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Investigation of midazolam electro-oxidation on boron doped diamond electrode by voltammetric techniques and density functional theory calculations: Application in beverage samples

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ABSTRACT

Midazolam (MID) is a sedative drug which can be added in beverage samples as drug-facilitated-sexual assault (date rape drug). This type of drug has short half-life in biological fluids (not detectable) which often prevents the correlation between drug abuse and crime. In this work, we described a simple and low-cost method for fast screening and selective determination of MID in beverage samples (vodka, whiskey and red wine). For the first time, the electrochemical oxidation of MID was used for this purpose. The oxidation mechanism was studied using electrochemical techniques (cyclic and square-wave voltammetry) and computational simulations (density functional theory calculations). Differential-pulse voltammetry, boron-doped diamond electrode (BDDE), and Britton-Robinson (BR) buffer (pH = 2) were selected as electrochemical analysis technique, working electrode and supporting electrolyte, respectively. Different linear response ranges (4–25 μmol L^{-1} with r = 0.9972; 1–10 μmol L^{-1} with r = 0.9951; 1–15 μmol L^{-1} with r = 0.9982) and limits of detection (0.46, 0.43 and 0.33 μmol L^{-1}) were obtained for the analysis of vodka, whisky, and red wine solutions, respectively. The precision and accuracy were satisfactory considering the low relative standard deviation values (RSD < 6.3%, n = 15) and minimal sample matrix effects (recovery values between 87 and 103%).

1. Introduction

Midazolam (MID) or 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo [1,5-a] [1,4]benzodiazepine (CAS number: 59467-70-8) is an imidazobenzodiazepine commonly used as tranquilizer, sedative hypnotic and anticonvulsant drug [1,2]. MID differs from other benzodiazepines due to its fast absorption and solubility in aqueous solutions, which enables its use in many types of beverage samples [2] as a facilitated-sexual or date rape drug [3,4]. MID has a synergic effect when it is consumed with alcohol, enhancing its sedative, hallucination and memory loss effects and, as result, the victims do not remember the events and can be exposed to sexual assaults or robbery [5,6]. In addition, this type of drug and its metabolites have short half-life in the human body, which makes difficult the detection of MID in biological samples to find evidence of criminal activities [7]. In this case, the determination or rapid screening of MID in beverage samples becomes an alternative evidence in crime investigation [4].

Some analytical techniques, such as high performance liquid chromatography [8,9], gas chromatography [3,4], spectrophotometry [10,11], capillary electrophoresis [12] and micellar electrokinetic capillary chromatography [13,14] have been employed for MID determination. However, these methods commonly involve high cost instrumentation, time-consuming, use of organic solvents and present difficulties for use on-site. Electrochemical methods are attractive for determination of MID, because of their fast response, high sensitivity, low cost, minimal sample manipulation and potential for portable forensic applications [15]. Electrochemical methods were also explored for the determination of MID. In 1987, the electrochemical behavior of MID was studied for the first time by Vire and Patriarche [16]. In this work, differential-pulse polarography was selected to quantify of MID by its electrochemical reduction in standard solutions. Afterwards, other electrochemical methods were also reported to determine MID [2,17–26] through electrochemical reduction of the azomethine group. However, according to our knowledge, the electrochemical oxidation of MID has not been shown before. In recent years, boron-doped diamond electrode (BDDE) has been attractive in the development

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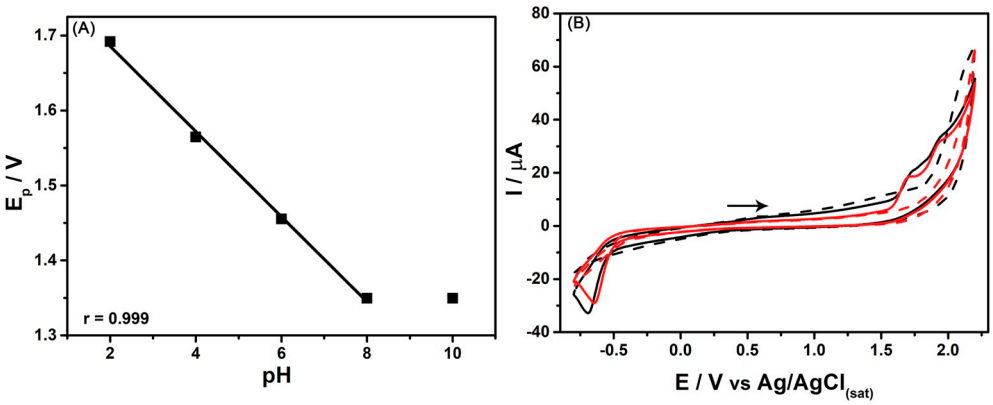

