

## CHAPTER 2

### LITERATURE REVIEW

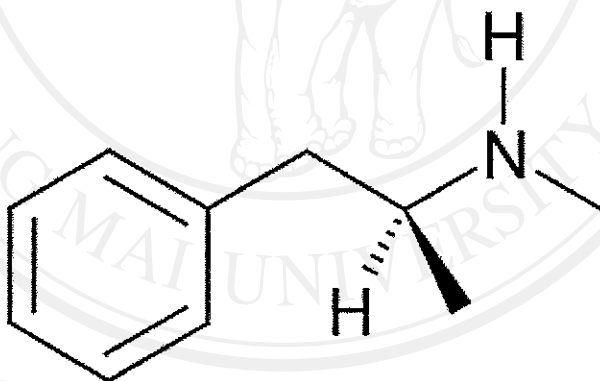
#### 2.1 The Amphetamines

##### 2.1.1 Background

Amphetamine was first synthesized in Germany by the German pharmacologist L. Edeleano in 1887 (2). Nothing was done with the drug, from its discovery (synthesis) until the late 1920's, when it was seriously investigated as a cure or treatment against nearly everything from depression to decongestion. In the 1930's, amphetamine was marketed as Benzedrine in an over-the-counter inhaler to treat nasal congestion. In 1935 physicians successfully used it to treat narcolepsy (a condition characterized by brief attacks of deep sleep that can occur at anytime of the day). In 1937 amphetamine was found to have a positive effect on some children with attention deficit hyperactivity disorder (ADHD). People with ADHD have difficulty concentrating. By 1937 amphetamine was available by prescription in tablet form. During World War II, amphetamines were widely used to keep the fighting men going (during the Vietnam war, American soldiers used more amphetamine than the rest of the world did during World War II). In a period after World War II, many physicians prescribed amphetamine routinely for depression. Side by side with the expansion of the legal market for prescribed amphetamines, a modest black market in the drugs also grew up. Early black market patrons included in particular truck drivers trying to maintain schedules which called for long over-the-road hauls without adequate rest periods. Students, who had long used caffeine tablets, now turned instead to these amphetamines when cramming for exams. In fact, some use of amphetamine by athletes and by businessmen had been reported as early as 1940. Users purchased Benzedrine inhalers, broke them open and ingested amphetamine found inside. Later Benzedrine inhalers were withdrawn from the market; they were replaced by inhalers that do not contain amphetamine (3).

Methamphetamine, more potent and easier to make than amphetamine, was synthesized in Japan in 1919 by a chemist A. Ogata (4). Methamphetamine is a powerfully addictive stimulant that dramatically affects the central nervous system,

including a strong feeling of euphoria highly addictive. Pure methamphetamine is a colorless, bitter-tasting crystalline solid. The chemical name of methamphetamine is (S)-N,α-dimethylbenzene-ethanamine. The structure is illustrated in figure 1. The drug is made easily in clandestine laboratories with relatively inexpensive over-the-counter ingredients. These factors combine to make methamphetamine a drug with high potential for widespread abuse. Methamphetamine is commonly known as "speed," "meth," and "chalk". In its smoked form, it is often referred to as "ice," "crystal," "crank," and "glass". Methamphetamine's chemical structure is similar to that of amphetamine. It is slightly less potent than amphetamine as a pressor drug, though clearly more potent as a central nervous system stimulant (5). Like amphetamine, it causes increased activity, decreased appetite, and a general sense of well-being. The effects of methamphetamine can last 6 to 8 hours. After the initial "rush," there is typically a state of high agitation that in some individuals can lead to violent behavior.



**Figure 1 Chemical Structure of Methamphetamine**

### 2.1.2 Patterns of use.

Methamphetamine can be smoked, "snorted" (inhaled through the nose), injected or ingested orally. Amphetamine is manufactured in Europe, while methamphetamine is manufactured in Asia and North American. In Asia, methamphetamine is sold in pills and in crystal form. Distinct sub-regional manufacturing, marketing and abuse patterns have been identified within the Asian region. Pills predominate in South and

