DETERMINATION OF CHEMICAL ATTRIBUTION SUBSTANCES IN METHAMPHETAMINE TABLETS BY GAS CHROMATOGRAPHY-MASS SPECTROMETRY

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by

MOHAMMAD ZAWAWIS BIN MOHAMMAD ZABIDI

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CERTIFICATE

This is to certify that the dissertation entitled **"DETERMINATION OF CHEMICAL ATTRIBUTION SUBSTANCES IN METHAMPHETAMINE TABLETS BY GAS CHROMATOGRAPHY-MASS SPECTROMETRY"** is a genuine record of the research work conducted by Mr. **"MOHAMMAD ZAWAWIS BIN MOHAMMAD ZABIDI"** from October 2024 to February 2025 under my supervision. I have read this dissertation and, in my opinion, it meets the acceptable standards of scholarly presentation. It is fully adequate in scope and quality to be submitted in partial fulfilment of the requirements for the degree of Bachelor of Science in Forensic Science (Honours) at Universiti Sains Malaysia.

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DECLARATION

I hereby declare that this dissertation is the result of my own research, except where due acknowledgment has been made. I further confirm that it has not been previously or concurrently submitted, in whole or in part, for any other degree at Universiti Sains Malaysia or any other institution. Additionally, I grant Universiti Sains Malaysia the permission to utilize this dissertation for teaching, research, and promotional purposes.

….. …….

(MOHAMMAD ZAWAWIS BIN MOHAMMAD ZABIDI)

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF SYMBOLS

%	Percentage
±	Plus-minus
°C	Degree Celsius
°C/min	Degree Celsius per minute
µL	Microlitre
µm	Micrometer
g	Gram
kg	Kilogram
m/z	Mass-to-charge
min	Minute
mg	Milligram
mg/mL	Milligram per millilitre
mL	Millilitre
mL/min	Millilitre per minute
mm	Millimetre
ng/mL	Nanogram per millilitre

LIST OF ABBREVIATIONS

ADHD	Attention deficit hyperactivity disorder
ASYN	Alpha-synuclein
ATS	Amphetamine-type stimulants
CAS	Chemical attribution substances
CMP	1-(1',4'-cyclohexadienyl)-2-methylaminopropane
DDA	Dangerous drug act
et al.	*et alia* – and others
FTIR	Fourier-transform infrared spectroscopy
GC	Gas chromatography
GC-MS	Gas chromatography-mass spectrometry
GC-FID	Gas chromatography-flame ionization detector
HI	Hydriodic acid
HIV	Human immunodeficiency virus
HPLC	High performance liquid chromatography
LC-MS	Liquid chromatography-mass spectrometry
MS	Mass spectrometry
NADA	National Anti-Drug Agency
NDTA	National Drug Threat Assessment
NSPs	Needle and Syringe Programmes
NIST	National Institute of Standard and Technology
OTC	Over-the-counter
P2P	Phenyl-2-propanone
RMP	Royal Malaysian Police
TFA	Trifluoroacetic acid
UNODC	United Nations Office on Drugs and Crime
USM	Universiti Sains Malaysia

PENENTUAN BAHAN ATRIBUSI KIMIA DALAM TABLET METAMFETAMINE OLEH KROMATOGRAFI GAS-SPEKTROMETRI JISIM

ABSTRAK

Penyalahgunaan metamfetamine merupakan satu kebimbangan global yang signifikan. Bahan atribusi kimia (CAS) dalam tablet metamfetamine, termasuk bahan pengaduk, pelarut, dan bendasing, memainkan peranan penting dalam penyiasatan forensik dengan memberikan maklumat mengenai kaedah pembuatan dan trend pemalsuan. Walau bagaimanapun, analisis forensik rutin biasanya memberi tumpuan kepada pengecaman dan pengkuantitian komponen utama dalam tablet metamfetamine yang dirampas, dengan kurang penekanan kepada pengesanan CAS. Oleh itu, kajian ini bertujuan untuk mengenal pasti CAS dalam tablet metamfetamine yang dirampas dengan menggunakan kromatografi gas-spektrometri jisim (GC-MS) bagi menentukan profil kimia dan trend pemalsuan. Dalam kajian ini, sebanyak 161 tablet metamfetamine yang dirampas oleh Polis Diraja Malaysia di negeri Kelantan telah dianalisis menggunakan GC-MS. Sampel tersebut diekstrak menggunakan metanol, diikuti dengan pemisahan kromatografi dan pengecaman menggunakan spektrometri jisim. Kehadiran metamfetamine dan kafein telah dikesan dalam semua sampel yang diuji. Nisbah metamfetamine kepada kafein didapati berbeza antara sampel, menunjukkan ketidakkonsistenan dalam proses pembuatan dan kemungkinan perbezaan dalam sumber atau kaedah sintesis. Sebilangan besar sampel mempunyai nisbah dalam julat 0.6 hingga 0.65, dengan 39 sampel mewakili 24.22% daripada jumlah keseluruhan. Kesimpulannya, kajian ini dapat menyumbang kepada perisikan dadah forensik dengan membantu dalam penentuan sumber tablet methamphetamine serta trend pembuatan.

Penetapan profil CAS boleh meningkatkan penyiasatan forensik dengan menghubungkan sampel dadah haram kepada laluan pengeluaran tertentu, sekali gus menyokong usaha penguatkuasaan undang-undang dalam membanteras pengedaran dadah.

