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Green aspects in the procedure of detection ketamine, flunitrazepam, and diazepam in drinks based on dried sample spot analysis

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ABSTRACT

A new methodology for the detection of ketamine, flunitrazepam, and diazepam in beverage samples by the dried sample spot method was developed. The method is characterized by very low LODs in all tested types of beverages (100 ng/mL for ketamine, 25 ng/mL for flunitrazepam and diazepam) and great precision at the concentration of 100 ng/mL for all analytes. The significant advantages of this method are the consumption of fewer amount of samples and the possibility of securing the beverage samples on DBS cards at room temperature. The proposed method was evaluated by the innovative WAC approach according to Green Analytical Chemistry. The results of the evaluation indicate the best results of this method in terms of analytical quality compared to the other methods from the literature, however other aspects such as green chemistry and economical are also good. The DBS/MAE/LC-MS method could be used for qualitative analysis for drugs detection in cases of date-rape drugs analysis.

1. Introduction

Date-rape Drugs (DRD) are substances used in Drug-facilitated Sexual Assaults (DFSA). Ketamine and benzodiazepines, in particular flunitrazepam and diazepam, are the most popular DRD. Ketamine is a substance that acts as an antidepressant, anesthetic, and analgesic. The drug is used to treat depression, alleviate pain and perform surgeries. At high doses, ketamine causes hallucinations and withdrawal from reality. Additionally, the use of this drug may lead to memory loss [1]. Benzodiazepines can cause central nervous system depression. The effect of taking them are somnolence, calming down and muscle relaxation [2]. These medicines are some of the most commonly prescribed psychotropic drugs in developed countries. Some studies showed that most of the medicines of the benzodiazepine group are prescribed by primary care physicians. The widespread use and easy access to these drugs are currently a serious social problem [3]. Analysis of drinks for substances from the DRD group content is important and necessary due to the fact that these substances have many features to facilitate their secret addition to alcoholic and soft drinks. Symptoms of intoxication by DRD usually develop within 30 min after ingestion. However, their detection in biological samples is only possible for about two days [2]. Analysis of drinks for DRD content could be considered as supporting evidence in DFSA cases due to the fact that there are difficulties in the detection of these substances in biological samples [4].

Nowadays, due to the fact that club drugs have become more common at parties (club parties, raves, house parties) and easier access to medicines (such as benzodiazepines, and antidepressants), the phenomenon of the secret addition of drugs to drinks has occurred frequently. The importance of the safety of drinks in clubs for their consumers can be demonstrated by the rapid development of solutions that make it difficult to manipulate the composition of the original drink and the more common education to minimize the likelihood of adding foreign ingredients to the drink [5]. The rapid development of handheld tests for the self-detection of xenobiotics in beverages is also observed, for example, color-change reagent test Drink Safe Technology Version 1.2 [6], colorimetric paper-based sensor [7] or drink coaster with test spots [8]. The developed tests are often insufficiently specific and sensitive, therefore the analysis performed in the laboratory is needed to eliminate false positive or negative results. In this respect, it is necessary to develop protocols to enable the take the sample of a suspect drink and send it to the laboratory.

The sample preparation of alcoholic and non-alcoholic beverages for ketamine and benzodiazepines determination was usually developed based on the use of liquid-liquid extraction [9,10] or only direct dilution of the tested drink [11]. The techniques commonly used in the analysis of beverages are separation techniques such as gas chromatography [9,12], high-performance liquid chromatography [4], and capillary electrophoresis [13,14]. Currently, many innovative methods of ketamine and benzodiazepine detection based on the new sensors are being developed. For example, Yehia et al. [15] developed a paper-based microfluidic device with three types of detection zones: fluorometric, potentiometric, and colorimetric combined with using carbon dots-gold

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nanoparticles and cobalt thiocyanate to detect ketamine in an energy drink. They obtained the lowest detection limit equal to 0.76 mg/L by the potentiometric detector. Tseliou et al. [16] used a sensor based on printed electrochemical cell and cyclic voltammetry measurement combined with single graphite screen-printed electrodes for the detection of flunitrazepam in a variety of drinks. Another new approach is proposed by de Paula et al. [17] who applied paper spray mass spectrometry in the determination of selected benzodiazepines in different alcoholic and non-alcoholic drink samples. By this approach, they obtained a limit of detection of diazepam in beer equal to 0.05 μg/L.

