 ± 0.0031	0.011 ± 0.0035	0.0058 ± 0.0012	0.064 ± 0.014
	Chamomile	0.063 ± 0.011	0.016 ± 0.0014	0.036 ± 0.0010	0.059 ± 0.0063

[a] AADES 2 (β-alanine:citric acid:water); [b] AADES 3 (β-alanine:xylitol:water); [c] Recoveries (%) obtained for CRMs analysis; [d] Certified value = 1.69 mg kg^{-1}; [e] Certified value = 0.06 mg kg^{-1}.

geous, compared to other techniques, as it does not require a previous solvent synthesis step, which considerably reduces the total time required for analysis (DES synthesis and sample preparation time), representing an increase in energy efficiency, in agreement with the principles of GAC [15,75–79]. The total time for As determination by UA-MSPD was 60 min, while for other methods it was up to 165 min [56–58]. The fastest methods found were applied using a large volume of HNO_3 (7 mL) after extraction with DES [72] or using MAE [80], with high costs associated with the acquisition of equipment and electric energy consumption. The UA-MSPD method also stands out in relation to other MSPD methods for As determination using DES as eluting solvent, as it was not necessary to use any other dispersing adsorbent, only the AADES precursors [37–42].

Table 3
Analytical comparison of methods reported in the literature using DES as extracting solvents for determination of elements in different matrices.

Elements	Matrix (sample mass, mg)	Method	DES (volume, mL)	Extraction time (min)	Analytical technique	LOQ (μg kg^{-1})	Recovery (%)	Ref.
As, Ca, Cd, Cr, Cu, Fe, K, Mg, Mn, Na, P, and Zn	Mineral supplement and rock phosphate (100)	UAE	CA-XY; CA-MA (9)	45	ICP-MS ICP OES	n/a[a]	81–120	[56]
As, Cd, and Pb	Plant tissue (90)	UAE	CA-XY; MA-XY; CA-MA (9)	45	ICP-MS	0.013–8.71	90–225	[57]
As, Ca, Cd, Cu, K, Mg, Mn, Na, and P	Plant tissue (90)	UAE	CA-XY; MA-XY; CA-MA (9)	45	ICP-MS ICP OES	n/a[a]	70–114	[58]
Cd	Rice (300)	UAE	ChCl-XY (2)	60	GF AAS	n/a[a]	90	[73]
As, Cr, Mo, Sb, Se, and V	Soil (100)	UAE	ChCl-OX (10)	5	ICP OES	0.03–0.3	98–102	[75]
As, Cd, and Pb	Plant tissue (90)	MAE	CA-XY; MA-XY; CA-MA (9)	20	ICP-MS	0.0051–7.98	92–127	[57]
Cu, Fe, Ni, and Zn	Marine biological (100)	MAE	ChCl-OX (2.5)	20 s	ICP OES	n/a[a]	96–98	[72]
Cu, Mn, Mo, and Zn	Plant tissue (50)	Vortexing	ChCl-CA; ChCl-GLU; ChCl-GLY; BET-CA; BET-GLU; BET-GLY; ALA-CA (2)	30	ICP-MS/MS	0.5–1.5	48–131	[74]
As and Cd	Fish and shellfish tissue (90)	UAE	MA-XYL (9)	45	ICP-MS	12.7 and 0.1	85–120	[76]
Co, Cu, Mn, Mo, and Zn	Plant tissue (50)	Vortexing	ChCl-GLY; ChCl-EG; ChCl-EG-BET; ChCl-MA; ChCl-CA; ChCl-FRU; CA-FRU; ChCl-GLU; ALA-MA (1)	30	ICP-MS	0.05–1.2 μg/L	90–103	[77]
Cd, Cu, Fe, Mn, and Zn	Plant tissue (150)	MAE	ChCl-OX (3)	35 s	ICP OES	0.02–1.10 (mg kg^{-1})	87–109	[80]
As	Plant tissue (200)	MAE	ALA-CA; ALA-XY (5)	40	ICP-MS	0.0048–0.011 (mg kg^{-1})	77–83	This study
As	Plant tissue (50)	UA-MSPD	ALA-CA (5)	60	ICP-MS	0.130 (mg kg^{-1})	95–101	This study

Ultrasound-assisted extraction (UAE), microwave-assisted extraction (MAE), ultrasound-assisted matrix solid-phase dispersion (UA-MSPD), graphite furnace atomic absorption spectrometry (GF AAS), inductively coupled plasma mass spectrometry (ICP-MS), inductively coupled plasma optical emission spectrometry (ICP OES), citric acid (CA), xylitol (XY), malic acid (MA), choline chloride (ChCl), oxalic acid (OX), glucose (GLU), glycerol (GLY), betaine (BET), ethylene glycol (EG), fructose (FRU). [a] Not informed (n/a).

