

Review

Applications of Gas Chromatography and Gas Chromatography-Mass Spectrometry for the Determination of Illegal Drugs Used in Drink Spiking

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Abstract: Drink spiking is a significant public safety issue, often linked to crimes such as theft and sexual assault. The detection of drugs used in these incidents is challenging due to the low concentrations (<ng) and complex matrices involved. This review explores the application of gas chromatography (GC) and gas chromatography-mass spectrometry (GC-MS) to identify drugs in spiked beverages. GC-MS offers high sensitivity and specificity, and is capable of detecting drugs at ng/mL levels and distinguishing between compounds with similar structures. This review highlights the advantages of GC-MS, including its ability to simultaneously analyze multiple substances and provide detailed molecular information. Various methods for detecting gamma-hydroxybutyrate (GHB), benzodiazepines, and other drugs in beverages are discussed, emphasizing the importance of derivatization to enhance their volatility and the method's chromatographic performance. The paper also addresses the challenges of analyzing complex beverage matrices and the need for continuous improvement in detection techniques to keep pace with the evolving drug market. Overall, GC and GC-MS are powerful tools for forensic analysis in drink spiking cases, offering reliable and accurate results, which are essential for legal and investigative processes.

Keywords: gas chromatography (GC); mass spectrometry (MS); drink spiking; forensic analysis; gamma-hydroxybutyrate (GHB); benzodiazepines; ketamine; drug-facilitated sexual assault (DFSA)



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1. Introduction

Drink spiking, or spiking, is the illicit addition of drugs or alcohol to a beverage belonging to a victim without their knowledge, leading to the victim experiencing drowsiness, confusion, nausea, and, potentially, memory loss. In more severe cases, victims may be rendered unconscious and experience harmful long-term psychological effects. Spiking events most often occur in bars, nightclubs, house parties, or other situations involving crowds of people, such as music festivals. A person might be spiked to make them vulnerable for various reasons, for example, as a prank or to enable a theft or sexual assault to be committed. It is believed that drug-facilitated sexual assault (DFSA) is underreported, but evidence suggests that it is becoming an increasingly common offence [1,2]. Countries vary in how they address DFSA, with some focusing on punitive measures while others emphasize prevention and education. In the United Kingdom [3], spiking offences could lead to a perpetrator being prosecuted under several laws, including the Offences Against the Person Act 1861 [4], the Criminal Justice Act 1988 [5] and, if an individual has attempted a DFSA

against a victim after they may have become disorientated or incapacitated, the Sexual Offences Act 2003 [6]. Depending on the severity of an offence, an individual prosecuted under these laws may be required to pay substantial fines and could face a sentence ranging from several years to life imprisonment. In a recent King's Speech, the UK government at the time proposed introducing new legislation to make drink spiking a specific criminal offence with strict liability. This would mean that intent would not need to be proven for a conviction, potentially increasing conviction rates due to the challenges in proving intent. Identifying spiked drinks can be difficult, as many drugs used for spiking are chosen for their ability to dissolve without noticeable visual changes in the drink. This makes it hard for unsuspecting victims to notice the addition of a drug to their drink and to identify the perpetrator. Such factors lead to a general underreporting of drink spiking incidents, complicating legal actions and victim support. Efforts to combat drink spiking include awareness campaigns, improved venue security, and the development of detection tools like drink-testing coasters [7] and wearable sensors [8]. These measures, however, have not yet been widely implemented and can often be circumvented. Overall, drink spiking remains a significant public safety issue, requiring continued efforts towards education, prevention, and support for victims. The detection of drugs used in DFSA is challenging due to the short biological half-lives [9] of these substances and the frequent delays in reporting by victims. Similarly, the analysis of small sample volumes with potentially degraded contents is required. Training responders to gather comprehensive data and encourage early sample collection is essential. The continuous improvement of detection methods is necessary to keep up with the evolving drug market.

The focus of this review is on the detection of drugs used in drink-spiking-related DFSA. There have recently been reports of DFSA resulting from what has been termed needle spiking, which is also known as injection spiking. Here, individuals are surreptitiously injected with drugs in crowded environments like nightclubs. Victims are reported to feel a sudden pinprick sensation, followed by symptoms such as dizziness, confusion, and blackouts. Despite numerous reports, there is skepticism among experts about the feasibility of such injections being administered unnoticed in crowded settings.

Nevertheless, methods for the simple sample preparation of syringe residues for subsequent gas chromatography-mass spectrometry (GC-MS) analysis have been given [10]. Here, fresh portions of methanol are repeatedly drawn into the syringe, expelled, and then collected in a test tube. These are then concentrated under nitrogen and reconstituted in a known solvent volume for GC-MS analysis.

Costa et al. [11], in 2020, reviewed the drugs that were most commonly reported in DFSA. They highlighted that ethanol, benzodiazepines, ketamine, and gamma-hydroxybutyrate were the most widely reported. However, a more recent review by Burrell et al. [12] revealed that, other than ethanol, these drugs are rarely detected. For instance, they highlighted that Scott-Ham and Burton [13] found no covert use of the commonly DFSA-associated benzodiazepine Rohypnol, and that Caballero et al., in 2017, [14] reported commonly perceived 'date rape drugs' in only 3 out of 152 DFSA cases. More recently, Orts et al. [15] have highlighted the emergence of so-called designer benzodiazepines, such as clonazolam and flubromazepam. In other regions of the world, such as Iran, opioids such as dextromethorphan, the antihistamines promethazine and cyproheptadine, and the antiemetic metoclopramide are the most commonly reported [16]. Many other substances, including over-the-counter medications and prescription drugs, can also be used to commit these crimes [9]. These substances can have stronger effects when combined with alcohol and are often easier to obtain. Such findings highlight the need for analytical techniques that are capable of dealing with the complexity and changing demands of this issue.

Gas chromatography and GC-MS offer several key advantages in the determination of drug spiking cases. They can detect very low concentrations of drugs, often in the ng/mL range, and, in the case of GC-MS, can be used to identify unknown sample components. The chromatographic element allows for the analysis of beverages that may contain various ingredients and additives, and can simultaneously identify multiple different drugs and their metabolites in a single sample. This is important, as drink spiking can involve a variety of substances. The mass spectrometry component provides detailed molecular information in the form of mass spectra, allowing for the precise identification of compounds. This helps in distinguishing between substances with similar structures, reducing false positives.

Gas Chromatography

Gas chromatography, as with all chromatographic separations, is based on the partitioning of compounds between two phases. Unlike in high-performance liquid chromatography (HPLC), the mobile phase in GC is an inert gas that plays a smaller role chromatographically, serving as a carrier to move components through the GC column, where they can interact with the column stationary phase. For the sample to be carried effectively by the gas, it needs to be vaporized and converted into a gaseous state. For this, a small sample volume (typically 0.1–1.0 µL) is introduced into the injection port using a micro-syringe, either manually or via an autosampler. The injection port is heated to a temperature higher than the boiling points of the analytes to ensure rapid vaporization. The carrier gas sweeps the vaporized analytes into the analytical column. Initial chromatographic focusing of the sample can then be achieved by either cold trapping or solvent focusing [17]. In cold trapping, the initial section of the column is kept at a low temperature to condense and focus the analytes into a narrow band. This is achieved by programming the oven temperature or using a cryogenic cooling system. In solvent focusing, the solvent vaporizes first and then condenses at the front of the column, carrying the analytes with it. The column oven is then programmed to follow a temperature gradient. Initially, the temperature is kept low to allow for the chromatographic focusing of the analytes. It is then slowly increased, allowing for the separation of the analytes based on their volatilities and interactions with the column stationary phase.

Components with a low affinity for the stationary phase exit the column quickly, while those with higher affinities take longer. The separation is influenced by the analyte's vapor pressures and their interactions with the stationary phase. Early GC methods used a single temperature (isothermal), but modern techniques employ temperature programming, starting at a low temperature and gradually increasing it to separate components more effectively. This approach achieves high chromatographic efficiencies, with modern capillary columns offering theoretical plate values exceeding 100,000 [18], which is notably higher than those obtained by other commonly applied separation techniques such as high-performance liquid chromatography (8000–12,000 plates) [19].

As the separated components exit the column, they pass through to a detector, which generates a signal proportional to the amount of each component. The detector's signal is recorded as a chromatogram, a plot of the detector's response versus the time. Each peak on the chromatogram corresponds to a different component of the sample, allowing for qualitative and quantitative analysis. There are a number of different types of detectors, including the electron capture detector (ECD) [20], the flame photometric detector (FPD), and the nitrogen-phosphorus detector (NPD) [21], that have been used with GC. Mass spectrometry has become a preferred detector for GC over traditional detectors for several reasons. MS can identify a wide range of compounds, including those that are not easily detected by other detector formats. It provides both quantitative and qualitative data, allowing for both the quantification of a substance and its identification, as well as the possi-

bility of identifying unknowns. Nevertheless, flame ionization detection (FID) [22] remains popular for GC due to its cost-effectiveness, robustness, and sensitivity to hydrocarbons coupled with a wide linear dynamic range.

