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Research Article

Detection of 3-4 Methylenedioxyamphetamine from Drug Abuser's Fingers and Toenails using Liquid Chromatography with Mass Spectroscopy

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ABSTRACT

Nails can stably accumulate substances for extended periods of time, thus providing retrospective information regarding drug abuse and pharmaceutical use. In recent years, drug analysis in human nail clippings has proven its significant value in forensic toxicological applications, identification of in utero drug exposure, monitoring of drug treatment programmes, and therapeutic drug monitoring. Nails have various advantages over conventional matrices (blood and urine), which include a longer detection window (months to years), non-invasive sample collection, and easy storage and transportation. These aspects make nails a very significant matrix for forensic toxicology and therapeutic drug monitoring. Because of the low concentrations of drugs of abuse and pharmaceuticals present in nails and the complexity of the keratinized matrix, analytical techniques need to be more sensitive, and sample preparation is crucial. The aim of the present study is to develop a simple, high-performance liquid chromatography-mass spectroscopy (LC-MS) method for the identification and quantitation of 3,4-methylenedioxyamphetamine (MDA) in fingernail and toenail clippings. Finger and toenail clippings were collected from six users undergoing treatment at a rehab center in Ujjain, M.P., India. Nail clippings were initially decontaminated, then hydrolyzed in 1 M NaOH at 370°C, extracted with ethyl acetate, diluted with methanol, and then subjected to LC-MS analysis. The calibration curve was constructed over the 0.5 to 30 ng/mL concentration range using the MDA reference standard. The limit of detection was calculated at 1.10 ng/mL and the limit of quantification was recorded at 3.67 ng/mL in standard solutions, whereas the respective values in spiked nail clippings were 1.21 and 4.6 ng/mg. The developed method has obtained significant results in original nail clippings with mean concentration ranges of 0.12 ng/mg in fingernails and 0.08 ng/mg in toenails in six abuser samples. The new method developed has been found to be capable of detecting the 3,4-methylenedioxyamphetamine MDA drug in nail clippings even after 90 days of drug intake.

INTRODUCTION

MDMA, also known as 3,4-methylenedioxymethamphetamine, is one of the drugs that is abused the most around the world. It is also known as ecstasy or molly. This synthetic substance was first synthesized in 1912 as a precursor to the production of hemostatic agents. Its origins can be traced back to the year of its conception. Ecstasy is the popular or "street" name for a drug that is chemically known as N-methyl-3,4-

methylenedioxyamphetamine or 3,4-methylenedioxy-methamphetamine MDMA. [1-3] According to Mass *et al.* [4] and Verebey *et al.* [5] MDMA is easily absorbed from the digestive tract and reaches its peak plasma concentration about 2 hours after oral consumption. The primary metabolites of MDMA are 3,4-methylenedioxyamphetamine (MDA), 4-hydroxy-3-methamphetamine (HMMA), and 4-hydroxy-3 methoxyamphetamine (HMA), with the metabolic intermediates 3,4-dihydroxyamphetamine

