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## ANALYTICAL CHEMISTRY | RESEARCH ARTICLE

# Qualitative and quantitative analyses of methamphetamine in hair following derivatization with trifluoroacetic acid or heptafluorobutyric acid anhydride

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**Abstract:** Illicit drug use and its consequence necessitate the development of identification methods for the target drugs in biological materials. Methamphetamine (MA) is a psychotropic substance with short elimination half-life in urine and blood; however, negative consequences of MA use may last for a long time. So, its diagnosis is essential even long after MA exposure. A total of 50 hair specimens were obtained from those with a history of MA abuse from addiction treatment camps. A gas chromatography–mass spectrometry (GC-MS) analysis was developed to identify MA using trifluoroacetic acid (TFA) or heptafluorobutyric acid anhydride (HFBA) as two derivatization agents. It was indicated that these subjects were 80 and 8% negative for MA following derivatization with HFBA and TFA, respectively. The limits of detection and quantitation for derivatization with TFA were 0.2 and 0.6 ng/mg. In conclusion, use of TFA in GC-MS can afford to effectively dissolve MA out of the hair matrix. This dissolving procedure has easy procurement with high applicability and validity.

**Subjects:** Analytical Chemistry; Addiction - Drugs - Adult; Laboratory Medicine

**Keywords:** methamphetamine; human hair; GC-MS; TFA; HFBA

### 1. Introduction

The central nervous system is strongly stimulated by methamphetamine (MA), the abuse of which is on the rise in many countries, having led to acute poisoning and death. MA has also become one of the major public health concerns in Iran as the most populated Persian Gulf country (1). Some recent surveys have indicated an approximately high prevalence of MA use among adults in the general population of Tehran (7%), nationwide truck drivers (73.9%) and male body builders in Tehran

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Mehdi Forouzesh is a faculty member, Department of Forensic Medicine, Iranian Legal (Forensic) Medicine Organization, Tehran, Iran. His main focus includes forensic anthropology, forensic medicine, clinical toxicology, forensic toxicology and so forth. Of his many published articles, “Variation in Anatomical Position of Vermiform Appendix among Iranian Population: An Old Issue Which Has Not Lost Its Importance”, “Case Report: Sudden Death of a Healthy Body Packer: A Case Study” or “Complementary strategies in DNA identification of specific cases of Mina disaster victims” can be noted.

### PUBLIC INTEREST STATEMENT

Drugs of abuse, of note methamphetamine, has garnered much attention across the globe to not only identify abusers, but also to manage unprecedented consequences. As a result, this study proposed two methods how to detect methamphetamine using a direct derivatization with trifluoroacetic acid or heptafluorobutyric acid anhydride. The best method should confer easy procurement with high applicability and validity.

(13.3%) (2–4). They have pinpointed increasing physical energy, wakefulness, pleasure-seeking and professional performance as the chief cause behind MA use (2–4). On the other hand, MA use causes physical and psychological impairments in the Persian community (5, 6). Moreover, the role of MA has been specified in various fatalities, traffic and violence offences in particular (7). It has been reported that illicit drug manufacturers employ various methods and precursors for MA synthesis, thus continuous analysis of such drugs is of utmost significance in Iran (8).

