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Chemical Profile of Ecstasy Tablets – a Review

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Abstract. Ecstasy is a popular name of a substance called 3,4-methylenedioxymethamphetamine (MDMA). Pharmacologically it displays effects related to amphetamine-type drugs like restlessness, well-being, and others. The Ecstasy is seized as tablets with a large variety of symbols and colors and an extremely diverse content. Also MDMA, other psychoactive compounds may be present, with or instead of, LSD, amphetamine, heroin, cocaine, and others. Considering the illicit production of ecstasy tablets, the raw materials used can be contaminated with several impurities and, multiple synthesis routes can be used generating a great variety number of sub-products and contaminants. The goal of this article is to evaluate the different methods of analysis described in the literature commonly used to determine the chemical profile of ecstasy tablets and use the analysis as a strategy to produce a database of ecstasy tablets seized at Rio de Janeiro State that will provide additional information for drug traffic repression. The interchange with others databases in Brazil and outside will evaluate the origin of these ecstasy tablets.

Keywords: MDMA, detection methods, ecstasy tablets, chemical profile, drug intelligence investigations.

1. Introduction

Ecstasy is a popular name of a substance called 3,4-methylenedioxymethamphetamine (MDMA). This name initials (MethyleneDioxyMethAmphetamine) are the origin of the term MDMA. This

substance is a methamphetamine derived known on the streets as “candy”, “XTC”, “Adam” and others.

The name “Ecstasy” used in a non-selective form, have been applied to designate 3,4-methylenedioxymethanphetamine (MDA) and 3,4-methylenedioxyethylanphetamine (MDEA), the last one is also known as “Eve”. These three compounds are chemically and biologically related.

In historical terms, the MDMA use was preceded by the MDA, as Jackson & Reed[1]related that MDMA was refereed as the “the love pill” by the recreational users in Wiscosin. Renfroe[2] analyzed 610 pills of MDA and MDMA sent anonymously to his lab between 1972 and 1985. He verified that all the amounts sent before 1975 was composed restrictedly by MDA. The first tablet with MDMA was found only in 1975, the second in 1976, and during the next years the number of MDMA tablets increase gradually. On the early’s 80’s the proportion of the amounts containing MDMA was much more than the tablets with MDA. Shulgin and Nichols[3] were the firsts to describe the psychopharmacology of MDMA, a compound with “occasionally incidence in the illicit street’s market”. Among the first publications that used the term “Ecstasy” is the West Coast Publication “MDA/MDMA: the components of Ecstasy”[4] while the name “XTC”, on this time, was also used[5].

Like others amphetamines, MDA and MDMA are synthetic substances, although they may have natural precursors. All three substances were firstly synthesized over a century ago: amphetamine in 1885[6], MDA in 1910 and MDMA in 1912[7].

In 1985, the amphetamines derivatives methylenedioxy and methoxy were placed in the Class 1 of the restricted substances’ list from USA[8] and, later, were classified in the same way on Canada (Class III of Controlled Drugs and Actives Substances) and in UK (Class A in the Active Substances of Restricted Use). In Brazil, the substances MDA, MDMA and MDEA are listed in the F2 list – Psychotropic Prohibited Substances – and are illicit.

Ecstasy is illicitly sold in tablet form, and typically prepared in a professional manner with a great variability of colors and symbols. Like all the abuse drugs illegally commercialized, the contents of this tablets are much diversified.

Also MDMA others psychoactive compounds may be presents, with or instead of like LSD, amphetamine, heroine, ketamine, cocaine and others. As a drug produced in illicit labs, it may be used, in their synthesis, impure precursors.

Furthermore, a great number of synthetic routes may be used generating a large number of products, sub-products and contaminants. These contaminants are usually organic substances and result from the secondary reactions in the synthetic route, or from the precursor's contaminations, or even from inefficient purification methods and also may be presents in contaminated packets[9].

Characterization studies of drugs may supply useful information to police authorities for combating drug dealing. Chemical connections between amounts may be established and materials from different seizures may be allocated in groups of similar characteristics. Furthermore, connections can be established between users and suppliers, a drug distribution pattern could be identified, and the different routes used by drug trafficking and the production sources, including the geographical origin may become clear[10].

