Original article

Analysis of amphetamine and methamphetamine contents in seized tablets from Jazan, Saudi Arabia by liquid chromatography-mass spectroscopy (LC-MS/MS) and chemometric techniques

Hassan A. Alhazmi [a,b,*], Waquar Ahsan [b], Mohammed Al Bratty [b], Sadique A. Javed [b], Karam A. El-Sharkawy [b], Asaad Khalid [a], Hussain M. Alsalem [c], Ahmed M. Hakami [c], Mohammad A. Attafi [c], Magbool E. Oraiby [c]

[a] Substance Abuse and Toxicology Research Centre, Jazan University, P. Box No. 114, Jazan, Saudi Arabia
[b] Department of Pharmaceutical Chemistry, College of Pharmacy, Jazan University, P. Box No. 114, Jazan, Saudi Arabia
[c] Poison Control and Medical Forensic Chemistry Center, General Directorate of Health Affairs, Jazan, Saudi Arabia

A R T I C L E I N F O

A B S T R A C T

A number of illegal amphetamine tablets were seized from three different cities of Jazan province of southern Saudi Arabia and were analyzed for amphetamine and methamphetamine contents using LC-MS/MS technique. Analyses were performed using a previously reported method taking 0.1 M ammonium formate buffer (85%) and 15% acetonitrile with 0.1% formic acid as mobile phase with a total runtime of 12 min. This method was successfully applied for the routine analysis of amphetamine and methamphetamine in the seized tablets using amphetamine-D5 and methamphetamine-D5 as internal standards. Hierarchical cluster analysis was performed to establish the similarity between samples. The retention times (RT) for internal standard, amphetamine and methamphetamine were observed to be within 6.0–7.1 min. Ten tablet samples from each city were subjected to analysis and the amount of amphetamine in all the samples were found to be in the range of 9.07–14.77 mg, whereas, the amount of methamphetamine ranged from 0.12 to 0.24 mg in each tablet. Hierarchical cluster analysis showed presence of five clusters of samples indicating different characteristics and possible sources of amphetamine tablets. The largest cluster consisted of 15 samples which are expected to be of the same origin. Both amphetamine and methamphetamine are considered to be illegal products and their illegal trade and use is banned in many countries including Saudi Arabia. Therefore, there is an urgent need of strict regulations worldwide to check the illicit trafficking of these psychoactive substances and should be considered on priority.

1. Introduction

Amphetamine, chemically, alpha-methylphenethylamine belongs to the phenyethylamine class of substances known for their potent central nervous system (CNS) stimulating action. Therapeutically, it is used for the treatment of attention deficit hyperactivity disorder (ADHD), obesity and narcolepsy (sleep disorder).

Sometimes, it is prescribed off-label for the treatment of chronic pain as well as for depression (Stahl, 2017; EPI, 2016; Bett, 1946). Amphetamine was first discovered in the year 1887 and generally exists in two enantiomeric form, dextroamphetamine and levoamphetamine. It is the parent compound of several structurally related derivatives which have similar CNS stimulating action. It is also chemically and structurally related to several neuromodulators produced in our body such as phenylehtylamine and N-methylphenethylamine.

Amphetamine and its congener methamphetamine (Fig. 1) are identified as one of the most commonly used illicit drugs owing to their psychostimulant properties leading to mood elevation (euphoria) as well as increased self esteem and physical and mental capacity. The major mechanism by which the amphetamine-like substances act is their ability to stimulate the release of newly synthesized dopamine from the dopaminergic neurons (Stahl,
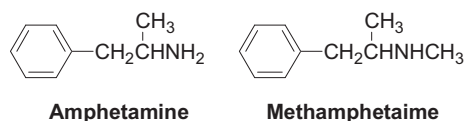
Fig. 1. Structures of amphetamine and its congener methamphetamine.

2017). The legal restrictions for these drugs are because of the dose dependent serious toxic effects such as hallucinations, confusion, tremors, cardiac arrhythmias and hypertension. Moreover, these drugs are known for the development of physical dependence and tolerance to the users.

The theophylline derivative of amphetamine, known as fenethylline hydrochloride shows similar effects to that of amphetamine and is marketed as "Captagon". It was generally used to treat the hyperactivity disorders such as ADHD, but is also a drug of abuse and is no longer produced today or used for therapeutic purposes (Sweetman, 2002). Primarily, Captagon has been marketed in Middle Eastern Countries including Saudi Arabia, Qatar and Kuwait, where it is very popular among the adolescents (DEA, 2003a,b). Previously, Alabdalla et al conducted the study to determine the chemical composition of counterfeit captagon tablets from Jordan (Alabdalla, 2005) using GC–MS and reported the absence of fenethylline in all the tablets, whereas, amphetamine was detected in the tablets along with several other additives. Similarly, the illegal productions of tablets having captagon logos were discovered in Turkey (Seven et al., 2003) and Serbia (Nevešćanin et al., 2008; DEA, 2003a,b; Nichols et al., 2015), where the identification of amphetamine and other additives were performed using FT-IR and GC–MS techniques. The analysis of these counterfeit captagon tablets has revealed the presence of amphetamine and its derivatives with absence of fenethylline.

