Characterisation of Seized Clandestine Methamphetamine in Malaysia

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ABSTRACT: Malaysia has been identified as one of the clandestine drug laboratory operation hotspots in this region as indicated by the increasing number of clandestine laboratories being dismantled. Methamphetamine is one of the major illicit drugs manufactured in these laboratories. This study aims to characterise methamphetamine manufactured in Malaysia via different analytical techniques to trace down to their synthetic pathway, namely colour screening test, Fourier transform infrared spectroscopy with attenuated total reflectance (FTIR-ATR) analysis, high performance liquid chromatography (HPLC), gas chromatography-mass spectrometry (GC-MS) and inductive coupled plasma-mass spectrometry (ICP-MS). Our results gave useful forensic information on the identity of the samples, enantiomers of methamphetamine and impurities present that can be used to characterise the seized samples to its possible pathway of synthesis.

Keywords: methamphetamine, drug clandestine laboratory, characterisation, synthetic pathway

Introduction

Amphetamine-type Stimulant (ATS) are well established on the illicit drug markets worldwide and their use are continuingly to equalise that of opiates and cocaine. The use of ATS was estimated at 33.8 million users, recording at 0.7% among the world population [1-3]. Recently, the market of ATS is showing an expanding sign where the levels of seizures and consumption are increasing, along with the spreading of manufacture as well as the development of new markets [2].

ATS is a group of synthetic drugs which can be synthesised and manufacturing in a laboratory. In 1990s, the incidence of illicit drug production become much more widespread [4], and continued as a major problem until recent years [2]. Up to 99% of the detected clandestine synthetic drugs laboratories process ATS and they are reported in all parts of the world regardless of geographical restriction [5]. To date, methamphetamine continues to be the mainstay of the ATS business, in which 71% of global ATS seizures were accounted in 2011 [2], and with more than 80% from all the clandestine laboratories reported worldwide [1-2]. The growing popularity in the production of methamphetamine can be due to its simpler manufacturing procedure; the detailed instructions that are readily available in books and internet, and also the available of chemicals easily acquired in daily life [5].

In Malaysia, an estimated of 8% of total drug users consumed ATS after heroin as the primary abused drug (48%) [6]. The demands for synthetic drugs in domestic market and a small proportion for regional supply, particularly methamphetamine, have raised the setting up of clandestine laboratories. Malaysia has become a significant methamphetamine manufacturing locations, demonstrating the shift in pattern of clandestine manufacturing, trafficking as well as the use [5-6]. According to Royal Malaysia Police, the numbers of seized clandestine laboratories were reported with an increasing trend, and the operations were often assisted by clandestine chemists. The statistics reveals the seizures of 30 and 32 clandestine laboratories in 2011 and 2012, respectively [7], and a total of 115 cases within the duration of six years between year 2007 to 2012 [7]. In 2012 alone, 20 out of 27 clandestine laboratories reported by UNODC were found with crystalline methamphetamine manufacturing [6]. Until today the drug-related problems, especially on ATS are continuingly reported from time to time, with

most recent case involving a house-based clandestine laboratory producing methamphetamine in Sepang involving eight people from three countries [8].

In this study, the methamphetamine profiles from the seized samples were developed to determine the types and sources of this drug besides gathering the information for legal authorities. In general, methamphetamine is produced chemically with end product containing traces of precursor chemicals, intermediates and by-products in many instances [9]. We aimed to gain the information of the drugs seized from clandestine laboratory prevalence in Malaysia, including the identification of the source of origin, starting chemicals and chemical process involved through the analytical techniques, with the hope to apply it as the routine drug characterisation in our forensic laboratory.

Materials and methods

Sample collection

Twenty drug samples were obtained from the Narcotic Section, Department of Chemistry Malaysia, Petaling Jaya. Note that the samples included in this study were those produced by the clandestine laboratories dismantled in Malaysia from 2011 to 2012 and available for research purposes. All the samples were homogenised, sealed securely in a brown vial and properly labelled. Due to legal restrictions and to comply with the laboratory requirements, these samples were kept in a secured room in Department of Chemistry Malaysia.

Preliminary spot test

Approximately 1 mg of sample was placed on a porcelain spot plate and 1-2 drops of each test reagents (*i.e.* Froehde reagent, Janovsky reagent, Marquis reagent and Simon reagent) were dropped into the well. The immediate colour change was documented.