The analysis of dried spot is widely used in the analysis of biological samples (for example Dried Blood Spot method – DBS), especially whole blood samples [18–20]. The extensive advantage of the DBS method is the possibility of self-collection of a blood sample by the patient, which turned out to be a significant advantage during the COVID-19 pandemic, allowing the patient to collect the sample himself and send it to the laboratory [21]. Due to the other advantages of this method, such as the stability in room temperature of the wide range of analytes in samples collected on DBS cards, the ease of storage of collected samples [22,23], using DBS cards seems to be an excellent tool in the collection and secured of non-biological samples and analysis dried samples spots of different matrixes. For example, Świądro et al. [24] performed tests showing the feasibility of using the DBS procedure developed for whole blood samples to analyze samples of alcoholic and non-alcoholic beverages containing ketamine. Preliminary results showed the possibility of using the DBS cards in the qualitative analysis of beverages.

The aim of these studies was to investigate the possibility of using the developed DBS procedure [25] for the analysis of dried spots of various alcoholic and non-alcoholic beverages to detect selected DRD: ketamine, flunitrazepam, and diazepam. Moreover, the presented DBS/MAE/LC-MS method was assessed based on the White Analytical Chemistry (WAC) method. We believe that the method developed for forensic toxicology could also be used in the analysis of beverages of various compositions. The proposed application of the already developed and used method in the human blood analysis could be promising in the analysis of dried spots of beverage samples enables to easiest security of the sample at the crime scene and will allow minimizing the amount of sample consumption according to the WAC principles.

2. Material and methods

2.1. Chemical and reagents

The following reagents were used in the experiment: ethyl acetate (purity class for analysis, > 99%, Merck, Germany), 35–38% hydrochloric acid (purity class for analysis, > 99%, POCH, Poland), borax (sodium tetraborate, decahydrate, purity 99%), acetonitrile (hypergrade for LC-MS, ≥ 99.9%), formic acid (for analysis, > 98%), and methanol (hypergrade for LC-MS, ≥ 99.9%) (Sigma-Aldrich, USA). Ultrapure water (18.2 MΩ/cm, less than 3 ppb TOC) was generated with the Mili-Q Plus system (Merck-Millipore, Germany) and technical nitrogen with 90–99% purity (Air Products, Poland) were used. Additionally, in the research were used: Coca-Cola (Coca-Cola Company®, USA), Tyskie beer (Tyskie Browary Książęce, Poland), Ballantine's whisky (George Ballantine & Son Ltd., Scotland), orange juice (Tymbark-MWS Sp. z o.o., Poland), Don Raffiano semi-sweet white wine (Castillo de Landa, Spain) and Carlo Rossi semi-dry red wine (CEDC International Sp. z o.o., USA).

Whatman FTA DMPK C cards and a Harris Unicore puncher (6 mm) were obtained from Sigma-Aldrich (USA). Falcon vials (15 mL) were purchased from Nest Biotechnology (China). Vials and inserts (200 μL) were produced by VWR (USA). Eppendorf vials (1,5 and 5 mL) were obtained from Eppendorf AG (Germany).

2.2. Standard solutions

Standard solutions of analytes in methanol: ketamine, flunitrazepam, diazepam, and diazepam-d_5 (internal standard) were purchased from Lipomed AG (Arlrshein, Switzerland) at a concentration of 1 mg/mL. All standards were stored in a freezer at −20 °C.

2.3. Instrumentation and conditions

For the analyses following devices were used. The nitrogen evaporator was purchased from Lieblisch Labortechnik (Germany). Allegra X-30R centrifuge was produced by Beckman – Coulter (USA). Reax control shaker from Heidolph (USA). Automatic pipettes with variable capacity from Hirschmann and Sartorius (Germany). The extraction process was carried out with MARS 5 microwave-assisted sample preparation system (CEM, Matthews, USA) equipped with Teflon vessels Xpress®PFA. The UltiMate 3000 RS liquid chromatography system (UHPLC; Dionex, Sunnyvale, CA, USA) and Hypersil Gold Phenyl column (50 mm × 2,1 mm ID, particles 1,9 μm; Thermo Scientific, Bremen, Germany) were utilized for chromatographic analyses. The liquid chromatography system was coupled to a MicroTOF-Q II mass spectrometer from Bruker (Bremen, Germany) with an electrospray ionization source (ESI) and time of flight analyzer (TOF).