In continuation to the ongoing analysis of illegal products in collaboration with Poison Control and Medical Forensic Chemistry Center of Jazan (Al Bratty et al., 2019; Alhazmi et al., 2018), the analysis of seized tablets from Jazan province of Saudi Arabia for the determination of amount of amphetamine and methamphetamine present in each tablet was intended to perform using a fast and validated LC-MS/MS method.

2. Materials and methods

2.1. Chemicals and reagents

The vials containing standards (1 mg/mL) for each analyte amphetamine and methamphetamine and their internal standards (amphetamine-D5 and methamphetamine-D5) were purchased from Lipomed AG (Cambridge, USA). Dichloromethane, isopropyl alcohol, ammonium hydroxide, methanol, acetic acid and acetonitrile were purchased from Sigma Aldrich (Germany). All chemicals were of HPLC grade. De-ionized (DI) water was prepared using Millipore purification system. SPE cartridges (CSDAU203) were purchased from United Chemicals Technologies (Philadelphia, USA).

2.2. Collection of samples

Samples were seized and collected by local police by raiding vehicles at the border of Saudi Arabia and Yemen as well as inside the cities of Jazan province. Tablets were obtained from three cities of Jazan Province, Ahad Al Masariha, Al-Darb and Gizan. Randomly 10 tablets from each city were collected for analysis. Tablets were seized and sent to the Poison Control and Medical Forensic Chemistry Center of Jazan for subsequent analysis of amphetamine and methamphetamine contents in the tablets. Samples were coded according to the name of cities as **A1-A10**, **D1-D10** and **G1-G10**.

2.3. Preparation of standard solutions and calibration curve

For the preparation of calibration curve, working solution containing amphetamine and methamphetamine at concentration 10 μg/mL in methanol was prepared from amphetamine and methamphetamine stock solution (1 mg/mL). Calibration curve was plotted using dilutions of 50, 100, 250, 500, 1000 and 2000 ng/mL concentration. The concentrations of the internal standards in the calibration curve solutions, quality control samples and the treated sample for injection were 375 ng/mL and 1000 ng/mL for amphetamine and methamphetamine respectively.

2.4. Sample preparation

Samples were extracted by solid phase extraction method for unknown screening using SPE cartridge (Telepchak, 2014). The weight of tablets were found to be in the range of 159–175 mg with an average weight of 167 mg. Briefly, half tablet was dissolved in 3 mL of methanol and two aliquots of 100 μL were taken in two separate 4 mL glass tubes A and B for amphetamine and methamphetamine analysis respectively. Subsequently, 1 mL deionized water and 1 mL phosphate buffer (pH 6) were added to each tube and mixed. Further, to solution A, 100 μL of internal standard amphetamine-D5 solution (500 μg /mL), and to solution B, 40 μL of methamphetamine-D5 internal standard solution (250 μg/mL) solution were added and mixed properly. The SPE cartridge was pre-conditioned with 3 mL methanol followed by 3 mL deionized water and 1 mL phosphate buffer (pH 6). Thereafter, the samples, calibrators and QC samples were loaded and eluted. The SPE cartridge was rinsed with 3 mL deionized water, 1 mL of 0.1 M acetic acid and 3 mL methanol. It was then allowed to dry under nitrogen stream using TurboAir evaporator at < 40 °C. The compounds of interest were eluted into clean 6 mL glass tube using 3 mL of a mixture of dichloromethane, isopropyl alcohol and ammonium hydroxide (78:20:2). The elution solvent was then evaporated under nitrogen stream and the residues thus obtained were reconstituted by 200 μL of mobile phase (0.1 M ammonium format buffer (85%) and 15% acetonitrile with 0.1% formic acid). Further dilutions were made to measure the target drug concentration from calibration curve. For amphetamine analysis, 150 μL of solution A was taken in a 100 mL volumetric flask and the volume was made up using mobile phase (diluted 666.66 times). Similarly, for methamphetamine analysis, 200 μL of solution B was taken in a 10 mL volumetric flask and the volume was made up using mobile phase (diluted 50 times).

Three quality control (QC) samples of concentration 1800 ng/mL (HQC), 900 ng/mL (MQC) and 100 ng/mL (LQC) for each analyte were prepared and used to validate the whole method. An aliquot of 200 μL of QC sample was taken and introduced for solid phase extraction method as mentioned above. The residues were reconstituted by 200 μL of mobile phase and used directly for analysis without further dilution

2.5. LC-MS/MS analysis

The analysis was carried out using LC-MS/MS system consisted of a LCQ Fleet Single quadrupole Ion Trap Mass spectrometer (Thermo Scientific) equipped with Thermo Finnigan Surveyor MS Pump and Thermo Finnigan Surveyor Autosampler.