In recent years, liquid chromatography-mass spectrometry (LC-MS) has become an increasingly more frequently reported analytical method for the determination of drugs in many matrices, including determination in drink spiking. Gas chromatography-mass spectrometry systems are often more cost-effective to operate and maintain compared to LC-MS systems. The equipment and consumables required for GC-MS tend to be less expensive. It is particularly effective for substances that can be readily vaporized without decomposition. This technique has been widely used for decades and is well-established in many laboratories. Having a long history of use in various fields compared to LC-MS, GC-MS is an established analytical technique that has led to the fabrication of proven methodologies and protocols, making it easier to find validated methods and reference materials for specific applications.

A number of advantages can be gained from the application of GC with MS detectors. Single-quadrupole MS systems can be operated in two modes: either in full scan mode or selected ion monitoring (SIM) mode [23]. In the full scan mode, scans are made sequentially over a range of mass values, generally in the range m/z 50– m/z 500, providing a complete picture of the sample and detecting any ionizable compounds and their fragments in that range. The mass spectra that are obtained can be matched against established library spectra to identify unknowns. This mode also allows for post-run analysis, in which specific ions can be extracted and displayed in an ion extracted chromatogram (EIC) [23], which allows for compounds of interest to be selected and highlighted from the full scan data. The SIM mode focuses on specific fragments (m/z values), increasing the method's sensitivity by scanning a smaller range, and thus reducing interference, improving the signal/noise ratios, and enhancing the method's detection limits.

Various detectors are available in single-dimension, classical GC-MS, such as ion trap and time-of-flight detectors, but quadrupole-based systems are the most common due to their simplicity and cost-effectiveness. Quadrupole systems are also prevalent in gas chromatography tandem mass spectrometry (GC-MS/MS). The primary difference [23,24] between GC-MS/MS and conventional GC-MS systems is that GC-MS/MS has three quadrupole mass filters in series, with the middle quadrupole acting as a collision cell for secondary fragmentation, whereas GC-MS has only one.

Gas chromatography requires the analytes to be volatile and thermally stable. In the case of illicit substances with higher molecular weights, in contrast to small metabolites, derivatization is often required to improve their volatility and chromatographic performance. Common derivatization methods include the formation of trimethylsilyl derivatives. Trimethylsilylation involves introducing a trimethylsilyl (TMS) group ($-\text{Si}(\text{CH}_3)_3$) into a molecule. This is usually undertaken using reagents such as *N,O*-bis(trimethylsilyl)acetamide (BSA), *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide (MSTFA), and trimethylsilyl chloride (TMSCl). The TMS group reacts with functional groups such as hydroxyl ($-\text{OH}$), carboxyl ($-\text{COOH}$), amino ($-\text{NH}_2$), or thiol ($-\text{SH}$) groups in the compound [25]. Trimethylsilylation significantly increases the volatility and thermal stability of the compound, making it more amenable to GC analysis. Water and oxygen can cause significant issues during TMS derivatizations. Trace amounts of water can lead to partial or complete desilylation [26], resulting in unexpected peaks in the mass spectrum or the formation of the original compound and trimethylsilanol via hydrolysis. This is particularly challenging when attempting to isolate illicit substances from spiked beverages. A number of different derivatization methods have also been developed, such as those based on the formation of methyl esters via transesterification using methanol and a mineral acid

catalyst or via the application of diazomethane [27]. However, these are beyond the remit of this review.

2. Methods

Google Scholar, Web of Science, and the University of the West of England Library were used to obtain the papers described in this review. We used filters to include only papers for which full access was available and which were published in English to avoid translation issues and ensure consistency. The search terms used were as follows: GC or GC-MS, combined with the AND Boolean operator, followed by one or more of the following: drugs AND beverages or drink. We did not impose an exclusion date range due to the limited nature of the existing literature.

3. Results

3.1. Ethanol

The presence of ethanol is commonly determined by gas chromatography in investigations of both product quality [28] and alcohol consumption [29]. The application of head-space gas chromatography (HS-GC) for determining blood alcohol ethanol levels was developed in the late 1960s [30,31] and is now a routinely used method for ethanol determination. This process allows for the detection of ethanol at very low concentrations, often in the range of mg/L or even lower in complex sample matrices such as blood. This is, of course, an attractive feature for trace determination. However, ethanol and other compounds such as methanol, isopropanol, and acetone can be present in beverages at percentage levels, in the higher g/L range. As a result, the less sensitive (LOQ = 5 mg/L) liquid injection of aqueous solutions of beverage samples has also been recently reported [32]. In several countries, headspace gas chromatography has also been reported as an official method of analysis for determining other volatiles in alcoholic beverages [33]. It is also commonly used to analyze ethanol levels in food and beverages such as vinegar [34]. The forensic application of a headspace gas chromatography flame ionization detector (GC-FID) to determine ethanol in blood has recently been described [35]. However, little exists in the literature on the application of GC or GC-MS for determining ethanol in beverages associated with DFSA. Recently, the presence of ethanol and other alcohols, such as the more toxic methanol [36], in beverages has been determined using headspace GC-FID. One study reported methanol levels of between 32.0% and 58.3% *v/v* in samples of illicit alcoholic beverages taken from various parts of Rwanda. The ethanol content was reported to have ranged from 3.8% to 98.9% (*v/v*). Of the investigated samples, 6.6% exceeded the methanol limit (0.5% *v/v*), with 16.9% exceeding the ethanol limit (45% *v/v*). Notably, no samples tested positive for both methanol and ethanol simultaneously. Determining both the type and concentration of the alcohol present in beverages is highly important.

3.2. Gamma-Hydroxybutyric Acid and Gamma-Butyrolactone

The structures of gamma-hydroxybutyric acid (GHB) and its lactone, gamma-butyrolactone (GBL), are shown in Figure 1. These are central nervous system depressants that have been misused for their euphoric and relaxing effects. They are also used in DFSA due to their sedative and amnesic properties at higher doses [37]. Their increased abuse and involvement in criminal cases have led forensic laboratories to develop methods to detect these substances in various samples. Restrictions on the availability of GHB [38,39] have led to consumers turning to its pro-drug, gamma-butyrolactone (GBL) [40,41], which is easier to obtain due to being commercially available as an industrial solvent [42]. Gamma-butyrolactone can be readily converted to GHB through simple chemical reactions or enzymatically in the body [43]. More recently, in the UK, the 2022 regulations [44] have

placed GBL and the related 1,4-butanediol (1,4-BD) under stricter control, requiring industrial users to obtain a controlled drugs license. From the 13th April of 2022, GHB has been reclassified as a Class B drug along with GBL and 1,4-BD [44].

Gamma-hydroxyvaleric, a 4-methyl analogue of GHB, has also been abused and marketed as a dietary supplement. Studies by Carter et al. [45] aimed to compare the pharmacological and behavioral profiles of GHV and GHB. However, GHV showed a lower affinity, did not significantly affect the GABAB receptors, and did not mimic the discriminative effects of GHB or those of the muscle relaxant drug baclofen. However, GHV did share other effects like sedation, catalepsy, and ataxia at higher doses.

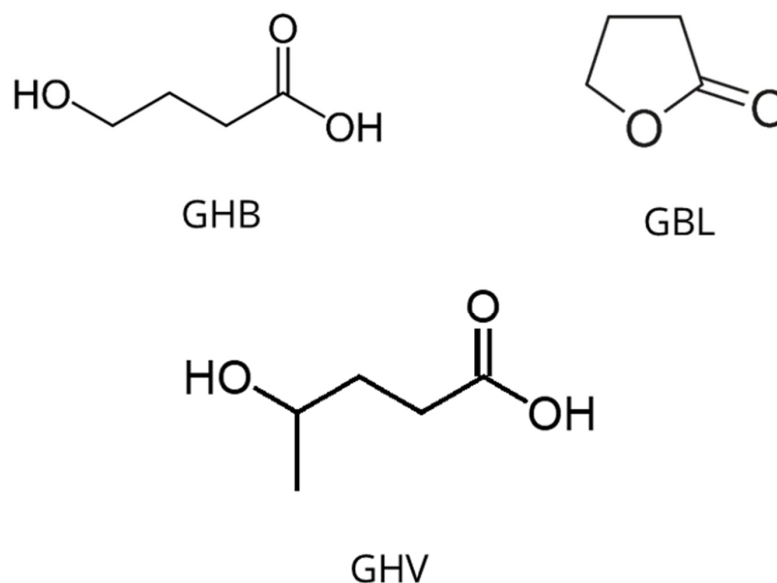


Figure 1. Structures of gamma-hydroxybutyric acid (GHB), gamma-butyrolactone (GBL), and gamma-hydroxyvalerate (GHV).