DETERMINATION OF CHEMICAL ATTRIBUTION SUBSTANCES IN METHAMPHETAMINE TABLETS BY GAS CHROMATOGRAPHY-MASS SPECTROMETRY

ABSTRACT

Methamphetamine abuse is a significant global concern. Chemical attribution substances (CAS) in methamphetamine tablets, including adulterants, diluents, and impurities, play a crucial role in forensic investigations by providing insights into manufacturing methods and trends in adulteration. However, routine forensic analyses typically focus on identifying and quantifying the primary drug component in seized methamphetamine tablets, with less emphasis on detecting CAS. Therefore, this study was aimed to identify and characterise CAS in seized illicit methamphetamine tablets using gas chromatography-mass spectrometry (GC-MS) to establish chemical profiles and assess trends in adulteration. In this study, a total of 161 methamphetamine tablets, seized by the Royal Malaysian Police in Kelantan state, were analysed using GC-MS. These samples were extracted with methanol followed by chromatographic separation and mass spectrometric identification. The presence of methamphetamine and caffeine were detected in all tested samples. The methamphetamine-to-caffeine ratio was found to be varied across samples, indicating inconsistencies in manufacturing processes and possible differences in source or synthesis methods. Most samples fell within the ratio range of 0.6 to 0.65 with 39 samples, representing 24.22% of the total samples. To conclude, this study could contribute to forensic drug intelligence by aiding in determining methamphetamine tablet sources and manufacturing trends. Establishing CAS profiles could enhance forensic investigations by linking illicit drug samples to

specific production routes, supporting law enforcement efforts in combating drug trafficking.

CHAPTER 1

INTRODUCTION

1.1 Background of Study

Methamphetamine, a potent central nervous system stimulant, is a prominent member of the amphetamine-type stimulants (ATS) class. It is the second most used illegal drug worldwide, with its highest prevalence reported in North America, Asia, and Oceania (UNODC, 2022). ATS, which include amphetamine, methamphetamine, and their derivatives, are psychoactive substances that stimulate the release of neurotransmitters such as dopamine, serotonin, and norepinephrine (Paz-Ramos *et al.*, 2023). The prevalence of ATS has been increasing globally, accounting for approximately 5% of the illicit drug market in 2019 (Dragan *et al.,* 2021). The rise in their production, facilitated by numerous clandestine laboratories, combined with their easy distribution within society, represents two of the primary challenges in the fight against illicit drugs.

Methamphetamine is available in various forms in the black market, including in the forms of crystal, tablet or liquid (UNODC, 2020). Each form caters the different user preferences and market demands, with variations in production methods could also have been influenced by regional precursor availability and trafficking operations. The most common form is the crystalline methamphetamine referred to as "ice" or "shabu" and tablets often branded as "yaba" in Southeast Asia. Methamphetamine is particularly potent due to its higher lipid solubility, enabling it to cross the blood-brain barrier more effectively than other ATS (Maas *et al.,* 2018). Its abuse is associated with a range of harmful side effects, both short-term and long-term. Short-term effects include the increased alertness, energy, and euphoria (Panenka *et al.,* 2013). However, these are often accompanied by adverse reactions such as insomnia, paranoia, and aggressive

behaviour. If an individual uses the drug of abuse for an extended duration, he or she may suffer complications such as myocardial infarction, strokes, and gastrointestinal damage, significantly impacting overall the health of that individual (Edinoff *et al.*, 2022).

Chemical attribution substances (CAS) refer to the chemical markers or impurity profiles that can be used to trace the origin and synthesis of illicit drug (Zhang *et al.*, 2024). A study on chemical profiling of illicit drugs street samples and their cutting agents by Żubrycka *et al*. (2022) found that methamphetamine sample contain amphetamine (51.0%), caffeine (42.9%), pseudoephedrine (2.0%), α-methylaminohexanophenone (2.0%) and dipentylone (2.0%). This information is crucial for linking substances found at crime scenes to their sources, enhancing the understanding of chemical profiles of illicit drugs.

Various sensitive and suitable analytical methods, mainly based on high resolution chromatography, have been applied to the analysis of illicit drugs to obtain specific fingerprints which are very useful in comparative drug samples analysis. Gas chromatography-mass spectrometry (GC-MS) is considered as a "gold standard" for the identification of forensic drug samples (UNODC, 2006). This technique combines the separation capabilities of gas chromatography (GC) with the identification of compound by mass spectrometry (MS), allowing the accurate and precise determination of compound in a drug sample. Therefore, in this study, GC-MS was used to analyse the methamphetamine tablets to identify the CAS present in these samples, including active ingredients, adulterants, and diluents. This approach enables a comprehensive understanding of the tablet composition, which is crucial for forensic investigations, determining trends in adulteration and synthesis method.

1.2 Problem Statements

Methamphetamine abuse has become a significant public health issue globally due to its widespread misuse and its potent, highly addictive effects on the central nervous system. In 2022, approximately 8,682.04 kg of methamphetamine were seized in Malaysia (UNODC, 2022). To get more profits, manufacturers often adulterate methamphetamine tablets with various adulterants and diluents. Commonly identified adulterants include caffeine, fentanyl, and ketamine are found mixed with methamphetamine, altering its pharmacological profile and increasing the risk of adverse effects. (Awang *et al.,* 2022; Paz-Ramos *et al.,* 2024; McKetin and McLaren, 2004). Additionally, sugar compounds such as lactose, dextrin, glucose, sucrose, and sorbitol, as well as other inorganic compounds such as silicates and magnesium salts could be used as diluents to increase the bulk of the tablets. (Haywood and Glass, 2011).