Settings of the mass detector, gradient program, and composition of the mobile phase were chosen based on previous research on psychoactive substances [19,26]. The mobile phase consisted of two eluents: eluents A (0.1% formic acid in ultrapure water) and eluent B (acetonitrile). The flow rate of the mobile phase was 0.3 mL/min and the column temperature was set to 35 °C during the entire measurement. Eluents A and B were mixed during analysis according to the following gradient. First, the content of eluent B increased from 15% to 40% (0.0–4.0 min). For the next 3 min, the content of eluent B was constant at 40% (4.0–7.0 min) and then increase to 70% in 3 min (7.0–10.0 min). Next, the content of eluent B was decreased to 15% in 2.5 min (10.0 – 12.5 min) and held for 4.5 min (12.5–17.0 min) to stabilize the column before the next injection. The injection volume was 5 μL.

The mass detector parameters were as follows. The detector operated in the positive ionization mode with a capillary voltage of 4.5 kV. The nebulizer pressure was 2.5 bar. The dry gas flow was 5.5 L/min and the dry gas temperature was 200 °C. The detector operated in the scanning mode in the range of 50–800 m/z. From the recorded chromatograms, selected values of $[M+H]^+$ ions corresponding to the tested substances were extracted. Extracted $[M+H]^+$ values for analytes and internal standard (IS) are present in Table 1.

The data analysis and LC-MS operation were performed using: Chromeleon 6.8, HyStar 3.2, microTOFcontrol (Bruker, Germany), Compas DataAnalysis 3.2 software (Bruker, Germany), and Excel 2019 (Microsoft, USA).

2.4. Standards solution preparation

First, from stock solution at a concentration of 1 mg/mL intermediate solutions of ketamine, flunitrazepam, diazepam, and diazepam-d_5 were prepared at a concertation of 10 μg/mL in methanol. Then, by diluting the intermediate solutions, mixtures of analytes (ketamine, flunitrazepam, and diazepam) and internal standard solution (diazepam-d_5) were prepared at a concentration of 1 μg/mL separately.

Table 1
Formula and values of monitored ions for analytes and internal standard (IS).

Analyte/IS	Formula	Monitored ion $[M+H]^+$	Retention time t_r (min)
Ketamine	$C_{13}H_{16}ClNO$	238.0993 ± 0.0050	1.62 ± 0.02
Flunitrazepam	$C_{16}H_{12}FN_3O_3$	314.0935 ± 0.0050	6.64 ± 0.02
Diazepam	$C_{16}H_{13}ClN_2O$	285.0789 ± 0.0050	6.91 ± 0.02
Diazepam-d_5 (IS)	$C_{16}D_5H_8ClN_2O$	290.1103 ± 0.0050	6.86 ± 0.02

2.5. Sample preparation

The sample preparation protocol was based on previous research in our laboratory [25]. Into the 1.5 mL Eppendorf vials, 20 μL of analytes mixture was pipetted and the solution was dried under nitrogen gas at 40 ˚C. Next, 200 μL of drink, which did not contain the tested analytes, were added to a vial with dried residue and vortexed for 5 min. The steps of preparation spiked samples of each tested beverage were the same. The samples were applied on the DBS cards as two drops (25 μL each) and then dried at room temperature for 1 h.