Forensic and clinical practices can substantiate its abuse typically through analyses of MA and/or its metabolites performed on urine and blood samples obtained from abusers. It has been observed that some factors exert undesirable effects on urine and blood analyses of the parent drugs, namely short drug-detection window following their intake and the pH of urine. Accordingly, another more appropriate biological material, of note hair, is required to determine drug use over a long period of time (9–11). Hair holds a history of drug usage due to its slow growth and absorption of any drugs and their metabolites over a very long period in comparison with other biological materials (12). More to the point, hair has special features including easy procurement, stable structure, small size, low amount of artificial additives, low potential of contamination with diseases, desirable for replicate measurements using the same specimen and easy storage at ambient temperature (13). Several chromatographic methods have been proposed to examine concentration of amphetamines for extraction of the targets from hair matrix (14–16). The determination of free amphetamines by employing gas chromatograph (GC) or gas chromatograph coupled with mass spectrometry technology (GC-MS) encounters some challenges in terms of sensitivity and reproducibility as a result of adsorption on and interaction with the column (17). Additionally, interference is another notable issue for MA owing to the similarity in the degradation pattern (18). These reasons necessitate derivatization for the GC analysis of these types of compounds. A great variety of derivatization agents for detection of MA by GC-MS has been documented in the pertained literature, such as the trifluoroacetylation reagent *N*-methyl bis(trifluoroacetamide) (19), *N*-methylbis trifluoroacetamide, *N*-methyl-*N*-trimethylsilyltrifluoroacetamide and trimethylchlorosilane (20), 2,2,2-trichloroethyl chloroformate (21), (*S*)-heptafluorobutylpropyl chloride (13), *N,O*-Bis(trimethylsilyl)trifluoroacetamide (BSTFA) (22). Considering the characteristics of high accuracy, specificity and simplicity, GC-MS methods have been vastly applied for the analysis of MA and other drugs (13). Overall, GC-MS is founded upon electron ionization, however, positive and negative chemical ionization has currently been utilized, as well (23, 24). Previously, liquid chromatography with tandem mass spectrometry (25, 26) and hyphenated with time-of-flight (TOF) MS (26, 27) or ion trap MS (28) have been shown promising utility for screening of drugs of abuse in hair analysis that enjoy promoted sensitivity along with detection of thermally labile compounds. Cordero et al. employed presented a method to simultaneously quantify opiates, amphetamines, cocaine, diazepam and its metabolites. Using a selected ion-monitoring programme and full scan, maximum information can be obtained from a single sample of hair (20). Orfanidis et al. employed a simple and fast method with considerable sensitivity and accuracy to extract drugs of abuse from three major classes at the same time using small quantities of hair (22). Liu et al. proposed a relatively simple protocol to simultaneously detect drugs/metabolites derived from both amphetamine and opiate drug categories without any chemical derivatization step (13). Indeed, many of these methods consist of a long extraction step, incubation for 12–18 h, and derivatization. To perform such analyses within a short period of time, some have reported new methods with no derivatization procedure (25, 29). Yet, derivatization appears necessary to enhance the chromatographic behaviour and detection response of drugs. The present study aimed at developing direct derivatization of the extract with trifluoroacetic acid (TFA) or heptafluorobutyric acid anhydride (HFBA) and compare the potential of each extraction method.

## 2. Materials and methods

### 2.1. Chemicals and reagents

Water for chromatography, 2-propanol and methanol for analysis were purchased from Merck (Darmstadt, Germany). Trifluoroacetic acid (TFA) and heptafluorobutyric acid anhydride (HFBA) for

GC derivatization were obtained from Sigma-Aldrich (Buchs, Switzerland). All organic solvents such as NaOH and ethyl acetate were purchased from Merck (Germany, analytical grade).

## **2.2. Biosamples**

The study was given approval by the Research Deputy in Iranian Legal (Forensic) Medicine Organization. Hair samples were obtained from three addiction treatment camps in Zanzan, Iran. Written consent was obtained from all the subjects. They were all male who admitted to these camps within 10 days following acceptance into the programme. Moreover, they had used MA at least three consecutive months prior to their admission in these camps. Those participants with dyed hair or using cosmetic/hygienic treatment were ruled out from the study. Therefore, all hair samples had natural colour. Hair sampling was performed from posterior vertex. A tuft of hair about 1 cm wide and 3 cm long was taken at scalp level. Of all hair specimens collated, 50 samples were fixed in aluminium foil for transferring into the Department of Forensic Medicine in Zanzan.