2.5.1. Chromatographic separations

The chromatographic separations were obtained using a validated LC method which was developed in our lab and is used for the routine analysis of amphetamine and related compounds (Mohan et al., 2016). Aliquots (10 μL) of samples, calibrators and quality controls were injected and the analytes were separated

on a Hypersil GOLD column (150 × 3 mm i.d.: 5 μm, Thermo Scientific, USA). The compounds were eluted by isocratic mobile phase made from 85% of 10 mmol ammonium formate buffer and 15% of 0.1% formic acid in acetonitrile. The total run time was 12 min with a flow rate of 0.3 mL/min.

2.5.2. Mass spectrometry conditions

After chromatographic separation, amphetamine, methamphetamine and internal standards (amphetamine-D5 and methamphetamine-D5) reached the Electrospray Ionization (ESI) interface and positively charged. The ESI conditions were 5 kV spray voltage, 275 °C capillary temperature, 50 V capillary voltage, 110 V tube lens voltage and 30 arb flow rate of nitrogen sheath gas. The analysis was performed in the multiple reaction monitoring (MRM) mode, and the following transitions: m/z 136 → 119 and m/z 136 → 91 for amphetamine, m/z 150 → 119 and m/z 150 → 91 for methamphetamine, m/z 141 → 124 for amphetamine-D5 and m/z 155 → 121 for methamphetamine-D5 were monitored. Helium gas was used as fragmentation gas in the Collision-induced decompositions (CID). The collision energy (CE) values were found to be 19, 23, 20 and 23 eV for amphetamine, methamphetamine, amphetamine-D5 and methamphetamine-D5, respectively. The above method was validated for amphetamine quantitation in Jazan poison control center with LOD 13 ng/mL and LOQ 40 ng/mL.

2.6. Hierarchical cluster analysis

The obtained analytical data were analyzed using NCSS statistical program 2019 Version 19.0.3. (NCSS LLC, Utah, USA). A widely employed multivariate Chemometric statistical analysis known as Hierarchical Cluster Analysis (HCA) was employed to interpret the data considering amounts of amphetamine and methamphetamine as variables expressing 2 columns and tablet samples constituting 30 rows. The analysis was performed to determine significant groups/clusters of samples having similar characteristics, which could have originated from a single source. Hierarchical cluster analysis was used to categorize the potential source of the tablets. Dendrogram plot was used to assess the cohesiveness of the clusters formed and can provide information about the appropriate number of clusters to keep. This plot was built using agglomeration schedule and average linkage. The used clustering method was unweighted pair-group (group average) with a Euclidean distance type and standard deviation as scale type. The two variables, amphetamine and methamphetamine contents were analyzed in all 30 samples. Grouping was done on the basis of similarities between the samples using the statistical software.

3. Results and discussion

The amount of amphetamine and methamphetamine in the tablet samples were analyzed using the LC-MS/MS method developed in our lab (Mohan et al., 2016). This method has been used for the routine analysis of amphetamine and related compounds. This method was continuously validated using different QC samples and the validation parameters were within acceptable limits. Amphetamine-D5 and methamphetamine-D5 were used as internal standards for the quantification of amphetamine and methamphetamine, respectively. Calibration curve was plotted using standard amphetamine and methamphetamine over the range 50–2000 ng/mL and a straight line was obtained with R^2 value 0.9964 (Fig. 2) and 0.9946 for amphetamine and methamphetamine respectively. Ten samples from each city were analyzed, and for each sample, amount of amphetamine and methamphetamine were calculated using the internal standard. The retention times (RT) for internal standard ranged between 6.50 and 6.58 min, however, amphetamine and methamphetamine were observed at RT 6.5–6.6 and 7.0–7.1 min. respectively. Figs. 3–5 shows the representative chromatograms obtained for samples, **A1**, **D1** and **G1** obtained from cities Ahad Al Masariha, Al Darb and Gizan respectively.

Three quality control (QC) samples of concentration 1800 ng/mL (HQC), 900 ng/mL (MQC) and 100 ng/mL (LQC) were used to validate the whole method. The recovery and precision values were within the acceptable limits with recovery ≥ 95% and precision < 2% (n = 3) for all QC samples in intraday and interday studies.

The calculated amounts of amphetamine and methamphetamine in the injected volume were obtained in nanogram which was multiplied with the dilution factor to get the total amount of amphetamine and methamphetamine in one tablet. The results are summarized in Table 1. As evident from the table, the amount of amphetamine in all the samples ranged from 9.07 to 14.77 mg, whereas, the amount of methamphetamine ranged from 0.12 to 0.24 mg in each tablet. The amphetamine to methamphetamine ratio was calculated to be from 57:1 to 110:1 in all tablets which indicated that methamphetamine could be present as an impurity in these tablets. These amounts of amphetamine were higher as compared to the recommended dose (5–10 mg per day) of amphetamine for the treatment of ADHD.