Fourier Transform Infrared Spectroscopy (FTIR)

All the twenty samples were analysed using a Thermo Fisher Scientific Nicolet^{TM} Magna 550 FTIR Spectrometer (Waltham, MA) with attenuated total reflection (ATR) accessory (Thermo Fisher Scientific, Waltham, MA). The ATR accessory composed of a single reflection diamond crystal with a refractive index of 2.40 and reflection angle of 42°. The resolution was set at 4 cm^{-1} with 32 scans between 400 cm^{-1} and 4000 cm^{-1}. Prior to the directly application of the sample onto the ATR crystal, the sample was finely powdered and homogenised in clean mortar and pestle to get the best contact with the crystal. With the help of the pressure arm on the ATR accessory, force was applied onto the samples to get a good contact with the crystal surface which leads to a thin film of the sample. The crystal surface of ATR was then cleaned with isopropyl alcohol. IR spectrum was collected using OMNIC E.S.P. *version* 6.1a software (Thermo Electron Corporation, Madison, WI). The resulting IR spectra were compared by performing library search.

Gas Chromatography-Mass Spectrometry (GC-MS)

All the 20 samples were individually homogenised with a clean mortar and pestle. 100 mg of the homogenised drug samples were then weighed into separate 10 mL glass capped centrifugation tubes, and dissolved with 2.0 mL of phosphate buffer, respectively. Phosphate buffer solution was prepared by dissolving the potassium phosphate monobasic (Sigma-Aldrich, St. Louis, MO) and sodium phosphate dibasic dehydrate (Sigma-Aldrich, St. Louis, MO) in distilled water, and subsequently adjusted to pH 10.5 by 10% sodium carbonate (Daiya, Japan). The solution was sonicated for 5 mins followed by agitation on vortex mixer for 1 min. Then, 400 µL of extraction solvent (ethyl acetate containing 0.05 mg/mL eicosane as an internal standard) (Thermo Fisher Scientific, Waltham, MA) was added and centrifuged for 5 mins [10]. The organic layer (top layer) was transferred into GC vial for GC-MS analysis. Standard reference of methamphetamine hydrochloride (Lipomed, Switzerland) in ethyl acetate containing eicosane was also injected for peak confirmation against the GC-MS library.

The analysis was performed by an Agilent 6890 GC and a 5973 Mass Selective detector (MSD) (Santa Clara, CA) equipped with an auto injector Model Agilent 7983 Series (Santa Clara, CA). Chromatography was achieved using a non-polar HP5 (25 m length, 0.2 mm i.d., 0.33 µm film thickness) purchased from Agilent Technologies (Santa Clara, CA). Purified helium gas (99.99%) was chosen as the carrier gas with a constant flow rate of 1.0 mL/minute. Splitless injection

mode was performed at 250. The oven initial temperature was set at 50C with an equilibrium time of 1 min. A temperature ramp of 10˚C/min was selected to reach the maximum of 300 ˚C and held for 15 mins. The detector temperature was set 300˚C. Hewlett Packard Chemstation® software (Agilent Technologies, Santa Clare, CA) was used for GC automation and data analysis. Peaks were integrated using the total ion chromatogram. Any compound that appears as peak in the chromatogram was identified by the comparing the retention time of the standard and also by library search.

High Performance Liquid Chromatography (HPLC)

One mg of drug sample was weighed into a 10 mL volumetric flask before filling to the mark with distilled water. The sample was sonicated for 5 min. Then, 1 mL of the sample solution was then transferred into GC vials for HPLC analysis. HPLC racemic standard, (±)-methamphetamine HCl was obtained from Lipomed, Switzerland and prepared according to above procedure. HPLC analysis was performed using a Shimadzu HPLC CLASS-VP version 6.1 equipped with auto-sampler and UV/PDA detector (SPD-M10AVP) (Kyoto, Japan). Separation was performed on a chiral column (5 µm particle size, length 150 mm, id. 4.6 mm). Samples were eluted with a mobile phase of acetonitrile:potassium phosphate monobasic (KH_2PO_4) (Sigma-Aldrich, St. Louis, MO; Redel-de-Haien, Germany) (80:20) at a 1.0 mL/minute flow rate, with UV (210 nm) detection and temperature at 25˚C. Total run time of analysis was 20 mins.