Fig. 1. (A) Relation between pH and peak potential (E_p) of electrochemical oxidation of MID in 0.12 mol L^{-1} BR buffer (pH adjusted with NaOH) using cyclic voltammetry and cathodic pre-treatment BDDE; **(B)** Cyclic voltammograms obtained for 1 mmol L^{-1} MID in 0.12 mol L^{-1} BR buffer (pH = 2.0) after anodic (black line) and cathodic (red line) pre-treatments of the BDDE and respective blank signals (dashed lines). Concentration of MID: 1 mmol L^{-1}; scan rate: 50 mV s^{-1}; step potential: 5 mV.

electroanalytical methods due to its attractive properties such as low and stable background current, favorable electron-transfer kinetics, wide potential window (especially in anodic potentials), surface inertness and robustness. These characteristics have been explored with great success in the last years [27,28].

Biological and chemical parameters, such as electronegativity and molecular electrostatic potential distribution of redox processes of organic molecules can be predicted using computational chemistry techniques [29]. Furthermore, the energy of the frontier orbitals (HOMO and LUMO) can be calculated and its values used to evaluate redox reaction kinetics [30,31]. Between all existent methods to perform theoretical calculations, density functional theory calculations represent a good choice due to its accurate level and low cost to calculate molecular parameters. In this work, electrochemical techniques and theoretical calculations were applied to investigate for the first time the oxidation mechanism of MID. Moreover, the attractive characteristics of BDD electrodes were used to develop a portable, rapid, and on-site method for fast screening and determination of MID in alcoholic beverages.

2. Experimental

2.1. Reagents and samples

Midazolam (MID) standard (99%, w/w) was received from Cristalia Laboratory (Itapira, SP, Brazil). Boric acid (99.8%, w/w) and sodium hydroxide (99%, w/w) were obtained from AppliChem Panreac (Barcelona, Spanish). Acetic acid (99.7%, w/v), phosphoric acid (85%, w/v) and ethanol (99.8%, w/v) from Synth (Diadema, SP, Brazil). Clonazepam (99%, w/w) and Diazepam (99%, w/w) from Pharma Mostra (Campinas, Brazil) and Flunitrazepam (99%, w/w) from Sigma Aldrich (Germany). All solutions were prepared with deionized water (Millipore Direct-Q3) with a resistivity not less than 18 Ω cm. All reagents were used without further purification.

Britton–Robinson (BR) buffer 0.12 mol L^{-1} (pH 2.0 to 10.0) was composed of a mixture of 0.04 mol L^{-1} acetic, boric and phosphoric acids. The pH of BR solutions was adjusted with 1.0 mol L^{-1} sodium hydroxide solution. Standard stock solutions of MID were prepared by dissolution in water. The alcoholic beverages (vodka, whisky, wine, and beer) were obtained from local supermarkets. Table S1 presents more information about the analyzed beverages. Before analysis, the samples were only diluted in supporting electrolyte.

2.2. Instruments and apparatus

Electrochemical measurements were performed employing a PGSTAT 128 N potentiostat (Metrohm Autolab B.V.) controlled by NOVA 1.11 software. As reference and auxiliary electrodes, a mini Ag/AgCl saturated with KCl [32] and a platinum wire were employed, respectively. The working electrode consisted of a thin film of BDD (1.2 μm of thickness) with a doping level of around 8000 ppm deposited on a polycrystaline silicon wafer (0.7 × 0.7 cm) with 1 mm of thickness (NeoCoat SA, La Chaux-de-Fonts, Switzerland).

Every day, before using of the BDDE, the material was electrochemically pretreated by applying +0.01 A for 1000 s in 0.04 mol L^{-1} Britton-Robinson buffer solution (anodic pretreatment). In a second step, −0.01 A was applied for 1000 s in 0.1 mol L^{-1} H_2SO_4 solution (cathodic pretreatment) prior to the electrochemical measurements. All results presented in the proposed work were performed without removal of the dissolved oxygen and at room temperature.

2.3. Molecular electronic structure calculations

The molecular orbital energies were calculated using the theoretical model composed by the hybrid functional B3LYP [33] and the base set 6-311G++ [34] using G09 software (Gaussian, Inc., Wallingford CT, 2016). The geometries were minimized to guarantee the more stable structures by confirming that there are no negative frequencies and this procedure was followed by single point and NBO (Natural Bonding Orbitals) calculations [35,36].