## **2.3. Sample preparation**

Hair specimens were washed and decontaminated by placing sequentially into 2 mL of water followed by three washes with 2 mL of 2-propanol, water and methanol. Every sample was exposed to every solution for 5 min and then removed by a sterile dressing. With drying at room temperature, the specimens were finely cut into under 2-mm fragments. Thereafter, 50-mg hair was mixed with a solution containing TFA:methanol (1:9). To accelerate extraction of hydrolyzed hair, the solutions were shaken in ultrasonic bath for 20 min, and incubated in water bath at 50°C for 20 min prior to the next ultrasonic shaking for 10 min. Afterwards, the solutions were centrifuged for 5 min at 3,500 rpm. The supernatant was removed and the remaining precipitate was dried with slow stream of nitrogen. A 0.5 mL of methanol was added to each sample before injecting into GC-MS.

As for HFBA, in a similar vein, hair specimens (50 g) were mixed with a 1 mL of 1 M NaOH at 50°C for 20 min. The samples were extracted with 1 mL of ethylacetate twice. After drying, 100 mL of methanol:HCl (99:1) was added to the samples, which were reconstituted in 50 µL of HFBA and 50 µL of ethylacetate at 60°C for 30 min. With shaking for 10 min, the extracts were dried with slow stream of nitrogen. 100 µL of ethylacetate was added to each extract and 1 µL of which was injected into GC-MS.

## **2.4. Instruments**

Analyses were conducted by employing an Agilent GC7890A GC equipped with an Agilent MC5975C MS. Moreover, an HP5-MS analytical column (30 m × 0.25 mm i.d.) was used with helium as carrier gas (1.5 mm/min). The temperature programme was in such a way that the initial temperature was 50°C for 1 min, and then reached to 300°C at a rate of 20°C/min. The temperature of injector, transfer line, ion source and quadrupole was 250, 300, 230 and 150°C, in order. An ionization energy was 70 eV (splitless mode, scan range 30–450 amu). The injection volume was 0.4 µL. Mass libraries included NIST, Wiley and Pest. In the long run, MPV was also used for interpretation of the database results from extraction with TFA.

## **2.5. Preparation of standard solutions and method validation**

Methamphetamine hydrochloride (MA-HCl, 99.42% purity) from Sigma-Aldrich (USA) was used as a standard stock solution to obtain three different concentrations 1,500, 250 and 35 ng/mL. Thereafter, a total of 1 mL was added to 50 mg blank hair samples to have corresponding concentrations of 30, 5 and 0.7 ng/mg of hair to measure the validity of direct derivatization with TFA. As for HFBA, these concentrations were 8, 15 and 40 ng/mg. The enrichment factor (EF) and extraction recovery (ER) were calculated as described by Xu et al. (30). Moreover, the accuracy and precision of the methods were measured using these three concentrations. Each measurement was carried out daily in five replicates. Limit of detection (LOD) and limit of quantitation (LOQ) values were investigated, as well.

**Table 1. Quantitative characteristics of the method containing derivatization with TFA**

Derivatization agents	Equation	$r^2$	LOD (ng/mg)	LOQ (ng/mg)	EF	ER (%)	Precision (%)	Accuracy (%)
TFA	$y = (0.9828 \pm 0.0748)x + (0.1578 \pm 0.3097)$	0.9998	0.2	0.6	18.5	92.6	7.5	8.1
HFBA	$y = (0.7692 \pm 0.1760)x - (0.6051 \pm 2.8439)$	0.9983	2.5	7.5	19.5	63.7	28.3	41.2