South-East Asia, while crystal methamphetamine (ice or shabu) is the main form in East Asia. China is the only country in which significant clandestine manufacture of both forms is reported (6). The literature on methamphetamine and amphetamine abuse is in agreement on some basic facts. Most amphetamine or methamphetamine users fall into one of two categories. In the first category are those who use an amphetamine or methamphetamine only on irregular occasions and usually for a specific purpose of postponing sleep: the student studying for an examination or the truck driver faced with a long trip. Users in the second category typically display a more familiar pattern of drug abuse, for their goal is purely hedonistic; they relished the “high” and the enhanced sense of self-confidence that stimulants can produce. Methamphetamine is a mild hallucinogen that stimulates the central nervous system giving rise to some behaviour changes, commonly referred to as “highs” and “lows”. The “high” effects include increased confidence, an elevated mood, prolonged awakeness, euphoria, empathy and heightened sexual activity. The “lows” on the other hand constitute nausea, dizziness, loss of appetite, anxiety, depression, insomnia and paranoid behaviour often end in suicide.

### **2.1.3 Medical aspects of methamphetamine abuse.**

Viewed pharmacologically, methamphetamine is itself dangerous, aside from its misuse as a stimulant and recreational drug. The most serious health implications of methamphetamine, resulting from chronic use, are dependence, characterized by compulsive drug-seeking and drug use, and a phenomenon known as amphetamine or methamphetamine psychosis. The latter is a mental condition similar to the psychotic episodes associated with schizophrenia. It is characterized by symptoms such as confusion, delirium and panic as well as hallucinations (visual, auditory or olfactory). It is accompanied by unrealistic suspiciousness and paranoid delusions. Intense paranoia subsequently may lead to aggressive behaviour or violence, including homicidal and suicidal tendencies. These behavioral changes can persist for years after drug use is discontinued. The medical complications of methamphetamine use are multiple and involve almost every major organ system. This drug can affect the cardiovascular system and potential complications include rapid heart rate, irregular heart rate, increased blood pressure, heart attacks. The central nervous system

complications may include seizures, chronic psychosis, strokes and spontaneous brain bleeds. The lungs can be affected as well because methamphetamine use can cause pulmonary edema (7).

#### **2.1.4 Overview of illicit methamphetamine problems in Thailand.**

The impact of methamphetamine abuse in Thai society over the past several years has reached crisis proportions. From an early user-base among sugar cane workers and long-distance truck drivers, methamphetamine has spread out to infiltrate homes, schools, offices and factories throughout the country. The pandemic of methamphetamine pills, which are called 'ya ba' in Thailand, has left in its wake a widening swathe of organized crime, official corruption, street violence and broken families. It is believed that Thailand is a major hub for drug trafficking, and has the highest methamphetamine abuse rates in the world (8). The impact among youths and students has been most severe. The government estimates that three million Thais, or five percent of the population are methamphetamine users (9). In February 2003, the Thai Government declared a "war on drugs". In term of police reports on activities, this "war" has produced some results: methamphetamine seizure cases reported decreased by one-third from the year 2002 to 2003 (10). However, methamphetamine is still the main illicit drug causing problems in Thai society. The problems in Thailand are also having effects outside Thailand. The methamphetamine pills from Thailand are also found to be smuggled to the other regions in the world--for example, in 2001, Swiss authorities broke a crime syndicate smuggling methamphetamine pills from Thailand, linked with trafficking in women. Switzerland's authorities were able to seize 450,000 methamphetamine pills throughout their country, and each pill had a brand "WY" on it. Taiwan and some Asian countries, that employ a large number of Thai laborers, were also reported to frequently detect methamphetamine pills in their countries (11). Methamphetamine pills from Thailand have also appeared in Southeast Asian communities in California (12).

Lying behind many car accidents and criminal cases, methamphetamine is misused by many people as a way of coping with extended working hours, as they turn to the drug's stimulating effect on the central nervous system to "keep going" at

work. When used by drivers to extend driving hours, methamphetamine lies behind many severe car crashes due to direct effects and the after-effects seen when it wears off leaving the user with withdrawal symptoms such as insomnia, restlessness, mental confusion, depression and a severe craving for the drug. Compounding the social problems is the fact that methamphetamine is also popular as a recreational drug amongst young people.