However, routine forensic analyses typically focus on identifying and quantifying the primary drug component in seized methamphetamine tablets, with less emphasis on detecting CAS (Awang *et al.,* 2022). The presence of these substances is not always apparent through simple physical examination or basic chemical tests. Advanced analytical techniques, such as GC-MS can be required to accurately detect and identify the wide range of compounds present in the seized methamphetamine samples. Therefore, this study allows for the determination of CAS in methamphetamine tablets seized in Kelantan state to gather information regarding the similarities and differences in their chemical profiles.

1.3 Objectives

1.3.1 General Objective

This study was aimed to investigate the CAS in seized illicit methamphetamine tablets using GC-MS.

1.3.2 Specific Objectives

I. To detect and identify CAS in methamphetamine tablets using GC-MS.

II. To compare the chemical profiles among the methamphetamine tablets for determining the trends in adulteration.

1.4 Significance of Study

This study has the potential to assist law enforcement authorities to obtain important information regarding the similarities and differences among illicit methamphetamine tablets. This approach is particularly beneficial for sample-to-sample, case-to-case, and seizure-to-seizure comparisons. Furthermore, it significantly contributes to forensic drug intelligence by, to some extent, by tracing the source or production process of methamphetamine tablets. The chemical profiling of methamphetamine tablets can also reveal patterns in the types and ratios of adulterants, diluents, and cutting agents used. These patterns can provide valuable insights into the manufacturing techniques used in clandestine laboratories, aiding efforts to trace the origin and production methods of methamphetamine.

1.5 Scope of Study

This study focused exclusively on the CAS in methamphetamine tablets, covering only the drug samples, seized by Royal Malaysian Police in Kelantan,

Malaysia, during the period from July 2017 to August 2019. This regional specificity is significant, as it may provide information into the trends in adulteration and chemical profiles of methamphetamine tablets circulating in this area. By limiting this study to methamphetamine tablets, we aimed to develop a comprehensive understanding of the chemical composition of methamphetamine tablets and focused on qualitative analysis rather than quantitative measurement, including the identification of CAS using the GC-MS technique.

CHAPTER 2

LITERATURE REVIEW

2.1 Methamphetamine

Methamphetamine, scientifically known as N-methyl-1-phenylpropan-2-amine, is a synthetic ATS that produces powerful effects on the central nervous system. Its chemical structure is a derivative of amphetamine, with the addition of a methyl group bonded to the nitrogen atom (Maas *et al.,* 2018). Addition of the methyl group is responsible for the potentiation of effects as compared to the related compound amphetamine that making it more lipid soluble and easy to transport across the blood brain barrier with high potency and long duration of effects (Maas *et al.,* 2018).

The first synthesis of methamphetamine was reported in 1919 in Japan, where it was derived from ephedrine for the treatment of respiratory diseases (Maas *et al.,* 2018). However, methamphetamine became widely abused during World War II when countries such as British, Japan and United States provided the drug to their military forces (Andrighetto *et al.,* 2016). It was prescribed to boost soldiers' endurance, enhance their alertness and focus, and improve overall performance in combat situations (Andrighetto *et al.,* 2016). Figure 2.1 demonstrates the chemical structure of methamphetamine.

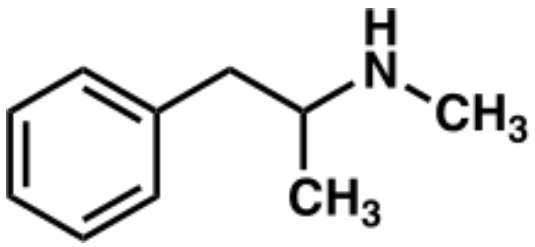

Figure 2.1 Chemical structure of methamphetamine.

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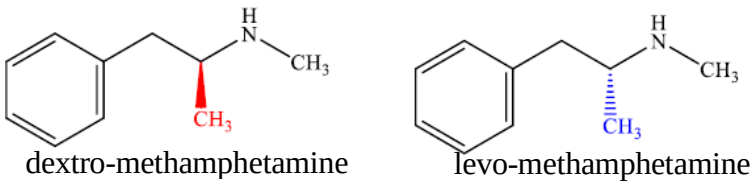
As shown in Figure 2.1, the chemical formula of methamphetamine is $C_{10}H_{15}N$ with 149.2337 g/mol molecular weight. Methamphetamine is made up of two enantiomers which are levo-methamphetamine (L-methamphetamine) and dextro-methamphetamine (D-methamphetamine) due to presence of chiral carbon in its chemical structure (Nigar *et al.*, 2021). The pharmacological and physiological effects of methamphetamine differ significantly between its two enantiomers, despite their chemical similarity. According to Ward *et al.* (2016), L-methamphetamine produces a weaker and shorter effect compared to the D- methamphetamine. Therefore, D-methamphetamine is also widely abused for its ability to produce intense euphoria, contributing to its role in the illicit drug market.

L-methamphetamine can be found in over-the-counter (OTC) nasal decongestant products, such as Vicks™ inhaler, where it is used to alleviate symptoms of the common cold (Andrighetto *et al.*, 2016). Conversely, D-methamphetamine is present in certain prescription medications, such as Desoxyn, which is used for treating attention deficit hyperactivity disorder (ADHD) and obesity (Ward *et al.*, 2016). As shown in Figure 2.2, the marker red in the chemical structure of methamphetamine on the left showing the bond is projecting out towards the viewer and the marker blue in the chemical structure of methamphetamine on the right showing the bond is projecting out away from the viewer.



