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Validation Method of 3,4-Methylenedioxymethamphetamine (MDMA) Analysis Using Gas Chromatography Mass Spectroscopy

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ABSTRACT
MDMA is known as a narcotic and stimulant is a drug that is often abused, both in pill and powder form. Therefore, it is important to have an accurate and sensitive analysis method to detect the presence of MDMA especially in urine samples of drug users. In this work, optimization of the GC-MS method was carried out to obtain the best separation conditions and the highest sensitivity using the GCMS instrument. This study aims to develop a validation method for the analysis of 3,4-methylenedioxymethamphetamine (MDMA) using the Gas Chromatography-Mass Spectrometry (GCMS) technique. The results of the analysis showed that the accuracy, precision, linearity, limit of detection, limit of quantification and selectivity were respectively: 97.53%, 3.66%, $R^2 \geq 0.99$, LOD 0.7 ppm, LOQ 2.35 ppm, and Rs 19.83. The results of the study showed that this method has good accuracy with acceptable precision values and low enough LOD and LOQ to detect MDMA at appropriate concentrations. Thus, this validated GC-MS method can be effectively applied for the analysis of MDMA in various urine sample matrices, especially in the development of the field of analytical chemistry.

Keywords: Analysis, GCMS, MDMA, Narcotics, Validation.

ABSTRAK
MDMA dikenal sebagai narkotika dan stimulan merupakan obat yang sering disalahgunakan, baik dalam dalam bentuk pil meupun serbuk. Oleh karena itu, penting untuk memiliki metode analisis yang akurat dan sensitif untuk mendeteksi keberadaan MDMA khususnya dalam sampel urin pengguna narkotika. Pada penelitian ini, optimasi metode GCMS dilakukan untuk memperoleh kondisi pemisahan terbaik dan sensitivitas tertinggi menggunakan instrument GCMS. Penelitian ini bertujuan untuk mengembangkan metode validasi analisis 3,4-methylenedioxymethamphetamine (MDMA) menggunakan teknik Gas Chromatography-Mass Spectrometry (GCMS). Hasil analisis menunjukkan bahwa akurasi, presisi, linieritas, batas deteksi, batas kuantifikasi dan selektivitas berturut – turut adalah : 97,53%, 3,66%, $R^2 \geq 0,99$, LOD 0,7 ppm, LOQ 2,35 ppm, dan Rs 19,83. Hasil Penelitian menunjukkan bahwa metode ini memiliki akurasi yang baik dengan nilai presisi yang dapat diterima serta LOD dan LOQ yang cukup rendah untuk mendeteksi MDMA pada konsentrasi yang sesuai. Dengan demikian, metode GCMS yang telah divalidasi ini dapat diterapkan secara efektif untuk analisis MDMA dalam berbagai matriks sampel urin terutama dalam pengembangan bidang kimia analitik.

Kata kunci: Analisis, GCMS, MDMA, Narkotika, Validasi.

1. Introduction

3,4-Methylenedioxymethamphetamine (MDMA), also known as ecstasy, is a synthetic psychoactive compound that possesses both stimulant and hallucinogenic characteristics [1-2]. However, excessive use of MDMA can cause euphoria, increased energy, and excessive empathy. In addition, MDMA also poses serious risks such as perceptual disturbances, hyperthermia, nervous system damage, depression, and potential

psychological dependence [3-4]. Therefore, the use of MDMA has been banned in various countries including Indonesia. Despite its use being banned, MDMA remains popular among teenagers and young adults, especially at music events and night parties [5].

In 2022, European Drug Report estimated that 20–22 million people aged 15–64 years have used MDMA in the past year, representing approximately 0.4–0.6% of the global population [6]. Meanwhile, the Indonesian National narcotics Agency (BNN) reported that over 3.3 million Indonesians (1.73%) aged 15-64 had utilized narcotics including ecstasy in 2023 [7]. This disorder poses a global health danger. Consequently, it is imperative to implement effective, efficient, and highly accurate early detection of MDMA to address this issue.