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HHMA and 3,4-dihydroxymethamphetamine (HHMA) and hypomethylating agents HMA.^[5-9] structure of MDA shown in Fig. 1. and Metabolism of MDMA into MDA and HHMA and HMA shown in Fig. 2. The National Crime Record Bureau (NCRB, India) reports a rise in the number of crimes that have been facilitated by illicit drug use in recent years. A significant number of cases, including those involving methamphetamine, have been registered under the NDPS Act.^[10] Such cases are occasionally referred to forensic science laboratories to determine whether abused MDMA was found in the body.^[11-15] To tackle this issue, forensic laboratories use biological matrices such as blood, urine, and saliva, which have a shorter detection period. Therefore, unusual, keratinized matrices, such as nail samples, could be evaluated for monitoring illicit drug use. Apart from this, nail analysis can also be useful in various pharmacokinetics studies, such as cases of alcohol and drug use during pregnancy, which can lead to miscarriage, premature birth, increased mortality, congenital abnormalities, and retarded physical and mental development.^[16,17] Newborn nails are formed during the second trimester of pregnancy,^[18] grow continuously, and persist after birth, thus providing an opportunity to assess in utero drug exposure. Research in 58 newborns indicated the significance of neonatal nails for detecting in-utero drug exposure to cocaine, opioids, caffeine, nicotine, and cotinine.^[19] Another application of drug analysis in nails consists of the possibility of detecting the presence of an antimycotic at the site of action during antifungal therapy for patients with onychomycosis. In previous research, patients with fungal infections of the nail have traditionally been treated with orally administered griseofulvin and ketoconazole following the failure of topical administrations.^[20] With the advancement of research and to improve the efficacy of onychomycosis treatment, these antifungal agents are delivered into the nail through the nail matrix, with slow incorporation into the newly formed nail.^[21,22] Abuse of alcohol and other drugs has detrimental effects on both individuals and society. Nail analysis can be helpful for patient monitoring in drug addiction treatment settings. It could also be used to formally identify patients who relapse during treatment and might require additional treatment. Monitoring methadone maintenance programmes is one instance. In patients following such a programme, nail analysis proved to be useful for assessing compliance with the treatment scheme.^[23] However, there is currently no evidence supporting the use of nails in treatment programmes to track abstinence from alcohol and/or drugs. Indeed, nail has a wider detection window, non-invasive sample collection, and minimum transportation.^[24,25] The present study focuses on the analysis of 3-4 methylenedioxyamphetamine detection from fingers and toenails after three months of drug consumption by using the liquid chromatography-mass spectroscopy (LC-MS)

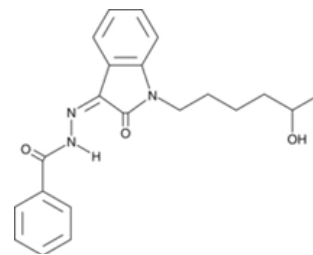


Fig. 1: 3,4-methylenedioxyamphetamine (MDA)

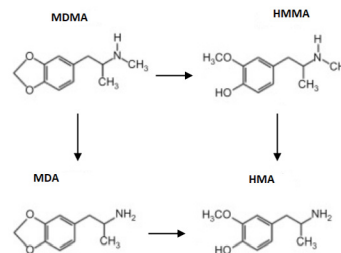


Fig. 2: Metabolism of MDMA into MDA and HHMA and HMA^[8]

method. Thus, the samples may be useful for both for forensic and pharmaceutical studies.

MATERIAL AND METHODS

Specimens

Finger and toenail clippings were collected from six subjects from a rehabilitation center in Ujjain (Parivartan Nasha Mukti Kendra) after 90 days of their admission to the rehab center. Nail samples were collected from all five fingers and toes to overcome ambiguity in the concentration of MDA in nails due to variable nail growth rates and other factors. The healthy volunteers kindly provided blank nail samples for spiking and recovery studies.

Inclusion Criteria

- Only those subjects were considered who had been admitted to the rehabilitation center within three months of the date of sample collection.
- Only those subjects were considered who had taken drugs within a period of three months prior to admission.
- Healthy subjects aged between 18 and 40 years were considered for this study.

Exclusion Criteria

- Subjects admitted to the rehabilitation center before and after the date of sample collection were not considered for the study.
- Subjects who had not taken drugs within a period of three months prior to admission were not considered for the study.
- Subjects showing any psychotic disorder or any other physical illness were excluded from this study.

- Subjects who had undergone any kind of cosmetic nail treatment were excluded from the study.

Chemicals and Reagents

Each of the chemicals that were used in this investigation was of LC-MS grade. Standard reference solution of MDA was obtained from Sigma Aldrich through S.K. Trader, Indore, and analytical grade chemicals: sodium hydroxide, ethyl acetate, acetonitrile, and methanol were procured from S.K. Trader in the city of Indore, M.P., India.