3. Results and discussion

3.1. Electrochemical behavior of midazolam

Initially, the electrochemical behavior of MID was investigated in 0.12 mol L^{-1} Britton Robinson buffer (BR, pH = 2.0–10.0) by cyclic voltammetry using BDDE as the working electrode (Fig. 1A). It was observed that MID exhibits two oxidation peaks at around +1.7 and + 2.0 V and one reduction peak at −0.6 V (Fig. 1B). Both oxidation and reduction processes are independent because both oxidation peaks (+1.7 and + 2.0 V) were observed in an independent anodic scan (0.0 to +2.1 V) and the reduction peak in an independent cathodic scan (0.0 to −0.8 V). These results (not shown) also indicate that both electrochemical processes are irreversible (without reduction peak in the reverse cathodic scan and without oxidation peak in the reverse anodic scan). The electrochemical reduction process of MID was previously explored by other authors which associated this process with the irreversible reduction of the C=N group generating hydroxylamine as an intermediate in this reaction, such as others 1,4-benzodiazepines molecules described in the literature [19,20,37,38]. On the other hand, to our knowledge, this is the first time that the electrochemical oxidation of MID was achieved. The best results (peak shape and current intensity) were obtained using BR buffer 0.12 mol L^{-1} (pH = 2.0) as the supporting electrolyte (Fig. 1B). The electrochemical oxidation of MID was studied after anodic and cathodic surface pre-treatments of the BDDE. The results obtained with BDDE showed more defined oxidation peaks at +1.69 V and +1.93 V (Fig. 1A) after both anodic and cathodic

pre-treatments. These procedures were carried out at the beginning of each workday. Other conditions (first cathodic and then anodic or just one of them) were also tested, but without greater success. Thus, both anodic and cathodic pre-treatments (in this sequence) and the supporting electrolyte composed of BR buffer 0.12 mol L^{-1} (pH = 2) were used in subsequent studies. As this is the first report on the electrochemical oxidation of MID, there is no information available in the literature about the electrochemical reaction for this process, which was the motivation to investigate and propose a mechanism.

It was demonstrated that the oxidation peak of MID is linear pH-dependent from 2.0 to 8.0 (Fig. 1A), with a slope of 56.8 mV pH^{-1}, indicating that the mechanism of the electrochemical oxidation of MID involves the transfer of equal number of electrons and protons [38,39]. In the following studies, the cyclic voltammetric technique was replaced by square-wave voltammetry because better peak shapes were obtained with this technique under the selected experimental conditions (oxidation peak in the presence of high background current). Fig. S1A (supplementary material) shows the effect of the frequency (10 - 70 s^{-1}) on square wave voltammograms of a solution containing 50 µmol L^{-1} of MID. Fig. S1B (supplementary material) showed that the plot of square root of frequency and current peak was linear (r = 0.998), which indicates a diffusion-controlled oxidation process [40,41]. The increase in potential values with the increase of f (Fig. S1C; supplementary material) is also indicative of the irreversible behavior of the oxidation process of MID. This result is in agreement with the results obtained by cyclic voltammetry (Fig. 1B). For irreversible electrochemical processes, the plot of E_p *vs.* log f (Fig. S1D; supplementary material) can be used to estimate the number of electrons involved in the oxidation process, considering the Lovric equation [40]:

$$\frac{E_p}{\log f} = -\frac{2{,}3RT}{\alpha nF}$$

where F is the Faraday's constant, T the temperature, R the universal gas constant, n the number of electrons involved in the redox process, α the coefficient of electron transfer and E_p the peak potential. Therefore, assuming a value of $\alpha = 0.5$, as described for organic molecules with irreversible electrode processes [42], the number of electrons involved in the electrochemical oxidation of MID was calculated as 1. A summary of parameters calculated from data of Fig. S1 is available in Table 1.

According to these results, a mechanism for the electrochemical oxidation of MID was proposed at the BDDE electrode in BR buffer (pH = 2). The oxidation of MID probably occurs at the imidazole group, involving the transfer of one electron and one proton, yielding a cation radical (Fig. 2), which may undergo rapid dimerization of imidazole radical group as described by other authors [39,43,44].

3.2. Molecular modeling of MID

In order to obtain additional mechanistic insights on the electrochemical oxidation of MID, computational simulations based on density functional theory calculations were carried out. The theoretical model was used to calculate the total energies and the natural bond orbital (NBO) interactions. Table 2 shows the calculated energies of MID and of possibly radicals formed in its electrochemical oxidation. Fig. 3 shows the structures of the two possible radicals (RAD1 and RAD2).

As can be seen in Table 2, the total energy values show that the RAD1 (Fig. 3A) is more stable than RAD2 (Fig. 3B) by an amount of almost ~31.643 kcal mol^{-1} (1 Hartree = 627.51 kcal mol^{-1}). These results show that the proposed mechanism for the electrochemical oxidation of MID (through the formation of RAD1) is in accordance with the calculated energy values.