In 1976, GOMM *et al* compared amphetamine tablets and LSD blotters based only in the dimensions and in the microscopic exam. Nowadays, a reliable chemical profile of the illicit drugs combines physical, chemical, and statistical techniques to establish connections between different seizures[11].

The complete chemical profile of Ecstasy tablets requires five main analytical tools: physical characterization of the tablets, which characterizes the samples by size, color, logotype and shape; active substance analysis to verify the presence of MDMA in the tablets and to determine the presence of others psychoactive substances (illicit or not) in the tablets; organic impurities analysis, evaluating the presence of sub-product routes; metallic traces which help in the identification of the synthetic route when they are used as catalysts in MDMA synthesis; excipients analysis which helps in the identification of similarity in the compression process of the tablets (same relation drug:exciepient)[9].

The goal of this paper is to describe the different tools used to trace physical and chemical profiles of ecstasy tablets and to evaluate the advantages and disadvantages of these tools; this will aid police in creating a database of ecstasy tablets seized at Rio de Janeiro State, wich will permit provide additional information for drug traffic repression. The interchange with others databases in Brazil and outside will evaluate the origin of these ecstasy tablets.

2. Methodology

The electronic search was made using “Medline/PubMed” databases. There were used strategically words like “MDMA”, “Ecstasy”, “Chemical Profile”, “Separation Methods”, Impurities Profiles” and “Synthetic Routes”. An initial analysis was achieved verifying the paper titles and their abstracts. After this trial, all the papers selected were obtained and reviewed.

3. Results

3.1 Physical Aspects of the Tablets

Among abuse drugs, ecstasy tablets are known for their extremely variable physical aspects. It’s common to find variable physical patterns in different ecstasy manufactures; these characteristics could be used in tablets individualizations.

Physical characteristics are labeled in the tablets and provide additional information for the chemical analysis. Both are important to the tablet characterization, since each one highlights a different phase of clandestine ecstasy production. For example: the organic impurities are generated during MDMA synthesis, but the physical patterns result from the physical process of tablets compression[12].

On the other hand, the unique information of similar physical aspects doesn’t imply that tablets are part of the same batch or producer. Different physical aspects could be found on tablets with similar chemical aspects, since the same producer can use different dyes and labels in tablets production. Cheng et al (2003) conducted a survey to study the ecstasy tablets seized in Hong Kong between 2000 and 2001. In this study, they compared physical attributes, including size, color, and logo, with the chemical aspects of the tablets. They related that, while in many cases, tablets with different physical aspects have similar chemical compositions, some tablets have chemical compositions that different from that expected by their physical characteristics. This study confirms that physical aspects could not be reliably used to predict the chemical composition of ecstasy tablets[13].

3.2 Analysis of the active compounds present in ecstasy

The term ecstasy is a generic one, since tablets sold as ecstasy may not present the MDMA compound, they could show an association between MDMA and other

amphetamines derivatives or they could even have different substances in their composition such as: caffeine, ketamine, diazepam, phenobarbital, and others[13].

The most useful techniques in ecstasy tablets active compounds determination are thin layer chromatography (TLC), high performance liquid chromatography (HPLC) with diode array detectors (DAD) and gas chromatography (GC) with mass spectrometry detection (MS)[13]. These techniques allow the identification of MDMA, and other common substances, in ecstasy tablets. Depending of the technique additional reference materials could be necessary. In the absence of reference materials, the MS detector can be used to elucidate the chemistry structure of the unknown compounds.

3.3 Organic impurities analysis

The organic impurities analysis can be used to help in the linkage of different seizures originated from the same laboratory and, possible, from the same batch of the illicit drug[9].

The impurities can either be found in the precursors or can be produced during the MDMA synthesis, besides the ones present in the additives and in the diluents that could appear during the tablet production[9]. The impurities analysis is not restricted to the detection of the synthesis reaction byproducts, but the possibility of the byproducts react themselves generating further byproducts must be considered. So it is important to develop a broad method that allows the identification of these residues.

In Ecstasy tablets, MDMA is considered the main illicit compound. Pathways of MDMA synthesis involve the use of isosafrole, safrole, piperonal and 3,4-MDP-2-P as precursors[11]. The two main routes are the Leuckart reaction and the reductive amination[11,14].