The therapeutic doses of amphetamine leads to a number of cognitive and emotional effects including euphoria, increased wakefulness and changed sexual desire. The physical effects at this dose include short reaction time, increased muscular strength and decreased fatigue. Amphetamine is not used clinically anymore; however, the illicit use of amphetamine has increased over the past
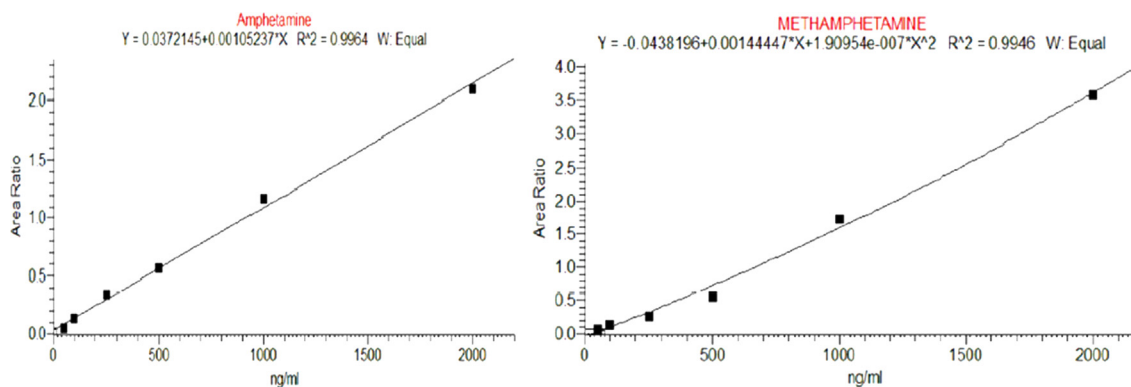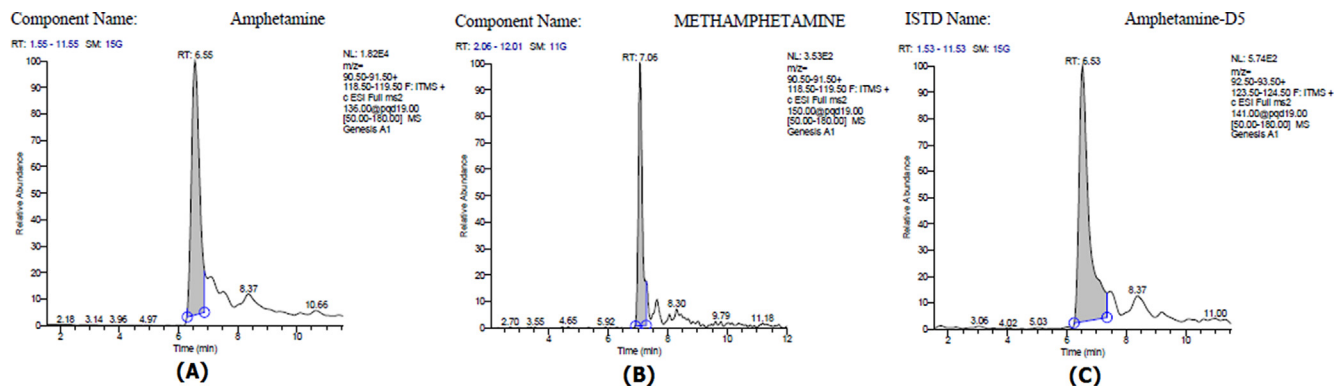

Fig. 2. Calibration curve obtained for standard amphetamine and methamphetamine over the range 50–2000 ng/mL.