### **2.1.5 Manufacture of methamphetamine in Thailand**

The amphetamine family of drugs was first introduced to Thailand in 1957. Initially the substances were imported in the form of white pills with a horse logo, which became popularly known as “horse pills”. The active ingredient of these “horse pills” was found to be amphetamine. By 1974, methamphetamine had replaced amphetamine as an active ingredient in the pills (13). At that time, purified methamphetamine was being imported from other countries and then formulated into pills in Thailand. This situation was to change for the worse, as local manufacturing began to take place. By 1987, clandestine methamphetamine laboratories had been identified around the central areas of Thailand. Clandestine methamphetamine laboratories were being moved to the northern region of Thailand by 1994, and then moved to the Thailand-Myanmar border, and finally deep into certain Myanmar regions by 1995 (14). Beginning at that time and into the present, it is believed that most or all methamphetamine present in Thailand is produced in Myanmar and sent over the border to be sold in Thailand. About 800 million methamphetamine pills were smuggled into Thailand during the year 2002 (15). During 2001/2002, seizures of illicit drugs throughout Thailand still increased, especially, methamphetamine seizures. Twenty major seizures of methamphetamine pills (a major seizure defined as involving above 1 million pills per case) were made from the early 2001 till the mid of 2002. There were 152,773 cases with 163, 425 offenders dealing only with methamphetamine seizures in the year 2001 (10). The intelligence sources estimate that, of the approximately forty clandestine laboratories active on the Myanmar side of the border with Thailand, only a minority is refining heroin. Most are manufacturing methamphetamine and are responsible for the bulk of the illegal shipments of that drug to Thailand. However, only five laboratories were reported to

the United Nation Office on Drugs and Crime in 2001, possibly a consequence of the remote location of most of the laboratories. All five were pilling laboratories. It is estimate that the majority of laboratories in Myanmar are high capacity laboratories. For some of the more recently uncovered 'pill laboratories' capacities of up to 100,000 pills per day are reported, representing a requirement for approximately three kilograms of methamphetamine per day. While three kilograms of methamphetamine may seem only a relatively small quantity, it does represent a three-fold increase on known outputs in the past. However, within Thailand, clandestine 'pill laboratories' continue to exist, as seen in the seizure of mixing and pilling machines with dies and punches for the typical logo seen in South-East Asia (6). The manufacture of methamphetamine is relatively simple and concealable because it does not require agricultural production, specialized equipment, or advanced technical training. Tanks of hydrogen gas, mason jars, coffee filters, gas stoves, rotary evaporators, gallon buckets, pillow cases, funnels, pH meters or litmus papers, suction pumps, shakers, fans, balances and tableting machines are commonly found in illicit methamphetamine laboratories. This equipment is used for laboratory functions supporting manufacturing processes. The ease with which methamphetamine can be manufactured is a major contributing factor to the increase in its use. As noted, methamphetamine in Thailand is mainly sold in pills. The illicit drugs policy of the Thai Government is predominantly focused on suppression and control of narcotic and psychotropic substances. Responding to this focus, drug producers continually modify their products, changing shape, colour and logo of methamphetamine pills as well as modifying the active ingredients. Their goal is to avoid arrest by the police authorities and also, to enhance marketing effectiveness through gaining new synergistic effects which would attract new buyers and maintain "brand" loyalty from existing users.

## **2.2 Related drug characterization study review**

Characterization of seized drug samples through laboratory analysis has long been recognized as making a valuable contribution to the body of information used in interdicting clandestine drug production and trafficking. Opium provides an example. An international program for opium research was initiated in the 1940's as a result of

concerns about the prevailing global situation with regard to availability of opium and the multiplicity of source countries. To some extent physical and chemical criteria had always been used in judging the origins of opium. The general appearance, colour, texture, oiliness or lack of it and morphine content as well had been noted and used to help identify opium origins. For example, Turkish opium has a morphine content around 12-13% generally as compared with 9-10% for Indian opium. The lower morphine content of Indian opium is chiefly due to a different method of collection. The oily character of Indian opium had been noted because the opium cultivators in central India customarily added some oil to their opium (16). To better apply identification techniques, methods for determining the origin of opium by scientific means were developed. Methods of assay of opium for morphine and codeine content were also developed and put to use in determining drug origins (17). The development of methods for the characterization of opium was discontinued in the late 1960s, when efforts began to focus on heroin, a substance being increasingly abused. The identification of diluents and impurities provided evidence for determining the origin of heroin, and colouring agents and adulterants could be indicative of the source of heroin as well. The proportions of morphine, codeine and acetyl products and the ratios of morphine to codeine and heroin to acetylcodeine were used as basic criteria for determining the origin of illicit heroin samples (18). In South Africa, seized Methaqualone which was an important substance which caused abuse potential effect was studied on physical and chemical characteristic. The database was established using seized Methaqualone that was received by the South African Police Service Forensic Science Laboratory. Forensic Drug Intelligence Database was an important part of a protocol on Combating Illicit Drugs in South Africa. The database would provide the strategic and operational intelligence that can be used to combat organized crime. The police station, police area and province of origin, substance type, quantity and physical characteristics were some of the data being captured for each drug exhibit received. The physical characteristics used to classify pills were the imprint/brand name, the diameter and colour. The data could be used as a tool for linking seizures and for establishing a graphic representation of the distribution of the drugs (19).

