PERFORMANCE ASSESSMENT OF PORTABLE RAMAN SPECTROSCOPY FOR ANALYSIS OF ECSTASY TABLETS

NG CHOON HIANG

UNIVERSITI SAINS MALAYSIA

2024

PERFORMANCE ASSESSMENT OF PORTABLE RAMAN SPECTROSCOPY FOR ANALYSIS OF ECSTASY TABLETS

by

NG CHOON HIANG

Thesis submitted in fulfilment of the requirements
for the degree of
Master of Science

September 2024

ACKNOWLEDGEMENT

First and foremost, I would like to express my greatest gratitude to my supervisor, Associate Professor Dr. Ahmad Fahmi Lim Abdullah for his advice, guidance, and encouragement throughout my postgraduate study. Special thanks to my co-supervisor Dr. Chang Kah Haw for being endless helpful in providing his valuable suggestion and endless patience with my continual questions at all stages of my research. Words can never express how thankful I am for everything they have done for me.

I would also like to specially thank to the Dean of the School of Health Sciences, Universiti Sains Malaysia who has unconditionally supported my application. A special acknowledge to the science officers of the school for assisting me to conduct the research.

A big thank you to Puan Halimah Abdul Rahim, the former Director-General of the Department of Chemistry Malaysia, and Dato' Hj. Mohamed Zaini Bin Abdul Rahman, the former Director-General who permitted me to pursue my postgraduate study. My warmest thanks to all managements and staffs in Department of Chemistry Penang Branch for their helps and supports. It would not have been possible without them.

Last but not least, my sincere thanks go to my wife Chong Evien, my child, parents, and family members for their continuous love, support and considerations during my hard time.

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LIST OF ABBREVIATIONS, SYMBOLS AND ACRONYMS

%	Percentage
°C	Degree Celcius
°C/min	Degree Celsius per minute
µL	Microliter
µm	Micrometer
5-HT	5-hydroxytryptamine
Al/Hg	Aluminium mercury amalgam
ATS	Amphetamine type stimulant
B	Boron
C	Carbon
CC	Correlation coefficient
CE	Capillary electrophoresis
CHAMP	Collaborative Harmonisation of Methods for Profiling of Amphetamine Type Stimulants
Cl	Chlorine
cm	Centimeter
GC	Gas chromatography
GC-MS	Gas Chromatography-Mass Spectrometry
GC-FID	Gas Chromatography-Flame Ionization Detector
et al.	*et alia* – and others
eV	Electron Volts
g/mol	Grams per mole
FID	Flame Ionization Detector
FTIR	Fourier transform infrared
FMA	Fluoromethamphetamine
FN	False negative
FP	False positive
H	Hydrogen
HPLC	High performance liquid chromatographic
HCA	Hierarchical cluster analysis
HIV	Human immunodeficiency virus
kg	Kilograms

LSD	Lysergic acid diethylamide
LOD	Limit of detection
m	Meter
m/z	Mass-to-charge
MBZP	Methylbenzylpiperazine
MDA	Methylenedioxyamphetamine
MDEA	Methylenedioxyethylamphetamine
MDMA	Methylenedioxymethamphetamine
MDP2P	Methylenedioxyphenyl-2-propanone
MDPBP	Methylenedioxyphenyl-2-bromopropane
mg	Milligram
mg/ml	Milligram per milliliter
mg/l	Milligram per liter
min	Minute
mins	Minutes
mL	Milliliter
mm	millimeter
MMC	Methylmethcathinone
MS	Mass spectrometery
MSD	Mass spectrometry detector
mW	Milliwatt
N	Nitrogen
NADA	National Anti Drug Agency
NBCT	North butterworth container terminal
NIR	Near-Infrared
nm	Nanometer
NPS	New psychoactive substances
NIST	National Institute of Standard and Technology
O	Oxygen
OTC	Over the counter
pFPP	1-(p-fluorophenyl) piperazine
PMA	Para-methoxyamphetamine
PMK	Piperonyl methyl ketone
PMMA	Para-methoxymethamphetamine

PTSD	Post traumatic stress disorder
RSD	Relative standard deviation
SWGDRG	Scientific Working Group for the Analysis of Seized Drugs
TIC	Total ion chromatogram
TN	True nagative
TNR	True negative rate
TP	True positive
TPR	True positive rate
UNODC	United Nations Office of Drugs and Crimes
UNCND	United Nations Commission on Narcotics Drugs (UNCND)
USM	Universiti Sains Malaysia
WHO	World Health Organization
Wt%	Percentage by weight

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PENILAIAN PRESTASI SPEKTROSKOPI RAMAN MUDAH ALIH UNTUK ANALISIS TABLET ECSTASY

ABSTRAK

Tablet *ecstasy* merupakan sejenis dadah berbahaya yang asalnya mengandungi 3,4-methylenedioxymethamphetamine (MDMA). Dadah sedemikian memberi kesan psikoaktif perangsang dan halusinogen. *Ecstasy* biasanya ditemui di kelab malam, pesta muzik atau peristiwa rekreasi lain yang dipercayai dapat membina pengalaman santai untuk pengguna. Daripada perspektif forensik, apabila penyalahgunaan dadah disyaki dalam senario sedemikian, anggota penguatkuasa undang-undang memerlukan suatu kaedah yang mudah, cepat dan tepat untuk mengesan kewujudan dadah berbahaya tersebut sebelum rampasan dan pemeriksaan forensik seterusnya. Dalam kajian ini, prestasi spektroskopi Raman mudah alih telah dinilai sebagai alat utama dalam analisis tablet *ecstasy*. Sebanyak 130 sampel tablet *ecstasy* telah diperiksa secara fizikal. Selepas itu, tablet tersebut telah dianalisis dengan spektroskopi Raman dan dicirikan dengan kromatografi gas-spektrometri jisim (GC-MS). Prestasi spektroskopi Raman telah dinilai selanjutnya dari segi ketepatan, kepekaan, dan spesifikasi berbanding dengan keputusan GC-MS yang sepadan. Dari kajian ini, pemeriksaan fizikal menunjukkan bahawa tablet *ecstasy* wujud dalam pelbagai reka bentuk dan warna. MDMA merupakan dadah berbahaya yang mendominasi komposisi tablet *ecstasy* yang diperoleh daripada sampel kes dalam kajian ini. Spektroskopi Raman mudah alih menunjukkan ketepatan 85.4% dalam menganalisis tablet *ecstasy*, manakala kepekaan dan spesifikasi masing-masing adalah 85.2% dan 100%. Tiada positif palsu bagi MDMA atau dadah lain telah dilaporkan. Untuk tujuan pemprofilan dadah, analisis kelompok hierarki (HCA) telah membentuk lapan kelompok utama

bagi tablet *ecstasy*. Gabungan keputusan GC-MS dan spektroskopi Raman membenarkan pembezaan sampel tablet sehingga 41 kumpulan. Sebagai kesimpulan, spektroskopi Raman mudah alih adalah suatu teknik yang sesuai untuk penentuan bersasar bagi kehadiran tablet *ecstasy*, terutamanya dalam kes forensik yang memerlukan teknik mudah alih, tidak merosakkan sampel, pantas dan membenarkan penyaringan secara besar-besaran ketika pemeriksaan di tempat kejadian jenayah oleh anggota penguatkuasa undang-undang.