To date, Gas Chromatography-Mass Spectrometry (GC-MS) is a commonly applied technology for analyzing MDMA due to its sensitivity and specificity advantages. In addition, it is able to identify and measure MDMA accurately down to very low concentrations, separate complex components well, produce consistent data, analyze multiple substances simultaneously, and can be applied to a wide range of biological samples i.e urine, hair, and blood [8-9]. In contrast, GC-MS also has weaknesses in detecting MDMA, including the potential for matrix interference from complex biological samples and the need for derivatization of certain compounds to make them more volatile and stable [10-11]. Therefore, validation of the GC-MS method is essential to ensure accuracy, precision, linearity, detection limit, sensitivity, and selectivity under actual analytical conditions.

Several previous studies have shown significant progress in developing of GC-MS validation methods. Bouzoukas et al. (2025) had developed and validated a GC-MS technique for quantifying 9 amphetamine-type stimulants (ATS), 7 synthetic cathinones (SCs), and 5 phenethylamines (PEAs) in blood and urine[12]. This method showed a limit of detection (LOD) between 0.70 to 7.0 ng/mL and a limit of quantification (LOQ) between 2.0 to 20 ng/mL, with acceptable accuracy and precision. As well as, Orfanidis et al. (2025) had developed and validated a GC-MS/MS approach for determining 11 amphetamines and 34 synthetic cathinones in whole blood [13]. However, both studies have a broad focus on various types of substances, without emphasizing MDMA detection specifically. In addition, the sample matrices are still limited to blood and urine, whereas MDMA detection in other matrices such as hair can provide more accurate information on long-term use. In addition, there are not many studies that optimize GC-MS instrumental parameters specifically to increase the sensitivity of MDMA detection in very low concentrations in complex samples.

This project aims to construct and validate a more sensitive and specific GC-MS technique in detecting MDMA in urine matric. On the other hand, this study also aims to address the existing research gap by optimizing analysis parameters, thereby making significant contributions to forensic testing and substance abuse diagnosis.

2. Materials and Methods

2.1Materials and Instrumentation

Certified Raw Material (CRM) MDMA, $Methanol_{(l)}$, $Sulfuric\ Acid_{(l)}$, $Ammonium\ Hydroxide_{(l)}$, $Acetone_{(l)}$,, $Formaldehyde_{(l)}$, $1\text{-}Butanol_{(l)}$, $Ethanol_{(l)}$, $Ammonium\ Carbonate_{(l)}$, $Ammonium\ Phosphate_{(l)}$, $Ammonia_{(l)}$, $Formaldehyde_{(l)}$, $Chloroform_{(l)}$, $2\text{-}Propanol_{(l)}$, $Ethyl\ Acetate_{(l)}$, $Methanol_{(l)}$, $Aquadest_{(l)}$, Urine from narcotic users obtained from the Bidlabfor Polda Sumut. The instrumentation used was a GCMS.

2.2 Procedure

MDMA Extraction from Urine Sample

25 mL of urine was added with 1 mL of ammonia and homogenized. Then, 25 mL of chloroform:2-propanol (1:1 v/v) solutions were introduced and homogenized. This resulted in two layers: the organic layer and the urine layer. The organic layer was then analyzed further.

2.3 Chemical Spot Test

A sample of MDMA solution with a concentration of 6 ppm and the extracted urine sample were placed on a spotting plate. Marquis reagent was applied, and the result showed a dark purple color.

2.4 TLC Test

In this work, silica gel GF254 TLC plate was prepared, and a 6 ppm MDMA solution sample was applied. The plate was eluted with a mobile phase of ethyl acetate:ammonia:25% ammonia (17:2:1). After the plate

dried, it was sprayed with Marquis reagentThe Rf value was compared between the CRM MDMA solution and the urine sample.