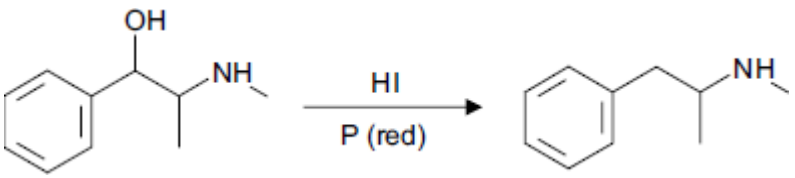
dextro-methamphetamine levo-methamphetamine

Figure 2.2 Chemical structures of dextro-methamphetamine (left) and levo-methamphetamine (right).

2.2 Synthesis Route of Methamphetamine

Methamphetamine can be synthesized through six chemical reactions, namely Leuckart, Reductive amination, Birch reduction, Nagai, Rosenmund, and Emde methods (Mat Desa and Ismail, 2017). Ephedrine or pseudoephedrine is used as the starting material for the Nagai, Birch reduction, Rosenmund, and Emde methods, while both the Leuckart and Reductive amination methods use phenyl-2-propanone (P2P) as the starting material (Mat Desa and Ismail, 2017). Among these methods, the most common synthetic routes for methamphetamine involve the use of ephedrine or pseudoephedrine as precursors, rather than P2P (UNODC, 2020).

In 1981, clandestine laboratories in the United States commonly employed the Nagai method, which involves the reaction of ephedrine with hydriodic acid (HI) and red phosphorus to produce methamphetamine. This method was extensively studied by Frank et al. (1983). The process involves mixing ephedrine with red phosphorus and HI, followed by heating. The heated product is then filtered, made basic, extracted, and crystallised as hydrochloride salt using an ether/acetone mixture and hydrochloric acid. The synthesis process via the Nagai method is illustrated in the Figure 2.3.



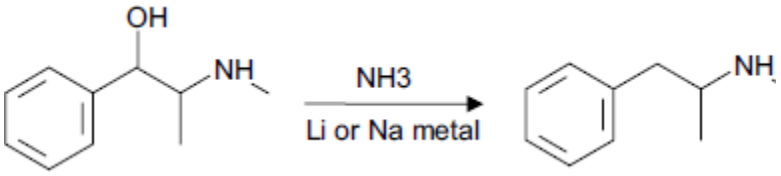
Ephedrine or pseudoephedrine

methamphetamine

Figure 2.3 Methamphetamine synthesis via Nagai method.

A study conducted by Person *et al.* (2005) aimed to study the lithium-ammonia reduction method also known as Birch method to synthesise methamphetamine. The

Birch synthesis route of methamphetamine involves the reduction of ephedrine or pseudoephedrine using lithium and liquid ammonia which act as reducing agents, producing methamphetamine. This process is notable for its ability to convert the hydroxyl group of ephedrine into a more reactive form, facilitating the formation of methamphetamine while also producing byproducts such as 1-(1',4'-cyclohexadienyl)-2-methylaminopropane (CMP). The synthesis process via Birch Method is illustrated in the Figure 2.4.

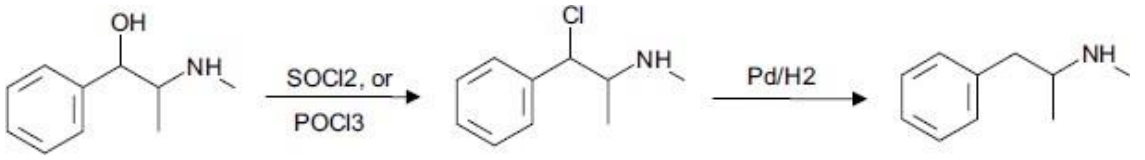


Ephedrine or pseudoephedrine

methamphetamine

Figure 2.4 Methamphetamine synthesis via Birch method.

According to UNODC (2020), Emde method is a method that commonly used to synthesise methamphetamine in clandestine laboratories. Ephedrine or pseudoephedrine typically reacts with thionyl chloride to give the intermediate chloroephedrine, which is then hydrogenated over a platinum or palladium catalyst to yield methamphetamine. In GC-based analytical schemes, the chloroephedrine intermediate is rarely found as an impurity, because it decomposes during analysis to form aziridines. Chloroephedrine also decomposes rapidly during basic extraction of methamphetamine. The synthesis process via the Emde Method is illustrated in the Figure 2.5.



Ephedrine or pseudoephedrine

chloroephedrine

methamphetamine

Figure 2.5 Methamphetamine synthesis via Emde method.

Kunalan *et al.* (2009) studied the methods used to synthesis methamphetamine from phenyl-2-propanone (P2P). Two widely employed methods for methamphetamine synthesis from P2P are the Leuckart method and the Reductive Amination method using aluminium/mercury amalgam. The authors discussed that the Leuckart method involves the reaction of P2P with N-methylformamide at elevated temperatures (165–170°C) for 24–36 hours, producing N-formylmethamphetamine as an intermediate. This intermediate is subsequently hydrolysed to yield methamphetamine. In contrast, the reductive amination method employs methylamine and aluminium amalgam as reagents. The reaction proceeds through the formation of an imine intermediate, which is then reduced to methamphetamine under controlled temperature conditions (Kunalan *et al.*, 2009).