Inductively Coupled Plasma-Mass Spectrometry (ICP-MS)

One hundred mg of sample was weighed into a 10 mL polypropylene tube and 10 mL of 10% nitric acid (Merck, Whitehouse Station, NJ) was added. The tubes were placed on an Edmund Buhler Swip KS-10 rotatory shaker (Hechingen, Germany) overnight. The solution was then filtered with a regenerated cellulose syringe filter (25 mm diameter and 0.45 µm pore size) (Sigma-Aldrich, St. Louis, MO). The 26 elements were analysed in multi element analysis (obtained from Agilent Technologies, Santa Clara, CA) with ICP-MS, namely lithium (Li), boron (B), sodium (Na), magnesium (Mg), aluminium (Al), potassium (K), calcium (Ca), scandium (Sc), vanadium (V), chromium (Cr), manganese (Mn), iron (Fe), nickel (Ni), copper (Cu), zinc (Zn), arsenic (As), selenium (Se), rhodium (Rh), argentums (Ag), cadmium (Cd), indium (In), antimony (Sb), barium (Ba), mercury (Hg), lead (Pb) and bismuth (Bi). A Thermo Electron Corporation X-Series II plus quadrupole ICP-MS instrument (Thermo Fisher Scientific, Waltham, MA) was used with a CETAC ASX-520 autosampler (Teledyne CETAC technologies, Omaha, NE). The instrumental operating conditions used were 1400 W RF forward power; 13 L/min plasma flow, 1.0 L/min nebulizer flow and 0.8 L/min auxiliary flow, respectively. A sample flush time for the ICP-MS was 60 sec, a wash time of 90 sec and a peak hopping scan mode was used with a dwell time per isotope of 10 msec. A solution of 1.0% nitric acid was used as a wash solution.

Results and Discussion

Preliminary spot test

The reference standard of methamphetamine hydrochloride gave positive results with Marquis reagent, producing an orange-brown coloured solution and also with the Simon reagent, giving a dark blue coloured solution. No reaction was observed with both the Froehde and Janovsky reagents. All the 20 samples in our work showed positive colour change when reacted with Marquis and Simon reagents, separately. The results indicated that all the samples could be of ATS drug group with the presence of secondary amine functioning group. Note that the Marquis reagent does not distinguish between ATS such as amphetamine and methamphetamine [11], but Simon reagent is common of differentiate methamphetamine from amphetamine [12]. Our spot test results have suggested that the secondary amine, including methamphetamine, could have present in all the samples. The preliminary test provided us the information to select the appropriate testing procedure for subsequent characterisation and confirmation of the drug substances.

FTIR

The spectrum of methamphetamine hydrochloride standard acquired using ATR-FTIR is shown in Fig. 1. Note that all the spectra were expressed in transmittance spectra for the ease of comparison with library spectra and those found in literatures and

guidelines. For better data treatment, the spectrum was divided into 18 regions (Fig. 1) to facilitate band assignment and subsequent comparison with clandestine sample. Two regions of importance were found to be in the range of 2500-3000 cm^{-1} (region D and C) that features the secondary amine hydrochloride and region 750-700 cm^{-1} (region R and S) that shows the characteristics of monoaromatic ring [13].