PERFORMANCE ASSESSMENT OF PORTABLE RAMAN SPECTROSCOPY FOR ANALYSIS OF ECSTASY TABLETS

ABSTRACT

Ecstasy tablet, a type of street drug originally consists of 3,4-methylenedioxymethamphetamine (MDMA), provides stimulant and hallucinogen psychoactive effects. They are frequently found in night clubs, musical festivals, or other recreational events believed to create relaxing experience for the users. From the forensic perspective, when the drug of abuse is suspected in such scenarios, the law enforcement personnel would then require an easy-to-perform, quick and accurate method to detect the existence of such controlled substance prior to seizure and subsequent forensic examination. In this study, the performance of a portable Raman spectroscopy was assessed as the primary aid in determining ecstasy tablets at the point of use. A total of 130 ecstasy tablet samples were physically examined. Subsequently, they were analysed by Raman spectroscopy and characterised by gas chromatography-mass spectrometry (GC-MS). The performance of Raman spectroscopy was further assessed in terms of its accuracy, sensitivity, and specificity corresponding to the GC-MS results. From the study, the physical examination showed that the ecstasy tablet appeared in various design and colour. MDMA dominated the composition of ecstasy tablets obtained from case samples in this study. Portable Raman spectroscopy showed an accuracy of 85.4% in analysing the ecstasy tablets, while the sensitivity and specificity were determined as 85.2% and 100%, respectively. No false positive of MDMA or other drug were reported. For drug profiling, the hierarchical cluster analysis (HCA) had formed eight major cluster of ecstasy tablets. The combination of GC-MS and Raman spectroscopy results allowed for the discrimination of tablet

samples up to 41 groups. To conclude, portable Raman spectroscopy is a suitable technique for targeted determination of the presence of ecstasy tablets, especially in forensic cases that require technique, which is portable, non-destructive, rapid, and allows for mass screening during on-site testing by the law enforcement personnel.

CHAPTER 1

INTRODUCTION

1.1 Background of the study

According to the World Drug Report 2023 by the United Nations Office on Drugs and Crime (UNODC), it was estimated globally number of drug users grew from 240 million in 2011 to 296 million people in 2021. Such figures account for a 23% increase. Cannabis or marijuana continues to be the world most widely used drug with estimated 219 million users in 2021. An estimated 60 million people had used non-medical opioid, 36 million people had used amphetamine, 22 million had used cocaine and 20 million had used ecstasy-type substances in 2021 (UNODC, 2023).

The use of illicit drugs not only creates social problem and crimes, but also increases the risk of overdose and prevalence of various infectious disease. As stated in the World Drug Report 2023, 13.2 million out of 296 million people who use drugs were intravenous drugs abuser (through injecting drug). It was revealed that half of the above-mentioned number were infected with hepatitis C, 1.6 million with human immunodeficiency virus (HIV), and 1.4 million with both. Besides health risk, there are 39.5 million people suffering from drug use disorders, account for a 45% increase over the past ten years, but only 1 in 5 people with drug use disorder received drug treatment (UNODC, 2023).

Ecstasy rank from number 5 on the preference list in the World Drug Report 2023 (after cannabis, opioids, amphetamine, and cocaine) with an estimation of 20 million people had used ecstasy by 2021 worldwide. The proportion of female users in ecstasy was around 38%, estimated 7.6 million out of 20 million people (UNODC, 2023). The term ecstasy was primarily applied to tablets containing MDMA. However,

over the last several years, the content of ecstasy tablets available on illegal drugs market has changed significantly (Brunt et al., 2011; UNODC, 2014).

In 2005, the ecstasy market went through a worldwide change triggered by a shortage of MDMA, because of the successful control of its precursor. The continuing demand for ecstasy led to the use of alternative chemical to MDMA which mimicked the effects of ecstasy group substances to fulfil the existing drug market. Analysis of seized ecstasy tablets revealed that ecstasy tablets in current drug market consisted mainly a blend of non-controlled substances such as new psychoactive substances (NPS) as opposed to MDMA. NPS such as synthetic cathinones and piperazines were among the common substances used to substitute MDMA (Brunt et al., 2011). The emergence of NPS and changing nature of ecstasy is overwhelming as MDMA may soon be merely of historical value (UNODC, 2014).

The use of drug abuse has grown significantly, and it brings new challenges in seized drug analysis. Today, one of the greatest challenges faced by the forensic seized drug analysis are issue of increasing of workload and backlogs when the drug abuse problems get more serious. Materials suspected of being drug of abuse, are regularly submitted to forensic laboratories by law enforcement agencies for further analysis. The samples submitted may consist of single exhibit, multiple packages with different type of drugs, or bulk samples for trafficking cases. The laboratories are continuing to look for new approaches or methods to ease the burden of backlogs (Sisco et al., 2022).

Another bottleneck for forensic seized drug analysis is analytical method challenges. Nowadays, traditional approaches such as colour tests and gas chromatography-mass spectrometry (GC-MS) may not be sufficient for current challenges. Colour tests are purely presumptive, rapid, inexpensive, and most

importantly high level of scientific knowledge is not required to perform the tests and interpret the results. Traditionally, colour spot tests are used as screening test in laboratory or on-site although their applicability is only limited to a particular group of drugs. Colour test usually involves a chemical reaction between strong acids and suspected material, thus may pose a safety risk to the analysts. Furthermore, ecstasy tablets have a large variety of colours which may interfering the interpretation of colour test results (Philp & Fu, 2018).