In ecstasy tablets, an elemental analysis could show important information about the: catalyzer agent, the reducing agent used, the materials used during the synthesis and the excipients added to powder MDMA in the compression process[15].

Gimeno et al (2002) have described a GC-MS method to evaluate the chemical impurities of ecstasy tablets. In this method several intermediate compounds were found, such as: amphetamine, methanphetamine, safrole, piperonal and isosafrole. These substances found on the tablets, prevented an exact determination of the synthetic route used to obtain MDMA, as there are some

common impurities that participate in two or more synthesis route. It was important to identify the tablets from the same batch that exhibited the same impurity profile. The primary MDMA precursor found was safrole, probably obtained from sassafras oil. Amphetamine and methamphetamine was found as impurities due to bottles used in synthesis process contaminations.

3.4 Elemental analysis (metals)

Metal residues could be found in ecstasy pills as a result of their use as catalysts and reducing agents or as components of the dyes used in the tablets, as well as contaminants of the materials used as additives and excipients during tablets production[9].

This analysis could also help in the synthetic route elucidation, especially when this information is associated with the organic impurities analysis, bringing up complete information about MDMA synthesis. The most analyzed metals are: sodium, aluminum and mercury. The first one could be used as a reducing agent in sodium borohydride ($NaBH_4$) or in cyano sodium borohydride ($NaBH_3CN$). Aluminum and mercury could be found as contaminants from the mercury amalgam used in MDMA synthesis reactions[16].

There are diverse spectroscopic techniques in the literature for the metals analysis in ecstasy pills. Among them, the most used are: the flame atomic absorption spectroscopy, the eletrotermic atomic absorption spectroscopy, and the inductively coupled plasma emission spectroscopy[17,15,18,19].

Koper et al (2007) have described the main synthetic routes of MDMA based on reducing reactions using catalysts. Using the Inductively Coupled Plasma Mass Spectroscopy they have proposed a methodology that identify the synthetic route by the evaluation of Pt, B and Hg as the main catalysts residues. This work has proven that Pt was the main reducing agent in Holland MDMA production.

3.5 Excipients analysis

BELL et al (2000) have demonstrated that the excipients used in ecstasy tablets, the relation of drug:excipient, and even the hydration level of the illicit compounds, especially MDMA, could be used to discriminate different batches from the same seizing or to determinate the routes of drug trafficking. The spectroscopic techniques are the most used in these analyses, since the spectrum generate could serve as a “fingerprint” of drug samples[20].

The most used technique with the “fingerprint” intention is Raman Spectroscopy. This technique provides a spectrum with plenty of information without sample preparation, allowing the use in tablets, powders and liquids analyses[20]. When it is associated with a statistical treatment it may to differentiate excipients compositions in ecstasy tablets[21]. The Raman spectrum is ideal because it can be subtracted from the excipients spectrum, generating unquestionable information in samples identifications[20].

3.6 N isotopic ratio analysis in MDMA

The Isotope Ratio Mass Spectrometer (IRMS) is an analytical tool that exhibits a wide application in forensic science[22,23]. In this analysis, the sample is firstly converted in gas, for example, CO_2, N_2, CO, H_2 and SO_2 these gases are analyzed in a mass spectrometry at the same time that a reference material is analyzed. The IRMS are instruments with a unique magnetic focus where the isotopes are continuously and simultaneously detected by a multi-collector beam. The stable isotopes measurements are expressed as delta values (δ) according to the formula:

$$\delta^{13}\mathrm{C}(\%) = \frac{\left((\mathrm{R}^{13}{}_{sample} - \mathrm{R}^{13}{}_{reference}) \times 10^{3}\right)}{\mathrm{R}^{13}{}_{sample}}, \quad (1)$$

where $\mathrm{R}^{13} = {}^{13}\mathrm{C}/{}^{12}\mathrm{C}$.

The greatest carbon isotope abundance (^{13}C) is 11.000ppm (0,011) in relation to its principal isotope (^{12}C). Others abundance values are: ^{2}H/^{1}H = 158ppm, ^{15}N/^{14}N = 3.700ppm, ^{18}O/^{16}O = 2.000ppm and ^{34}S/^{32}S = 42.000ppm. The positive delta values indicate a greater percentage from the heavier isotope in relation to the reference one. The differences between samples from different batches of MDMA production could be solved by coupling gas chromatography to IRMS and analyzing the isotope ratio of nitrogen. In MDMA synthesis other amines are used as precursors and these compounds could be determined by the nitrogen analysis in their chemical structure[24]. A similar approach was used in the determination of heroin origin[25].