Gas chromatography has been commonly used to detect GHB and the related compounds GBL and 1,4-BD in beverages and biological fluids. Methods for its detection generally involve the derivatization of GHB to its trimethylsilyl derivative, which is then analyzed by GC-MS. This approach enhances the volatility and, as a result, the chromatographic behavior of GHB. Alternatively, by acidifying the sample, GHB can be converted to its less polar, more volatile form, GBL. However, such approaches have been questioned as they can affect the equilibrium levels of GHB and GBL that may be present in the sample. Beverages such as beer, wine, rum, tequila, fruit juice, and tonic water naturally contain ng/mL levels of GHB [46–48], which can complicate understanding of the detected GHB levels. However, the GHB levels that are commonly reported in drink spiking and sexual assaults are generally much greater, in the g/L region.

Knowledge of the endogenous levels of GHB in beverages is essential in forensic investigations as it is important to identify whether the levels are consistent with those commonly seen in a given beverage or indicate possible spiking. Tucci et al. [46] employed the ion-exchange solid phase extraction of GHB, followed by full GC-MS, to determine the low endogenous levels of GHB in alcoholic and non-alcoholic beverages. Beer, vodka, tequila, rum, and red and white wine, orange and tomato juices, tonic water and lemon tonic water were all investigated. The BSTFA-TMCS derivatized extracts were then introduced to the GC-MS and monitored using the ions m/z 117, 147, 204, 233, 234, and 235 for GHB and m/z 120, 206, 239, 240, 241 for the internal standard, GHB- d_6 . The concentrations of GHB were found to be in the ng/mL to low $\mu\text{g/mL}$ range for all of the investigated beverages. Notably, levels in the range of 9.3–12 $\mu\text{g/mL}$ for red wine and 2.5–3.2 $\mu\text{g/mL}$ for white wine

were reported. However, this was reported to be notably lower than generally expected in drink spiking incidents, where levels of 2000 µg/mL were reported to be more likely.

In a separate study, Elliott and Fais [47] investigated the concentrations of naturally occurring GHB in various non-alcoholic beverages including tonic water and lemon-flavored tonic water, which were purchased from local stores to provide further evidence of the endogenous presence of GHB. Each beverage was sampled at 0, 24, and 96 h after opening. The samples were degassed in an ultrasonic bath for 15 min before extraction. The analysis was performed using gas chromatography coupled to tandem mass spectrometry (GC-MS/MS) on an Agilent 6890/7000C Triple Quadrupole. The method involved liquid–liquid extraction with acidified ethyl acetate and MSTFA derivatization. The sensitivity of the method was determined with a limit of quantitation (LOQ) of 2.5 ng/mL and a limit of detection (LOD) of 1.3 ng/mL. Calibration curves and quality controls were used to ensure accuracy. GHB was detected in all beverage samples at very low concentrations, ranging from 89 to 145 ng/mL (0.089–0.145 mg/L). There was no significant variation in the GHB concentrations over the 96-h period. The study confirmed that the detected GHB levels were far below those required to produce any pharmacological effect. GHB was detected in all beverage samples at very low concentrations, ranging from 89 to 145 ng/mL (0.089–0.145 mg/L).

The levels of GHB reported by Elliott and Fais are lower than those previously reported by Elliott and Burgess [48]. It was reported that endogenous GHB and GBL were detectable in beverages obtained from the fermentation of white grapes, at levels between 3 and 9.6 µg/mL, and, especially, red grapes, at levels from 4.1 to 21.4 µg/mL. Their investigation reported no detectable levels of GHB or GBL in drinks such as beer, juice, spirits, and liqueurs. GHB/GBL were detected in red wine vermouth at a level of 8.2 mg/L, in sherry at 9.7 mg/L, and in port at the limit of detection. Their study utilized GC-FID to detect GHB and GBL, indicated as “total GBL” because the complete conversion of the GHB to GBL before analysis was required. This was undertaken by acidification with 6 M sulfuric acid and extraction with chloroform, using hexanoic acid as an internal standard. The levels of GHB were determined by full scan mode GC-MS following derivatization with TMS, using GHB-D₆ as an internal standard.

Meyers and Almirall [49] developed a solid-phase microextraction (SPME) method to extract GHB from water and beverage samples followed by on-fiber derivatization and analysis via GC/MS. The method demonstrated linearity from 0.01 mg/mL to 0.25 mg/mL for the detection of GHB in aqueous samples, without the need for sample manipulation that could lead to the interconversion of GHB and its lactone GBL. The method was successfully applied to detect GHB in spiked water and beverage samples. The SPME fiber was immersed in a solution of aqueous GHB for 15 min, stirring for 15 min. The exposed fiber was then exposed to the atmosphere for 1 min before being exposed to the headspace of 50 µL of BSTFA–TMCS (99:1) at 60 °C for 40 min. The fiber was then exposed to the atmosphere for 1 min and then placed in the GC injection port, which was set to 220 °C, to desorb for 12 min. Figure 2 shows the resulting mass spectrum that was obtained. Under the conditions used for analysis, an ionization voltage of 70 eV, no molecular ion was detected. This is common for TMS ethers as they tend to fragment easily under electron ionization (EI) conditions. A common fragmentation pathway involves the loss of a methyl group, which results in a significant loss of m/z 15, rather than the molecular ion itself. The molecular ions of TMS ethers can be unstable and may decompose before detection. This instability can be exacerbated by the presence of trace amounts of water or oxygen, which can lead to partial or complete desilylation. Even when molecular ions are formed, they are often of low abundance compared to other fragment ions. This makes them harder to detect and less prominent in the mass spectrum. Therefore, the authors utilized the peak at m/z 233 ($[M-15]^+$ peak) to show the presence of the derivatized GHB. Another ion that

is indicative of derivatized GHB is m/z 159, as it results from the further loss of a TMS group. However, the base peak, the m/z 147 ion, is not indicative of GHB, but is commonly observed in mass spectrometry of trimethylsilyl (TMS) derivatives in general [50]. Similarly, in TMS derivatization, the ion m/z 73 corresponds to the fragment $(CH_3)_3Si^+$, which is the trimethylsilyl cation. This ion is formed during the EI process when a TMS group is cleaved from the molecule. The stability of the trimethylsilyl cation makes it a common and prominent fragment in the mass spectra of TMS derivatives.

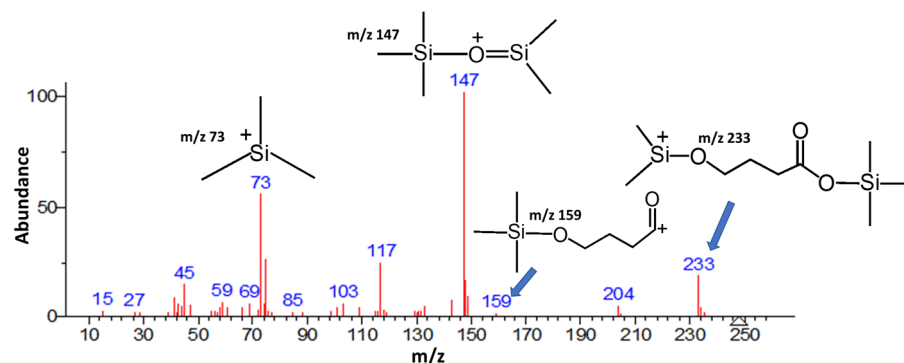


Figure 2. Mass spectrum of derivatized GHB after Meyers and Almirall [49].

Total vaporization solid-phase microextraction (TV-SPME) involves heating the sample to completely vaporize the analytes, which are then adsorbed onto a solid-phase microextraction fiber. The fiber is coated with a sorbent material that selectively captures the analytes. This offers greater sensitivity compared to traditional liquid injection and SPME methods, making this method suitable for detecting low-concentration analytes. Davis et al. [51] used a TV-SPME-based GC-MS approach to determine the levels of both GHB and GBL in water, beer, wine, liquor, and mixed drinks. The SPME fiber was first modified with BSTFA +1% TMCS vapor. It was then exposed to sample vapor that was generated by heating at 60 °C for 10 min. The drug absorbed on the fiber then underwent derivatization at the BSTFA–TMCS-modified fiber. This was then desorbed in the GC inlet at 250 °C and the desorbed derivatized GHB focused on the analytical column held at 60 °C. The oven temperature program was then initiated and the eluting compounds were monitored over a mass range from m/z 40 to m/z 550. Extracted ion profiles were then obtained, and compound identification was undertaken using either SWGDRUG and/or NIST libraries.