LC-MS Procedure

The Agilent Q-TOF G6550B connected to the Agilent 1260 Infinity II LC system was used for the analysis of analytes. The column dimension was the Agilent Poroshell 120 HPH-C18, 100 × 4.6 mm, 2.7 microns. The column temperature was maintained at 250°C. As Micheal SY *et al.* suggested, 20 mM ammonium bicarbonate in water and methanol in gradient chromatographic conditions (Table 1) were used for the detection.^[26] The mobile phase flow rate was maintained at 0.2 mL/minute with a total run time of 20 minutes. The detection was carried out using electrospray ionization operated in the positive ionization mode. The mass spectral parameters are optimized to obtain the best results, as mentioned in Table 2.

Sample cleanup and extraction

Finger and toenail clipping analysis includes the following steps: Sample decontamination, digestion, or extraction of the nail samples, and finally, the quantification of various analytes of the MDA drug.

Table 1: Chromatographic gradient conditions

Time (min)	%Mobile phase A	%Mobile phase B
0	80	20
2	80	20
9	50	50
15	0	100
16	0	100
16.5	80	20
18	80	20

Table 2: Ion source parameters

Parameter	Range
Nebulizer gas temperature	290°C
Sheath gas temperature	350°C
Drying gas	121/min
Nebulizer gas	35 psi
Sheath gas flow	111/min
Capillary voltage	3500 V
Nozzle voltage	1000 V

Step 1 : sample decontamination

Every finger and toenail clippings were first weighed and then washed with 1-mL of dichloromethane for 15 minutes three times at 37°C and then the layer was discarded, again washed with water, and subsequently with methanol for 15 minutes on an ultrasonicator to remove contamination. Samples were then air-dried overnight.

Step 2: Sample digestion or extraction

Finger and toenail clippings were then incubated with 1-mL of 1M sodium hydroxide solution at 90°C and extracted with 5 mL of ethyl acetate. The organic layer was dried and reconstituted with 1-mL of methanol.

Step 3: Quantification of the analyte

Quantification of various analytes was performed with a LC-MS (Agilent Q-TOF G6550B connected to an Agilent 1260 Infinity II LC) using a developed method.

Preparation of standards

A stock standard solution of MDA was prepared in methanol at a concentration range of 100 ng/mL and stored at -180°C. Under this condition, it was found to be stable for six months. The stock standard solution was used to prepare six working standards.

To find the optimum protocol for sample preparation and maximum recovery, nail samples were spiked with 200 µL of a standard solution of MDA and incubated overnight at room temperature until they were completely dry. As mentioned below, the analysis protocol was followed for the finger and toenail samples under analysis. Then the residue was reconstituted to volume with 200 µL of methanol and injected into the LC-MS system. The protocol was optimised in terms of solvents, temperature, and sonication time.

Method Validation

The method was validated in terms of linearity, precision, accuracy, selectivity, and sensitivity. A standard calibration curve was obtained by preparing 50 mg of authentic spiked blank nail clipping containing 0.5, 0.8, 1, 10, 12, 20, and 30 ng/mL of MDA, followed by extraction and LC-MS analysis. Linearity studies were performed by triplicate analysis covering the entire working range, and the least squares linear regression coefficient was used to calculate the slope, intercept, and coefficient determination. The limits of detection and quantification were calculated by the 3.3 and the 10 S/N ratios, respectively.

Selectivity was examined by analyzing blank samples and was assessed by the absence or presence of a peak at the retention time of the MDA drug.

RESULTS

Under the chromatographic conditions applied for standard MDA at 20 ng/mg, the extracted nail samples of one subject.