GC-MS has been the "Gold Standard" in the field of drug analysis for many decades because of its sensitivity, selectivity, and flexibility (Borden et al., 2020). However, GC-MS also have its own limitation in seized drug analysis, especially most NPS are isomers. Various difficulties are encountered in identifying the active ingredients of NPS due to the presence of isomers and possible similar chemical structure between certain compounds of the same class. For example, it is not always possible for GC-MS to distinguish different synthetic cannabinoids from the JWH class, as isomers with similar structures may co-elute at the same retention time (UNODC, 2014, 2018).

To address these challenges, forensic laboratories may seek out new analytical instrument and method to serve as an alternative to support the current toolkit. In past decade, portable spectroscopic techniques such as Fourier transform infrared (FTIR), Raman spectroscopy and near-infrared (NIR) spectroscopy have emerged as new alternative technique for performing rapid, high selective, and non-destructive examination, either in forensic caseworks analysis or for on-site drug screening.

1.2 Problem statement

Ecstasy tablets are frequently found different in their colours, logos, shapes, and sizes (Togni et al., 2015), seized in night club, music festivals, or any recreational events to create relaxing experience. Therefore, in most instances, they require immediate detection for forensic seizure and investigation by the law enforcement teams. The current practice, namely the presumptive colorimetric tests could be used for on-site testing or as screening test in laboratory; however, they exhibited limitations (Kranenburg et al., 2021; Philp & Fu, 2018). Reagents of colorimetric tests are found to be selective which potentially lead to false negative (FN) results. If a tested sample contained more than one active substance or with interfering colour, false positive (FP) could be resulted. Moreover, the law enforcement personnel might expose to significant safety concern due to the involvement of hazardous substances during casework applications (Philp & Fu, 2018). Furthermore, the ecstasy market has changed when NPS appeared as new alternative to replace MDMA, current colorimetric tests might not be sufficient to detect the NPS in ecstasy tablets.

Raman spectroscopy, being portable, offers a non-contact and non-destructive technique in forensic testing that can be used for on-site drug screening and analysis. Direct identification at the scene of crime enables enforcement agencies to make rapid decisions and leads to considerable efficiency and cost benefits. However, studies focusing on the performance of a portable Raman spectroscopy towards the detection of ecstasy tablets were limited. Therefore, forensic drug testing laboratories have the responsible to further explore the applicability of portable Raman spectroscopy in the analysis of ecstasy tablets.

During routine laboratory analysis, seized ecstasy samples submitted to forensic laboratories are physically examined and screened by Marquis test and Simon's test. The presence of active ingredients in ecstasy samples are then confirmed by GC-MS and subsequently quantified by gas chromatography-flame ionisation detector (GC-FID). In this study, the visual and physical characteristics of ecstasy tablets were examined and measured to gather more information related to ecstasy for drug intelligence purpose. Apart from that, both handheld Raman spectroscopy and GC-MS were carried out to identify the active ingredients in the ecstasy tablets.

1.3 Aim and Objectives

This study was aimed to evaluate the performance of a portable Raman spectroscopy for the analysis of ecstasy tablets. To achieve the aim, three objectives were set as follows:

i. To evaluate the physical characteristics of ecstasy tablets through visual examination and measurement for drug intelligence purpose.

ii. To determine the chemical profiles of 130 ecstasy tablets through portable Raman spectroscopy and GC-MS analysis.

iii. To evaluate the performance of a portable Raman spectroscopy by comparing the Raman's result to its corresponding GC-MS results.

1.4 Scope of the study

The ecstasy samples tested in this study was only limited to those samples sampled from seized samples that submitted to the Narcotic Laboratory of the Department of Chemistry, Penang Branch from January 2018 until January 2023. Prior

to chemical analysis, the visual (colour, shape, and score) and physical characteristics (diameter, weight, and thickness) of ecstasy tablets were examined and measured to gather more information related to ecstasy for drug intelligence purpose. Subsequently, each tablet was examined by a portable Raman spectrometer to obtain their respective profiles The presence of active ingredients in ecstasy samples were then confirmed by the findings of GC-MS. The results from both portable Raman spectroscopy and GC-MS were compared to assess the performance of portable Raman spectroscopy. Lastly, the physical characteristics and chemical profiles of ecstasy tablets were combined for drug intelligence purpose.

1.5 Significance of the study

This study would benefit the forensic laboratories and law enforcement agencies such as airport security, border security, custom officers and raiding officers who are required to perform on-site screening whenever possible. The current study utilised a portable Raman spectroscopy for analysis of the illicit ecstasy tablets, and the performance of Raman spectroscopy could provide useful clue or data to support forensic laboratories and law enforcement personnel during forensic testing and investigation. To certain extent, the drug profiling of ecstasy would allow the establishment of their possible source of distribution network, which useful for investigation of drug trafficking activities.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

Through the review of literature reviews on ecstasy with particular focus on 3,4-methylenedioxymethamphetamine (MDMA), an overview on origin of MDMA, the degree of ecstasy problems in Malaysia, trend of ecstasy, and manufacturing process of ecstasy tablets were described. The analytical techniques related for ecstasy tablets analysis were also discussed. A brief overview on drug intelligence on ecstasy tablets, including statistical analysis, grouping of ecstasy tablets, and identification of synthetic route were included.

2.2 Ecstasy – An amphetamine type stimulant (ATS)

The term "ecstasy" is a street name commonly referred to N-methyl-3,4-methylenedioxy-amphetamine or 3,4-methylenedioxymethamphetamine (MDMA). They are commonly come in tablet form. The initial letters of the major portions of the latter name (methylenedioxy-methamphetamine) give rise to the acronym MDMA (Kalant, 2001). Beside ecstasy, other terms that have been used to refer MDMA included "E", "X", XTC", "Molly" and "Adam" (Shulgin, 1986). "Molly" (short form for "molecule") has also been the street name for powder or crystalline MDMA that are usually kept in capsule (Palamar, 2017).

MDMA is a derivative of amphetamine, and its chemical structure is shown in Figure 2.1. The molecular formula for MDMA is $C_{11}H_{15}NO_2$ with a molecular of 193.2 g/mol. Like the amphetamine, MDMA are amines that can exist either as salts of various acid or as free base. As a free base, MDMA is a white, musty smelling oil with a searing taste, soluble in most organic solvents but insoluble in water. MDMA forms salts with

several acids and the most common salt form found in the drug markets is the hydrochloride salt ($C_{11}H_{15}NO_2$.HCl). MDMA hydrochloride appears as a white or off-white powder or crystal that are readily water soluble and bitter to taste (Shulgin, 1986).