Meng et al. [52] have applied dispersive liquid–liquid micro-extraction (DLLME) followed by GC-MS/MS for the determination of GHB in both beverages and hair. A 1.0 mL aliquot of the beverage samples was added to a centrifuge tube and, following the addition of the internal standard, GHB- d_6 , the sample was adjusted to pH 4.3 by saturating the solution with ammonium dihydrogen phosphate. An aliquot of 180 μ L of ethyl acetate was added as the extractant. The tube was then sealed and sonicated to form a cloudy suspension, allowing the transfer of target analytes to the ethyl acetate. Following centrifugation, 30 μ L of the upper ethyl acetate layer was removed and derivatized with 30 μ L of BSTFA. Determination was then undertaken by GC-MS/MS in the full scan mode, from m/z 40 to 500, with quantitation being made in the MRM mode using the mass transitions of m/z 233/147 and 233/73 for GHB-TMS and m/z 239/147 and 239/73 for GHB- d_6 -TMS, with m/z 233/147 and 239/147 being used for quantification. GHB was reported to be in the range of 10.3–16.3 μ g/mL in red wine, 8–10 μ g/mL in white wine, and 0.87–1.89 μ g/mL in beer. These levels are similar to those reported by Elliot and Burgess [48] et al.

The possible advantages of GC-MS compared to HPLC in the determination of GHB and gamma-hydroxyvalerate (GHV) (Figure 1) have been investigated by Mercer et al. [53], in which the determination of GHB in various beverages, including water, Riesling white wine, cranberry vodka cocktail, Coca Cola, Guinness, and Coors beer was conducted. Using 1,5-pentanediol as an internal standard and 1,2-hexanediol as a surrogate standard, a reported percentage recovery of 97% was achieved. Additionally, investigations into the possibility of determining GHB using reverse-phase HPLC with UV detection at 254 nm found it to be less sensitive, with a limit of detection of 0.05 µg on a column being reported. In an attempt to improve on this, based on the number of interferences that were observed from the beverage sample, LLE was undertaken prior to HPLC analysis. However, this resulted in a notable decrease in sensitivity (LOD 100 µg on column) and inconsistent peak profiles. Taken together, both GC and GC-MS have been successful multiple times in detecting GHB and GBL at forensically relevant concentrations.

3.3. Xylazine

Sadiq et al. [54] developed GC-MS and GC-FID methods for the determination of xylazine (Figure 3) in various beverage samples. Qualitatively, xylazine was identified by GC-MS from its base peak of m/z 205.1 and a molecular ion of m/z 220.1, with quantification being achieved by GC-FID. The used samples included water, energy drinks, carbonated drinks, and fruit-based drinks. Three different drink sample types were investigated: a liquid drink by itself, droplets of drink residue, and dry drink residue. For the extraction of the liquid drink, 1.0 mL of the sample was taken and subjected to liquid–liquid extraction (LLE). Droplets of drink residue and dry drink residue were recovered by rinsing with 1.0 mL of distilled water, and the resulting sample extract was then subjected to LLE. Higher recoveries of xylazine were achieved from the liquid samples (77.2–97.3%) compared to the droplets (50.8–80.0%) and dry samples (39.8–66.9%). The LOD and LOQ were 0.08 µg/mL and 0.26 µg/mL, respectively. Xylazine was shown to be chromatographically separated from several drugs, including paracetamol, caffeine, ketamine, codeine, morphine, 6-monoacetylmorphine, and heroin.

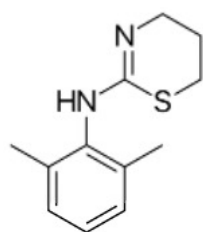


Figure 3. Structure of xylazine.

3.4. Benzodiazepines

1,4-benzodiazepines are commonly used as tranquilizers and antidepressants in clinical practice. However, their availability and synergistic effects with alcohol make them appealing for criminal misuse. Screening for benzodiazepines can also be carried out using HPLC with UV detection, but this technique lacks both the sensitivity and specificity required for forensic applications. Furthermore, some of the low-dosage benzodiazepines, like flunitrazepam, which also exhibit shorter biological half-lives, require identification at low levels. The native fluorescence of 1,4-benzodiazepines is low, but their fluorescence emission can be markedly enhanced after acidic [55] base hydrolysis. However, this is time-consuming and is not generally attempted in modern applications. Benzodiazepines are well-suited for determination by GC-MS. A number of them are chemically stable and volatile, allowing them to be determined directly. They can also be readily derivatized,

enabling more sensitive MS responses. Their mass spectra often exhibit distinctive fragmentation pathways, aiding in precise structure determination. However, being bases, they can readily react with active sites such as the GC inlet liner, which causes problems in analysis at low levels.

Alternatively, LC-MS/MS is quite often the method of choice; it offers the ability to handle polar and thermally labile compounds without derivatization, as well as higher sensitivity. GC-MS requires derivatization but can provide more robust and reproducible results for thermally stable compounds. It is less affected by matrix effects compared to LC-MS/MS and gives spectra that can be searched against commercially available databases. Milk-based alcoholic drinks, such as whiskey creams, are a popular beverage, but represent a complex sample matrix due to containing proteins and fatty acids, several of which can interfere with extraction and quantification. Famiglini et al. [56] have investigated the possibility of determining the eight benzodiazepines, diazepam (Valium), chlordiazepoxide (Librium), clobazam, flunitrazepam (Rohypnol), bromazepam, flurazepam, nitrazepam (Mogadon), and clonazepam (Figure 4) in milk-based alcoholic drinks (whiskey creams) using a QuEChERS-based extraction method before quantification by GC-MS. To simulate realistic crime scene scenario conditions, 0.5 mL of whiskey cream (the typical residue volume found at the bottom of a glass) was diluted with Millipore water to a final volume of 10 mL. An aliquot of 10 mL of acetonitrile was added, and the resulting mixture was manually shaken for one minute before being placed in the extraction tube. This was stirred for one minute and then centrifuged. The supernatant (10 mL) was collected and concentrated to 1 mL under a nitrogen flow. The final volume was transferred to the purification tube, manually shaken, and centrifuged. The supernatant (0.5 mL) was collected, and the final volume was adjusted to 0.5 mL with acetonitrile. A 5.0 μ L aliquot of internal standard (Medazepam) was added to give a final concentration of 0.5 μ g/mL. One microlitre of the resulting solution was then introduced to the GC-MS. The mass spectrometer was operated in SIM mode, and the limits of detection and limits of quantitation were determined to be in the range of 0.02–0.1 and 0.1–0.5 μ g/mL, respectively. Whiskey cream beverages fortified with commercial drugs at 20 μ g/mL gave percentage recoveries of between 47% and 64% and RSDs between 11% and 14% for all eight benzodiazepines.

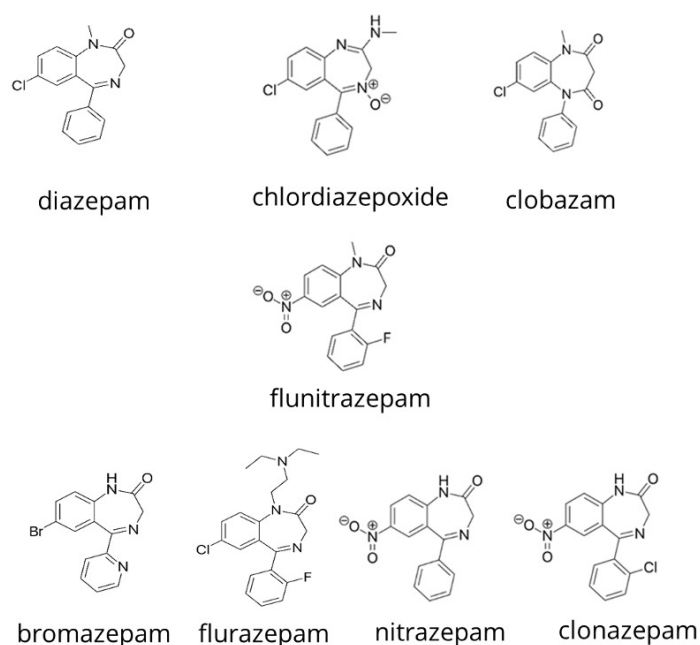


Figure 4. Structures of benzodiazepines studied by Famiglini et al. [56] in milk-based alcoholic drinks, such as whiskey creams.