2.5 GCMS Analysis and Validation Method

MDMA solutions with concentrations of 5 ppm, 4 ppm, and 3 ppm, which have been adsorbed with CHA, as well as urine solution samples 1 and 2 that have been prepared and adsorbed with CHA, were analyzed by GC-MS using an Agilent 7890 B GC system and Agilent 5977A MSD, equipped with a DB-5MS column, 30 m in length, 250 µm inner diameter, and 0.25 µm film thickness with a stationary phase mixture of 5% Diphenyl and 95% Methyl polysiloxane. The injector temperature was set to 300°C, the interface temperature to 290°C, and the ion source temperature to 230°C. The constant flow rate was 1 mL/min with a split ratio of 50:1, and a solvent delay of 2 minutes. Mass scanning was set from 50 to 500 m/z. The injector was set to splitless mode with a sample injection volume of 1.0 µL at a constant injector temperature of 250°C. The initial oven temperature was set to 100°C, held for 0 minutes, then increased by 15°C per minute to 280°C, where it was held for 5 minutes. Validation method includes accuracy, precision, linearity, LoD, and LoQ tests[14]. Several steps involved in validation methods are as follows[15]:

1. *Accuracy:* Accuracy is a definitive measure of a technique, whereas analysis refers to the degree to which measurement findings converge with the value deemed accurate, whether it be the reference value, the actual value, or the standard value. The accuracy measurement is conducted by quantifying the amount of analyte successfully recovered following its addition to the sample. For drug compound testing, accuracy is determined by comparing the measurement results with the Certified Reference Material (CRM) is presented in Eq.1

$$\%\ Recovery = \frac{(CF-CA)\ x\ 100\%}{C^{*}A} \quad \text{(Eq.1)}$$

CF = Analyte concentration obtained from the measurement after adding the standard material
CA = Analyte concentration before adding the standard material
C*A = Concentration of the standard material (analyte) added[15][12]

2. *Precision:* Precision quantifies the repeatability of a technique of analysis, usually expressed as the relative standard deviation of a statistically significant sample set (Eq.2).

$$RSD = \frac{SD\ x\ 100\%}{x} \quad \text{(Eq.2)}$$

x = Mean concentration of the sample
SD = Standard Deviation
RSD = Relative Standard Deviation

3. *Linearity*: Linearity is ability of an analytical method to produce response that is proportional to the concentration of the analyte within a certain range. Linearity indicates how well the relationship between the instrument response (y) and the concentration of the analyte (x) is through a calibration curve. Evaluation of linearity is done by measuring the response at various concentration levels individually. Linearity is measured by performing single measurements at different concentrations (Eq.3) [16].

$$Y = bx + a \quad \text{(Eq.3)}$$

Y = Instrument response (e.g., peak area, absorbance)
x = Analyte concentration
b = Slope (line gradient; sensitivity)
a = Intercept (y-axis intercept)

4. *Limit of Detection*: Limit of Detection (LoD) is the lowest concentration of an analyte in a sample that can still be detected by the method, although the analysis may not be able to quantify it accurately. The International Council for Harmonisation (ICH) introduced this signal-to-noise ratio method, although ICH also provides two alternative methods for determining LoD: the non-instrumental visual method and the calculation method. The non-instrumental visual method is used in thin-layer chromatography techniques,

and in titrimetric methods, LoD can be determined using the standard deviation (SD) of the response and the slope (S) of the calibration curve at levels approaching the LoD is displayed in Eq.4 [15].

$$LoD = \frac{3\,SD}{b} \quad \text{(Eq.4)}$$

LoD = Limit of Detection
b = Slope (y-axis intercept)

5. *The Limit of Quantification*: Limit of Quantification (LoQ) is the lowest concentration of an analyte in a sample that can still be measured accurately and precisely within acceptable limits according to the operational conditions of the method used. Similar to LoD, LoQ is also expressed in units of concentration. LoQ determination is often based on a signal-to-noise ratio of 10:1. Although this approach is commonly used, it is important to understand that LoQ reflects a balance between concentration, precision, and accuracy. As the LoQ concentration decreases, precision usually decreases; therefore, if high precision is required, the reported LoQ tends to be higher, as explained in Eq 5 [12].

$$LoQ = \frac{10\,SD}{b} \quad \text{(Eq.5)}$$

LoQ = Limit of Quantification
b = Slope (y-axis intercept)