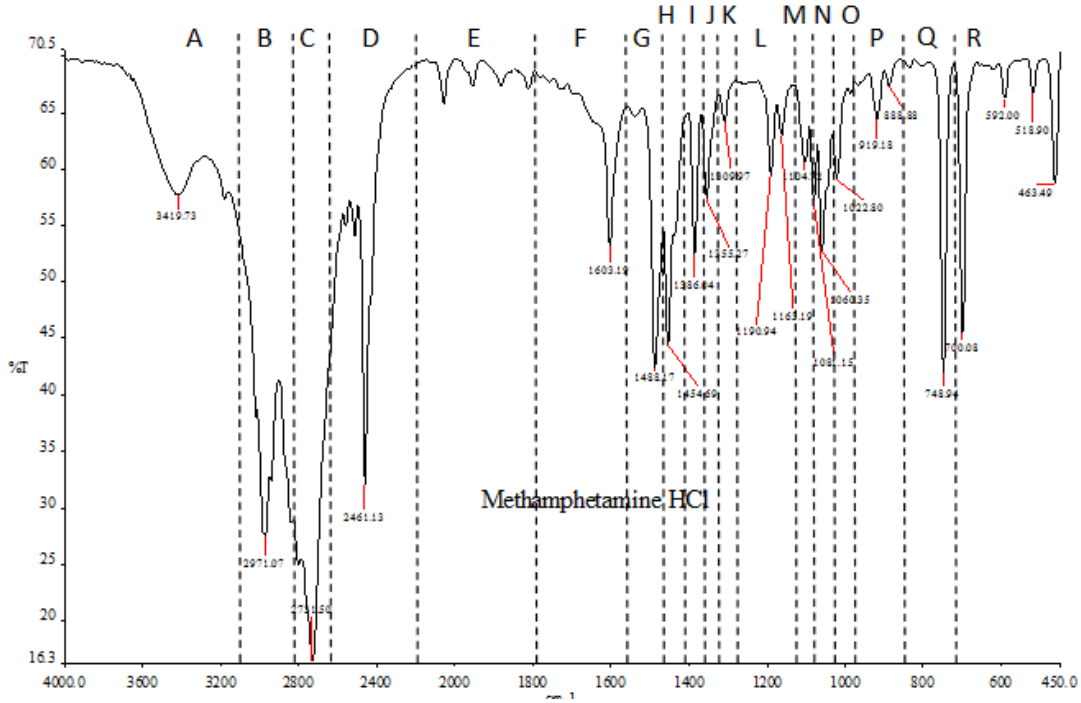

Fig. 1: Infrared spectrum of methamphetamine hydrochloride standard with regions

By comparison of the spectra of our samples with the standard, similar infrared spectra was observed except one sample showing a single largest peak at the regions of 3800-2500 cm^{-1}, followed by a large peak at 1078 cm^{-1}, 1640.7 cm^{-1}, and a few minor peaks at 1459 cm^{-1}, 1286.6 cm^{-1}, 746 cm^{-1} and 703.5 cm^{-1}. Similar signal characteristics were observed in the 18 regions based on the vibration band assignments. Our results suggested that the 19 out of 20 of the clandestine laboratory samples were of certain high degree of purity.

Fig. 2 and Fig. 3 illustrate the total ion chromatogram of methamphetamine hydrochloride standard and internal standard, as well as the mass spectrum of methamphetamine at the retention time of 8.159 min.

Domination of an ion at 58 m/z was due to alpha-cleavage of methamphetamine, as the hallmark of molecules containing similar nitrogen groups such as methamphetamine, pseudoephedrine/ephedrine and methcathinone. The peak at 148 m/z was the molecular mass peak (M-1) with the removal of one electron during ionisation, involving the loss of a hydrogen redical. The fragmentation at the peak of 58 m/z and 134 m/z, respectively, was a result of α-cleavage of the amine while peak of 91 m/z is due to charge migration during α-cleavage of the benzyl ion [14-15] or as a result of ring opening and closing between the benzyl ion and tropylium ion [15].

From the analysis of drug samples, the base peak was appeared at 8.159 (± 0.04) min, with was eluted at the time similar to the standard of methamphetamine. From our observation, peaks were also observed at 9.08 min, 11.30 min and 11.50 min in one of the drug samples (Fig. 4). From the library search, the peak of 9.08 min had a 60% match with α-rimethyl-α-N-benzeneethanamine (phenethylamine), whereas the peaks at 11.30 min and 11.50 min had a match of 83% to the spectrum of methyl-ephedrine and methyl-pseudoephedrine, respectively.

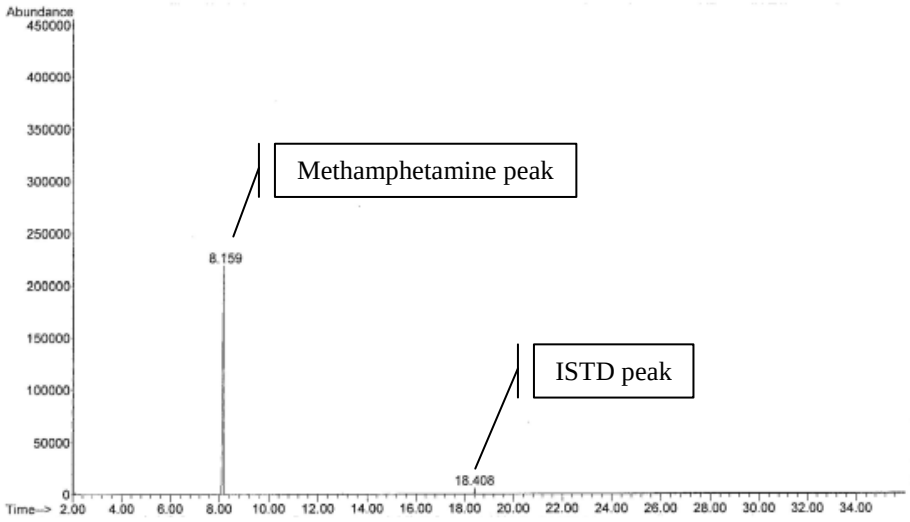

Fig. 2: Total ion chromatogram of methamphetamine hydrochloride standard and ISTD