3.4. Greenness assessment

The sustainability characteristics of the sample preparation methods were evaluated using the Analytical Eco-Scale [81] and the RGB model [82]. The Analytical Eco-Scale is applied to assess whether a method complies with the GAC principles, with penalty points being subtracted from a total value of 100, based on the following parameters: reagent volume multiplied by its potential risk; safety to man and the environment; instruments used in sample preparation and analysis; electricity consumption; occupational risk; and generation of chemical residues [81]. For MW-AD, a score of 76 was obtained, resulting from penalties related to the use of HNO_3 and H_2O_2 (8 points), acid steam generation (3 points), acid residue generation (3 points), safety (2 points), and use of ICP-MS (1 point). A score of 92 points was obtained for MAE, with penalties associated with the use of AADES (1 point), biodegradable waste generation (4 points), energy expenditure per sample (2 points), and use of ICP-MS (1 point). For UA-MSPD, 94 points were obtained, with deductions due to the use of AADES (1 point), biodegradable waste generation (4 points), and use of ICP-MS (1 point). In this approach, a score higher than 75 points indicates an excellent green analysis, while values close to 100 reflect near-ideal sustainability.

The RGB model is based on the White Analytical Chemistry (WAC) concept, using the primary colors red, green, and blue (RGB), in addition to considering the GAC principles [83]. In evaluation of the white characteristics of a procedure, the red color considers attributes inherent to analytical efficiency, namely the parameters necessary for validation (accuracy, precision, LOD, and LOQ). The green color is related to compliance with the principles of GAC (considering the toxicity of reagents, impacts on humans and the environment, consumption of reagents/energy, and waste generation). The blue color represents the practical and economic efficiency of the procedure, considering the factors cost, time, and operational simplicity [82]. For the application of this tool, values from 0 to 100 are assigned to each parameter evaluated using the WAC approach, individually considering the sample preparation methodologies, as explained by Nowak et al. [83], where obtaining a score close to the maximum value represents high compliance with the WAC principles, so the method could be considered as being completely acceptable for the desired application [83].

The RGB model results for each sample preparation method are shown in Fig. 4. The lowest score was obtained for MW-AD (77 points), due to factors related to reagent toxicity, generation of harmful residues, and higher sample consumption, in addition to high cost and a

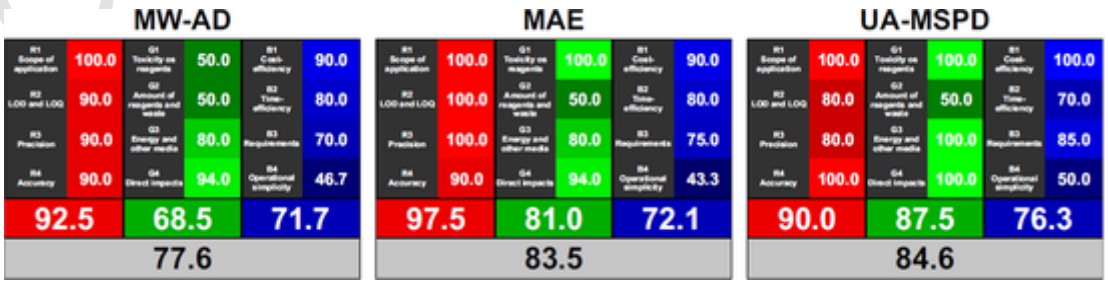

Fig. 4. Greenness comparison of the MW-AD, MAE, and UA-MSPD methods, based on application of the RGB model.

long process. The Analytical Eco-Scale indicated that the UA-MSPD method was most advantageous (84 points), despite a long execution time and higher LOD and LOQ values (although they were nonetheless completely acceptable). The MAE method (83 points) presented disadvantages in terms of high cost, a long process time, and greater sample consumption.

The differences between the scores obtained for the MAE and UA-MSPD methods were mainly related to energy expenditure, since the use of microwaves requires energy consumption higher than 1.5 kWh/sample, while an ultrasonic bath requires 0.1 kWh/sample, as well as to the cost of the necessary instruments, since an ultrasonic bath is a much cheaper option.

Considering the costs of precursors and also the consumption of electricity for the synthesis of AADES and for the proposed sample preparation methods (always considering 5 mL of AADES), it was possible to calculate total expenses of USD $1.14/sample for application of MAE/AADES 2, USD $1.75/sample for MAE/AADES 3, and USD $0.79/sample for UA-MSPD/AADES 2, where the low values reflected the fact that no energy expenditure was required for synthesis of the AADES. For MW-AD, total expenditure of USD $2.22/sample was obtained, due to the consumption of energy by the microwave (USD $0.17/sample) and the cost of the reagents used (USD $3.20/sample for 6 mL of HNO_3 and 2 mL of H_2O_2). The results highlighted the advantage of using AADES, in terms of cost reduction, especially for the UA-MSPD methodology, which proved to be most economical. These costs per sample were calculated considering the values (in Brazilian reals) of the reagents obtained from Sigma-Aldrich, as well as the electricity tariff for São Paulo, Brazil.