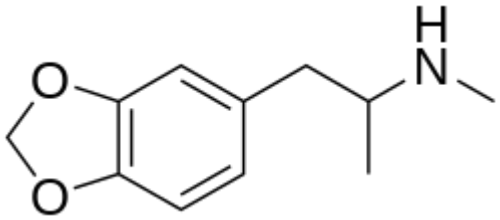


Figure 2.1: Chemical structure of 3,4-MDMA.

MDMA differs from methamphetamine and amphetamine in one important aspect. MDMA is a psychoactive substance that chemically similar to the hallucinogen mescaline and the nervous system stimulant methamphetamine. As shown in Figure 2.2, MDMA has a methylenedioxy (-O-CH_2-O-) group attached to the positions 3 and 4 of the aromatic ring of the amphetamine molecule, and it resembles the structure of the hallucinogenic mescaline. As a result, the pharmacological effects of MDMA are a combination of those amphetamine and mescaline.

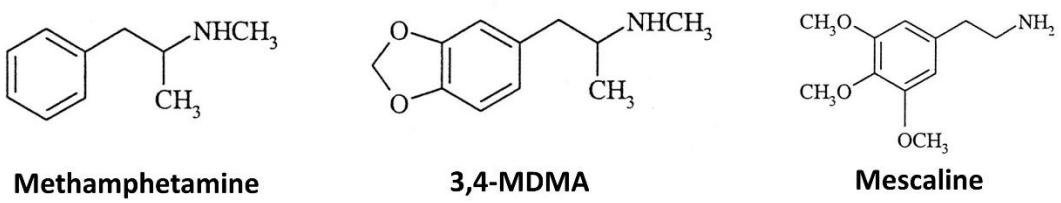


Figure 2.2: Chemical structures of methamphetamine, 3,4-MDMA, and mescaline.

2.2.1 Origin and history of MDMA

MDMA related literature suggested that MDMA was synthesised by the German pharmaceutical company Merck in 1912 to develop an "appetite suppressor", just before World War I according to Freudenmann et al. (2006) It was true that the origin of MDMA could be dating back to as earlier as years 1912. It was first synthesised by the above-mentioned company could be proved by two documents (Freudenmann et al., 2006). Figure 2.3 shows the German patent (Patent-Urkunde) with the number 274350. According to the patent instrument, the patent no 274350 was assigned to the company E. Merck in Darmstadt by the German Imperial Patent Office in Berlin. In the patent specification (Patentschrift), MDMA appeared only as a chemical formula "CH_2-O_2:C_6H_3-CH_2-$CH(CH_3)$-NH-CH_3", and not under the name "MDMA" as shows in Figure 2.4 (Bernschneider-Reif et al., 2006).


PATENT-URKUNDE

№ 274350

AUF GRUND DER ANGEHEFTETEN PATENTSCHRIFT IST DURCH BESCHLUSZ DES KAISERLICHEN PATENTAMTES

an die Firma E. Merck in Darmstadt

EIN PATENT ERTEILT WORDEN.

GEGENSTAND DES PATENTES IST:

Verfahren zur Darstellung von Alkyloxyaryl-, Dialkyloxyaryl- und Alkylendioxyarylaminopropanen bzw. deren am Stickstoff monoalkylierten Derivaten.

GESETZ V. 7. APRIL 1891

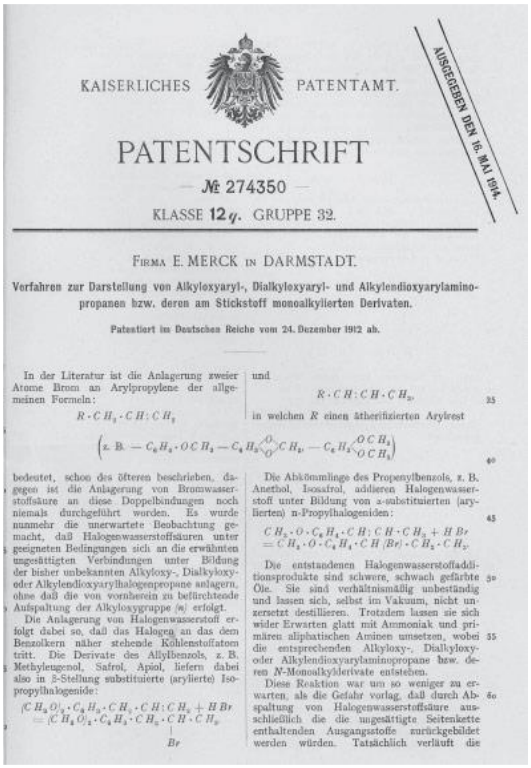
ANFANG DES PATENTES: 24. Dezember 1912.

DIE RECHTE UND PFLICHTEN DES PATENTINHABERS SIND DURCH DAS PATENTGESETZ VOM 7. APRIL 1891 (REICHS-GESETZBLATT FÜR 1891 SEITE 79) UND DURCH DAS GESETZ VOM 6. JUNI 1911 (REICHS-GESETZBLATT FÜR 1911 SEITE 243) BESTIMMT.

ZU URKUND DER ERTEILUNG DES PATENTES IST DIESE AUSFERTIGUNG ERFOLGT.

KAISERLICHES PATENTAMT.

Figure 2.3: Patent Instrument no. 274350 (Patent-Urkunde). The text states: "Subject of the patent is: Procedure for the manufacturing of alkyloxyaryl-, dialkyloxyaryl- and alkylendioxyarylaminopropanes and their at nitrogen monoalkylated derivatives. Beginning of the patent: December 24th 1912" (Freudenmann et al., 2006)



KAISERLICHES PATENTAMT.

AUSGEGEBEN DEN 16. MAI 1914.

PATENTSCHRIFT

№ 274350

KLASSE 12 q. GRUPPE 32.

FIRMA E. MERCK IN DARMSTADT.

Verfahren zur Darstellung von Alkyloxyaryl-, Dialkyloxyaryl- und Alkylendioxyarylamino-propanen bzw. deren am Stickstoff monoalkylierten Derivaten.

Patentiert im Deutschen Reiche vom 24. Dezember 1912 ab.