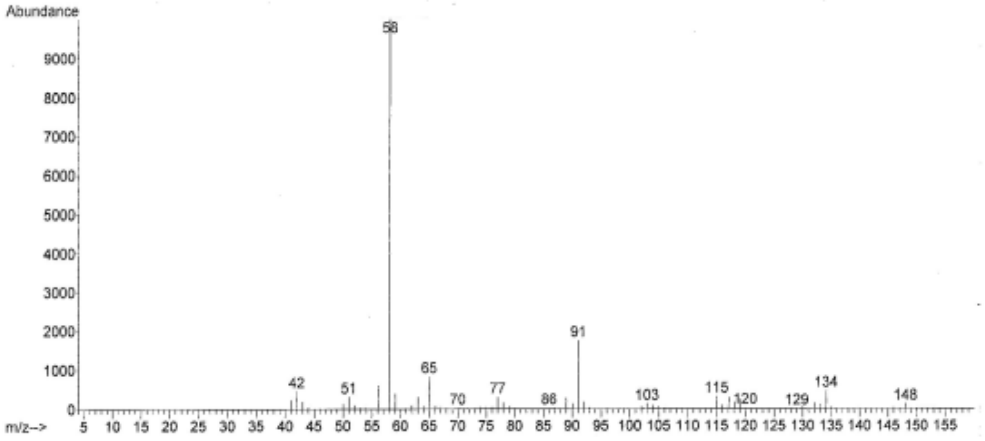

Fig. 3: Mass spectrum of methamphetamine at the retention time of 8.159 min

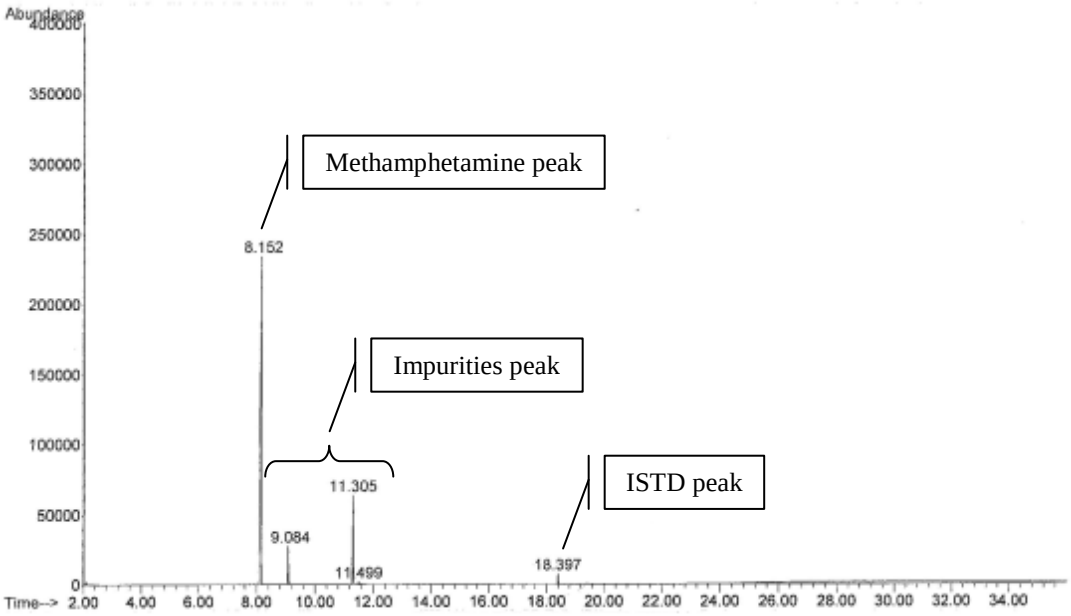

Fig. 4: Total ion chromatogram of drug sample

The synthesis of illicit drug in a clandestine laboratory could introduce impurities into the end product due to improper purification, nature of precursor used, incomplete reactions and presence of adulterants. Eleven out of 20 of our samples contained no detectable impurities under the basic extraction protocol and experimental parameters in this study.

Eight of them showed the presence of chloroethene and dichloroethene, which could have originated from the solvents. Traces of ephedrine, pseudoephedrine or by product such as phenethylamine were detected in two samples, and this observation was not surprising when they are being used as the precursors during the synthesis process. From the GC-MS analysis, 90% of the samples were with no traceable impurities detectable under our experimental protocols, leading to difficulty in source and synthesis pathway determination.