The possibility of determining benzodiazepines in beer and peach juice by full scan GC-MS has been reported [57]. The compounds were extracted from spiked drinks by LLE with chloroform/isopropanol 1:1 (*v/v*). Benzodiazepine pills containing flunitrazepam, clonazepam, alprazolam, diazepam, and ketamine (Figure 5) were used to fortify samples of peach juice and beer. The samples were fortified at concentrations that reflect the approximate doses that cause peak drug response and amnesia. An aliquot of 1.0 mL of the fortified beverage was then extracted with 1 mL of a 1:1 (*v/v*) solution of chloroform/isopropanol. The resulting organic extract was then evaporated under nitrogen, reconstituted in 0.5 mL internal standard (medazepam) solution, and introduced to the GC-MS using a scan range of *m/z* 50–600. The extracted ion chromatograms were used to resolve the analytes and internal standard peaks from the total ion chromatograms.

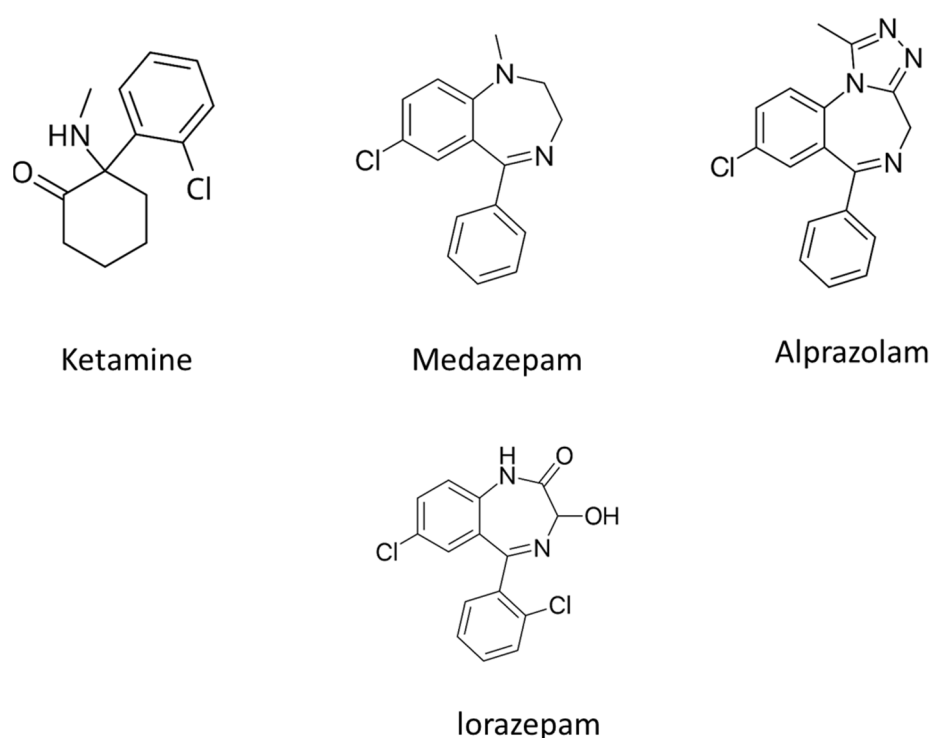


Figure 5. Structures of ketamine and the benzodiazepines studied by Acikkol et al. [57] in peach juice and beer.

Blood and urine samples are commonly collected in cases of DFSA. However, a number of these drugs have short half-lives [9]. Accordingly, there is interest in alternative samples such as the possibly spiked beverages and their residues. Consequently, there is interest in understanding the stability of drugs in various beverages. Gautam et al. [58] investigated the behavior of three benzodiazepines (diazepam, flunitrazepam, and temazepam) in five drinks: an alcopop (flavored alcoholic drink), a beer, a white wine, a spirit, and a fruit-based non-alcoholic drink (J2O). The stability of the benzodiazepines under two different storage conditions, uncontrolled room temperature and refrigerator (4 °C), were observed over a 25-day period. Reportedly, all drugs could be detected in all beverages investigated over this period. Diazepam was found to be stable in all beverages, except in J2O, under both storage conditions. The stability of flunitrazepam changed after being stored in both wine and J2O. This was concluded to be due to the pH or alcohol content, as both beverages have a pH of 3.2, and the investigated wine had an ethanol concentration of 12.5%, while J2O was alcohol-free. Temazepam is also degraded in all drinks apart from beer stored at 4 °C. The stability of the benzodiazepines varied by beverage type, with J2O showing significant changes for all substances investigated. Factors like the pH, alcohol content, extraction,

and method of analysis might affect the stability of the drugs, but this investigation was unable to reveal any clear patterns.

Solid-phase extraction (SPE) combined with dispersive liquid–liquid microextraction was used to extract trace amounts of diazepam, midazolam, and alprazolam from water, tap water, fruit juices, and urine [59]. The analytes were adsorbed onto octadecyl silica SPE columns from 60 mL sample volumes. After elution with acetone, the eluent was injected into water, extracted, and centrifuged. The sedimented phase was analyzed by GC-FID. The method showed low detection limits (0.02–0.05 µg/L), with a linear range (0.1–100 µg/L).

Jain et al. [60] explored the possibility of using fabric phase sorptive extraction (FPSE) combined with GC-MS for the determination of sedative-hypnotic drugs in food and drink samples. Fabric phase sorptive extraction is a sample preparation technique where the extraction medium is a fabric substrate coated with a sol-gel sorbent, a thin layer of an inorganic or organically modified inorganic polymer, enhancing the ability of the fabric to interact with and retain analytes. The FPSE membrane is immersed in the sample and stirred to enhance interaction between the analytes and the FPSE membrane. After extraction, the membrane is back-extracted in a small volume of solvent, and the resulting solution is introduced to the GC-MS. Beverage samples of flavored milk, juice, water, tea, and beer, along with food samples of chocolate, cream, and cake, were investigated. Sol-gel-coated FPSE membranes were coated with Carbowax 20M (CW-20M) and used for the extraction of food and drink samples that were fortified with diazepam, chlordiazepoxide, and ketamine and diluted with ultrapure water adjusted to pH 12. Extraction was undertaken following the dilution with ultrapure water and adjustment to pH 12. The FPSE membranes were then immersed in the prepared sample, which was stirred for 45 min. The exposed membrane was then transferred to an Eppendorf tube containing 0.5 mL of methanol for 10 min to desorb the analytes. A suitable aliquot of this was then examined by GC-MS. Ion-extracted chromatograms were obtained using full scan GC-MS with subsequent processing. The method was reported to be linear over the 0.3–10 µg/mL range, with the R^2 values ranging from 0.996 to 0.999. Detection limits of between 0.020 and 0.069 µg/mL for the liquid samples and 0.056 and 0.090 µg/g for the solid samples were reported. The FPSE-based GC-MS method was successfully applied to real forensic food samples involved in drug-facilitated crimes, demonstrating its effectiveness in detecting diazepam, chlordiazepoxide, and ketamine residues.

Jain et al. have also investigated the use of the related technique of cellulose paper sorptive extraction (CPSE) [61] for the determination of lorazepam residues in food and tea samples using GC-MS (Figure 6). Samples of tea were diluted and adjusted to pH 12. Pieces of cellulose paper (1.5 cm × 1.5 cm) were introduced into the diluted food matrices and stirred on a rotary shaker at 200 rpm for 30 min. The cellulose papers were then dried and the adsorbed lorazepam was back-extracted into 2 mL of methanol. The methanol extract was investigated by GC-MS in the SIM mode using m/z 275, 303, 239. The method was reported to be linear over the 0.2–10 µg/mL range, with R^2 values ranging from 0.996 to 0.998. A LOD of 0.054 µg/g for cream biscuits and 0.05 µg/mL for the tea samples, with a LOQ of 0.18 µg/g for cream biscuits and 0.16 µg/mL for the tea samples, was reported. The method was applied to real forensic food samples involved in drug-facilitated crimes, demonstrating its effectiveness in obtaining cleaner extracts for the determination of lorazepam residues.