6. *Selectivity/Specificity*: In analytical methods involving chromatography, selectivity is determined through the calculation of the resolution power. The formula used is displayed in Eq.6:

$$Rs = \frac{2\,(Rt_2 - Rt_1)}{W_1 + W_2} \quad \text{(Eq.6)}$$

Rs: Resolution
Rt 1: Retention time of peak area compound 1 (minutes)
Rt 2: Retention time of peak area compound 2 (minutes)
W 1: Width of peak area compound 1 (minutes)
W 2: Width of peak area compound 2 (minutes)[15]

3. Results and Discussion

3.1 Chemical Spot and TLC Test

Chemical spot and Thin Layer Chromatography (TLC) tests were performed to identify the presence of MDMA in the sample. This test aims to detect compounds based on chemical color changes and their Rf values (retardation factor), which are indicators of the characteristics of compounds in certain solvent systems. The resulting test is illustrated in Table 1.

Table 1. Chemical spot and TLC test results

Sample	Colour	Rf
MDMA	Purple (++)	0.555
Urine	Purple (++)	0.555

The results of the chemical spot and TLC tests in Table 1 show that both pure MDMA samples and urine samples produce a dark purple color (++), indicating a positive reaction to MDMA. In addition, both samples have the same Rf value, which is 0.555. The retardation factor (Rf) value is the ratio of the distance of compound migration to the solvent, and the similarity of this value between the urine sample and pure MDMA indicates that the compound found in the urine is most likely MDMA. The similarity of color and Rf value strengthens the indication that MDMA was successfully detected in the urine sample, and shows that the TLC method used is quite effective in separating and identifying the presence of MDMA in biological matrices such as urine [17].

3.2 GCMS Analysis

To ensure the presence and measure the concentration of MDMA in urine samples, the analysis was conducted utilising GCMS. The results of the chromatogram and mass spectrum of MDMA are shown in Figure 2, while quantitative data in the form of MDMA concentrations in standard and urine samples are shown in Table 2. MDMA chromatogram (a) and MS spectrum (b) is presented in Figure 2 below:

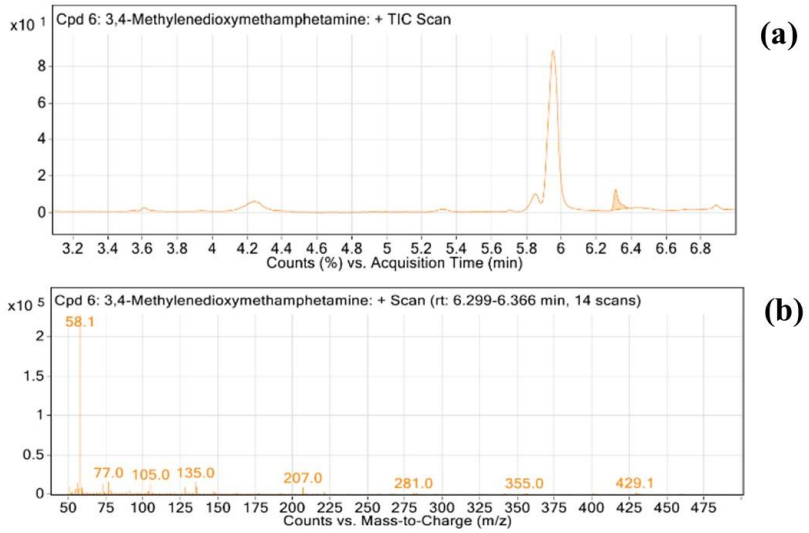

Figure 2. MDMA chromatogram (a) and MDMA MS spectrum (b)