HPLC

The presence of a chiral carbon in methamphetamine structure contributes to an optically active property, either in pure and racemic mixture form [16]. These two enantiomers could have different physiological effects as such the dextro- (*d*) is more potent that the levo-methamphetamine (*l*) [17-18]. Stereochemistry properties are closely related with the synthetic routes during manufacturing process, thus the isomer identification of methamphetamine could help to establish its possible synthetic pathways [19]. In our work, the enantiomeric separation of methamphetamine samples was determined by a validated chiral HPLC procedure, which was also served as the confirmatory test [20]. Fig. 5 illustrates the chromatogram of the racemic methamphetamine standards, reflecting a good separation and resolution of the enantiomers where (*d*)-methamphetamine standard eluted at 10.244 min and (*l*)-methamphetamine standard at 13.593 min.

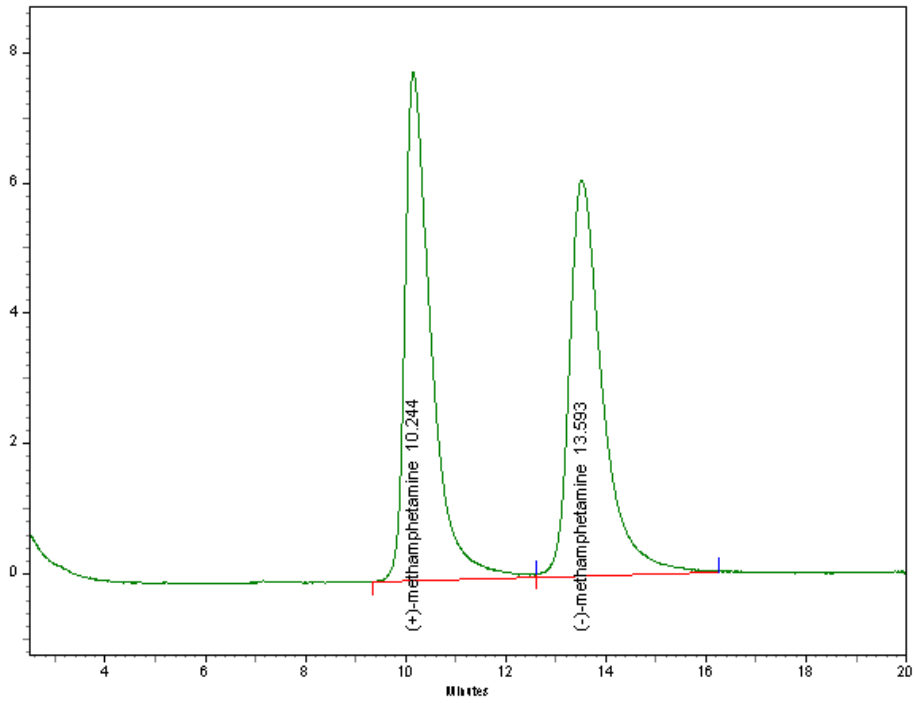

Fig. 5: (*d*)-methamphetamine and (*l*)-methamphetamine standard by chiral column

Our HPLC analysis positively identified the presence of methamphetamine substances in all the samples. Interestingly, eight out of twenty samples demonstrated only the presence of (*d*)-methamphetamine, indicating the detection of pure drugs from clandestine preparations. The samples showed only a single peak at 10.55 min (Fig. 6). Other samples detected the presence of racemic methamphetamine mixtures.