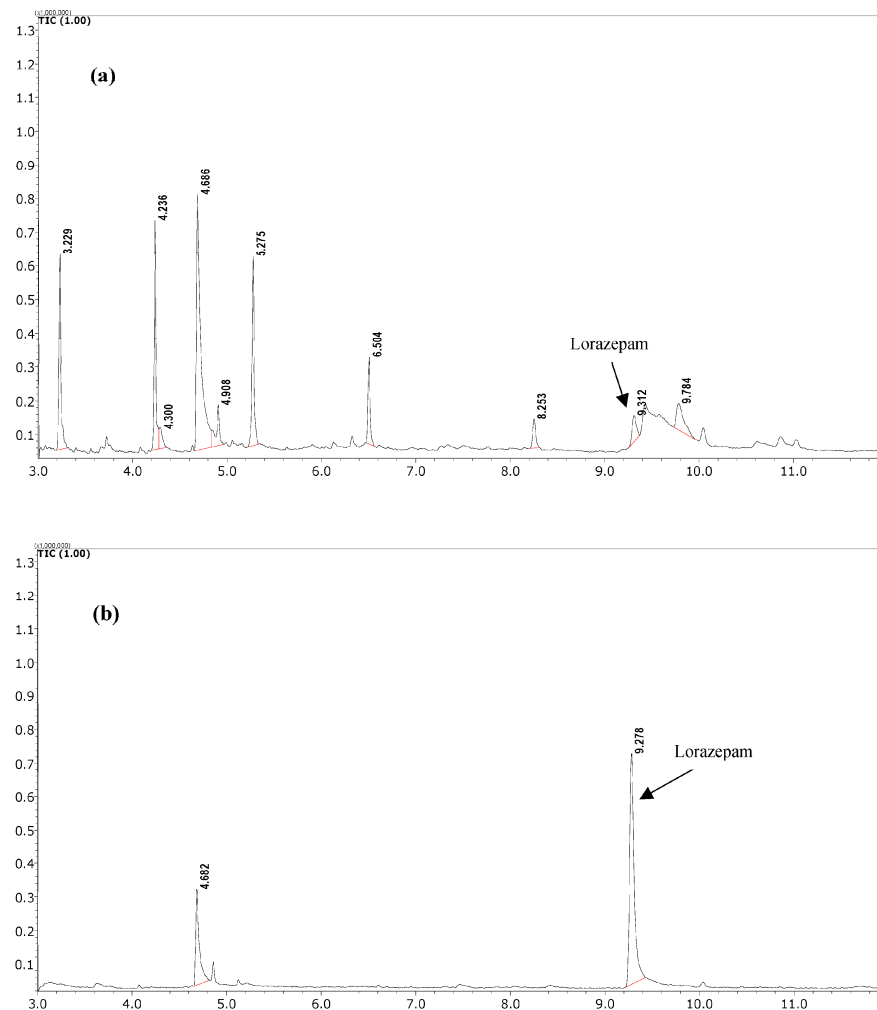


Figure 6. Comparison of sample clean-up capacity of (a) LLE and (b) CPSE in a real forensic sample (tea sample from case 1) in TIC mode. Peak identification: caffeine at 4.68 min; lorazepam at 9.29 min. From reference [61].

3.5. Other Drugs

As well, reports have also shown issues relating to the deliberate use of drugs in the manufacture and formulation of beverages themselves. The composition and drugs used to formulate these beverages are broad, and the resulting names they are known by are equally broad. One notable example is that which is commonly sold as “Dirty Sprite” [62], a preparation prepared from mixing soft drinks with cough medicines containing codeine and promethazine. The GC-MS determination of both codeine and promethazine in such beverages has been recently reported by Rosenberger et al. [62]. Samples were extracted following a modification of the liquid–liquid extraction method described by Meatherall [63]. Following adjustment to $\text{pH} \geq 9$ with ammonium hydroxide solution, a sample aliquot of 1.0 mL was extracted with an equal volume of 1-chlorobutane. The resulting extract was then blown down to dryness, reconstituted in 0.1 mL of methanol, and introduced to the GC-MS. Screening was undertaken by GC-MS and was reported to reveal the presence of promethazine, dihydrocodeine, codeine, and cocaine (Figure 7). Quantification was undertaken using the SIM mode, and concentrations of between 68 and 75 mg/L of promethazine and 130 mg/L of codeine were recorded. The presence of other drugs, such as cocaine at 3.4 mg/L and dihydrocodeine at 91 mg/L, was also reported. Further screening by LC-MS/MS did not reveal the presence of any other drugs.

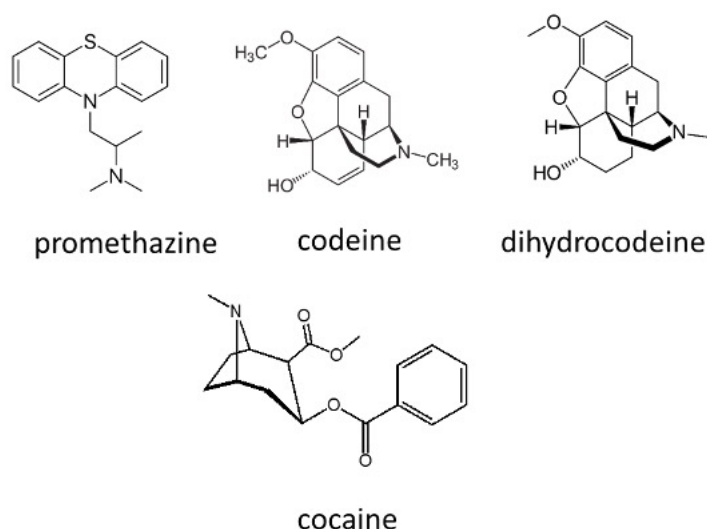


Figure 7. Structures of promethazine, codeine, dihydrocodeine, and cocaine.

Phonchai et al. [64] have investigated what is known colloquially as a “lean cocktail”, an improvised drink made from mixing cough or prescription medicines with a beverage. It is also sometimes referred to as a “dirty sprite” amongst other names. The Phonchai et al. [64] investigation focused on the determination of tramadol, diphenhydramine, codeine, promethazine (Figure 8), and caffeine in “Lean Cocktails” obtained from five high schools located in the Songkhla, Satun, and Yala provinces of Southern Thailand. The authors developed a “dilute and shoot” GC-FID-based method for nine “Lean cocktail” samples. Aliquots of 1.0 mL of the sample were filtered and then diluted with 1:5 methanol, and a suitable aliquot was directly introduced to the GC-FID. Three of the samples were reported to have contained just tramadol at levels between 195 and 859 mg/L, and another three only contained promethazine at levels between 71 and 87 mg/L. Both tramadol and promethazine were detected in a further three of the samples at levels between 179 and 576 mg/L and 7 and 47 mg/L, respectively. None of the samples were reported to have contained caffeine, codeine, or diphenhydramine. The injector was held at a temperature of 260 °C, with the initial GC column temperature being set at 120 °C for 1.0 min before being ramped to 240 °C at a rate of 10 °C/minute and held isothermal for 4.0 min. The temperature was then increased to 280 °C at 20 °C/minute and held at this temperature for 4.0 min.

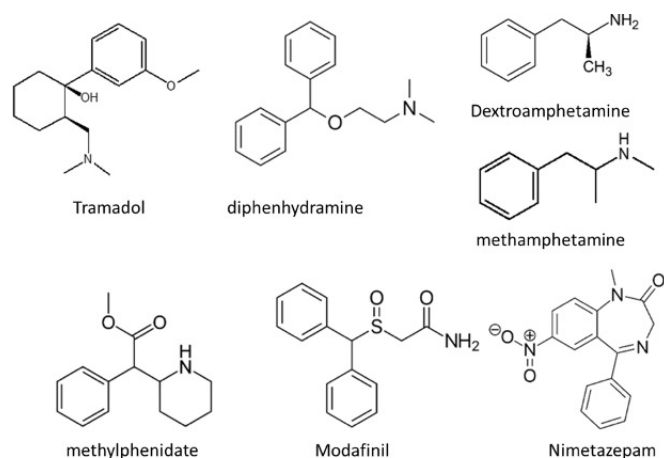


Figure 8. Structures of tramadol, diphenhydramine, dextroamphetamine, methamphetamine, methylphenidate, modafinil, and nimetazepam.

The fabrication of SPME fibers modified with graphene oxide and the metal–organic framework (MOF), zeolitic Imidazolate Framework-8 (GO@ZIF-8 MOF), along with a molecularly imprinted polymer (MIP), has recently been reported [65]. The SPME was used for the extraction of the amphetamines dextroamphetamine, methamphetamine, methylphenidate, and modafinil (Figure 8). Their levels were then determined by GC-MS in the SIM mode in several beverages and snacks. Following the optimization of the GO@ZIF-8 MOF MIP SPME, a linear range of 0.1–400 µg/L with an $R^2 > 0.9976$ was reported for the compounds that were investigated. The detection limits for amphetamine derivatives were reported to range from 0.023 to 0.033 µg/L. A wide array of samples was investigated, including cappuccino, espresso, Nescafe coffee, energy drinks, and ginseng drinks. Food samples, including breakfast cereal, dark chocolate, Gummi candies, truffles, marshmallows, and toffee, were also investigated. This was undertaken by, first, homogenizing 10 g of the sample. A 500 mg aliquot was then taken and dissolved in 200 mL of water with the aid of ultrasound. Following further dilution with deionized water and adjustment to pH 3.5, the sample was then extracted with the GO@ZIF-8 MOF/MIP-SPME by immersing 1 cm of the fiber into the sample for 35 min with stirring. The fibers were then transferred into 1-octanol for desorption, which was aided by ultrasonication. The resulting solution was evaporated to dryness under nitrogen, and the residue was reconstituted in 20 µL of methanol for GC-MS analysis. The sample extracts were introduced in the splitless pulse mode with a temperature program that started at 67 °C and then ramped up to 270 °C.