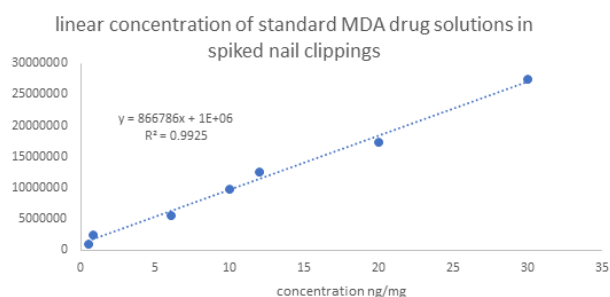


Fig. 3: Linear concentration of standard MDA drug solutions in spiked nail clippings

Linearity and sensitivity data are summarised in Table 3. The limits of detection and quantification were found to be 1.21 and 4.6 ng/mg for spiked nail clippings, whereas the respective values in the standard solution were 1.10 and 3.67 ng/mL.

The accuracy (assessed by the relative recovery percentage) was evaluated by the determination of MDA in nail clippings spiked at three concentration levels, such as 8, 20, and 40 ng/mg (Fig. 3). Repeatability was evaluated by analyzing samples spiked with MDA at three concentration levels in five replicates. Intermediate precision was assessed by the between-day study over a period of three days. The relative recovery rate was in the range of 95–105% with RSD values less than 15%. Accuracy and precision data are mentioned in Table 4.

Selectivity was assessed by the absence and presence of interference from the sample matrix in the same chromatographic condition. No interference was observed from the nail matrix.

A typical chromatogram of MDA in nail clippings spiked with a concentration of 10 ng/mg and an extracted nail sample of a drug addict is shown in Fig 4.

DISCUSSION

This study presented a fully validated method for the detection of MDA in human fingernail and toenail clippings.

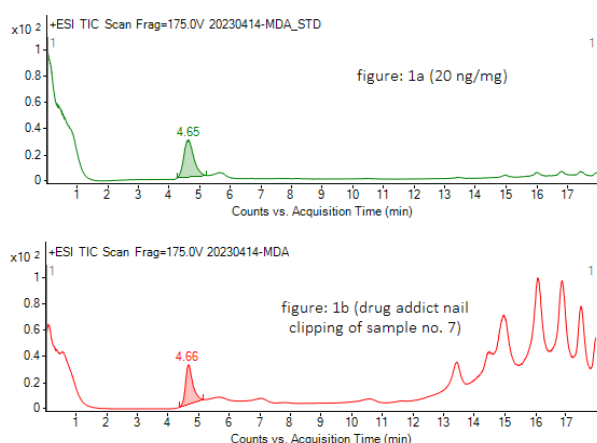


Fig. 4: Chromatograms of MDA obtained with (1a) a nail spiked with 20 ng/mg and (1b) an extracted nail sample of addict no. 7.

Table 3: Sensitivity and linearity data of the developed method

Matrix	Linear regression	R^2	LoD	LoQ
Standard solution (ng/mL)	$y = 827470x_1$	0.993	1.10	3.67
Nail clippings (ng/mg)	$y = 866786x_2$	0.992	1.21	4.6

X_1 = Concentration of MDA in standard solution

X_2 = Concentration of MDA in spiked nail samples (in ng/mg)

Table 4: Accuracy and precision data of the developed method (within day)

Matrix	Added (ng/mg)	Within day (n=5)		
		found $\pm$ SD (ng/mg)	RSD	Recovery (%)
Nail Clippings	8	7.8 $\pm$ 0.4	5.01	98.8
	20	20.5 $\pm$ 0.4	1.9	103.0
	40	40.3 $\pm$ 0.6	1.6	101.0

Table 5: MRM transitions of MDA analytes

Analyte	(Q1) m/z	(Q2) m/z	(Q3) m/z
MDA	180	135	163.1

In this study, we also investigated whether human fingernail and toenail clippings could be detected after 90 days of drug consumption in drug monitoring cases. The validated method was utilized to compare the detection of MDA in fingernail and toenail clippings by collecting and analyzing six samples of real drug consumers. This study found that MDA concentrations were significantly higher in fingernail clippings compared to toenail clipping specimens. The mean concentration of MDA in fingernail clippings and toenail clippings was 0.12 and 0.08 ng/mg, respectively. Our findings for the concentrations of MDA in fingernail and toenail clippings are consistent with those of previously published studies.^[27-36]