During the synthesis of methamphetamine, various chemical reactions introduce specific impurities into the end products, which can serve as markers of the synthesis route or precursor used. These impurities could also provide valuable forensic intelligence for identifying manufacturing methods and possible sources. However, the methods of methamphetamine manufacture in clandestine laboratories have evolved over time due to increasing regulations and control of precursor chemicals, making them more difficult to gather the important information (Andrighetto *et al.*, 2016).

Additionally, the precursors and synthesis pathways employed in clandestine drug laboratories are often influenced by the geographical regions. This is evident in the historical patterns of methamphetamine production, where specific methods and precursors have been linked to specific areas or regions (UNODC, 2020). These geographical variations further underscore the need for ongoing chemical profiling to understand and disrupt trafficking networks effectively.

According to the UNODC (2020), ephedrine and pseudoephedrine are commonly used as precursors in methamphetamine production in China, as the country is the world's leading producer of ephedrine and pseudoephedrine. This accessibility makes them the preferred starting materials for methamphetamine synthesis in the region. Similarly, in Australia, pseudoephedrine has been identified as the predominant precursor. Andrighetto *et al.* (2016) reported that in 2014, the Australian Crime Commission found that 91% of seized methamphetamine was synthesized using pseudoephedrine. This data was based on the detection of 448 major clandestine laboratories, emphasizing the widespread reliance on pseudoephedrine as the primary source for methamphetamine production in Australia.

2.3 Effects of Methamphetamine

Similar to other amphetamine groups, methamphetamine induces an initial state of euphoria and leads to dependence and psychosis. However, its long-term effects include weight loss, memory loss, psychosis, paranoia, hallucinations, and cardiovascular collapse, that can contribute to severe health complications and potential death (İvecen & Gokdemir, 2022). Additionally, Shrestha *et al.* (2022) also indicated

that methamphetamine dependence could result in long-term neuronal damage, as well as harmful effects on cognition, memory, and attention.

A study on the effects of methamphetamine induced neurotoxic diseases by Shrestha *et al.* (2022) found that methamphetamine abuse significantly increases the likelihood of developing neurotoxic conditions including Parkinson's disease, Alzheimer's disease, and other neurotoxic disorders. Specifically, methamphetamine elevates the risk of Parkinson's disease by increasing the expression of alpha-synuclein (ASYN). The authors mentioned that methamphetamine abuse is associated with a high risk of Alzheimer's disease and subsequent neurodegeneration, which may result from biological variations in brain regions or genetic and epigenetic factors.

Chen *et al.* (2024) investigated the toxic effects of methamphetamine on reproductive systems, embryo development, and newborns. Their findings revealed that methamphetamine abuse adversely affects the hypothalamic-pituitary-testicular axis, testicular structure, and sperm function in males. Similarly, it disrupts ovarian folliculogenesis, impairs oocyte quality, and hinders embryo development in females. Ultimately, these impacts lead to significant reproductive toxicity and developmental issues in both males and females, highlighting its detrimental effects on overall reproductive health.

Furthermore, a study conducted by Norrozi *et al.* (2016) on the effectiveness of Needle and Syringe Programmes (NSPs) in reducing Human immunodeficiency virus (HIV) incidence among people who inject drugs in Kermanshah, Iran. The authors have also mentioned that the risk of HIV transmission through sharing needles among people who inject drugs is significant. Key findings revealed that with insufficient coverage of NSPs, the HIV rate among these people increased to 4.04%.

Therefore, it can be concluded that the consequences of methamphetamine abuse range from acute psychological disturbances to chronic physiological damage, Notably, it significantly impacts cognitive health, cardiovascular function, reproductive health, and immune response underscoring its severe effects on overall well-being.

2.4 Chemical Attribution Substances

Chemical attribution substances in methamphetamine tablets, including specific adulterants, impurities or unique chemical profiles that can indicate the source or manufacturing processes that important for forensic traceability (Zhang *et al.*, 2024). Particularly, *Yaba* tablets, a common form of methamphetamine tablet, typically consist of a mixture of approximately 25–35 mg of methamphetamine and 45–65 mg of caffeine, as reported in Thailand (Siam Rehab, 2019). However, the composition can vary slightly, with some tablets containing about 90–100 mg per tablet (UNODC, 2006). Meanwhile, methamphetamine tablets in Australia are often combined with ketamine and sold in the party scene as ecstasy. (McKetin, R. andMcLaren, J., 2004).

Awang *et al.* (2022) conducted a study on the physical and chemical discrimination of methamphetamine tablets for forensic intelligence found that methamphetamine and caffeine were present in most samples. Using GC-MS, the authors analysed 164 methamphetamine tablets seized by the Royal Malaysian Police in Kelantan, Malaysia, and observed that most of the samples contained caffeine. However, this study focused solely on the detection and quantification of methamphetamine, without addressing CAS.

A study conducted by Adam *et al.* (2005) aimed to develop chemical profile of 298 *Yaba* tablets seized by the police in the northern region of Thailand. The authors

found that most methamphetamine tablets contain not only the active ingredient but were also adulterated with caffeine, with an average caffeine content of 62.43 mg per tablet. However, the ratio of methamphetamine to caffeine varied across the 298 methamphetamine tablets samples, indicating inconsistencies in the composition of the seized tablets.

Moreover, Mat Desa and Ismail (2017) have described a GC-MS harmonised method to study the impurity profiling of amphetamine and methamphetamine. Based on the findings, the identification of route specific impurities in methamphetamine samples showed that the presence of P2P is suggestive towards the possibility of synthetic route being either Leuckart's, nitrostyrene or aminative reduction pathway. It was important to identify the methamphetamine tablets from the same batch that exhibited the same impurity profile.