Figure 2 shows the chromatogram (a) and mass spectrum (b) of MDMA obtained by GC-MS analysis. The MDMA peak appeared at a retention time (RT) of 6.299 minutes, both in the standard sample and the urine sample, indicating the agreement of the chromatographic characteristics between the two. The mass spectrum of MDMA showed a major molecular ion peak at m/z 58, as well as characteristic fragments at m/z 105, 135, and 178, which were consistent with the typical fragmentation pattern of MDMA reported in previous literature [18], [19]. This indicated that the compound detected in the urine sample had identical structure and ionization properties to pure MDMA. The quantitative concentration of MDMA is shown in Table 2. The MDMA standard sample with a nominal concentration of 6 ppm produced an actual concentration of 5.965 ppm with an area of 829979.98, while in the urine sample, the peak area reached 1258358.00 but with a calculated concentration of 0.081 ppm. Although the instrument response was quite high in urine samples, the actual lower concentrations could be due to the influence of the biological matrix as well as the possible excretion of MDMA in the form of metabolites. Overall, the agreement between the retention time, mass spectrum fragmentation pattern, and quantification results indicates that the GC-MS method used has excellent ability to detect MDMA specifically and sensitively in complex samples such as urine.

Table 2. MDMA and urine concentrations

Sample	Area	RT	Concentration (ppm)
MDMA	829979.98	6.299	5.965
Urine	1258358.00	6.299	0.081

3.2.1 Method Validation

Accuracy Test

Accuracy testing was conducted using the percent recovery approach to evaluate the ability of the GC-MS method to accurately measure MDMA levels in urine matrices. Based on Table 3, the percentage recovery obtained at three variations of spike concentrations, namely 10 ppm, 50 ppm, and 100 ppm were 97.2%, 97.5%, and 97.9%, respectively, with an average recovery value of 97.53%. All recovery values are within the internationally accepted range for content analysis in biological matrices, namely 80–110% for concentrations above 1 ppm. This indicates that the method used has very good accuracy in detecting MDMA at various concentration levels. The absence of MDMA content in blank urine samples also strengthens that the measurement results come from the added target compound and not from contamination. Therefore, it can be concluded that the GC-MS method validated in this study meets the criteria for good accuracy for the analysis of MDMA in urine samples.

Table 3. Percentage Recovery Data

No	Spiked concentration (ppm)	Test results 1 (ppm)	Test results 2 (ppm)	Test results 3 (ppm)	Urine blank (ppm)	Mean (ppm)	Recovery (%)
1.	10	9.81	9.11	10.24	0	9.72	97.2
2.	50	49.13	48.97	48.20	0	48.76	97.5
3.	100	97.45	94.56	101.69	0	97.9	97.9

Precision Test

The precision test aims to assess the level of consistency of the analysis results by injecting a 100 ppm MDMA standard solution three times. The results of the precision test are shown in Table 4. Based on Table 4, the concentration values obtained were 97.451 ppm, 94.563 ppm, and 101.691 ppm, with an average of 97.902 ppm and a standard deviation (SD) of 3.585. The resulting Relative Standard Deviation (RSD) value was 3.66%, still below the maximum limit set, which is ≤5%. This shows that the GC-MS analysis method used has good precision and is able to provide consistent results between repeated measurements. Thus, this method is suitable for use in quantitative analysis of MDMA in various samples because it shows reliable stability of results.

Table 4. Precision test results

Measurenment	Results (ppm)
1.	97.451
2.	94.563
3.	101.691
Mean	97.902
SD	3.585
RSD (%)	3.66

Linearity Test

Linearity test was conducted to ensure that the analytical method provides a proportional response to the concentration of MDMA within a certain range. Based on Table 5 and Figure 3, the relationship between concentration (X) and absorbance area (Y) shows a linear regression equation $y = 260334x + 115612$ with a coefficient of determination (R^2) value of 0.9971. The R^2 value approaching 1 indicates that there is a very good linear relationship between the concentration of MDMA and the signal area produced by the instrument. In accordance with the validation criteria of the analytical method, the R^2 value ≥ 0.99 indicates that the method has adequate linearity and can be used for accurate quantification of MDMA within the tested concentration range. Therefore, the GC-MS method validated in this study meets the requirements of good linearity.