Fig. 3. LC-MS chromatograms obtained from sample (**A1**) procured from Ahad Al Masariha city. (A) Represents the chromatogram for Amphetamine at RT 6.55 min, (B) represents the chromatogram for Methamphetamine at RT 7.06 min and (C) represents the chromatogram for internal standard Amphetamine-D5 at RT 6.53 min.
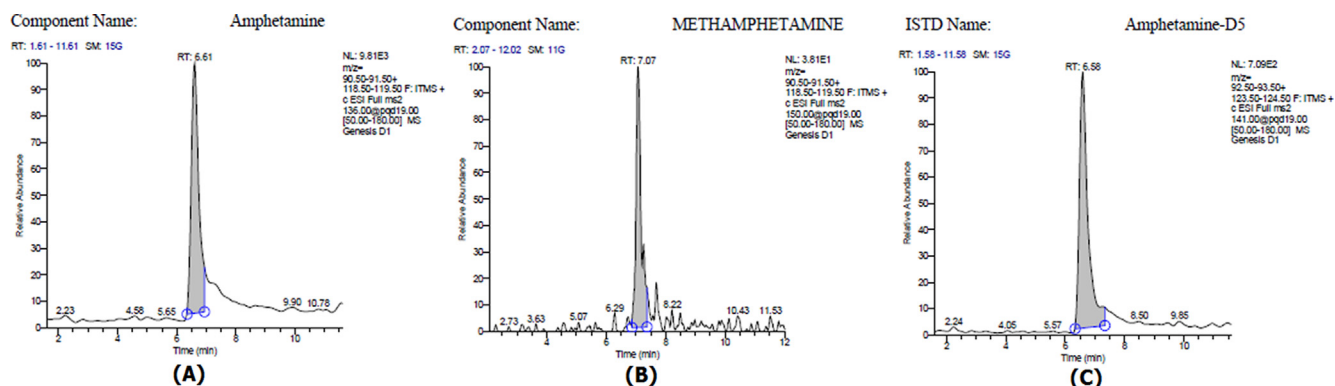
Fig. 4. LC-MS chromatograms obtained from sample (**D1**) procured from Al Darb city. (A) Represents the chromatogram for Amphetamine at RT 6.61 min, (B) represents the chromatogram for Methamphetamine at RT 7.07 min and (C) represents the chromatogram for internal standard Amphetamine-D5 at RT 6.58 min.
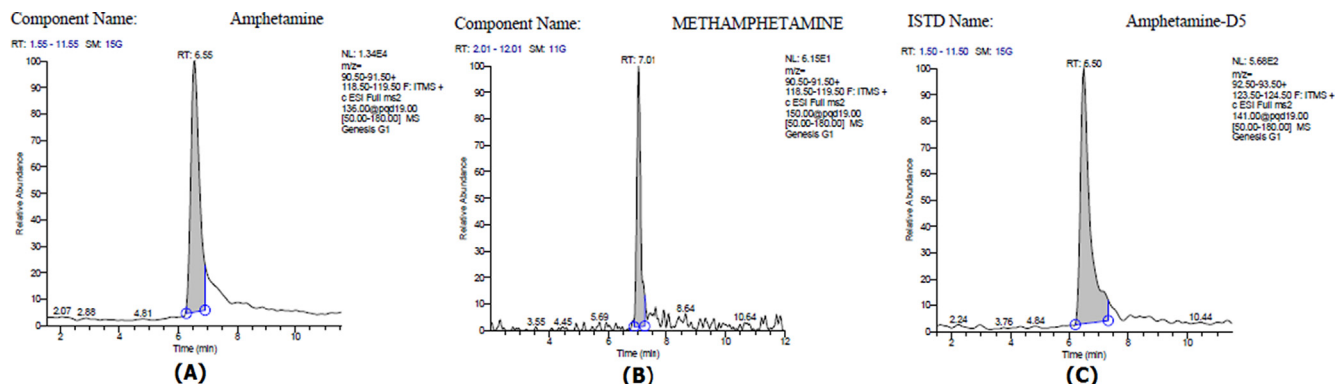
Fig. 5. LC-MS chromatograms obtained from sample (**G1**) procured from Gizan city. (A) Represents the chromatogram for Amphetamine at RT 6.55 min, (B) represents the chromatogram for Methamphetamine at RT 7.01 min and (C) represents the chromatogram for internal standard Amphetamine-D5 at RT 6.50 min.

several years. At larger doses, amphetamine and related substances are known to impair the cognitive functions and induce rapid muscular breakdown. Very high doses result in psychiatric illness such as delusions and paranoia and leads to addiction. Generally, addiction does not occur with therapeutic doses even given for long term, but the high recreational doses are always associated with addiction. These recreational doses are very high in comparison to the normal prescribed therapeutic doses and have greater chances of toxic effects. Previously, the effects of high doses of amphetamine given for long term was studied on animal models

and resulted in producing nerve damage along with abnormal dopaminergic system (Carvalho et al., 2012; Berman et al., 2008). On the other hand, it showed improved brain development and neuronal growth on human beings with ADHD, when given at prescribed dose (Hart et al., 2013; Spencer et al., 2013; Frodl and Skokauskas, 2012).

The Chemometric statistical multivariate analysis, Hierarchical Cluster Analysis (HCA) was also performed on the set of data obtained in order to establish similarities between the tablet samples. Samples were divided into clusters on the basis of

Table 1
The calculated amount of Amphetamine and Methamphetamine present in seized tablet samples from different cities.

Sample no.	Amphetamine		Methamphetamine	
	Retention time (min)	Calculated amount in one tablet (mg)	Retention time (min)	Calculated amount in one tablet (mg)
A1	6.6	14.77	7.1	0.24
A2	6.6	11.35	7.1	0.19
A3	6.6	12.52	7.1	0.15
A4	6.6	11.24	7.0	0.16
A5	6.6	11.45	7.1	0.17
A6	6.6	10.55	7.1	0.14
A7	6.6	13.15	7.0	0.14
A8	6.6	12.23	7.1	0.15
A9	6.6	12.49	7.1	0.15
A10	6.5	13.19	7.0	0.12
D1	6.6	9.07	7.1	0.13
D2	6.6	9.94	7.0	0.13
D3	6.6	11.82	7.0	0.14
D4	6.6	10.97	7.0	0.19
D5	6.6	14.05	7.1	0.18
D6	6.6	12.80	7.0	0.17
D7	6.6	9.27	7.0	0.12
D8	6.6	11.97	7.0	0.14
D9	6.6	11.95	7.0	0.13
D10	6.6	12.58	7.0	0.14
G1	6.6	12.98	7.0	0.13
G2	6.6	12.78	7.0	0.14
G3	6.5	13.87	7.0	0.14
G4	6.6	10.86	7.0	0.12
G5	6.6	11.17	7.0	0.13
G6	6.5	10.16	7.0	0.13
G7	6.5	11.83	7.0	0.13
G8	6.6	9.68	7.0	0.13
G9	6.6	11.43	7.0	0.13
G10	6.6	10.67	7.0	0.13