In der Literatur ist die Anlagerung zweier Atome Brom an Arylpropylene der allgemeinen Formeln:

$$R \cdot C H_2 \cdot C H : C H_2$$

und

$$R \cdot C H : C H \cdot C H_3,$$

in welchen R einen ätherifizierten Arylrest

$$\left(z.\ B. -C_6H_3 \cdot O C H_3 - C_6H_3\langle{}^{O}_{O}\rangle C H_2 - C_6H_4\langle{}^{O C H_3}_{O C H_3}\right)$$

bedeutet, schon des öfteren beschrieben, dagegen ist die Anlagerung von Bromwasserstoffsäure an diese Doppelbindungen noch niemals durchgeführt worden. Es wurde nunmehr die unerwartete Beobachtung gemacht, daß Halogenwasserstoffsäuren unter geeigneten Bedingungen sich an die erwähnten ungesättigten Verbindungen unter Bildung der bisher unbekannten Alkyloxy-, Dialkyloxy- oder Alkylendioxyarylhalogenpropane anlagern, ohne daß die von vornherein zu befürchtende Aufspaltung der Alkyloxygruppe (n) erfolgt.

Die Anlagerung von Halogenwasserstoff erfolgt dabei so, daß das Halogen an das dem Benzolkern näher stehende Kohlenstoffatom tritt. Die Derivate des Allylbenzols, z. B. Methylengenol, Safrol, Apiol, liefern dabei also in β-Stellung substituierte (arylierte) Isopropylhalogenide:

$$(C H_3 O)_2 \cdot C_6 H_3 \cdot C H_2 \cdot C H : C H_2 + H Br = (C H_3 O)_2 \cdot C_6 H_3 \cdot C H_2 \cdot \underset{Br}{C H} \cdot C H_3$$

Die Abkömmlinge des Propenylbenzols, z. B. Anethol, Isosafrol, addieren Halogenwasserstoff unter Bildung von α-substituierten (arylierten) n-Propylhalogeniden:

$$C H_3 \cdot O \cdot C_6 H_4 \cdot C H : C H \cdot C H_3 + H Br = C H_3 \cdot O \cdot C_6 H_4 \cdot C H (Br) \cdot C H_2 \cdot C H_3.$$

Die entstandenen Halogenwasserstoffadditionsprodukte sind schwere, schwach gefärbte Öle. Sie sind verhältnismäßig unbeständig und lassen sich, selbst im Vakuum, nicht unzersetzt destillieren. Trotzdem lassen sie sich wider Erwarten glatt mit Ammoniak und primären aliphatischen Aminen umsetzen, wobei die entsprechenden Alkyloxy-, Dialkyloxy- oder Alkylendioxyarylaminopropane bzw. deren *N*-Monoalkylderivate entstehen.

Diese Reaktion war um so weniger zu erwarten, als die Gefahr vorlag, daß durch Abspaltung von Halogenwasserstoffsäure ausschließlich die die ungesättigte Seitenkette enthaltenden Ausgangsstoffe zurückgebildet werden würden. Tatsächlich verläuft die

Figure 2.4: Patent Specification No. 274350 (Patentschrift). (Bernschneider-Reif et al., 2006)

The second document is the Annual Report for 1912 of Merck Scientific Laboratory. In the annual report, MDMA was referred to as “Methylsafrylamin”, “Safryl-methyl-amin” or “N-Methyl-a-methylhomopiperonylamin”. This compund was synthesized by Merck as a parent compound to synthesise a haemostatic substance (clotting agent) call methylhydrastinin (Freudenmann et al., 2006).

The available documents showed that Merck did not want to produce and patent an appetite suppressor when MDMA was first synthesised in 1912. A possible explanation for the association of MDMA with appetite suppressors might be the analogue of MDMA, namely the methylenedioxyamphetamine (MDA). MDA was studied for its potential as an appetite suppressor and anti-depressant between 1949 and 1977. Therefore, the “copy and paste” action in the literature may have contributed to the formation of myth that MDMA was developed as an appetite suppressor (Freudenmann et al., 2006).

2.2.2 Ecstasy as a drug of abuse

Abuses of "club drugs" have become more prevalent among youngster generation for recreational uses. Club drugs (also known as party drugs) refer to those drugs being used by young generation at bars, discos, parties, music festivals, or all-night dance parties, commonly known as "raves". One of the most common used "club drugs" encountered in Malaysia is ecstasy, usually in tablets form. In Malaysia Chinese society, ecstasy tablets are more commonly known as "Yao Tou Wan", literally meaning "Shaked Head Pills" (Cheng et al., 2006).

Ecstasy tablets gain popularity among teenagers and young adults as they widespread belief and perceived that ecstasy is a "safe drug" and relatively "harmless". The desired effects of MDMA are closely similar to those who using amphetamine derivatives. According to the World Health Organisation (WHO), physically desired effects include wakefulness, endurance and sense of energy, postponement of fatigue and sexual arousal. On the other hand, the accompanying psychological effects include the sense of euphoria, sense of closeness to other people, well-being and greater sociability (WHO, 2000).

Abuse of MDMA also has adverse effects on physical and psychological functions. The undesired physical symptoms of MDMA include headache, dry mouth, insomnia, nausea, tooth grinding loss of appetite and increase in body temperature. The undesired psychological effects often include mild hallucination, anxiety, agitation, depression, insomnia, and difficulty in concentrating (WHO, 2000).

2.2.3 Routes of administration

MDMA can be administered orally, intravenously or by snorting the powder. Ecstasy is mainly taken by the oral route in most region of the world, and it is frequently prepared as single-dose tablets for this purpose (Kalant, 2001; WHO, 2000).

2.2.4 Mechanism of MDMA

The biological mechanism involved in the MDMA intake are the changes in the serotonergic system, affecting the serotonin (5-hydroxytryptamine or 5HT) and dopamine (Mustafa & Mohamad, 2019). MDMA has high affinity for serotonin receptors and transports site, and acts by increasing the net release of the monoamine neurotransmitters such as noradrenaline, serotonin, and to a smaller extent, dopamine. MDMA compound does not involve in directly releasing serotonin, but by binding to the transports site and inhibition of the reuptake not only serotonin (Kalant, 2001; Shulgin, 1986). Serotonin plays a direct role in regulating aggression, sexual activity, mood, sleep, and sensitivity to pain. Besides, serotonin also plays important role in temperature and memory regulation (WHO, 2000).

In addition to serotonin, MDMA also induces a rapid and substantial increase of another neurotransmitter, namely dopamine. A similar but weaker mechanism is also inhibited the reuptake of dopamine (Kalant, 2001). Dopamine is important in the control of the cognition, movement, and motivation (WHO, 2000).