Next, from each sample, two 6-mm discs were cut out from the DBS card using a puncher and put into Teflon vessels. Then, 1 mL of pH buffer (pH = 9, containing sodium tetraborate and hydrochloric acid) and 3 mL ethyl acetate with internal standard (IS) at a concentration of 150 ng/mL were added to the vessels with cut discs. The microwave-assisted extraction (MAE) was carried out at 50 ˚C for 15 min. The temperature was ramped up in 10 min, using microwave power ranging from 480 to 800 W. After the extraction, the contents of the vessels were transferred to the 15 mL plastic tubes and centrifuged (4000 rpm, 4 ˚C, 5 min). Next, 2.5 mL of ethyl acetate from plastic tubes were transferred to a 5 mL Eppendorf vial and dried under nitrogen gas at a temperature of 40 ˚C. In the next step, a 500 μL portion of ethyl acetate was added to the residue, vortexed for 10 s, and centrifuged (10,000 rpm, 4 ˚C, 10 min). Then 450 μL of the solution was taken into the 1,5 mL Eppendorf vial and the mixture was again dried under nitrogen gas at 40 ˚C. Next, to the residue in Eppendorfs 50 μL of eluent A was added, vortexed for 10 s, and centrifuged (16,000 rpm, 4 ˚C, 15 min). Finally, 40 μL of the sample was placed into the 200 μL insert. The prepared samples were analyzed using liquid chromatography coupled with a mass spectrometer (LC-MS).

2.6. Validation

The validation process was performed according to the guidelines for method validation formulated by EURACHEM [27] and general tips for the validation process given by the European Medicines Agency (EMA) [28]. Repeatability, intermediate precision, and limits of detection (LOD) were determined for qualitative analysis of selected beverages using the proposed analytical procedure.

The LODs for all analytes in each studied beverage were estimated based on the signal-to-noise ratio (S/N) obtained based on 10 analyses of samples with a concentration of 100 ng/mL. In the next step, analysis of samples of each beverage at the concentrations of 25, 40, and 50 ng/mL were done to experimentally confirm estimated values. The lowest concentration at which the signal-to-noise ratio was equal to 3 and the signal was still visual detect was taken as the LOD.

Repeatability and intermediate precision were determined for samples at a concentration of 100 ng/mL. Three spiked samples for each tested beverage were analyzed and the analysis of each sample was repeated 3 times to calculate the coefficient of variation (CV%) for repeatability during one day. Intermediate precision was determined based on results obtained for 3 consecutive days.

3. Results and discussion

3.1. Validation process

Values of limits of detection (LOD) estimated based on the signal-to-noise ratio (S/N) and determined experimentally are presented in Table 2. Fig. 1. presents an example of extracted ions chromatogram for analytes and internal standard at a concentration of 100 ng/mL in a spiked whisky sample.

The experimental LODs for ketamine in all tested types of beverages were 100 ng/mL. These values are quite consistent with estimated values for beer, whisky, orange juice, and white wine samples. Only for coca-cola and red wine samples determined LODs are not consistent with estimated values – for samples of this kind of beverages signals of ketamine were not observed in the samples prepared at a concentration close to expected LODs. Signals for ketamine were not observed in samples at concentrations of 25, 40, and 50 ng/mL in each type of drink. This experiment shows that it is important to experimentally confirm the calculated limits of detection.

The experimental values of LODs for flunitrazepam confirm the estimated values. It is promising that the experimentally determined detection limits for this analyte are even lower than the estimated values such for whisky, white, and red wines samples.

The lowest LODs were obtained for diazepam, which is confirmed by both the estimated and experimental values. The experimental limits of detection for all kinds of beverages are 25 ng/mL. Observed signal-to-noise ratios for diazepam at the concentration of 25 ng/mL in beverage samples were close to 3 which indicated that determined limits of detection are the lowest concentrations that can be detected with a certain confidence by this method. Fig. 2. presents a chromatogram obtained for whisky, orange juice, coca-cola, and beer samples containing diazepam at the concentration of 25 ng/mL.

Values for repeatability and intermediate precision for beverages with analytes at the concentration of 100 ng/mL are presented in Table 3. Repeatability and intermediate precision for all analytes in tested drinks were in the range of 1.2–3.9% and 3.2–7.8%, respectively. The proposed method is characterized by a very good intra-day precision of determinations at the tested concentration level. Almost in all types of beverages, inter-day precision for ketamine and flunitrazepam do not exceed 5% (higher values were determined only for ketamine in orange juice – 5.1% and flunitrazepam in white wine – 6.7). Less intermediate precision was observed for diazepam, although CV% values for this analyte do not exceed 8% (for half of the tested beverages CV% is around 6%). Despite the lower intermediate precision for diazepam, the precision of the method could be considered satisfactory, especially due to the fact that the precision was tested on a relatively low concentration of analytes in the samples.