Table 5. Linearity data

Concentration (X)	Absorbance (Y)
10	2696899.11
1451909.04	94.563
1	445569.52
0.5	204969.77
0.2	201267.95
0.1	66657.31

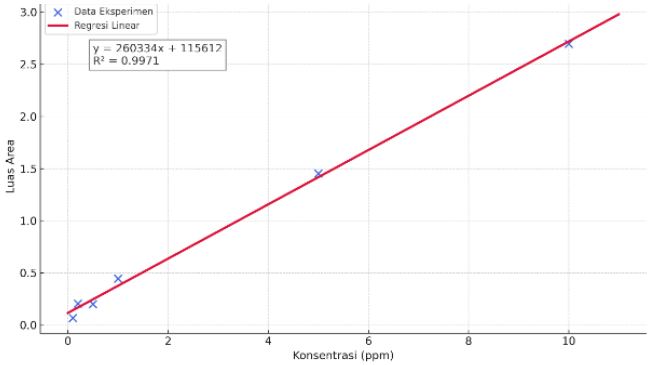

Figure 3. Concentration vs Area Calibration Curve Plot

Limit of Detection (LoD) and Limit of Qualification (LoQ) Test

The Limit of Detection (LOD) and Limit of Quantification (LOQ) tests aim to determine the minimum sensitivity of the method in detecting and quantifying MDMA compounds. Based on the calculations shown in Table 6, the residual standard deviation (SD) value is 61134.35. By using the slope of the calibration curve (slope) of 260334, the LOD and LOQ values are obtained at 0.70 ppm and 2.35 ppm, respectively. The LOD value indicates the lowest limit of MDMA concentration that can still be detected by this method, while the LOQ indicates the lowest limit that can be quantified with an acceptable level of accuracy and precision. These results indicate that the GC-MS method used is quite sensitive in detecting the presence of MDMA in low concentrations, making it suitable for forensic applications and monitoring of illicit substances in biological samples such as urine [1],[12].

Table 6. LOD and LOQ values

Concentration(X)	**Absorbance(Y)**	**y'**	**y- y'**	**(y-y)^2**
10	2696899.11	2718946.85	-22047.74	486102839.11
5	1451909.04	1417279.20	34629.84	1199225818.43
1	445569.52	375945.08	69624.44	4847562645.31
0.5	204969.77	245778.32	-40808.55	1665337345.02
0.2	201267.95	167678.26	33589.69	1128267543.01
0.1	66657.31	141644.90	-74987.59	5623139103.93
		Amount		14949635294.81
		Amount (y-y')^2/n-2		3737408824
		SD= SQRT x (y-y')^2/n-2		61134.35
		LOD= 3xSD/b		0.70
		LOQ = 10xSD/b		2.35

Selectivity/Specificity

The selectivity/specificity test aims to ensure that the GC-MS method is able to distinguish MDMA peaks from other compounds that may be present in the sample. The test was carried out by injecting blank solvent, MDMA standard solution, and Carisoprodol reference compound into the instrument. The results shown in Table 7 indicate that the MDMA peak appears at a retention time (Rt) of 6.299 minutes with a peak width (W) of 0.137 minutes, while Carisoprodol appears at Rt 8.860 minutes with a W of 0.134 minutes. The resolution value (Rs) obtained was 19.83, far above the minimum limit of Rs ≥ 10 which generally indicates very good separation. This confirms that the method used has high selectivity and is able to separate MDMA from other compounds without interference, making it valid for the analysis of this substance in complex matrices such as urine [2],[8].

Table 7. Selectivity/specificity data

Sample	**Results (ppm)**		***Carisoprodol***	
	Rt (minutes)	W (minutes)	Rt (minutes)	W (minutes)
Mean	6.299	0.137	8.86	0.134

3. Conclusion

The MDMA analysis using the Chemical Spot Test yielded a dark purple color and an Rf value of 0.555 from TLC. The urine sample tested positive for MDMA with an Rf value of 0.555. The method validation results showed that the accuracy, precision, linearity, detection limit, quantification limit, and selectivity were 97.53%, 3.66%, $R^2 \geq 0.99$, LOD 0.7 ppm, LOQ 2.35 ppm, and Rs 19.83, respectively. Therefore, this validated method is highly reliable and effective for sample analysis, with performance that meets the required standards.

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5. Conflict of Interest

The author declares no conflict of interest

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