2.2.5 Intoxication of ecstasy

MDMA related death and intoxication are complicated. As MDMA is usually consumed in dance clubs and music events, it is frequently involved in the context of polydrug or poly substances use, especially when MDMA is used in combination, mainly with alcohol (WHO, 2000).

Kłys et al. (2007) reported a case of fatal poisoning with MDMA of a 22-year-old male with documented history of drug abuse. The alcohol level analysis report revealed that the urine and blood of the deceased were free of ethanol. Toxicological analysis showed that MDMA and MDA were detected in postmortem blood, while MDMA and trace of amphetamine were detected in hair. The analysis of hair for third segment showed the presence of MDMA and amphetamine, indicating that the deceased had been using both MDMA and amphetamine at least approximately half year before death. The opinion on cause of death was based on the high level of MDMA in postmortem blood (1.42 mg/L), showing a fatal poisoning of MDMA.

Roxburgh and Lappin (2020) who analysed 392 cases of MDMA related deaths in Australia between 2001 and 2018 found that 244 death cases (62%) were attributed to drug toxicity. Approximately 55 death cases (14%) were attributed to MDMA toxicity alone, and 189 death cases (48%) to multiple drug toxicity. The remaining 148 death cases (38%) were due to other cause such as traumatic accident or violent suicide, with MDMA recorded as a contributory factor.

In 2003, Becker et al. (2003) reported a case report of a 22-year-old man died after taking the ingestion of ecstasy tablets containing para-methoxymethamphetamine (PMMA) and para-methoxyamphetamine (PMA). The victim was witnessed to be hallucinating in a part, after that he started to convulse and developed respiratory distress. The toxicological results analysis with GC-MS showed the present of high amount of PMMA (10.22 mg/L), PMA (6.37 mg/L), and trace level of cocaine metabolite benzolecgonine (0.02 mg/L) in deceased urine. Investigation of fatal intoxication in the case study have shown that approximately 50 mg of PMA or PMMA could led to spontaneous life-threatening increase of body temperature and blood

pressure. The case occurrence also reflected that the street ecstasy tablets might contain not necessarily MDMA, but other dangerous life-threatening ingredients.

In most MDMA-related deaths, the main cause of fatality was not due to overdose of MDMA. The deceased usually was found had only taken a dose of MDMA within normal range and without combination with other drugs. A detailed review of 87 published literature and case reports revealed that the two primary cause of MDMA related deaths were due to hyperpyrexia (n=30) and hyponatremia-related cerebral oedema (n=9) (Kalant, 2001).

The most frequently seen acute effects of recreational MDMA-use are hyperpyrexia (also known as hyperthermia and heatstroke). A normal dose of MDMA may raise body temperature and inhibit body's natural thermoregulation. The combination of the MDMA action, intense aerobic dancing in a hot environment, and insufficient water supplementation can contribute to the increase of body temperature. MDMA-induced vasoconstriction, which conserves blood volume, halts sweats production, and thus lead to an increase in body temperature (Kalant, 2001; van Amsterdam et al., 2021; WHO, 2000).

One side effect of the use of MDMA is the profuse sweating due to the pharmacological action of MDMA on the thermoregulatory mechanism and vigorous physical activity in hot environment (Kalant, 2001). Hyponatremia or water toxicity can be caused by excessive water intake following profuse sweating. Budisavljevic et al. (2003) reported a case of hyponatremia in 18-years-old woman that developed after taking one tablet of ecstasy. A detailed review of literature found 18 cases of hyponatremia were associated with MDMA abuse. 17 out of 18 cases were young women ranging from 15 to 30 years old, and three women were diagnosed with MDMA

associated hyponatremia died. Budisavljevic et al. (2003) also suggested that acute hyponatremia developed after MDMA abuse might be life threatening.

2.2.6 Legal status of MDMA

There are three International Drug Control Conventions issued by the United Nations Commission on Narcotic Drugs (UNCND), namely the Single Convention on Narcotic Drugs 1961, Convention on Psychotropic Substances 1971 and United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances 1988. There are four schedules of controlled substances under Convention on Psychotropic Substances 1971, ranging from Schedule I (most restrictive) to Schedule IV (less restrictive). According to a UNODC report in 1999, Schedule I mostly contain hallucinogenic drugs that are produced by illicit laboratories, while other three schedule are mainly for legally produced pharmaceutical. 3,4-MDMA is listed in Schedule I of the Convention on Psychotropic Substances 1971. For dangerous drugs that listed under Schedule I, it is believed that the dangerous drugs can create serious risk to public health.

Starting 1 July 2023, Australia has become the first country in the world to legalise and permit the prescribing of 3,4-MDMA by specifically authorised psychiatric for the treatment of post-traumatic stress disorder (PTSD). For the treatment of PTSD, MDMA is listed as Schedule 8 (Controlled Drugs) medicines in the Poisons Standard. However, MDMA still remains in Schedule 9 (Prohibited Substances) for all other uses which largely restrict their supply to clinical trials (Therapeutic Goods Administration, 2023).

In Malaysia, the Dangerous Drug Act 1952 (Revised 1980) is an act for the regulating of the importation, exportation, manufacture, sales and use of dangerous

drugs and substances. 3,4-MDMA is regulated under Schedule I of Dangerous Drug Act 1952. Any person who is found in possession of 50 gram or more 3,4-MDMA is consider as drug trafficking of the said drug and can be charged under section 39B. For instance, any person who found guilty under section 39B can be punished on conviction with death or imprisonment for life (Dangerous Drug Act 1952).

2.3 Ecstasy situation in Malaysia

2.3.1 Ecstasy tablets users in Malaysia

The National Anti-Drug Agency (also known as NADA or AADK) is the main and leading agency under the purview of the Ministry of Home Affairs in combating drugs and substances abuse in Malaysia. The vision of NADA is to achieve a "Drug Free Malaysia" through the following objectives:

(a) To prevent a person to be involved with drugs,

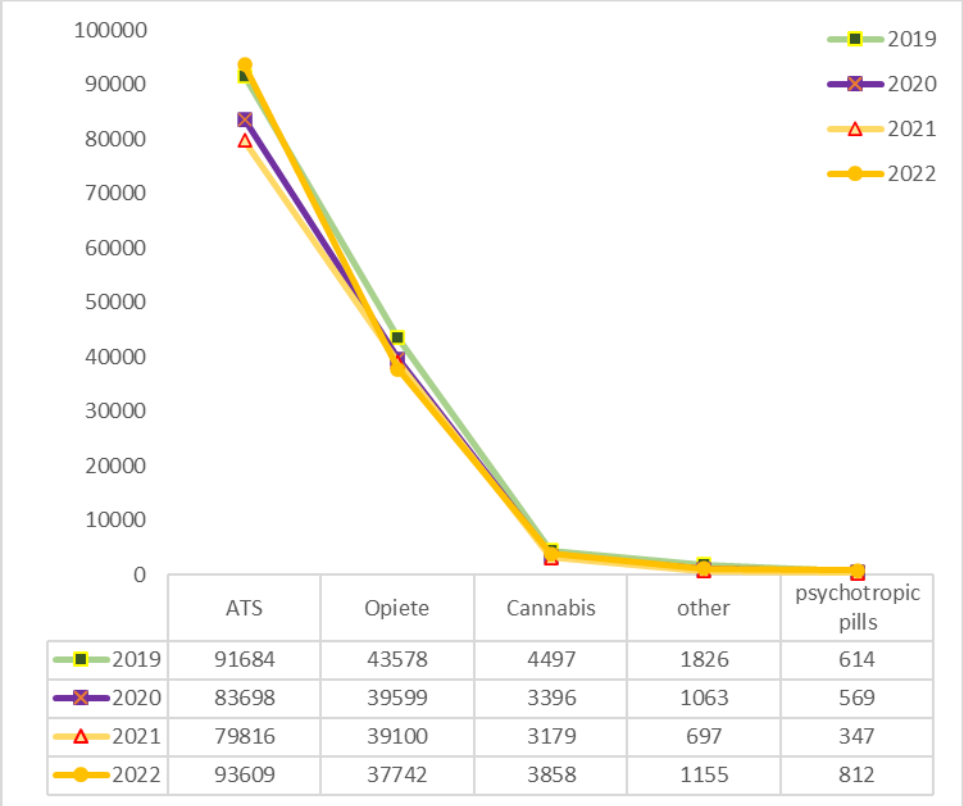
(b) To treat, and rehabilitate drug addicts,

(c) To prevent addiction relapse, and

(d) To eradicate the supply, trafficking, and abuse of drugs.

As stated in the latest report "Information on Drugs 2022" published by NADA, a total of 137,176 individuals were identified as drug user and addicts in Malaysia in 2022. Figure 2.5 shows the numbers of drugs and substance abusers and addicts according to drug Category from 2019 to 2022. From the total abusers, ATS group was the most misused drug with a total of 91,684 abusers (64.4%) in 2019, 83,698 abusers (65.2%) in 2020, 79,816 abusers (64.8%) in 2021, and 93,609 abusers (68.2%) in 2022. In 2021, younger generation formed the largest portion of the ATS abusers with a record at 31,424 abusers (83.2%) for youth (15-29 years old) and 58,641 abusers (63.3%) for adult (30-59 years old) (NADA, 2023). The total amount of ATS abusers was the sum

of abusers for methamphetamine (crystalline), methamphetamine tablets, ecstasy tablets, and amphetamine. Therefore, these statistics do not clearly reflect or state the exact abusers for ecstasy tablets individually.



	ATS	Opiete	Cannabis	other	psychotropic pills
2019	91684	43578	4497	1826	614
2020	83698	39599	3396	1063	569
2021	79816	39100	3179	697	347
2022	93609	37742	3858	1155	812

Figure 2.5: Number of Drug and substances abusers and addicts according to drug category from 2019 to 2022 (Source:NADA, 2023)

Illegal substances abuse has been increasing among university students and professional group in Malaysia. Chie et al. (2015) conducted a questionnaire study on 460 university students from Penang, Selangor, Kuala Lumpur, Sabah, and Sarawak to investigate the university students' perception on drug abuse. The first part of the questionnaire asked the student impression about commonality and availability of ten drug types, including ecstasy, heroin morphine, ketum, cannabis, opiates, methamphetamine, amphetamine, psychoactive tablets, and ketamine. As a result, ecstasy and cannabis were rated as the highest rank, indicating these two substances were the most known by the target subjects.

Du et al. (2020) conducted a wastewater-based epidemiology in Kuala Lumpur, Malaysia to estimate the consumption of common illicit drug in urban population. Influent wastewater samples were collected from two wastewater treatment plants in Kuala Lumpur from June to July 2017. Concentration of twenty-four drug biomarkers were analysed from the wastewater to estimate the drug consumption in Kuala Lumpur area. From the study, MDMA has the highest estimated per capital consumption, followed by methamphetamine and ketamine. As shown in Figure 2.6, it was interesting to note that the higher estimation of MDMA consumption in Kuala Lumpur than Netherland, the country with highest estimation MDMA consumption in European's study. The study also suggested that ATS were the most prevalent drugs in Kuala Lumpur region, replacing opiates in the illicit drug market.

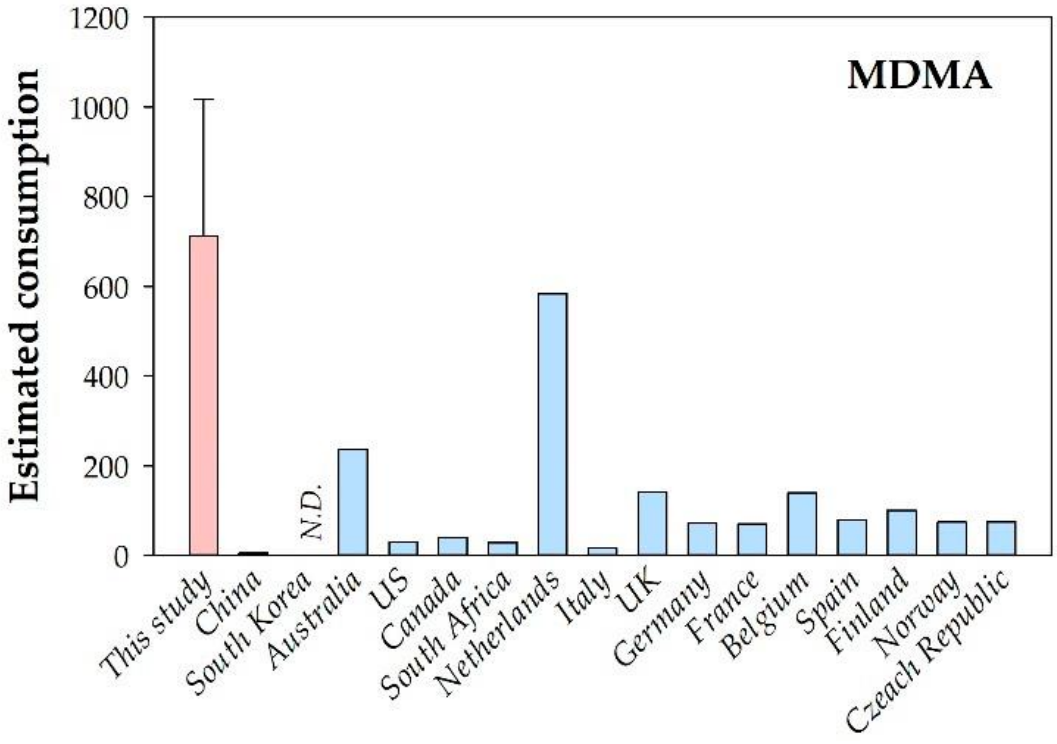


Figure 2.6: Estimated MDMA consumption (mg/1000 inh/d) in Kuala Lumpur and other countries (Du et al., 2020).