3.5. Application of the methods and risk assessment of the presence of as in medicinal herb samples

Table 2 shows the As concentrations measured in commercial fennel, yerba mate, lemongrass, and chamomile herbs, obtained to validate the optimized MAE and UA-MSPD methods, as well as the values obtained by MW-AD. The results using MW-AD were in agreement with those using UA-MSPD/AADES 2 for fennel, yerba mate, and chamomile, as well as using MAE/AADES 2 for yerba mate. The disparities observed for the other results could have been due to differences in the sample matrices (yerba mate are stems, lemongrass are grasses, chamomile are dried flowers, and fennel are seeds), the different AADES employed, and the sample preparation methods. The MW-AD method promotes mineralization of the sample by the acid and the auxiliary oxidizing agent, under high temperature and pressure [16]. The other extraction methods are performed under milder conditions, at lower temperature, while the UA-MSPD procedure is performed at ambient pressure [16].

The maximum permissible concentration limit established by ANVISA and MERCOSUL regulations is 0.60 mg kg^{-1} for As in herbs, yerba mate, and other plant tissues used for infusions. The As concentrations in the medicinal herb samples evaluated in the present work, determined by the MW-AD method, were below this limit, reaching 16 % of the maximum limit for yerba mate, 10 % for fennel and chamomile, and only 6 % for lemongrass.

The values obtained were in agreement with other studies investigating the presence of As in herbs used for infusions. Oliveira et al. [84] obtained an average of 0.21 ± 0.03 mg kg^{-1} for As in different herbs. Milani et al. [4] found 0.107 and 0.062 mg kg^{-1} for As in chamomile and yerba mate, respectively, and in earlier work reported 0.42 mg kg^{-1} for As in different leaves (including flowers and fruits) [85]. The As concentrations determined by the MW-AD method were used to calculate the potential risk posed by ingestion of As present in the medicinal herbs (**Eq. (1)**:

$$TMI = C \times \frac{R}{BW} \quad (1)$$

where, TMI is the tolerable monthly intake (μg kg^{-1}), C is the concentration of As in the infusion (μg L^{-1}), R is the average monthly infusion intake (L $month^{-1}$), and BW is the average body weight of an adult person (70 kg).

After the infusion process, the average percentage of the analyte extracted to the aqueous phase is around 20 % [86]. The average daily consumption of medicinal herb infusions by an adult person is approximately 263 mL, giving an R value of 7.9 L [87]. Hence, the calculated intakes of As were about 0.010 μg kg^{-1} for fennel herb, 0.017 μg kg^{-1} for yerba mate, 0.0038 μg kg^{-1} for lemongrass, and 0.0057 μg kg^{-1} for chamomile. The WHO has established a monthly reference dose limit for As of 3.0 μg kg^{-1}. Therefore, the As intake levels resulting from the daily consumption of these commercial medicinal herbs could be considered safe [88].

4. Conclusions

Ultrasound-assisted matrix solid-phase dispersion (UA-MSPD) and microwave-assisted extraction (MAE) were applied together with AADES for determination of As in medicinal herbs. Doehlert designs were used to optimize the conditions for application of these methods (60 min and 10:1 mg mL^{-1} for UA-MSPD, and 100 °C, 40 min, and 40:1 mg mL^{-1} for MAE). The techniques complied with the principles of the GAC, as confirmed by evaluation using the Analytical Eco-Scale and RGB 12 methodologies, providing high extraction efficiencies (77–101 %) and low limits of detection and quantification (0.015–0.039 and 0.0048–0.13 mg kg^{-1}, respectively). For the medicinal herbs evaluated, As concentrations above the WHO daily intake limit were not observed. The UA-MSPD method is highlighted as an innovative and advantageous methodology that dispenses with the AADES synthesis step, consequently facilitating the operation and reducing the time and costs for sample preparation.

CRediT authorship contribution statement

Taciana G.S. Guimarães : Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft. **Floriatan Santos Costa :** Methodology, Writing – original draft. **Iohanna M.N.R. Menezes :** Methodology, Writing – review & editing. **Ana P.R. Santana :** Writing – review & editing. **Daniel F. Andrade :** Writing – review & editing. **Andrea Oliveira :** Writing – review & editing. **Clarice D.B. Amaral :** Writing – review & editing. **Mario H. Gonzalez :** Conceptualization, Supervision, Project administration, Funding acquisition, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.molliq.2023.121801.

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