There are two possibilities of the radical formation in the MID structure and the calculation of total energy analysis predicts that the formation of RAD1 is preferable. Additionally, NBO analysis can be used to provide useful information about the stabilization of this structure. In the case of RAD1, the interactions between N20-C21 and N20-C23 stabilize the structure by 13.23 kcal mol^{-1} and 6.94 kcal mol^{-1}, respectively. These interactions involve bond orbitals of N20-C21 pair and antibonding orbitals located C1-C2 and C21-C22, among others. On the other hand, the bond N18-H7 stabilize the structure of RAD1 by 3.81 kcal mol^{-1} and the bond N20-H5 present in the RAD2 stabilizes its structure by an amount of 6.15 kcal mol^{-1}. For this amount only, the RAD2 is more stable than RAD1. However, the interactions between N18-C7 and N18-C8 stabilize the RAD2 structure by 6.32 kcal mol^{-1} and 8.06 kcal mol^{-1}, respectively (there are interactions with antibonding orbitals of C2-N17 or C3-C4 among others). Hence, considering only the interactions involving the N atoms, RAD1 is more stable than RAD2 by an amount of 3.45 kcal mol^{-1}, which represents more than 10% of the energy stabilization of RAD1 compared to RAD2.

Table 1
Parameters obtained from data shown in Fig. S1.

Parameters	I_p vs $\sqrt{f}$	E_p vs log f
r	0.9993	0.9956
Intercept	−0.345 ± 0.076 µA	1.4924 ± 0.00631 V
Slope	0.7133 ± 0.0128 µA $s^{-0.5}$	0.08931 ± 0.0042 V

3.3. Determination of MID in beverage samples

To obtain a better analytical performance, some parameters of the DPV technique (modulation amplitude, modulation time, and step potential) were optimized. The optimal values were chosen based on their effects on the voltammetric characteristics for MID detection, such as current response, peak shape, speed of analysis and sensitivity. Table S2 (supplementary material) presents the studied ranges and the selected optimal values used in subsequent studies.

Next, linear response ranges of the BDDE for MID determination were evaluated using standard (aqueous media) and alcoholic sample solutions (vodka, whisky, and red wine) spiked with MID (matrix-matched analytical curves). The analytical characteristics obtained from these studies are shown in Table 3. The limit of detection (LOD) was calculated using IUPAC definition as 3σ/s, in which σ corresponds to the standard deviation of baseline noise and s to the slope of the analytical curve.

As can be seen in Table 3, better slope and LOD values were obtained for MID in aqueous media (standard solutions). However, wider linear ranges were achieved for MID in sample solutions. According to the literature, the presence of ethanol in sample solutions can cause two phenomena, the reduction of the sensitivity (slope) due to the increase in the electrical resistance of the electrolyte (smaller dielectric constant of ethanol than water) [45–47], and delay or prevention of contamination of the BDDE surface (resulting in wider linear ranges) [48]. Probably, in the absence of ethanol (standard solutions), the partial blockage of the electroactive area of the BDDE already occurs in lower concentrations of MID. These results also indicate that the standard addition method need to be used for the determination of MID in the target beverage samples (due to the varied ethanol content).

In the next study, the stability and detectability of MID in the target beverage samples were evaluated. Table S3 (supplementary material) shows RSD values obtained for successive measurements of samples solutions (n = 3) diluted in supporting electrolyte under different volumetric ratios (1:10; 1:20; 1:50; 1:75; 1:100) in order to evaluate the effect of sample matrix. For all samples, no signals were observed after addition of MID (20 µmol L^{-1}) when the dilution of 1:10 (v/v) was used (decrease in the sensitivity). In the case of vodka samples, better results, in terms of sensitivity and stability (RSD < 3.1%; 20 µmol L^{-1}), were obtained with 20-fold diluted samples. The results found for the determination of MID in vodka samples are in agreement with those obtained in the determination of drug of abuse 4-hydroxybutanoic acid