In addition, Cui *et al.* (2020) conducted a study on the impurity profiling of seized methamphetamine tablets in China. Several intermediate compounds were identified in this study, including amphetamine, phenyl-2-propanone-oxime, N-formylamphetamine, ephedrine, bibenzyl, and α-methyldiphenethylamine. The findings revealed that the analysed methamphetamine tablets could be divided into two groups, one group used ephedrine as the precursor, while the other used P2P.

The pattern of chemical attribution substances may help law enforcement trace the origin of seized drugs, identify manufacturing methods, and potentially link specific batches to certain trafficking networks. By establishing unique chemical "fingerprints" of methamphetamine samples, forensic investigators can build a comprehensive database that helps in identifying the geographical origin, precursor chemicals, and synthesis methods used in drug production. (Andrighetto *et al.,* 2016). This information

not only enhances the ability to track down clandestine laboratories but also facilitates the identification of patterns in trafficking routes and networks.

2.5 Methamphetamine Market in Southeast Asia

The methamphetamine market in Southeast Asia has continued to expand significantly. Organised crime groups in the region have increasingly turned to the use of non-controlled chemicals to manufacture methamphetamine and other synthetic drugs. This shift in production methods has contributed to a further decline in prices across several countries in the region, making methamphetamine more affordable and accessible (UNODC, 2022). According to the UNODC, in Asia region, methamphetamine in the form of tablets and crystals is predominantly produced in the "Golden Triangle" region. The Golden Triangle is a region encompassing parts of Myanmar, Laos, and Thailand serves as a major hub to produce illicit drugs since 1950s (Chouvy , 2013). The methamphetamine is subsequently distributed to the Mekong regions and other Southeast Asian countries, using various trafficking routes to reach international markets. This highlights the significant role of the Golden Triangle as a hub for methamphetamine production and the complexity of the trafficking networks operating in the region. Figure 2.6 illustrates the perceived methamphetamine tablet trafficking flows in the Mekong region.

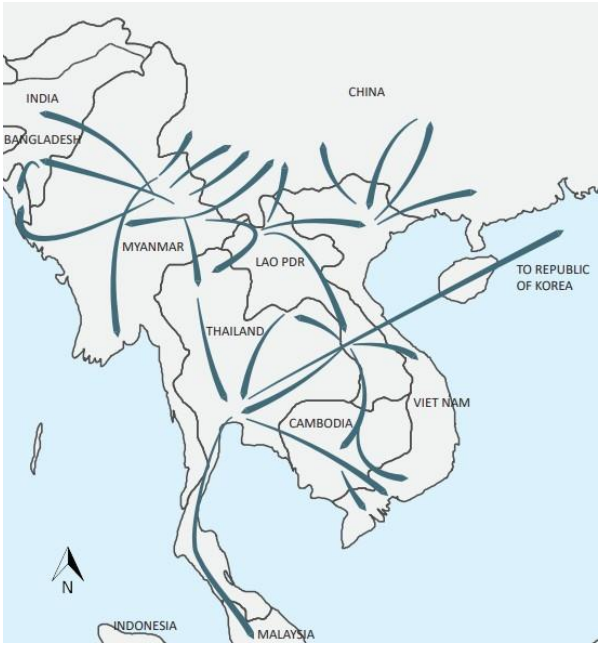


Figure 2.6 Perceived methamphetamine tablet trafficking flows in the Mekong region (Source: UNODC, 2019).

The Figure 2.6. highlights that Thailand has become as one of the primary routes for the entry of methamphetamine tablets into Malaysia (UNODC, 2019). This underscored Thailand's strategic role within the regional drug trafficking network and the challenges associated with controlling cross-border drug movement in the area. Furthermore, Malaysia has become a transit hub for the importation of methamphetamine to Australia and New Zealand (UNODC, 2019).

The Figure 2.7 shows the seizures of methamphetamine in the East and Southeast Asia, by region, 2011-2021, where in 2021 indicated that a record amount of methamphetamine, totalling 171.5 tonnes, was seized in the regions of East and Southeast Asia. The Southeast Asian region, particularly the lower Mekong sub-region comprising Cambodia, Lao PDR, Myanmar, Thailand, and Vietnam continues to account for a significant and growing proportion of methamphetamine seizures

(UNODC, 2022). In 2021, this subregion alone was responsible for nearly 89 percent of the total seizures reported in the region.