### 3. Results and discussion

The United Nations Office on Drugs and Crime (UNODC) emphasizes that around 5% of the total world's population reported illegal drug use in 2010 (31). More recently, MA use as a recreational drug has been on the rise so that it is now referred as the second most widely misused substance (32). Moreover, data from Asian countries substantiate great levels of use, which can be viewed as a cultural phenomenon (32). Noteworthy, MA plays a key role in criminality and social decline (33, 34). Accordingly, it constitutes a notable public health and social issue. Hair matrix provides a history of the drug use with enough of evidence based on a retrospective evaluation from months to years (35). There has been a myriad of investigations on this alternative to examine the common illicit drug exposure and interpret the resultant data in various clinical as well as legal settings. Of all techniques applied in this respect, the reliability of GC-MS is widely known, having led to the development and validation of specific and sensitive methods for determination of the drug in hair sample. In forensic context, a delay in sampling is more likely to occur, which, in turn, the frequency of negative results from the pertained analysis on blood and urine samples may increase. Thus, it is of utmost significance to have screening methods capable to detect the target drug in a single analysis and even applicable for large samples (36). Moreover, analysis of hair by means of GC-MS is contingent upon chemical derivatization, which is expected not to impose undesirable influences on the structure of the target drug while paving the way for identifying and confirming its usage. It has been reported that the direct derivatization procedure sounds more desirable than the other methods (21, 37). The present study deals with determination of MA in hair specimens by GC-MS following direct derivatization with TFA and HFBA. The participants of this study were all male with an average age of  $38.9 \pm 10.8$  years (Minimum: 21 years; Maximum: 63 years). Of all subjects, 88% were also found with simultaneous smoking. Non-therapeutic use of methadone and opium was reported by 62.1 and 52.1% of the participants. The findings exhibited that of the HFBA-derivatized samples, 80% were found negative for MA. This was a far cry from the results of derivatization with TFA indicative of 8% negative for MA; put differently, this method detected 92% positive for MA and accordingly appeared effective for these assessments in hair among MA abusers. Such conflicting findings maybe related to the dissolving procedures using acidic (TFA) and alkaline (NaOH) hydrolysis. Initially, 0.1 M NaOH was used for derivatization with HFBA, which further failed to digest the hair matrix at 45–50°C for 18 h. The subsequent addition of 0.1 M HCl can afford to dissolve out MA from the hair matrix; however, its structural integrity was lost. Therefore, the digestion system containing TFA (acidic hydrolysis) can afford to dissolve out MA without a solid-phase extraction (SPE) procedure and any negative impacts on its structure. What is more, analytical properties such as, LOD, LOQ, EF, ER, accuracy and precision were calculated for derivatization with TFA and HFBA. As can be seen in Table 1, the corresponding values for derivatization with TFA were 0.2, 0.6 ng/mg, 18.5, 92.6 and 7.5%, respectively. The related chromatograms of the standard, blank and hair samples were provided as Supplementary Materials.

Bassindale (38) in a quantitative analysis of MA utilized 0.1 M HCl at 37°C for extraction, which was adjusted to pH 7 by applying 1 M NaOH. To complete the extraction, SPE was also performed prior to the instrumental measurement by LC-MS/MS. The merit of the procedure used in this study regards hair digestion without using SPE and thereby saving time and costs. In another study, hair samples underwent alkaline digestion followed by extraction with ethyl acetate and derivatization with HFBA (39). On the contrary, we successfully dissolved MA out of the hair matrix without the use of HFBA,

which was associated with lower cost. Likewise, a mix of TFA and methanol was used for hair digestion before conducting microwave-assisted extraction. Although this procedure is of high potential, less time and simultaneous extraction, a microwave oven for the forensic laboratory use is associated with some limitations in working conditions (40).

#### 4. Conclusion

The findings of this study showed that GC-MS can successfully identify the presence of MA among drug-addicted abusers without the need for SPE and HFBA. Of two procedures used in this study, derivatization with TFA detected 92% positive for MA, suggestive of high applicability and appropriate reliability for effective hair testing. Moreover, use of TFA for both hydrolysis as well as derivatization in GC-MS measurement is time- and cost saving, which is paramount for large populations in the forensic evaluations.

#### Supplementary material

The supplementary material for this paper is available online at <https://doi.org/10.1080/23312009.2018.1453594>.

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#### Competing interests

The authors declare no competing interest.

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