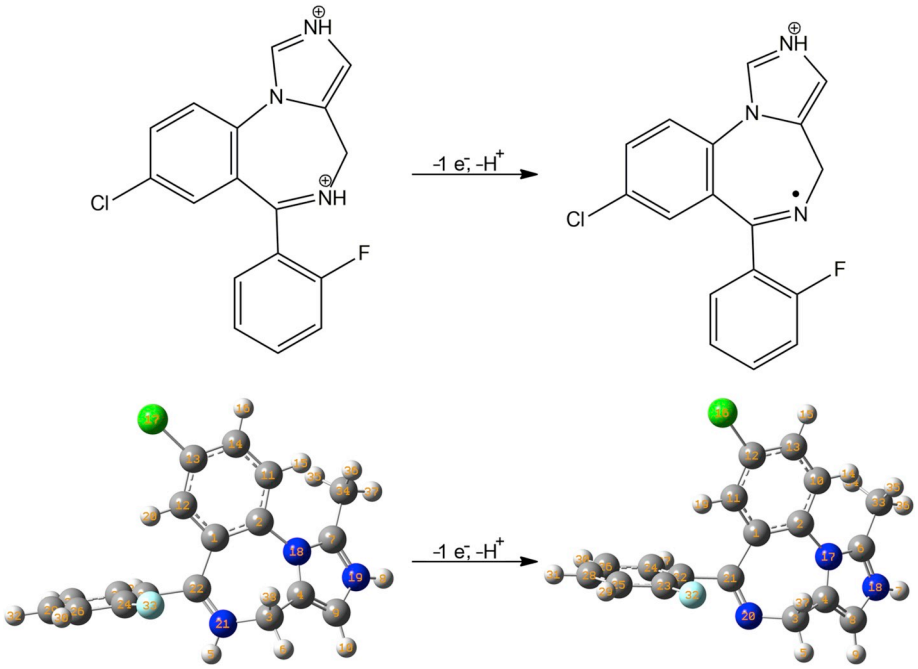

Fig. 2. Proposed mechanism of the electrochemical oxidation of MID using BR buffer (pH = 2) as the supporting electrolyte and BDD as the working electrode. Spheres: green (chlorine); white (hydrogen); gray (carbon); blue (nitrogen); cyan (fluorine).

Table 2
Total energy values of MID and of two possible radicals calculated by density functional theory.

Molecule	Total Energy (Hartree)
MID	−1418.6108063
RAD1	−1417.9434163
RAD2	−1417.8929891

(GHB) in vodka samples [49]. On the other hand, whisky and red wine samples presented more complex matrices and satisfactory results were only obtained when both samples were 100-fold diluted (Table S3). Probably, the matrix effect caused by the presence of other electroactive compounds was only minimized in this condition. Whisky is a distilled alcoholic beverage obtained from fermented cereals (barley, wheat, and rye) which typically contains in its composition phenolic compounds, different alcohols (1-propanol, isobutanol, ethylic alcohol, etc.) and sugars [49–51]. Red wine contains polyphenolic antioxidants (phenolic acids, flavanols, anthocyanins, oligomeric and polymeric proanthocyanins) and tartaric acid, which are described as electroactive molecules on carbon electrodes [52,53].

After selecting the best dilution rate for each sample, the standard addition method was used to quantify MID in three spiked beverage samples (vodka, whisky and red wine). Fig. 4 shows the DPV voltammograms and respective calibration curves obtained in the determination of MID. Table 4 summarizes the results obtained in the study.

As seen in Table 4, the recovery values (87–103%) demonstrated that the proposed method exhibited acceptable accuracy and is free from interference of sample matrices. Recovery studies were also carried out with beer samples spiked with MID. However, for beer samples, recovery values lower than 50% were obtained for all tested samples. In next step, the precision/stability of the proposed method was reassessed by successive analysis (n = 15) of a standard and three sample solutions (vodka, whisky and red wine) spiked with MID. The obtained RSD values were 3.5%, 6.3%, 4.4% and 4.9%, respectively. Finally, the performance of the proposed method was evaluated for fast screening of MID in different beverage samples. The addition of MID in beverage samples is prohibited and a simple and low-cost traceability procedure is very important [54]. Fig. S2 shows DP voltammograms obtained for 12 different beverage samples (3 wine samples, 2 vodka samples, 2 whisky samples, and 5 beer samples) before and after addition of MID (50 μmol L^{-1}). The detection of the presence of MID was possible in all

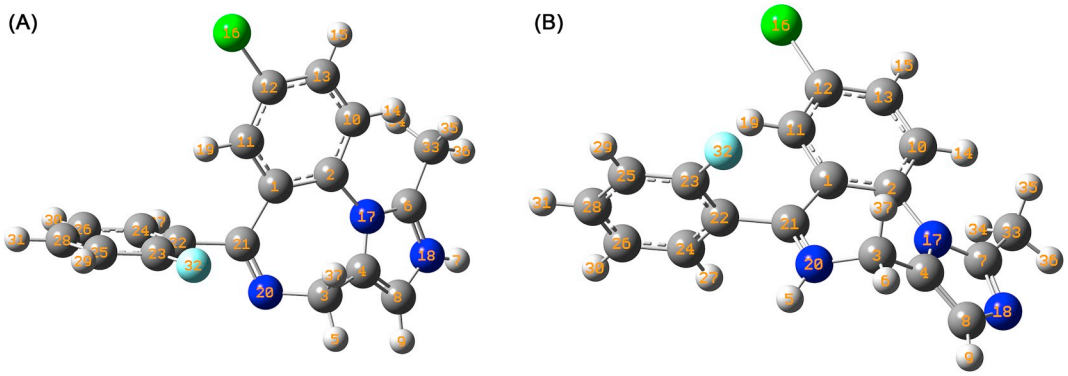

Fig. 3. Radical structures showing the Nitrogen atoms where the radical was placed to perform the calculations. (A) RAD1 and (b) RAD2. Spheres: green (chlorine); white (hydrogen); gray (carbon); blue (nitrogen); cyan (fluorine).