3.2. Method evaluation according to the WAC concept

The presented DBS/MAE/LC-MS method was assessed based on the White Analytical Chemistry (WAC) method [29]. The WAC approach is used to evaluate the method in terms of 12 WAC principles, which consider aspects related to the quality of the analytical method (red), green chemistry issues (green), and practical and economical use (blue). The method was compared with the other most widely used methods in laboratories: CZE-DAD [14], LC-MS [4], and GC-MS [9].

The evaluation of some principles included in the new WAC model was difficult. Due to this fact it was decided to evaluate those principles for the methods to each other, assigning a value of 100 for the best method to the others (subsequent methods received adequately fewer points). The assessment of some issues requires detailed information about the methods (e.g., consumption of energy and other media). In the case of those parameters, the same number of points were given to the methods to minimize its factor for the final evaluation score. The general results of the method evaluation are presented in Fig. 3.

The details of the evaluation of the WAC principles (R1-R4, G1-G4, B1-B4) and the procedure for justifying them are as follows. R1: Scope of application – assessed based on the number of analytes and number of types of tested beverages; R2: LOD and LOQ – due to the fact that the developed method is a qualitative method, only the LOD was assessed; method with the lowest LODs values was awarded 100 points; R3: Precision – method with the best repeatability was awarded 100 points; R4: Accuracy – accuracy was not evaluated; all methods were awarded 100 points and the impact of accuracy on the final evaluation of the methods was not considered; G1: Toxicity of reagents – evaluated based on the sum of pictograms of used reagents and their toxicity, the amount of organic solvents used; the lowest toxicity method was awarded 100 points;