3.7 Summary of Analytical Methodologies of Ecstasy Tablets

Table 1 summarizes the advantages and disadvantages of all the methods used to trace chemical profile of Ecstasy tablets.

Table 1: Summary of the main analytical methodologies to obtain the chemical profile of Ecstasy tablets. MDA: methylenedioxyamphetamine; MDMA: 3,4-Methylenedioxymethamphetamine; MDE: methylenedioxyethylamphetamine; MD-P2P: 3,4-methylenedioxyphenyl-2-propanone; MD-P2P-OH: 3,4-methylenedioxyphenyl-2-propanol; MD-P3B: 3-(3,4-methylenedioxyphenil)-3-beuten-2-one; MD-DPIA 1: di-[1-(3,4-methylenedioxyphenyl)-2-propil] amine 1; MD-DPIMA: di-[1-(3,4-methylenedioxyphenyl)-2-propyl]methylamine; GC: gaseous chromatography; MS: mass spectrometry; AAS: atomic absorption spectroscopy; ICP- EM: inductively coupled plasma mass spectrometry; FTIR: fourier transform infrared spectroscopy; HPLC: high performance liquid chromatography.

Analysis Tool	Main Analyzed Aspects	Main Analytical Methodologies	Advantages and Disadvantages	References
Physical Aspects of the Tablets	Color, dimensions, mass and logo	Do not Apply	Advantages: Easy characterization, do not require the use of equipment. Disadvantages: Tablets with similar physical aspects could not have the same Chemical Profile.	12, 26
Active Compounds Analysis	MDMA, MDA, MDE, MDEA, LSD, Amphetamine, Heroíne, Ketamine, mCPP, Cocaine, Methamphetamine	GC-MS	Advantages: Public Security: control and knowledge of the main illicit drugs consumed; Public Health: prevention and fighting against the consumption of theses substances. Disadvantages: the group of substances analyzed is restricted and insufficient to correlate different samples.	27,28, 29
Organic Impurities	MD-P2P, MD-P2P-OH, MD-P3B, N-formyl-MDMA, N-acetyl-MDMA, MD-	GC-MS	Advantages: Robust and complete tool to correlate distinct samples. Allows the determination of the possible synthetic route. Disadvantages: Requires equipment with great sensibility to perform trace analysis of these substances in the samples.	12, 30, 31

	benzyl-MDMA, MD-DPIA 1, MD-DPIMA			
Metals Trace	Li, B, V, Cr, Mn, Ni, Cu, Zn, Br, Sr, Sn, Ba, Pt and Pb	AAS, ICP-MS	Advantages: Indicated to help in the determination of MDMA synthetic route and in the origin of bulk production in ecstasy tablets. Disadvantages: Use of specialized equipment without application in organic chemistry.	32, 14, 17
Excipients Analysis	MgSO4, maltose, lactose, NaHCO3 and starch	FTIR, Raman, Capilar Eletroforesis, HPLC with light scattering	Advantages: Indicated to help in the determination of MDMA bulk production origin. Disadvantages: Does not provide information on the MDMA synthetic route and requires the use of two or more methodologies	19, 33

4. Discussion

In the linkage of different seized samples by using chemical analysis of the drug, it's important to consider the complex pathway traversed by the drug before it gets into the user's hands. Synthetic drugs are especially rich in chemical information due to the singular characteristics provided in each chain stage.

Physical aspects of the tablets do not give precise information, as laboratories use different dyes and labels of logos to produce ecstasy pills with diverse physical patterns using the same bulk batches[13]. Physical analyses help with the characterization, but relevant additional information that can be obtained from others analyses. There is value in these analyses, as they are the only ones that could provide information about the compression machines used in the tablets. In the case of a repetitive and outstanding defect in the pills, it could be related to a physical or mechanical defect in the machine[10].