Table 3
Comparison between analytical characteristics obtained for the detection of MID in standard and beverage sample solutions both prepared in supporting electrolyte.

Analytical characteristics	Samples			
	Standard solution	Vodka	Whisky	Red wine
r	0.9913	0.9972	0.9951	0.9982
Slope/μA L μmol^{-1}	0.342 ± 0.042	0.038 ± 0.002	0.116 ± 0.0006	0.065 ± 0.002
Intercept/μmol L^{-1}	0.476 ± 0.082	0.057 ± 0.023	−0.0645 ± 0.0048	−0.002 ± 0.0003
Linear range/μmol L^{-1}	1–3	4–25	1–10	1–15
LOD/μmol L^{-1}	0.074	0.46	0.43	0.33

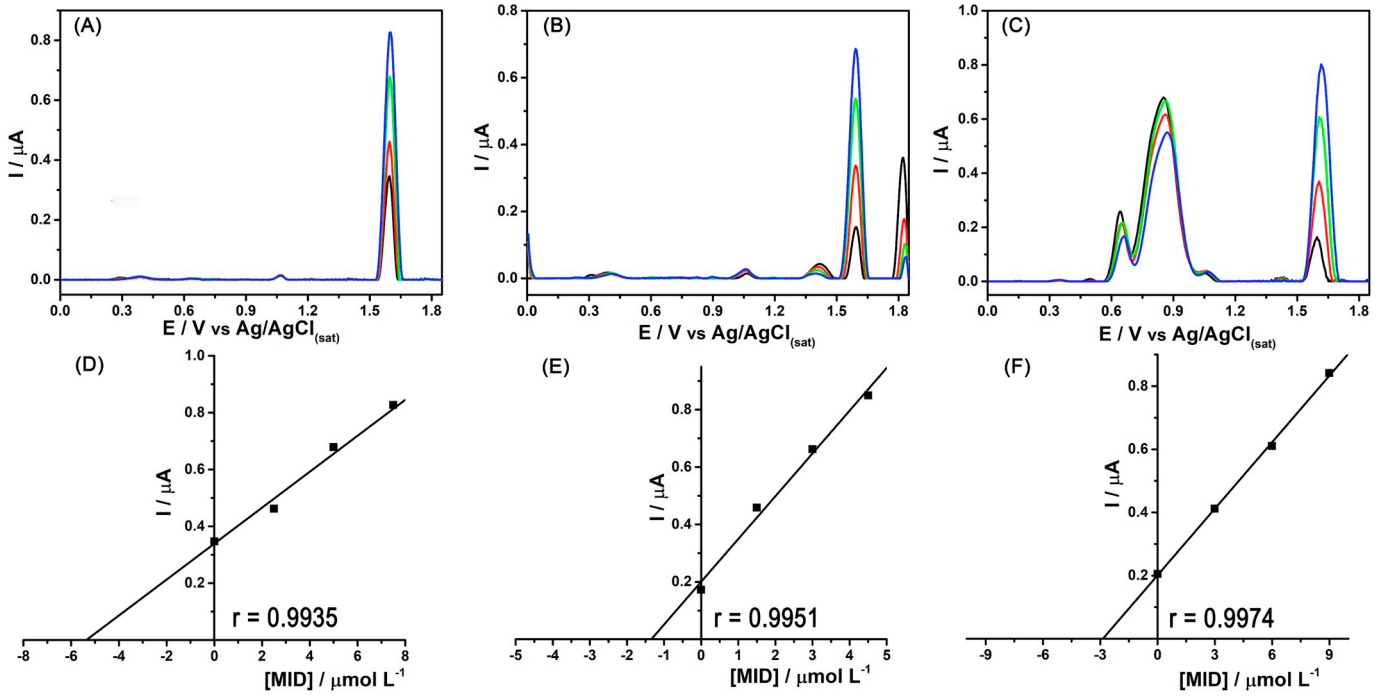

Fig. 4. Baseline-corrected DPV responses of alcoholic beverage samples spiked with MID and diluted in 0.12 mol L^{-1} BR buffer (pH = 2.0) before and after addition of increasing concentrations of MID. (A) vodka; (B) whisky; (C) red wine; (D, E, F) respective calibration curves (standard addition method). Supporting electrolyte: 0.12 mol L^{-1} BR buffer (pH = 2). DPV parameters: ΔEs = 5 mV; a = 70 mV; tm = 25 ms. Anodic scan (0 to +1.9 V).

Table 4
Results obtained in recovery experiments with beverage samples spiked with MID (n = 3).