Vortex-assisted dispersive liquid–liquid microextraction-gas chromatography (VADLLME-GC) has been investigated for the determination of ketamine, nimetazepam, and xylazine [66]. The study focused on the application of a novel extraction method for these drugs in various forms of spiked mineral water, carbonated drinks, tea, beer, and orange juice for quantification by GC-FID. Beverages were spiked with known quantities of the drugs and prepared in three forms: liquid, droplet, and dry residues. The extraction involved using dichloromethane as the extraction solvent and ethanol as the dispersive solvent. The study optimized the extraction parameters of the VADLLME procedure, including the choice and volume of solvents, the vortex agitation time, the centrifugation rate and time, and pH adjustment. The samples were vortexed and centrifuged, and the organic phase was collected and evaporated before introduction to the GC. The method was reported to give a LOD of 0.08 µg/mL for ketamine and xylazine, and 0.16 µg/mL for nimetazepam. Higher recoveries were achieved for the liquid samples (51–97%) compared to the droplet (48–96%) and dry samples (44–93%). The intra-day and inter-day precision (% RSD) were below 7.2% and the accuracy (% recovery) was between 92.8% and 103.5%.

4. Discussion

Gas chromatography is a powerful analytical technique. However, it has some limitations in the determination of drugs in beverages. It is best suited for the determination of volatile compounds, and many drugs and their metabolites are not sufficiently volatile without derivatization, making them unsuitable for direct GC analysis. Some drugs may also decompose at the temperatures required for GC analysis. A notable number of applications have focused on the determination of GHB. This is believed to reflect the general switch in analytical laboratories to using techniques based on liquid chromatography-mass spectrometry (LC-MS). Liquid chromatography-mass spectrometry is often preferred for analyzing drugs in beverages because it can handle non-volatile and thermally labile compounds more effectively. However, this is generally only true for compounds that can give ions or distinct transitions large enough to demonstrate some degree of uniqueness, which is a problem when attempting the determination of GHB by LC-MS. Different methods of

criminal spiking other than drink spiking should be investigated, for example, injection needle spiking and illegal additions to food.

Table 1 summarizes the GC applications given in this review. Papers published on the determination of drugs in beverage samples using GC or GC-MS have principally focused on GHB, GBL, and benzodiazepines. The predominance of work focused on GHB and GBL is believed to be the result of the problems these drugs present to the commonly employed alternative approach of LC-MS. The determination of GHB and GBL is complicated in LC-MS/MS analysis, with positive mode electron spray ionization producing only one product ion in significant enough abundance. In the alternative negative mode, three abundant transitions are recorded. This makes negative mode electron spray ionization potentially more attractive analytically in terms of its sensitivity and selectivity [67,68]. However, the prior reversed-phase chromatographic separation step requires the use of an acidified mobile phase for the separation of GHB to ensure that it is in its non-ionized, non-polar form. In addition, the use of a low-pH mobile phase means that negative mode electron spray ionization cannot be readily applied, as GHB will not be present as an anion (pKa 4.6).

Comparing the last 10 years' publications with those published in the previous 10 years, before 2015, shows there to be an equal number of publications made on the determination of benzodiazepines, GHB, and GBL in these two periods. However, the number of publications on the determination of other drugs has increased in the last 10 years compared to the previous 10-year period. It is presumed that this trend in analyzing drugs other than these main classes will continue to increase with the changing trends in drug usage.

The evolving drug market requires ongoing updates to analytical methods to keep pace with new substances. Gas chromatography can potentially detect these compounds, especially when it is coupled with sophisticated detectors such as mass spectrometry detectors.

Future developments in the application of gas chromatography (GC) to determine drugs in drinks and beverages should focus on several key areas. There is a growing emphasis on incorporating green chemistry principles into GC methods. This includes reducing the use of harmful solvents and minimizing waste to make the process more environmentally friendly. Advances in detector technology, such as developing more sensitive mass spectrometers, are improving the ability to detect and quantify trace amounts of drugs in complex beverage matrices. The trend towards the automation and miniaturization of GC systems is making their analysis faster and more efficient. Portable GC systems [69] are being developed for on-site testing, which could be particularly useful in forensic and regulatory settings. The use of comprehensive two-dimensional gas chromatography (GC $\times$ GC) is expanding [70]. This technique offers enhanced separation capabilities, allowing for a better resolution of complex mixtures and more accurate identification of compounds. Innovations in sample preparation, such as solid-phase microextraction (SPME) and dispersive liquid–liquid microextraction (DLLME), are being integrated with GC to enhance the extraction and concentration of drugs from beverages. The application of advanced data analysis techniques, including machine learning, is helping to interpret complex GC data more effectively. This can lead to the more accurate identification and quantification of drugs in beverages.

Table 1. Determination of drugs in beverage samples by gas chromatography and gas chromatography-mass spectrometry.

Analytes	Sample Matrix	Derivatisation	Sample Pre-Treatment	Type of GC	LOD/LOQ (mg/L)	Comments	Reference
GHB	Beer, wine, rum, Tequila, fruit juice and tonic water	BSTFA 1% TMCS	Ion-exchange solid phase extraction.	SIM GC-MS. HP-5MS (30 m × 0.25 mm I.D, 0.25 µm film	LOQ 0.0067 and LOD 0.0045.	Internal standard GHB-d ₆ . Naturally occurring levels of GHB determined.	[46]
GHB	Tonic water and lemon-flavored tonic water	MSTFA	liquid-liquid extraction with acidified ethyl acetate	MRM GC-MS/MS. HP-5MS column 30 m × 0.25 mm × 0.025 µm).	LOQ 0.0025 and LOD 0.0013	Internal standard GHB-d ₆ . Naturally occurring levels of GHB determined.	[47]
GHB and GBL	Beer, juice, spirits, liqueurs, sherry, port, white and red wine	TMS for GHB and conversion via acidification to give total GBL.	LLE with chloroform.	Full scan GC-MS and GC-FID. DB5 MS capillary column, 30 m × 0.25 mm, 0.25 µm film thickness.	GHB LOD 3.0	Internal standard GHB-d ₆ . Naturally occurring levels of GHB and GBL determined.	[48]
GHB	Water, Coca Cola, beer, lemonade.	On-fiber derivatization with BSTFA–TMCS (99:1).	SPME.	GC-MS. A 30-m HP5-MS column with a 0.25 µm film thickness and 0.25 mm	LOQ 1.5.	Internal standard GHB-d ₆ .	[49]
GHB and GBL	Water, beer, wine, liquor, coca cola and mixed drinks.	On-fiber derivatisation with BSTFA–TMCS (99:1).	Total vaporization SPME.	Full scan GC-MS. Extracted ion profiles were used to identify the analyte.	LOD 1.0.		[51]
GHB	Beverage samples and hair.	BSTFA 1%	Dispersive liquid-liquid microextraction with ethyl acetate following adjustment to pH 4.3 with ammonium dihydrogen phosphate.	GC-MS/MS. DB-5MS capillary column (30 m × 0.32 mm ID, 0.25 µm film.	LOD 0.0005.	Internal standard GHB-d ₆ .	[52]

Table 1. Cont.