The organic impurities are directly related to the synthesis process since they generally originated from drug synthesis[10]. However, these results are not, in the majority, conclusive alone, since the main synthetic MDMA routes include common precursors, and few compounds that could be used as markers to identify the synthetic route used. Cheng et al (2003) have shown that the precursor 3,4-(Methylenedioxyphenyl)-2-propanone (MDP2P) is common to the two main synthetic routes used, the Leuckart reaction and the reducing amination and, for this reason, its presence and the substances originated from side reactions with MDP2P are not able to determine the synthetic route used on their own. The presence of 3,4-methylenedioxy-N-methylbenzylamine (MDB) characterizes the presence of piperonal as a precursor to generate MDP2P by reducing amination and could be useful to distinguish the initial precursor. To elucidate the entire route, it is crucial to develop a deeper study of the reaction byproducts. This would allow for monitoring for the presence of new synthesis markers.

In 2005, Swist et al (2005)[35] presented an alternative way to produce MDMA from safrole. They described the safrole bromination that is a synthetic route different since MDP2P is not an intermediary. Safrole bromination is the only route that provides an exclusive marker such as N-methyl—N-[1-methyl-2-(3,4-methylenedioxyphenyl)-ethyl)]-3-(3,4-methylenedioxyphenyl)-propaneamine.

The tablets from the same batch are, in its majority, identified when their impurities profiles are compared. Tablets with the same impurities profile are associated to the same batch.

Metals could also give important information over the synthesis method, but it could also give data about the dyes added after the bulk production. These dyes could be added to the same batch during the bulk production or to different batches after their production. So, data about organic impurities and metal composition must crossover to give more precise information over the synthesis of MDMA.

The active compounds analysis provides the variations in MDMA concentrations over the years, and the substances that are used with MDMA in Ecstasy tablets. Cheng et al. have determined that other psychoactive compounds, such as ketamine and methamphetamine are present in some tablets instead of MDMA[13]. The complete analysis of active compounds found in ecstasy tablets could be used not only with an investigative purpose, but also to study the relations between the composition and toxicity of the tablets. In this context, some deaths have been related to ecstasy consumption, including the ingestion of only one pill, which composition has not been described[26].

The isotopic nitrogen ratio analysis using GG-IRMS is an excellent tool to establish links between different ecstasy tablets. PALHOL et al (2004) have related that the differences between the values of $\delta^{15}N$ of precursors and of MDMA observed in seized samples could be explained by the fractioning during MDMA synthesis, that is related to the production process and to the conditions used. This fractioning generates an isotopic ratio pattern in the samples that is characteristic to the synthetic route and which a statistical treatment of the data could serve to relate different samples and determine their synthetic route. A study of the influence of the manufacturing process in the isotopic ratio fractioning could generate additional information about this process[24].

5. Conclusions

Synthetic drugs, like Ecstasy, have altered the illicit drug market. The portability and effiveness of facilities stimulate their trafficking and complicate their identification by the police.

The elucidation of the chemical profile of Ecstasy tablets in a region would be enable the construction of a detailed database that could be linked to others databases in others regions. Partnerships between these regions could highlight the drug traffic routes, as well origins of drug production. This database could also be used to connect the seized drugs with specific regions of origin.

However, to obtain correct information regarding the differences and similarities between the chemical profiles analyzed, it is necessary to seek a deep knowledge of the chemical production of synthetic drugs. MDMA synthesis has common intermediate compounds, which makes the knowledge of impurities formation and its stabilities in reaction medium vital. the significance of some impurities in the synthetic route identification and, mainly, the interchangeability between impurities from distinct routes is of particular importance. It is therefore necessary to obtain new precursors as chemical markers to begin an ecstasy chemical profile study.

The use of equipment with sufficient sensibility and precision is vital to the impurities identification process, particularly if additional reference materials are unavailable. The use of gaseous or liquid chromatographs coupled to mass spectrometers is recommended and are indispensable in these studies. In metals analysis, it will be necessary the use of particulars equipments, such as: the atomic absorption spectrometer with flame ionization. Others techniques could provide additional data and could be useful in the characterization, such as: Raman Spectroscopy, near Infrared Spectroscopy, and others.

The chemical profile analysis of ecstasy tablets as a tool in the investigative intelligence is actuallt routine in European countries and in USA. In Brazil, and other developing countries, the forensics analyses of ecstasy tablets are restricted to the identification of the prohibited substances. Observing the strategic importance of these analyses, this new approach to drug analysis will be a reality in all the Forensic Laboratories around the world.

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