Sample	Spiked/μmol L^{-1}	Found ± SD/μmol L^{-1}	Recovery ± SD/%
Vodka	5.0	5.13 ± 0.36	103 ± 3
Whisky	1.5	1.32 ± 0.09	87 ± 3
Red wine	3.0	2.90 ± 0.19	97 ± 6

samples after simple dilution in supporting electrolyte. Therefore, we can conclude that the proposed method can be used to fast screening MID in adulterated alcoholic beverages after simple sample pretreatment (dilution in supporting electrolyte). The average sedative dose is estimated around 0.3 mg kg^{-1} [54,55]. Therefore, the sedative effect of MID in beverages will only occur for normal people (≈50 kg) if the concentration in a drink is around 15 mg per 100 mL (460 μmol L^{-1}).

3.4. Evaluation of the selectivity of the method

Other benzodiazepines also known as date rape drugs, such as clonazepam (CLO), flunitrazepam (FLU), and diazepam (DIA), may cause similar effects of MID if consumed with alcoholic beverages. According to the literature [4,56,57], similar to MID, these molecules can also be electrochemically reduced at more negative potentials. Fig. 5 exhibits a comparison between DPV voltammograms obtained for each molecule (CLO, FLU, DIA, and MID) by cathodic (Fig. 5A) and anodic (Fig. 5B) DPV scans.

As can be observed in Fig. 5A, electro-reductions of MID, DIA, FLU, and CLO occur at approximately −0.60, −0.77, −0,79 and −0.86 V, respectively. The reduction processes of benzodiazepines were previously studied by others authors [38,58] and involve the reduction of the azo group in the molecule with the transfer of equal number of protons and electrons [58]. Both CLO and DIA have reduction processes taking place at the same potential range of MID, which compromises the selectivity of the method. However, no oxidation peaks for DIA, CLO and FLU were observed in the anodic region (Fig. 5B), even when the concentration of these compounds exceeds the concentration of MID in 10 times. Thus, we can conclude that the selective determination of MID is only possible if the oxidation process is used (Fig. 5B).

Screening studies were also carried out with the target beverage samples in the cathodic region. Fig. 6 shows the DPV voltammograms obtained for sample solutions (dashed lines) and for a standard solution of MID (solid line). As can be seen, the red wine sample solution presents a broad voltammetric peak in the same potential region where occurs the reduction peak of MID. Therefore, we can conclude that the selective determination of MID in red wine samples is only possible if the anodic DPV scan is used (Fig. 4C). In the anodic region, the red wine sample also presents oxidation peaks relative to other compounds present in the sample, however, these peaks are well-separated

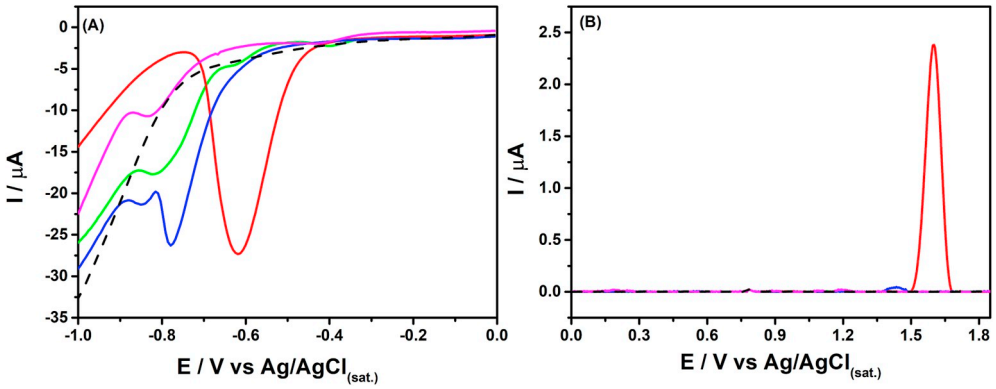

Fig. 5. DPV voltammograms obtained for: **(A)** 10 µmol L^{-1} of MID (red line), FLU (pink line), and CLO (green line), and 100 µmol L^{-1} of DIA (blue line) in the cathodic scan; **(B)** 100 µmol L^{-1} of FLU, CLO, and DIA and 10 µmol L^{-1} of MID in the anodic scan. The dashed lines are the blank signals. Other conditions see Fig. 4.