Analytes	Sample Matrix	Derivatisation	Sample Pre-Treatment	Type of GC	LOD/LOQ (mg/L)	Comments	Reference
GHB	Water, Tropicana's cranberry juice cocktail with Barton's vodka, Coca Cola, Guinness Stouts beer, Coors Lights beer, and Willi Haags Riesling.	BSTFA + TMCS	Dilution in internal standard solution.	GHB was quantitated using the peak area of the ion at m/z 233 and derivatized GHV was quantitated using the peak area of the ion at m/z 117. HP-5, 30 m × 0.25 mm i.d. × 0.25 µm film.	1.0 pg on column.	Internal standard 1,5-pentanediol. Reverse phase HPLC also investigated.	[53]
Xylazine	Energy drink, a carbonated drink, and a fruit-based drink.	None	LLE with dichloromethane following adjustment to pH 11 using 13% sodium hydroxide solution.	Full-scan GC-MS and GC-FID. 5%-phenyl-methylpolysiloxane (HP5) capillary column (30 m × 0.32 µm i.d., 0.25 µm film thickness,	LOD and LOQ were reported at 0.08 and 0.26 respectively by GC-FID.	Internal standard 2,2,2-triphenylacetophenone	[55]
Diazepam, chlordiazepoxide, clobazam, flunitrazepam, bromazepam, flurazepam, nitrazepam, and clonazepam.	Milk-based alcoholic drinks (whiskey creams).	None.	QuEChERS based extraction.	SIM GC-MS. HP-5MS (30 m 0.25 mm i.d., 0.25 µm film thickness	LOD and LOQ were in the range of 0.02–0.1 and 0.1–0.5, respectively.	Internal standard medazepam.	[56]
Flunitrazepam, clonazepam, alprazolam, diazepam and Ketamine	Peach juice and beer.	None.	LLE with chloroform: isopropanol 1:1 (v/v).	Full scan GC-MS (m/z 50–600). Ion extracted chromatograms used. HP-5MS 30 m × 250 µm i.d. × 0.25 µm film.	LOD between 1.3 and 34.2. LOQ 3.9 and 103.8.	Internal standard medazepam.	[57]

Table 1. Cont.

Analytes	Sample Matrix	Derivatisation	Sample Pre-Treatment	Type of GC	LOD/LOQ (mg/L)	Comments	Reference
Diazepam, midazolam, and alprazolam	Tap water, fruit juices, and urine	None.	SPE combined with dispersive liquid–liquid microextraction	GC-FID. HP-5 30 m × 0.32 mm and 0.25 µm film thickness	LODs of between 0.00002–0.00005		[59]
Diazepam, chlordiazepoxide, and ketamine	Flavoured milk, juice, water, tea and beer	None.	Fabric phase sorptive extraction (FPSE)	Full scan GC-MS with subsequent processing to give ion-extracted chromatograms	LODs of between 0.020–0.069	Food samples of chocolate, cream, and cake also investigated.	[60]
Lorazepam	Tea	None.	Cellulose paper sorptive extraction (CPSE)	GC-MS in the SIM mode using m/z 275, 303, 239. Txi-5Sil MS capillary column (30 m length × 0.25 mm internal diameter × 0.25 µm film thickness) with a stationary phase of 95% dimethylpolysiloxane and 5% phenyl.	LOD 0.05	Cream biscuits also investigated.	[61]
Codeine and promethazine	“Dirty Sprite” beverage formulated from a mixture of soft drink, and cough medicine.	None.	LLE with 1-chlorobutane following adjustment to pH ≥ 9 with ammonium hydroxide solution.	Full scan and SIM GC-MS. DB-5 ms, 30 m, i.d. 0.25 mm, film thickness 0.25 µm	LOD/LOQ were 0.3/0.9 for cocaine, 0.3/1.0 for promethazine, 0.3/1.0 for dihydrocodeine, and 0.3/1.0 for codeine, respectively.	Dihydrocodeine, and cocaine also determined. Internal standards: promethazine-D ₃ , codeine-D ₃ , cocaine-D ₃ and dihydrocodeine-D ₆ .	[62]

Table 1. Cont.

Analytes	Sample Matrix	Derivatisation	Sample Pre-Treatment	Type of GC	LOD/LOQ (mg/L)	Comments	Reference
Tramadol, caffeine, diphenhydramine, codeine, and promethazine	“Lean Cocktail” An improvised drink containing prescription drugs.	None.	Beverage filtered and diluted five times in methanol and introduced to the GC.	GC-FID. DB-5 capillary analytical column (30 m × 0.25 mm i.d. × 0.25 µm film thickness).	LOD 1.25 for tramadol and codeine and 2.5 for caffeine, diphenhydramine, and promethazine. LOQ 2.5 for tramadol and 5.0 for the other analytes.	“Dilute and shoot” method employed.	[64]
Dextroamphetamine, methamphetamine, methylphenidate, and modafinil.	Cappuccino, espresso, Nescafe coffee, energy drinks, ginseng drinks.	None.	GO@ZIF-8 MOF MIP SPME	GC-MS in the SIM mode. Column 25 m × 0.32 mm film thickness of 0.5 µm.	LOD between 0.000023 and 0.000033	Breakfast cereal, dark chocolate, gummi candies, truffles, marshmallows and toffee also investigated.	[65]
Ketamine, nimetazepam, and xylazine	Mineral water, carbonated drink, tea, beer, and orange juice	None.	Optimised VADLLME procedure	5%-phenyl-methylpolysiloxane (HP-5) capillary column (30 m × 0.32 µm i.d., 0.25 µm film thickness).	LOD, nimetazepam 0.16; ketamine and xylazine, 0.08. LOQ ranged from 0.26 to 0.53.	Internal standard 2,2,2-triphenylacetophenone.	[66]

BSTFA, N,O-bis(trimethylsilyl)trifluoroacetamide; GC × GC, two-dimensional gas chromatography; GO@ZIF-8 MOF MIP SPME, graphene oxide modified zeolitic imidazolate framework molecularly imprinted polymer solid-phase microextraction; HPLC, high performance liquid chromatography; LLE, liquid-liquid extraction; LOD, limit of detection; LOQ, limit of quantification; MIP, molecular imprinted polymer; MRM, multiple reaction monitoring; QuEChERS, quick, easy, cheap, effective, rugged, and safe; SIM, select ion monitoring; SPME, solid-phase microextraction; TMCS, trimethylchlorosilane; TMS, trimethylsilyl chloride; ZIF-8, zeolitic imidazolate framework; VADLLME, Vortex-assisted dispersive liquid-liquid microextraction.

5. Conclusions

Gas chromatography and gas chromatography-mass spectrometry are powerful analytical techniques for detecting drugs in beverages, particularly in cases of drink spiking. These methods offer high sensitivity and specificity, and can identify drugs at trace levels and distinguish between compounds with similar structures. This review highlights the effectiveness of GC and GC-MS in analyzing complex beverage matrices and their ability to simultaneously detect multiple substances, providing detailed molecular information essential to forensic investigations.

Despite their advantages, GC and GC-MS face challenges such as the need for derivatization to enhance the volatility and potential thermal instability of certain drugs. The evolving drug market necessitates continuous improvement in detection techniques to keep pace with new substances. Ongoing developments in GC technology, including green chemistry integration, enhanced detector sensitivity, automation, and advanced data analysis, promise to further improve the efficiency and accuracy of drug detection in beverages.

Overall, GC and GC-MS remain indispensable tools in forensic science, offering reliable and accurate results that are crucial to legal and investigative processes. Continued advancements in these techniques will enhance their application in combating drug-facilitated crimes and ensuring public safety.

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Abbreviations

The following abbreviations are used in this manuscript:

1,4-BD	1,4-butanediol
BSA	N,O-bis(trimethylsilyl)acetamide
BSTFA	N,O-bis(trimethylsilyl)trifluoroacetamide
CAF	Caffeine
COD	Codeine
CPSE	Cellulose paper sportive extraction
DCM	Dichloromethane
DLLME	Dispersive liquid-liquid microextraction
DPH	Diphenhydramine
ECD	Electron capture detector
EI	Electron ionization
EIC	Ion extracted chromatogram
FID	Flame ionization detector
FPD	Flame photometric detector
FPSE	Fabric phase sorptive extraction
GBL	Gamma-butyrolactone
GC	Gas chromatography
GC-FID	Gas chromatography flame ionization detector
GC-MS	Gas chromatography mass spectrometry
GC-MS/MS	Gas chromatograph tandem mass spectrometry
DFSA	Drug-facilitated sexual assault

GC × GC	Comprehensive two-dimensional gas chromatography
GHB	Gamma-hydroxybutyrate
GHV	Gamma-hydroxyvalerate
GO@ZIG-8 MOF	Zeolitic Imidazolate Framework-8
HPLC	High-performance liquid chromatography
LC-MS	Liquid chromatography-mass spectrometry
LC-MS/MS	Liquid chromatography tandem mass spectrometry
LLE	Liquid-liquid extraction
LOD	Limit of detection
LOQ	Limit of quantitation
MIP	Molecular imprinted polymers
MOF	Metal-organic framework
MRM	Multiple reaction monitoring
MSTFA	N-methyl-N-(trimethylsilyl)trifluoroacetamide
PRO	Promethazine
SIM	Selected ion monitoring
SPE	Solid phase extraction
SPME	Solid-phase microextraction
TMCS	Trimethylchlorosilane
TMS	Trimethylsilyl
TMSCI	Trimethylsilyl chloride
TRA	Tramadol
TV-SPME	Total vaporization solid-phase microextraction
VADLLME-GC	Vortex-assisted dispersive liquid-liquid microextraction-gas chromatography

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