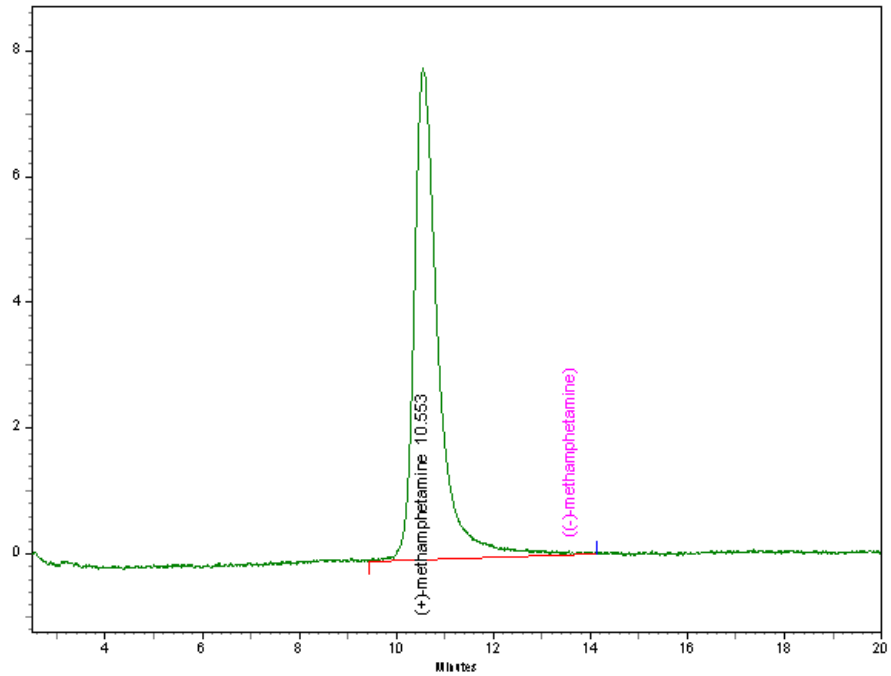

Fig. 6: (*d*)-methamphetamine peak eluted at 10.55 min by chiral column

From previous studies, production of methamphetamine by the reduction of (-)-ephedrine and (+)-pseudoephedrine is known to yield (+)-methamphetamine (Cantrell et al, 1998; Skinner, 1990). This suggested that some samples analysed in the work could tentatively were processed using the above mentioned precursors. Additionally, subsequent purification technique, known as enantiomeric enrichment of methamphetamine isomers, could also yield a non-racemic methamphetamine product during the clandestine preparation [19,21]. Several studies also reported on the presence of racemic methamphetamine as the product of utilising 1-phenyl-2-propanone as a starting material [9,22]. In many instances, there was also possibility to yield racemic form or unequal proportions of (*d*)- and (*l*)-methamphetamine [22]. 60% of our samples displayed racemic property, due to the fact of wider choice of starting materials, with either ephedrine or 1-phenyl-2-propanone. Note that these drug substances are less potent than the pure (*d*)-methamphetamine, which required no subsequent enrichment of the isomers by the clandestine operators.

ICP-MS

Elemental analysis performed on all 20 drug samples from clandestine laboratories could provide us the information on the presence of inorganic impurities, which might be related to the catalyst or reducing agent used during the synthesis process. From a total of 26 elements analysed, 22 elements (*i.e.* Li, B, Na, Mg, Al, K, Ca, V, Cr, Mn, Fe, Ni, Cu, Zn, As, Sc, Ag, Cd, Sb, Ba, Hg and Pb) were detected. Five of them, namely Li, Ba, Hg, Al and Na were found more prevalent than other elements during our experimental analysis, and the analytical results of all 20 samples are recorded in Table 1.

Out of the 20 samples, one of them recorded a relatively higher concentration of lithium at 0.034 mg/L, while all other samples were detected below 0.01 mg/L or remained undetectable. The sample with relatively higher level of lithium were also found with high concentration of elements including barium, mercury and aluminium as compared to other samples. Beside this drug sample, there were another two samples reporting with the presence of mercury, at a concentration level greater than 0.01 mg/L. Note that lithium and mercury are target impurities in Birch and Reductive amination pathway, respectively. The same sample also gave a relatively greater level of barium in the analysis, together with another nine samples with concentration greater than 0.01 mg/L. The presence of barium could be associated with the conversion of chlorophedrine to methamphetamine in Emde's methods, where barium sulphate was introduced as a reductive catalyst during the synthesis [23]. In addtional

to above sample, another drug sample was also found with relatively higher concentration of Al, but other elements were undetected under our experimental conditions. Note that all samples showed the presence of aluminium at different concentration of more than 0.05 mg/L. The contaminants from the usage of aluminium containers or utensils may lead to the high concentration of Al in the inorganic profile of the drug sample. Ten out of the total 20 samples were observed with greater level of Na as compared to others, which may relate them to the Nagai's and Emde methods which originated from sodium hydroxide and hydrochloric acid as the nuetralisation reagants [23]. From these results, it showed that traces of elements from reagent and catalyst remained in the final product [23], giving a clue on the possible synthetic pathway.