In a parallel way, drug characterization of methamphetamine has also been developed to help identify any links between two samples of seized drugs and monitor methods used in clandestine laboratories. In this development, it is combination of the findings from both chemical and physical examination that is seen as critical to the drawing of meaningful conclusions (1). In Britain, characterization of various illicit drugs such as amphetamine has been investigated for usefulness in providing scientific support for the work of the Central Drugs and Illegal Immigration Intelligence Unit. Dosage forms of drugs, bulking agents, colouring agents were all studied. For example, it was noted that illicit amphetamine pills were found to be pale blue, probably as an attempt to copy a particular brand of licit amphetamine pill. Techniques to link different seizures to the same source were proposed. In one investigation involving three amphetamine pills, by the application of a unique combination of chemical profiling data, a clear conclusion emerged to proceed on the assumption that all three physically different amphetamine pills were made by the same manufacturer, which later was proved to be the case (20). With the further development of physical profiling came greater potential to link seizures in an attempt to combat illicit drug trafficking. Physical examination of the synthetic drug ecstasy (3,4-metylenedioxyamphetamine, MDMA) was used to assess the potential for determining the type of pilling machine and tooling used (21, 22). A ballistic tracking of the illicit pills and capsules was also undertaken. Ballistic tracking is used on pills and capsules submitted to the U.S. Drug Enforcement Administration (DEA) laboratory as drug evidence--samples undergo a ballistic examination as part of the effort to determine the source of the drug. The ballistic examination consists of a macro- and microscopic physical examination and chemical analysis of the drugs to determine individual characteristics of the manufacturing process and of the tools with which the pills or capsules were made. The results of such examinations are computerized and compared with reference samples to provide indications of the drug source (23). Also, in Japan physical and chemical profiling of amphetamine-type stimulant pills was performed. Chemical characteristic of ecstasy pills were analyzed to determine their chemical characteristics. Physical characteristics, logo, diameter, thickness, weight, colour also were studied. The method for profiling amphetamine-

type stimulant pills was proposed (24). Impurities profiling in illicit methamphetamine was performed to help identify synthetic methods of methamphetamine (25). Impurities profiles of methamphetamine pills seized in Thailand have also been investigated. Nine compounds (1,2-dimethyl-3-phenylaziridine, ephedrine, methylephedrine, N-formylmethamphetamine, N-acetylmethamphetamine, N-formylephedrine, n-acetylephedrine, N,O-diacetylephedrine, methamphetamine dimmer) were identified as impurities in methamphetamine pills (26).

The primary identifying aspect of any illicit pill is the method of manufacture. The most common method of manufacture is that used in the pharmaceutical industry, involving the compression of a powder or granules in a die with the aid of punches. This can take the form of a single-punch or a multi-punch pill press. Other methods exist, such as moulding, and this is an attractive alternative for the illicit manufacturer, since it does not require expensive and heavy machinery. Although weight variation between moulded pills is much greater than with machine-compressed pills, it is possible by this technique to produce pills of basically uniform diameter and thickness (27). However this technique can only produce at a low rate of production. Quite small moulded, LSD (Lysergic acid diethylamine) pills known as Microdot were produced beginning from the early 1970s by this technique. However, despite the existence of the alternative of moulding, compression production methods dominate both licit and illicit industry, and compressed pills are widely produced by the pharmaceutical industry and by clandestine laboratories. The pills produced for the illicit "street" market are usually simple in design, plain, uncoated and capable of easy manufacture. A variety of compression production techniques have been used, ranging from hand compression to machine manufacture on a multi-punch rotary press. There was one report of amphetamine and ephedrine pills being produced from a simple hand-operated press. The pills were found to be  $5.05 \pm 0.01$  mm with thickness  $2.89 \pm 0.44$  mm and weight  $81.8 \pm 12.3$  mg. (27). A hand-operated press for producing methamphetamine pills was seized in Lumphun province, Thailand in 2002. Compressed-pill machines are frequently encountered in clandestine laboratories. Nineteen sets of methamphetamine pilling machines with a capacity to

produce 300 pills per minute were seized at Panshanmanu jetty in March 2000. Eighty sets of methamphetamine pilling machines were also seized in Kanchanaburi province in July 2001 (28).