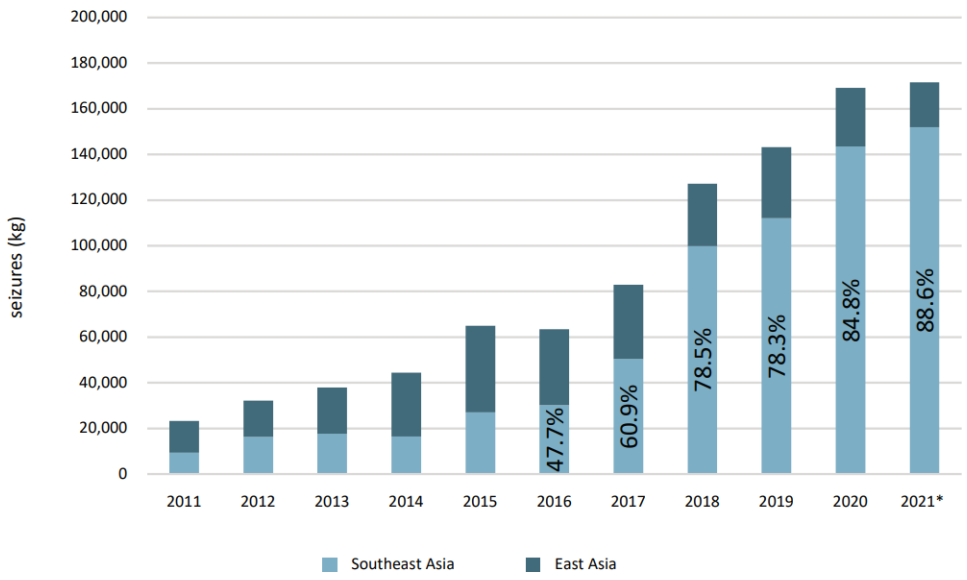


Figure 2.7 Changes in the seizure of methamphetamine in East and Southeast from 2011-2021 (Source: UNODC, 2022).

2.6 Trends of Methamphetamine Abuse in Malaysia

The widespread abuse of methamphetamine has caused serious problems in Malaysia. According to UNODC, approximately 8,682.04 kg of methamphetamine were seized in Malaysia in 2022. This huge number of methamphetamine seizures was influenced by various factors, especially due to close proximity of Sungai Golok to Thailand facilitates easy movement of drugs across the border (Redhuan *et al.*, 2024). Sungai Golok is a river demarcating the border between Malaysia's Kelantan state and Thailand, has long been a hotspot for illicit activities, notably drug smuggling. The river's extensive network of informal crossing points, often referred to as "rat lanes,"

facilitates the clandestine movement of narcotics between the two countries. Figure 2.8 shows a photo of Sungai Golok- Border of Malaysia and Thailand.

Figure 2.8 Sungai Golok- Border of Malaysia and Thailand (Source: Bernama, 2024).

Several significant seizures of methamphetamine tablets occurred in Kelantan in 2024. In December, the Royal Malaysia Police successfully apprehended a local people and two Thai nationals involved in a drug smuggling syndicate. Police seized 63,910 *Yaba* tablets and two kilograms of shabu, worth RM1.02 million, in Rantau Panjang, Kelantan. (Metro, 2024). Additionally, a significant drug-related case in November 2024 in Sungai Golok further emphasized the persistent issue of narcotics trafficking along the Malaysia-Thailand border. A popular modern female singer from Kelantan, along with five other Malaysians, were detained for allegedly possessing 6,000 *Yaba* tablets, a form of methamphetamine. (Bernama, 2024). This high-profile case underscored the involvement of individuals from various backgrounds in drug trafficking activities. Law enforcement authorities suspected that the *Yaba* tablets were

intended to be smuggled into Kelantan through Sungai Golok, a known hotspot for cross-border drug smuggling.

It was observed that crystalline and tablet form of methamphetamine seizures showed an increase over the five years, while liquid form of methamphetamine exhibited sharp spikes, peaking in 2020 before sharply declining, as shown in Table 2.1. Notably, the seizure of methamphetamine tablets demonstrated a gradual increase over the years, with a substantial rise observed from 2020 onwards. A sharp increase was recorded in 2021, with 357.45 kilograms seized. This upward trend continued in 2022, where the seizure amount increased to 383.63 kilograms. The growing prevalence of tablets may reflect increased demand for this form of the drug. Additionally, this trend was also influenced by the reduced price of methamphetamine tablets, making the illicit drug more affordable and accessible (UNODC, 2022), The price of a methamphetamine tablet in Malaysia has also decreased from RM20 to RM15 per tablet in 2019 (NADA, 2022).

Table 2.1 Seizures of methamphetamine drugs in Malaysia from 2018-2022. (Source: NADA, 2023).

Methamphetamine	**Unit**	**2018**	**2019**	**2020**	**2021**	**2022**
Crystalline	Kg	6,85179	5,302.38	7,644.47	9,682.07	8,298.41
Tablet	Kg	226.12	198.75	207.42	357.45	383.63
Liquid	Kg	269.89	308.40	864.95	188.52	49.59

2.7 Legislation of Methamphetamine in Malaysia

The Dangerous Drugs Act 1952 (DDA 1952) is Malaysia's primary legislation for regulating and controlling the possession, manufacturing, distribution, and use of

dangerous drugs, including methamphetamine. Methamphetamine is classified as a dangerous drug under this act, and its handling is strictly controlled to prevent misuse and harm to public health.

In terms of self-administration, Section 15(1)(a) of the DDA 1952 states that using methamphetamine or testing positive for its metabolites is a punishable offense. Offenders may face a fine of up to RM5,000, imprisonment for up to two years, or both. Furthermore, those convicted may be required to undergo mandatory rehabilitation at a *Pusat Serenti* (rehabilitation centre) for treatment and counselling. The duration of rehabilitation is determined by the National Anti-Drug Agency (NADA), aiming to facilitate recovery and reduce the likelihood of relapse.

In addition, the DDA 1952 addresses possession of methamphetamine under Section 39A, which categorises offenses based on the quantity in possession. For minor possession, defined under Section 39A(1) as 5g or more but less than 30g, offenders may be sentenced to imprisonment for a period ranging from two to five years and whipped between three to nine strokes. However, if the quantity in possession is 30g or more, it is classified as major possession under Section 39A(2). This offense carries significantly harsher penalties, including imprisonment for a period of 10 years to life, and offenders must also be subjected to a minimum of 10 strokes of whipping.