amphetamine and methamphetamine content present in them (variables). The results were obtained as a dendrogram tree which is presented as Fig. 6. The dendrogram tree clearly showed presence of five clusters with different number of samples. The cluster solution was observed as a sudden gap (jump) in the distance coefficient and the solutions which are before this gap were considered as good solution. The first cluster comprised of eight out of thirty samples including D7, D1, G4, G8, G6, D2, G10 and A6 with lesser distances showing much similarity between these samples. Samples under the same cluster signify that these are similar to each other as far as amphetamine and methamphetamine contents are concerned. Generally, the samples separated by lesser distance (<1) are considered to be similar and having same characteristics and the more dissimilarity increases the distance more. It can be observed that the samples present in the same cluster were separated by lesser distance (<1), whereas, the five clusters are separated with each other by comparatively larger distances (>1). The second cluster being the largest one, comprised of 15 samples including G3, G1, A10, G9, G5, G7, D9, D8, D3, G2, D10, A7, A8, A9 and A3, which indicates similar characteristics of these samples and are probably from the same source. Within this cluster, samples G9 and G5, G7 and D9, D8 and D3, G2 and D10 and A9 and A3 are separated by very short distance showing very similar characteristics of these samples. Interestingly, the third cluster comprised of only two samples, D6 and D5 which also were separated with each other by good distance (~0.7) and larger distances from other clusters of samples indicating different nature of samples probably having different origin. The fourth cluster comprised of four samples, A5, A4, D4 and A2 and surprisingly, the fifth cluster had only one sample A1 which means that this sample was different from all other samples and is separated by other samples at a much larger distance (>3) and had mush different characteristics than

other samples. It may be concluded that the samples present in the same cluster may have originated from the same source or from the same manufacturer and different clusters obtained indicates that different sources are present distributing samples at different places.

The illegal trafficking of amphetamine tablets has been a serious problem worldwide and many Middle Eastern and European countries are affected by it. A number of cases of seizure of captagon tablets have been reported from countries such as Saudi Arabia, Jordan, Iraq, Bulgaria, Lebanon, Turkey, Serbia and Yemen during the period 1992–2013 and is still counting. The forensic analysis of these tablets revealed the psychoactive agent amphetamine as the principle constituent, often present with other substances (Alabdalla, 2005; Dabbagh and Rawson, 2019; Al-Gharably and Al-Obaid, 1993; Dimova and Dinkof, 1994; Nevescanin et al., 2008; DEA, 2009; UNODC, 2009; TUBIM, 2013; Demirkiran et al., 2014). The amount of amphetamine varied in different seized tablets when analyzed, which varied from trace quantities to more than one third of the total tablet weight. Earlier, a forensic analysis of captagon tablets seized in Saudi Arabia led to the finding that nearly half of the seized tablets contained amphetamine in trace amount, whereas, the other half contained approximately 38% amphetamine which was highly significant (Dabbagh and Rawson 2019).