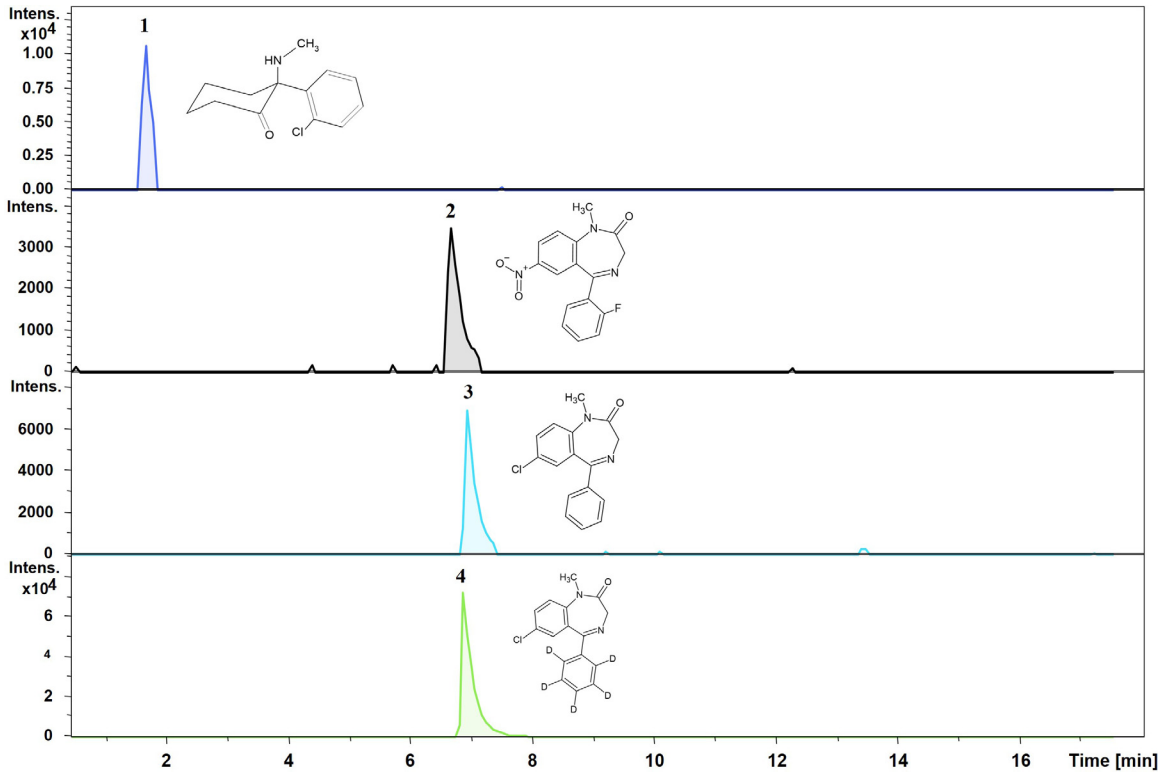

Fig. 1. Extracted ions chromatogram for analytes and internal standard at a concentration of 100 ng/mL in spiked whisky sample (1 – ketamine; 2 – flunitrazepam; 3 – diazepam; 4- diazepam-d5).

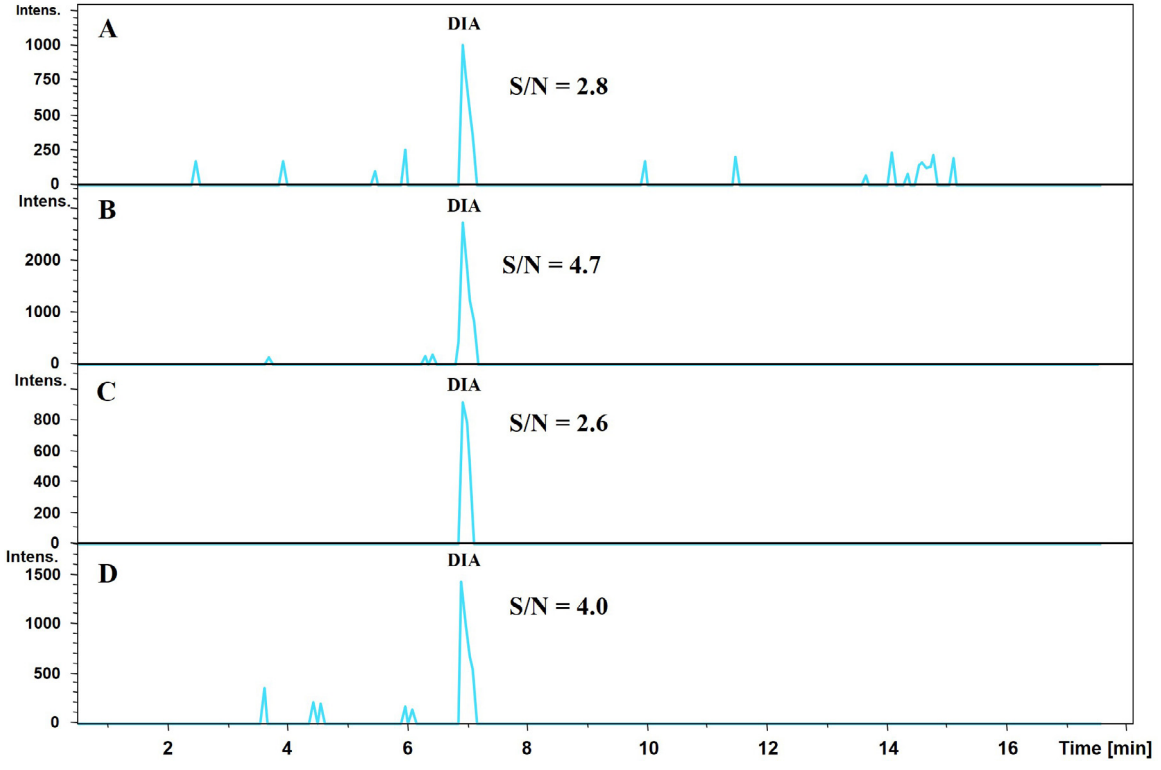

Fig. 2. Extracted ion chromatograms for whisky (A), orange juice (B,) coca-cola (C) and beer (D) samples contain diazepam at the concentration of 25 ng/mL.

Table 2
Limits of detections (LODs) of ketamine, flunitrazepam and diazepam for different beverages.