Moreover, the act imposes severe penalties for the unauthorized production or synthesis of methamphetamine under Section 39B. This offense is treated with utmost seriousness due to its role in drug trafficking networks. Individuals found guilty of manufacturing methamphetamine may face the death penalty. Nonetheless, recent amendments to the DDA 1952 allow courts the discretion to impose life

imprisonment instead of the death penalty, depending on the circumstances and severity of the case.

In brief, the Dangerous Drugs Act 1952 serves as a comprehensive legal framework to combat the misuse and illegal activities associated with methamphetamine. Through stringent penalties for self-administration, possession, and production, the act seeks to deter drug-related offenses and protect public health. Importantly, the inclusion of judicial discretion in certain cases demonstrates a balanced approach between strict enforcement and consideration of individual case factors

2.8 Analytical Methods for Methamphetamine Analysis

Various analytical methods are employed to detect and characterize methamphetamine and its related compounds, including chemical attribution substances. Common techniques include gas chromatography-mass spectrometry (GC-MS), which provides detailed chemical profiling, liquid chromatography-mass spectrometry (LC-MS) for high sensitivity in biological matrices, and Fourier-transform infrared spectroscopy (FTIR) for rapid qualitative identification. (Awang *et al.,* 2022). These methods ensure accurate detection, quantification, and differentiation of methamphetamine samples, supporting legal and forensic investigations. In this section, the most used method, namely GC-MS was described and explored.

The analysis of methamphetamine tablets using GC-MS is a critical method for detecting and quantifying. This technique is particularly valuable due to its sensitivity, specificity, and ability to analyse complex samples, making it essential for forensic and clinical applications. During the process, compounds are separated by GC and detected

by MS, and their spectra are compared to a database library to identify unknown substances in the drug (UNODC, 2006).

A study by Awang *et al.* (2022) on the physical and chemical discrimination of methamphetamine tablets for forensic intelligence, showed that the GC-MS method developed has provided excellent separation and detection of this drug. The study reported that solvent extraction using methanol to prepare methamphetamine samples resulted in optimal separation. Furthermore, the study highlighted that the GC-MS method is accurate, precise, and capable of providing reliable results, making it a robust technique for analysing methamphetamine samples.

Moreover, the parameters and conditions of GC-MS instrument need to be taken account for the optimal analysis of the narcotic sample. Putra *et al.* (2024) suggested that use of HP-5 column with specific temperature settings, demonstrating GC-MS's effectiveness in identifying illicit drugs, including methamphetamine tablets. Typical conditions include a column temperature ramp from 100°C to 280°C, with an injection port temperature around 250°C (Putra *et al.*, 2024). In this study, the authors analysed 500 samples using GC-MS and detected methamphetamine in 244 samples, representing 48.8% of the total analysed. These findings emphasised the importance of precise instrument settings for accurate detection and identification of methamphetamine.

Bonchev *et al.* (2017) improved the GC-MS method for methamphetamine analysis by simplifying sample preparation, utilising solid-phase extraction, and incorporating pentafluoropropionic anhydride for derivatisation, achieving a limit of detection of 10 ng/mL. Apart from that, the method also provided accurate and precise results within 100 minutes. Another study conducted by Saito *et al.* (2024) also

demonstrated the use of sample derivatisation with trifluoroacetic acid (TFA) for methamphetamine analysis. This derivatisation process significantly enhanced the efficiency of methamphetamine extraction and analysis by GC-MS, improving the sensitivity and reliability of the analytical method.

Although HPLC is another commonly used method for the analysis of illicit drugs, but the aim of this study is to determine the CAS in methamphetamine tablets. For this purpose, the database library from mass spectrometry plays a crucial role, as it offers detailed chemical profiling and precise identification of compounds present in the samples. This approach enhances the ability to detect adulterants, diluents, and other substances in methamphetamine tablets, providing a comprehensive understanding of their composition.

Therefore, in this study, a GC-MS method was used, aiming to achieve reliable detection and identification of CAS in methamphetamine tablets. The method was designed to ensure accuracy, precision, and reproducibility, providing a robust analytical approach for the profiling of methamphetamine tablets.

CHAPTER 3

METHODOLOGY

3.1 Introduction

The chemical analysis of methamphetamine tablets was carried out to identify the CAS present in the tablets using the GC-MS method. The analytical procedure began with sample preparation, sample dissolution followed by sample analysis via GC-MS. The chemical profiling focused on identifying the major and minor constituents, including adulterants, in each illicit drug sample. A comparative study was then conducted across all samples to identify potential differences, enabling an in-depth understanding of the composition of the seized methamphetamine tablets on a case-by-case basis. This analysis could provide valuable insights into the variability in the chemical composition and potential trends in the synthesis and adulteration of these drugs.

3.2 Materials, Apparatus and Instrumentation

Material and apparatus used in this study are listed below:

- Methanol GC grade (SupraSolv®, Sigma-Aldrich, United States).
- Micropipette P5000 (Pipetman®, Gilson, United States)
- Analytical balance (A&D HR-251AZ, A&D Company, Japan)
- Sonicator (Sonicor Ultrasonics, Sonicor, United States)
- GC vials (Hp vial, Hewlett Packard, United States)
- 0.45 µm PTFE syringe filter (Cronus, Cronus Technologies, United Kingdom)
- Mortar and pestle
- Syringe (5mL)
- Spatula