Interestingly, most of the previous studies did not report the presence of methamphetamine in the seized tablets (BKA, 2016; EMCDDA, 2018, ARTE, 2015; Orsini 2015; Des Déserts, 2016). However in this study, the analysis of tablets seized from Jazan showed presence of considerable amount of methamphetamine, although it was very less as compared to amphetamine. Nevertheless, the detected methamphetamine in the seized tablets could be considered as marker for its place or country of production and related suppliers. (UNODC, 2014).
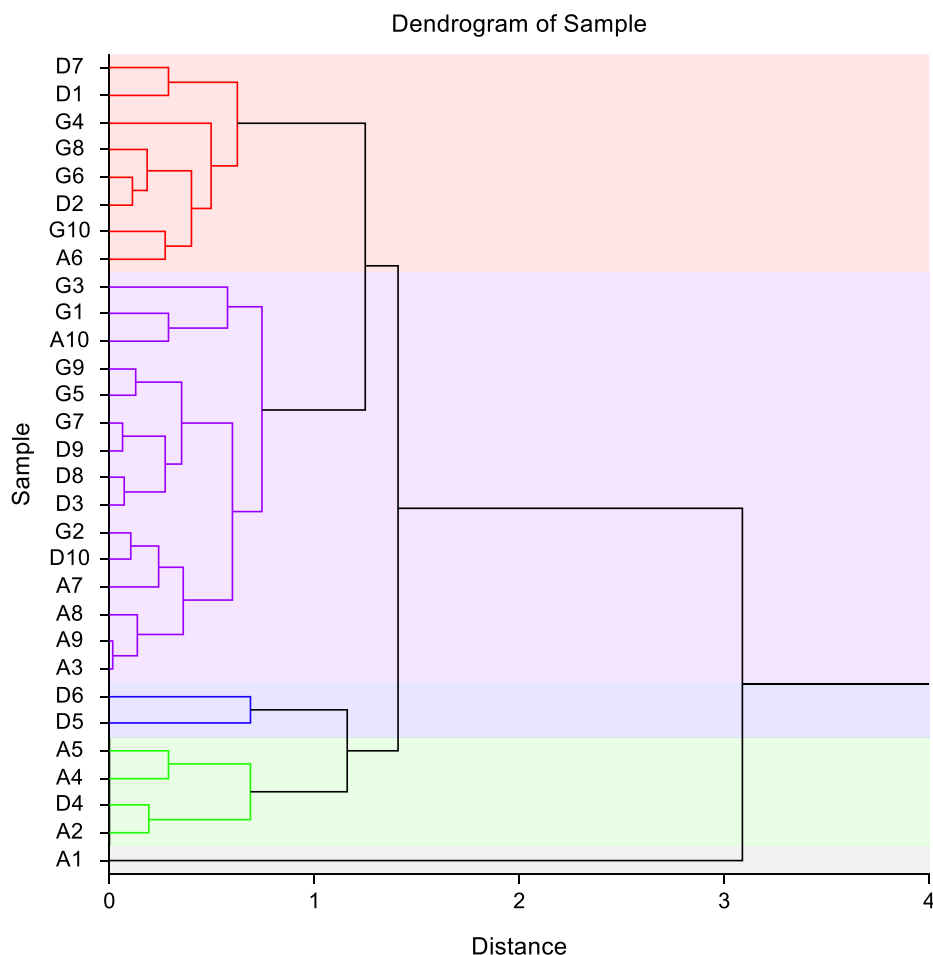
Fig. 6. Dendrogram tree obtained for amphetamine tablet samples using Average linkage (between groups) showing five clusters and distances between the samples.

4. Conclusions

Amphetamine and methamphetamine in the seized tablets from Jazan have successfully been detected and quantified using a fast and validated LC-MS/MS method. Total 30 samples from three cities (10 from each city) of Jazan province were randomly selected for the analysis and the results showed the presence of amphetamine as the major constituent in all the tablets in high concentration. Methamphetamine was present in a much lower amount in all the tested tablets as compared to amphetamine which indicated that it may be present as an additive to the tablets and were not aimed to exert any psycho stimulant activity. However, the presence of methamphetamine in the tablets could be used as a marker and could represent the common place of origin of these tablets.

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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References

Al Bratty, M., Ahsan, W., Alhazmi, H.A., Attafi, I.M., Khardali, I.A., Abdelwahab, S.I., 2019. Determination of trace metal concentrations in different parts of the khat varieties (*Catha edulis*) using inductively coupled plasma-mass spectroscopy technique and their human exposure assessment. Phcog. Mag. 15, 449–458.

Alabdalla, M.A., 2005. Chemical characterization of counterfeit captagon tablets seized in Jordan. Forensic Sci. Int. 152, 185.

Al-Gharably, N., Al-Obaid, A.R., 1993. The characterization of counterfeit Captagon tablets. J. Forensic Sci. Soc. 34, 165–167.

Alhazmi, H.A., Ahsan, W., Attafi, I.M., Khalid, A., Abdelwahab, S.I., Al Bratty, M., Sultana, S., 2018. Elemental profiling of smokeless tobacco samples using inductively coupled plasma-mass spectrometry, their chemometric analysis and assessment of health hazards. Phcog. Mag. 14, 587–596.

ARTE, 2015. 'La drogue de Daech', ARTE Journal, 20 May 2015.

Berman, S., O'Neill, J., Fears, S., Bartzokis, G., London, E.D., 2008. Abuse of amphetamines and structural abnormalities in the brain. Ann. N. Y. Acad. Sci. 1141, 195–220.

Bett, W.R., 1946. Benzedrine sulphate in clinical medicine; a survey of the literature. Postgrad. Med. J. 22, 205–218.

Carvalho, M., Carmo, H., Costa, V.M., Capela, J.P., Pontes, H., Remião, F., Carvalho, F., Bastos, M.L., 2012. Toxicity of amphetamines: an update. Arch. Toxicol. 86, 1167–1231.

Dabbagh, R., Rawson, R., 2019. Captagon Use in Saudi Arabia: What Do we Know?. Int. Addict. Rev. 2, 22–30.

Demirkiran, S., Zeren, C., Çelikel, A., Arslan, M.M., 2014. The captagon tablets captured in Hatay between 2011–2012. J. Foren. Med. 28, 17–23.