		Limit of detection (ng/mL)					
		Coca-cola	Beer	Whisky	Orange juice	White wine	Red wine
Ketamine	calculated	26	95	87	119	92	54
	determined	100	100	100	100	100	100
Flunitrazepam	calculated	26	43	51	33	49	46
	determined	25	50	25	25	25	25
Diazepam	calculated	21	25	43	31	31	38
	determined	25	25	25	25	25	25

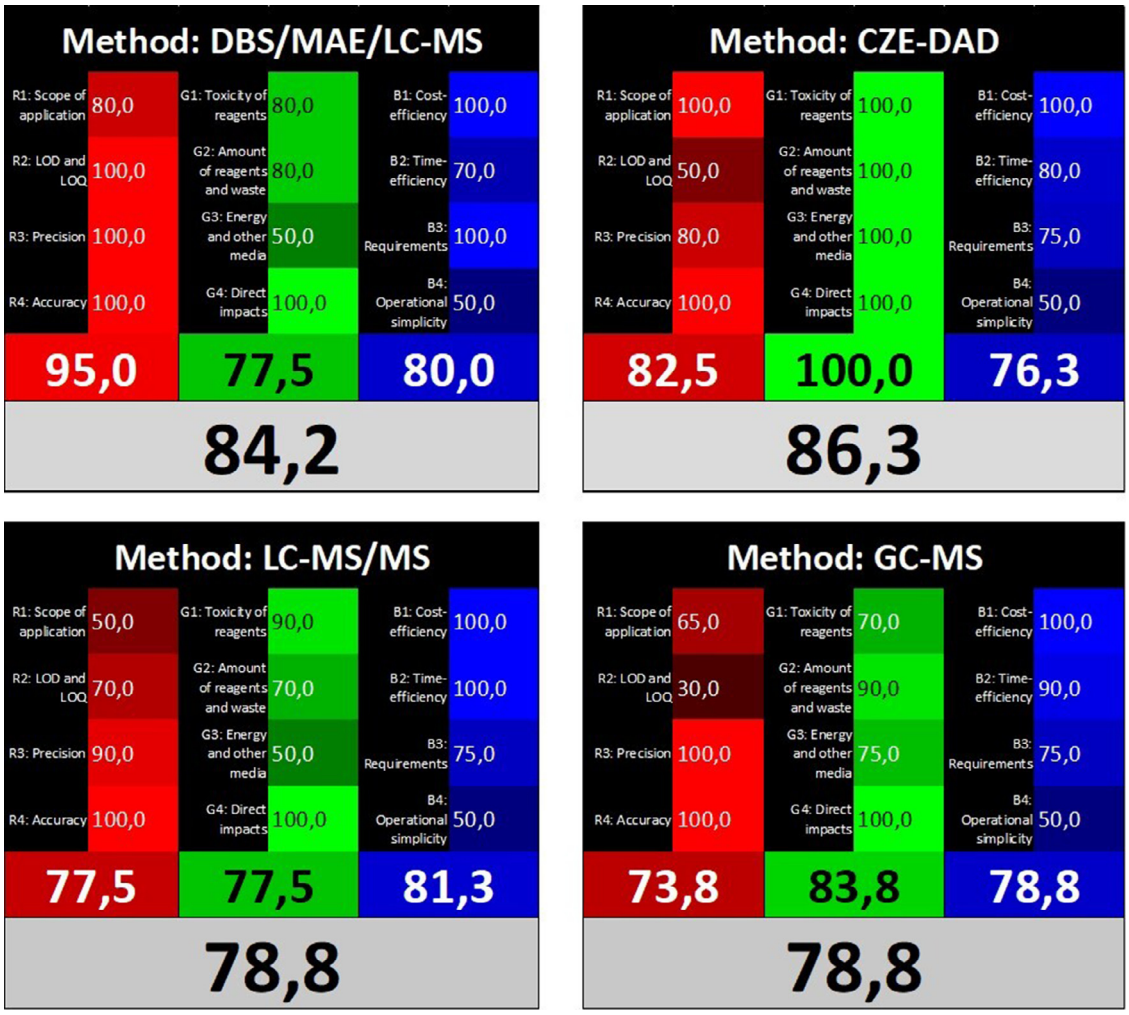

Fig. 3. Summary of the evaluation of selected analytical methods by the WAC approach.