2.3.2 Seizure of ecstasy in Malaysia

UNODC maintains data of drugs seized in Malaysia collected from several sources, including the Department of Chemistry, NADA, and Royal Malaysia Police. Table 2.1 tabulates the type and amounts of seized drugs in Malaysia from 2018 to 2022. In 2022, crystalline methamphetamine recorded the highest amount of seized sample with the record 8,329 kg, followed by 6,292 kg of cannabis. The seizure of MDMA was among the lowest in 2021 and 2022, with 293.1 kg and 312.6 kg, respectively. However, it was important to note that the data on the amount of ecstasy seizure might not have directly reflected the degree of problems of ecstasy abuse in Malaysia. Study on ecstasy tablets remains important.

Table 2.1: Type and amounts of seized drugs in Malaysia from 2018 to 2022.

Type of Drug	**Seizure of Drug (kg)**				
	2018	**2019**	**2020**	**2021**	**2022**
Methamphetamine (crystalline)	6,851.8	5,302.4	7,557.2	9,682.1	8,329.9
Cannabis	1,894.8	649.6	5,426.8	3,728.3	6,292.3
Heroin	731.5	709.9	930.3	2,166.5	580.4
Ketamine	217.1	1,261.0	3,004.2	474.6	2,860.0
Ecstasy	381.3	706.9	1,096	293.1	312.6
Erimin-5	912.4	683.2	925.4	-	-
Methamphetamine (Tablet)	226.12	198.75	207.42	357.45	383.63

In May 2023, The Royal Malaysian Customs Department had seized approximately 1,063 kg of ecstasy tablets worth more than RM 78 million in a container at the North Butterworth Container Terminal (NBCT). The container arrived from Europe contained 20 units of silent compressors where 14 units of the silent compressors were modified to hide the ecstasy tablets. Figure 2.7 shows the Customs director-general Datuk Zazuli Johan and his teams, showing the ecstasy tablets found hidden inside silent compressors.

Figure 2.7: Custom director -general and his team showing the seized ecstasy tablets concealed in specially-modified silent compressor units (Source: New Straits Times, 12 May 2023).

Another large seizure of ecstasy was reported in September 2023 by the Royal Malaysian Customs Department where 436.2 kg of ecstasy tablets worth RM 32 million were seized at Kuala Lumpur Airport Cargo Complex as shown in Figure 2.8. The customs officers conducted inspection on 36 boxes and found that 12 boxes of them containing ecstasy tablets while the remaining contained only brick. Preliminary investigation revealed that these ecstasy tablets had shipped from the Netherlands and Malaysia is its destination.

Figure 2.8: Custom director -general and his team showing the seized ecstasy tablets worth RM 32 million during press conference (Source: Kosmo, 6 September 2023)

2.3.3 "Happy Water" – An alternative to ecstasy tablet in Malaysia.

During the past few years, a new product known as "Happy Water" has emerged as an alternative to drug users at entertainment venues. "Happy Water" usually refers to sachet drink powder that containing various of illicit substances such as MDMA, methamphetamine, ketamine, nimetazepam, and caffeine. The drug syndicates usually produce "Happy Water" in two methods, the first method is to spike the mixture of drugs into commercially available drink sachets such as chocolate powder, lemon tea, and coffee package as shown in Figure 2.9. Another method is by manufacturing their own drink powders together with drugs (mostly with ecstasy tablet), and lastly packaging with their own attractive packages as shown in Figure 2.10.

Figure 2.9 Investigation officer Insp Mohd Faizul Fazri Padok showing the seized sachet drinks suspected containing illegal drugs. (Source: Sinar Harian, 24 Februari 2020)

Figure 2.10 Example of Sachet drinks received by Department of Chemistry that contained MDMA (ecstasy).

According to the document entitled "Synthetic Drugs in East and Southeast Asia 2023" reported by the UNODC, "Happy Water" have previously identified in China, Thailand, Malaysia, Singapore, Indonesia, and Philippines. The amount of MDMA in such sachet drinks vary significantly, ranging from 0.7% to 33.5%. The "Happy Water"

usually target university students or professional groups who seeking for temporary excitement at night clubs. The drug users of "Happy Water" believed that they would not addict to the trace level of MDMA but bringing mild effect of excitement. Additionally, the users believed that the "trace" amount of MDMA will not stay inside body for a longer time, therefore, not produce positive result in urine drug testing.

The production of "Happy Water" is very simple process as it involved open the sachet drinks packages, blending/mixing of drink powders with ecstasy tablets, ketamine, and Erimin-5 tablets, and lastly repackaging back in their original packages. Figures 2.11 and 2.12 show the dismantle of two small scale "Happy Water" clandestine laboratory by the police officers in Penang State, Malaysia. The exhibits that seized in these laboratories included ketamine, erimin-5 tablets, ecstasy tablets, sachet drink powders, blender, balances, and sealer.

Figure 2.11 Police officers showing the seized of a small scale of "Happy Water" clandestine laboratory in Georgetown, Penang (Berita Harian, 19 February 2021)

Figure 2.12 Police officers showing the seized of a small scale of "Happy Water" clandestine laboratory in Butterworth, Penang. (Kosmo, 09 November 2020)

2.4 Trend of ecstasy tablet

In the past few decades, "ecstasy" usually refers to tablets that containing MDMA as active ingredient. The profiling study of ecstasy tablets proved that the ecstasy compositions might vary from one geographical location to the other, and changing from time to time (UNODC, 2014). Table 2.2 summarises the active ingredients detected in the various profiling studies conducted at different countries and time periods.