Des Déserts, S., 2016. Captagon, enquête sur la drogue des terroristes', Vanity Fair, No 34, April, 2016.

Dimova, D., Dinkof, N., 1994. Psychotropic substances of the amfetamine type used by drug addicts in Bulgaria. Synthesis and medical forms, Analytical methods of identification, Scientific and Technical Notes, SCITEC/10, UNODC, Sofia.

Drug Enforcement Administration (DEA), 2003. Fenethylline and the Middle East. A Brief Summary, USA, DEA-03046.

Drug Enforcement Administration (DEA), 2009. Captagon mimic tablets (containing d,l-amphetamine, caffeine, theophylline, and other components) in Al Anbar Province, Iraq, Microg. Bull. 42, 28-29.

Drug Enforcement Administration, 2003. Fenethylline and the Middle East: a brief summary, DEA-03046.

European Monitoring Centre for Drugs and Drug Addiction, 2018. Captagon: understanding today's illicit market, EMCDDA Papers, Publications Office of the European Union, Luxembourg.

Evekeo Prescribing Information (EPI), 2016. https://www.evekeo.com/assets/evekeo-pi.pdf/ Arbor Pharmaceuticals LLC. pp. 1–2. (accessed 20 October 2019).

Frodl, T., Skokauskas, N., 2012. Meta-analysis of structural MRI studies in children and adults with attention deficit hyperactivity disorder indicates treatment effects. Acta Psychiatrica Scand. 125, 114–126.

German Bundeskriminalamt (BKA), 2016. 'Captagon', presentation, BKA (Germany), EMPACT Synthetic Drugs Meeting, Prague, 18-19 April, 2016.

Hart, H., Radua, J., Nakao, T., Mataix-Cols, D., Rubia, K., 2013. Meta-analysis of functional magnetic resonance imaging studies of inhibition and attention in attention-deficit/hyperactivity disorder: exploring task-specific, stimulant medication, and age effects. JAMA Psychiatry 70, 185–198.

Mohan, S., Abdelwahab, S.I., Hobani, Y.H., Syam, S., Al-Zubairi, A.S., Al-Sanousi, R., Oraiby, M.E., 2016. Catha edulis extract induces H9c2 cell apoptosis by increasing reactive oxygen species generation and activation of mitochondrial proteins. Phcog. Mag. 12 (S3), 321–326.

Nevescanin, M., Stevic, S.B., Petrovic, S., Vajs, V., 2008. Analysis of amphetamines illegally produced in Serbia. J. Serb. Chem. Soc. 73, 691–701.

Nevešćanin, M., Stević, S.B., Petrović, S., Vajs, V., 2008. Analysis of amphetamines illegally produced in Serbia. J. Serb. Chem. Soc. 73, 691–701.

Nichols, W., Kravitz, M., 2015. Soldiers of Abu Hilalain: An investigation into Captagon trafficking by Syrian war militants and what it means for U.S. foreign policy. Available at: http://imes.elliott.gwu.edu/sites/imes.elliot.gwu.edu/files/downloads/documents/Capstone-Papers-2015/CaptagonCapstoneFinalDraft.pdf (accessed 15 November 2019).

Orsini, A., 2015. Le Captagon, la 'potion magique' des djihadistes', L'Obs, 22 May 2015.

Seven, E., Bora, T., Çavuş, M., Inceoğlu, D.N., Azak, E.Ö., 2003. In: Proceedings of the 3rd EAFS Meeting, Istanbul, Turkey.

Spencer, T.J., Brown, A., Seidman, L.J., Valera, E.M., Makris, N., Lomedico, A., Faraone, S.V., Biederman, J., 2013. Effect of psychostimulants on brain structure and function in ADHD: a qualitative literature review of magnetic resonance imaging-based neuroimaging studies. J. Clin. Psychiatry 74, 902–917.

Stahl, S.M., 2017. "Amphetamine (D,L)" (https://books.google.com/books?id=9hssDwAAQBAJ&pg=PA45#v=onepage). Prescriber's Guide: Stahl's Essential Psychopharmacology (6th ed.). Cambridge, United Kingdom: Cambridge University Press. pp. 45–51. ISBN 9781108228749.

Sweetman, S.C., 2002. Martindale: the complete drug reference. The Pharmaceutical Press, London, p. 1509.

Telepchak, J.M., 2014. Forensic and Clinical Applications of Solid Phase Extraction. Springer.

Turkish Monitoring Centre for Drugs and Drug addiction (TUBIM), 2013. National report (2012 data) to the EMCDDA by the Reitox national focal point, TUBIM, Ankara.

United Nations Office on Drugs and Crime (UNODC), 2009. World drug report 2009, UNODC, New York.

United Nations Office on Drugs and Crime (UNODC), 2014. Global synthetic drugs assessment. Amphetamine-type stimulants and new psychoactive substances, UNODC, New York.