Table 1: Concentration level of Lithium, Barium, Mercury, Aluminium and Sodium in 20 drug samples by ICP-MS

Sample	Element (mg/L)				
	Li	Ba	Hg	Al	Na
1	*	*	*	0.10	925.11
2	*	0.01	*	5.03	869.41
3	*	0.01	*	0.12	S
4	*	*	*	0.05	983.34
5	*	*	*	0.17	730.52
6	*	0.01	*	4.35	393.51
7	*	0.04	0.01	0.69	S
8	*	0.06	*	0.21	S
9	*	0.01	*	0.14	S
10	0.04	101.8	0.07	327.49	S
11	*	0.01	*	0.62	17.34
12	*	*	*	0.06	1.95
13	*	*	*	0.18	2.35
14	*	*	*	0.15	1.64
15	*	0.04	0.01	0.81	13.26
16	*	*	*	1.15	2.41
17	*	0.01	*	5.32	20.80
18	*	*	*	80.96	3.36
19	*	*	*	0.39	2.22
20	*	*	*	0.18	1.97

Note: * indicates undetected or concentration level of less than 0.01 mg/L; S indicates saturated level of element under the experimental conditions

General Discussion

Characterisation of clandestine methamphetamine can serve as a strategy to provide the information to predict the potential origin or precursor and possible synthetic pathway of the drugs, and also to link the source to its syndicate operation or source of clandestine laboratories based on the profiles of these seized substances. Initial screening of any substance sampled from a clandestine laboratory or a crime scene allowed us to determine the subsequent analytical procedure. FTIR enabled the identification of functional groups in a group, and our results showed that the drugs samples were of certain high degree of purity. GC-MS results determined the presence of impurities (if any) in the samples, whereas HPLC identified the enantiomers of respective samples. The inorganic profiles of the drug samples by ICP-MS facilitated the discrimination to some extent on the basis of their synthetic pathway. Further characterisation strategy was taken by combining the information of all four analyses as shown in Fig. 7. Our work showed the reliability of the techniques used for the characterisation of methamphetamine.

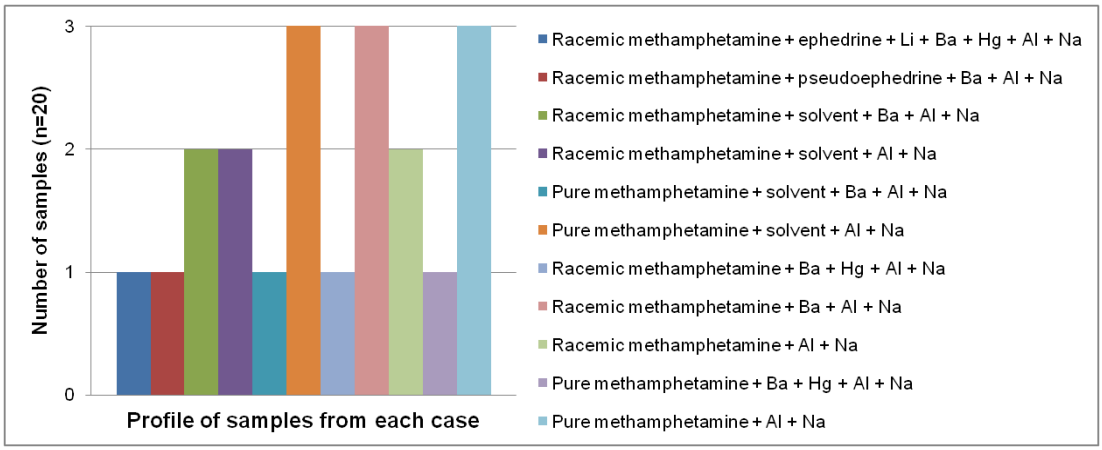

Fig. 7: Distribution of active ingredients, presence of precursor, stereochemistry and inorganic profiles according the number of samples

Conclusion

Methamphetamine continued to be in high demand, although the conventional drugs remain the top listed drugs of choice as well as the emergence of new psychoactive substances in the drug market. They were illicitly manufactured in clandestine laboratories in a steady growth since there was increase in seizure every year. Combat against these drugs and their manufacturing has been performed to ward off their threat to the national society but still facing huge challenges, especially with the shifting of large-scale laboratories to a smaller one. In this work, the analytical technique demonstrated the characterisation of methamphetamine samples on the basis of their possible starting materials and synthetic pathway. All the four analyses gave useful results, allowing us to compare the drug samples from different sources. These techniques can be easily adapted in forensic narcotic laboratories, which received the methamphetamine samples and could be contributed in the development of drug profile database. The information on the profile of seized drugs could serve for both intelligence and evidential purposes, to link the sources of samples or to relate a particular source to the distribution network in the illegal drug market.

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