G2: Amount of reagents and waste – the amount of reagents and waste were estimated and the number of points was awarded according to their amount and toxicity; G3: Consumption of energy and other media – were estimated on the basis of general knowledge on the energy consumption of used analytical instrument (e.g., methods coupled with mass detector was found to be more energy-consuming); the method with the lowest consumption of energy was awarded 100 points; G4: Direct impacts – the evaluated methods were considered as safe for personnel, all methods were awarded 100 points (methods do not pose any additional hazards); B1: Cost-efficiency – due to the difficulties with estimation, the assessed methods were considered as equally costly; this parameter has not been evaluated; B2: Time-efficiency – assessed based on the ranking of methods in terms of method time from sample preparation to analysis; the fastest method was awarded 100 points B3: Requirements – evaluated mainly on the basis of sample consumption, other needs were found to be similar in all assessed methods; B4: Operational simplicity – was not evaluated; all methods were awarded 50 points due to the fact that assessed methods are not miniaturized or portable.

Based on the evaluation results it should be underlined that the proposed method is the best in the analytical quality (red) issues. The DBS/MAE/LC-MS method has the lowest limits of detection for analytes compared with other methods. It is also characterized by the best precision and quite a wide range of potential applications. The weakness of the method compared to others is its greenness, which results mainly from the use of relatively energy-consuming equipment and the necessity to carry out the extraction process (which generates an additional amount of used reagents and waste). However, the significant advantage of the proposed procedure is the reduction of the sample volume used for analysis compared to other methods, which is also an important issue of the greenness of the method. Additionally, it should be emphasized

Table 3
The precision of ketamine, flunitrazepam, and diazepam determinations at the concentration of 100 ng/mL in different kinds of beverages.

	KET	FLU	DIA
Repeatability[1], CV (%):			
Coca-cola	1.2	2.0	2.1
Beer	1.6	2.2	3.9
Whisky	1.8	3.5	3.1
Orange juice	2.0	2.2	2.3
White wine	3.2	3.3	1.7
Red wine	2.6	1.7	2.0
Intermediate precision[1], CV (%):			
Coca-cola	4.1	4.1	3.2
Beer	4.6	4.9	7.8
Whisky	3.2	3.6	4.1
Orange juice	5.1	4.3	6.7
White wine	4.1	6.7	5.8
Red wine	4.9	2.7	5.0

[1] $n = 9$ for repeatability; $n = 27$ for intermediate precision.

that the developed method seems to be relatively better at economic and practical aspects (blue).

Besides the advantages based on the evaluation, the method has a lot of advantages regarding the use of the DBS cards: (1) a small amount of the sample is sufficient to carry out the analysis, (2) the use of a DBS card can be a helpful tool to secure a different kind of beverages samples without having to store it in the bottle in cooling conditions, (3) the possibility of analyzing only the dry residue after drying of the card with sample enables the removal of some volatile components of the sample matrix, e.g., ethanol.

4. Conclusion

The growing availability of illegal drugs and medications translated into more cases of interference with the original composition of alcoholic and non-alcoholic beverages consumed in bars or during parties. Properties of the commonly used date-rape drugs allow for secret addition to drinks without changing their taste, color, or smell. This work shows that the DBS cards, which are mainly used for blood analysis, could be also a very useful tool in the analysis of different types of beverages in application to forensic analysis. This procedure offers a lot of advantages such as the easy way of collecting and storing samples even at room temperature. The proposed DBS/MAE/LC-MS method is fit for alcohol and non-alcohol drinks analysis for drugs detection. The precision of detection of ketamine, flunitrazepam, and diazepam at a low concentration of 100 ng/mL in selected six types of beverages and low limits of detection indicate its possibility in use for qualitative analysis of beverages. The biggest advantage of this method is that it required only a small among of samples and by using a very sensitive mass detector it is possible to detect selected drugs at a trace level. Evaluation of the method by the WAC approach confirms that the proposed method is the best compared to other assessed methods in terms of analytical quality.

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.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.greeac.2022.100029.

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