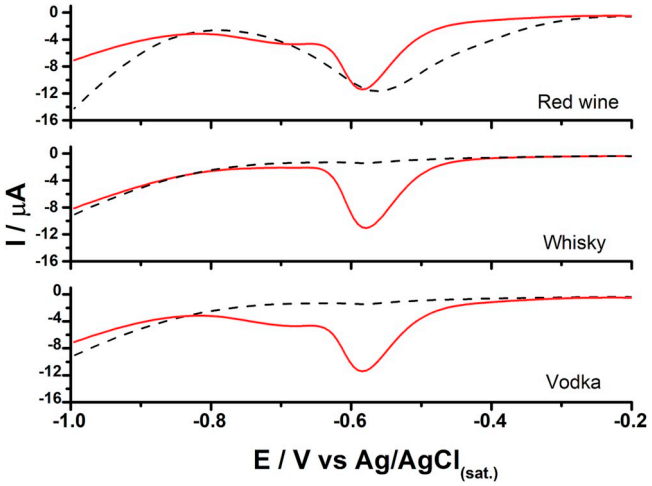

Fig. 6. DPV voltammograms obtained for sample solutions (dashed lines) and a standard solution of MID (solid line). Concentration of MID after sample dilution: 10 µmol L^{-1}. Cathodic scan (0 to −1.0 V). Other conditions see Fig. 4.

(~350 mV) from the oxidation peak of MID (Fig. 4C). Whisky and vodka samples did not present matrix effects or electroactive species that under electrochemical reduction processes at the same potential region for MID detection using its reduction process.

3.5. Comparison of the proposed method with other electrochemical methods for the determination of MID

The determination of MID through electrochemical oxidation was proposed for the first time. Therefore, the analytical characteristics obtained with the proposed method were compared with other electrochemical methods that used the electrochemical reduction for MID determination. As can be observed in Table 5, many proposed methods reported in the literature did not evaluate the analysis of real samples. In addition, some works require the use of a preconcentration step (adsorption on the electrode) and modified electrodes, which increase the analysis time. The presented work presents high precision and the limits of detection are comparable to the previous reported works.

4. Conclusions

The possibility of selective detection and fast screening of MID in beverage samples (vodka, whisky, red wine, and beer) based on its electrochemical oxidation is demonstrated for the first time. The use of the electrochemical reduction of MID for the analysis of beverage samples is limited by the interference of sample matrix (e.g., wine sample) and by the presence of other similar benzodiazepines (e.g., clonazepam, flunitrazepam, and diazepam). Thus, the detection of MID

Table 5
Comparison of some analytical characteristic of the proposed method with others electrochemical methods reported for MID determination.

Technique	Sample	LOD/µmol L^{-1}	LOQ/µmol L^{-1}	LR/µmol L^{-1}	Electrode	Reference
DPP	SS	0.06	NR	0.1–10	HMDE	[16]
NPAdSV	SS	0.00001	NR	3.6–36	HMDE	[17]
Potentiometry	Tablet	10	NR	10–10000	PVC	[18]
SWAdsCV	Tablet	0.016	NR	0.1–10	HMDE	[19]
DPAdsCV	SS	NR	NR	0.001–1.6	HMDE	[20]
Impedance	SS	NR	NR	10–400	Au-PoliAn	[21]
DPV	NR	NR	NR	46–2760	GCE	[22]
SWV	Urine	0.0017	0.0089	0.0005-0.1	MIP- CPE	[2]
SWV	Herbal	NR	NR	NR	GE-paraffin	[37]
SWAdSCV	Phytotherapic	NR	NR	NR	HMDE	[24]
Potentiometry	Blood serum	0.6	NR	10–1000	CPE	[25]
DPV	Vodka	0.46	1.51	4–25	BDDE	This work
	Whisky	0.43	1.42	1–10		
	Red wine	0.33	1.09	1–15		

LR: linear range; LOD: limit of detection; LOQ: limit of quantification; SS: standard solution.
Techniques: DPP – Differential Pulse Polarography; NPAdsV – Normal Pulse adsorptive cathodic voltammetry; SWAdsCV – Square wave cathodic adsorptive voltammetry; DPAdSCV – Differential Adsorptive cathodic voltammetry; DPV – Differential Pulse Voltammetry; SWV – Square wave voltammetry; **Electrodes:** HMDE – Hanging mercury drop electrode; PVC – PVC membrane; Au-PoliAn – Au electrode modified with polyaniline; GCE – Glassy carbon electrode; Nano-MIP- CPE – Molecularly imprinted polymer in carbon paste electrode; GE-paraffin – paraffin impregnated with graphite; CPE – Carbon paste electrode; BDDE – boron doped diamond electrode.

at very positive potentials on the BDDE is a relevant advantage of the proposed method (much more selective). A feasible mechanism for the electrochemical oxidation of MID was proposed based on voltammetric studies and computational simulations (density functional theory calculations). The developed method is simple, stable (RSD < 4.9%, n = 15), presented acceptable recovery values (88–107%), and can detect MID in beverages within concentration values used for criminal purposes. Additionally, the proposed method can be used in laboratories with limited infrastructure. The analysis is possible after very simple sample pre-treatment step (just dilution in supporting electrolyte).

Declaration of interest

No conflict of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.talanta.2019.120319.

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