Most drug substances require the addition of one or more excipients in order to assist in the preparation of granules and their subsequent compression into pills. Even though crude methods are used in the illicit manufacture and the end product may not be of the standard required by the pharmaceutical industry, the basic requirements remain the same if an acceptable pill is to be made in quantity at a reasonable rate of production. The excipients most commonly used in pill manufacture are as follows:

(i) **Diluents** Where a drug dose is measured in a few milligrams such as amphetamine, a diluent is used to give the pill sufficient bulk for ease of handling. Among the substances frequently employed in the pharmaceutical industry are sucrose, lactose, mannitol and calcium phosphate. Illicit pills usually contain a wide variety of diluents which can serve to characterize a source. These diluents are available in the black markets.

(ii) **Adhesives or binders** These substances are added to the powdered ingredients in order to increase the cohesive strength of the diluent and assist in converting the fine powders into a coarser, free flowing form of granule. The adhesives are added in concentrations of between 1% to 10%. Powdered binders such as acacia or gelatin have traditionally been used. The simple formulations used in the clandestine production of illicit pills are likely to contain a natural gum or possibly a starch.

(iii) **Lubricants** These agents are most important in pill formulation, as they are associated with three aspects of pill manufacture: the flow of the granulates, the adhesive of material to the punches and dies and the release of the completed pill from the die. The most frequently used materials are magnesium stearate, calcium stearate and talcum.

(iv) **Disintegrants** The purpose of the disintegrant is to ensure that after the pill has been swallowed it will quickly break down to release the drug for absorption by the body. The most widely used disintegrant is powdered starch.

(v) **Colourants** These are added to a wide variety of pills for aesthetic appeal

and in order to distinguish one product from the other, that is, illicit methamphetamine manufacturer would seem to use dyes not only for visual appeal, but also to enable their products to be readily identified on the drug scene.

Changing the formulation especially the major excipients, can affect the character of the pills. The mean weight of ten tablets taken from two batches of illicitly produced amphetamine tablets of the same diameter and similar thickness made on the same single-punch machine but with different major excipients, will likely be different, as in this example: batch A containing lactose, the average weight of the pills was  $173.9 \pm 8.3$  mg; batch B containing calcium phosphate, the average weight was  $238.9 \pm 5.9$  mg. A wide variation of weight between batches can indicate a change in excipients (27).

The identification of dyes in illicit pills can be used in conjunction with knowledge of other components to relate seizures from different locations. The identification of dyes could also help to link the precursor supply chains. Soluble food dyes are a very common form of colouring agents found in the illicit pills and the HPLC method has been found to be of value in distinguishing the differences which occur in the number and nature of impurities present in these dyes from different manufacturers or batches (29). The identification of soluble food dyes has been developed using Thin Layer Chromatography (TLC), visible spectrophotometry and reverse - phase ion-pair high performance liquid chromatography (HPLC) (30).

There are many procedures available to examine and describe illicit tablets. Examination of pill shape and colour is easy to accomplish and, when combined with such characteristics as diameter and weight, provide an excellent means for the initial comparison of illicitly produced pills. Pharmaceutical tablets are characterized or described by a number of specifications. These include the diameter size, shape, thickness, weight, hardness, disintegration time and dissolution time. The diameter and shape depend on the dies and the punches selected for the compression of the tablet. The top or lower surface may be embossed or engraved with a symbol or letters which serve as an additional means of identifying the source of the tablets. The specifications assure the manufacturer that the tablets do not vary from one production lot to another. These are some tablet properties which depend

predominately on the formulation and method of manufacture, for example, hardness, disintegration and dissolution (31). The tests used in pharmaceutical industry for quality control procedures can be useful tools to help understand the techniques used in clandestine methamphetamine laboratories.



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