The first reported instance of nails being utilized for the purpose of detecting illicit drug abuse was in 1984 with the detection of methamphetamine and amphetamine in the nails of methamphetamine users^[27] and it was concluded that these drugs can be detected in fingernails for up to 3 to 5 months and for toenails for up to 15 to 20 months, but the author didn't show any data related to MDA drugs. In their work, samples were randomly donated by the police department. This was followed three years later by a second report detecting methamphetamine, amphetamine, and their metabolites in nails for up to 45 days.^[28] Subsequently, Cirimele *et al.*^[29] research was the first to detect amphetamine, MDA, and MDMA in one fingernail sample, but no time duration was reported. However, David L. Lin, *et al.*^[30] reported the detection window of amphetamine and methamphetamine in fingernail clipping for up to 12 weeks or 3 months in 6 subjects. After that, there were three consecutive studies by Kim *et al.*^[31-33] where the growth rate was associated with the drug detection time duration for both fingernail

Table 6: Details of individuals (MDA Addicts) from Rehabilitation Centre and quantity of MDA detected in fingernails (FN)

S. No.	Samples code and number	Age	Daily Dose (g)	Duration of Addiction (yrs.)	Presence of MDA after 90 days (ng/mg)
1	FN-1P	24	1	5	0.23
2	FN-2P	35	2	15	0.12
3	FN-3P	44	5	20	0.18
4	FN-7P	19	2	4	0.04
5	FN-12P	21	3	6	0.09
6	FN-15P	39	5	10	0.06
Mean concentration					0.12

FN denotes fingernail, and P denotes Parivartan Rehab Centre in Ujjain

Table 7: Details of individuals (MDA addicts) from Rehabilitation Centre and quantity of MDA detected in toenails (TN)

S. No.	Samples code and number	Age	Daily Dose (g)	Duration of Addiction (years)	Presence of MDA after 90 days (ng/mg)
1	TN1P	24	1	5	0.09
2	TN-2P	35	2	15	0.18
3	TN-3P	44	5	20	0.07
4	TN-7P	19	2	4	0.07
5	TN-12P	21	3	6	0.01
6	TN-15P	39	5	10	0.06
Mean concentration					0.08

TN denotes toenail and P denote Parivartan Rehab Centre, Ujjain

Table 8: Previous studies and their concentration values

S. No.	Drug	Concentration (ng/mg nail)	Matrices	Method used	Reference
1.	AP, MA, MDA and MDMA	MA - 0.32 to 17.7 ng/mg (mean 4.75 ng/mg) in FN, 0.06 to 9.93 ng/mg in TN, AP -0.03 to 0.40 ng/mg (mean 0.14 ng/mg) in FN, 0.03 to 1.60 ng/mg in TN	Finger and toenail clippings	GC-MS	O. Suzuki <i>et al.</i> (1984) ^[27]
2.	MA and AP	MA - 0.4 to 642 ng/mg in nails AP - 0.3 to 23.2 ng/mg in nails	Fingernail clippings	Mass fragmentography	S. Suzuki <i>et al.</i> (1989) ^[28]
3.	AP, MDA, MDMA	9.7 ng/mg of MDA and 60.2 ng/mg of MDMA	Fingernails scraping	GC-MS	Cirimele <i>et al.</i> (1995) ^[29]
4.	MA, AP	MA -0.46 to 61.50 ng/mg and for AP 0.20 to 5.42 ng/mg	Fingernail clippings	GC-MS	Lin DL <i>et al.</i> (2004) ^[30]
5.	AP, MA, MDA, MDMA, Delta9-THC, THCCOOH	MA, AP, and THCCOOH were 0.10 to 1.41, 0.12 to 2.64, and 0.20 ng/mg	Fingernail clippings	GC-MS	Kim JY <i>et al.</i> (2008) ^[31]
6.	MDA	>0.094 ng/mg LoD and 0.314 ng/mg LoQ	Fingernail Clipping	GC-MS	Kim <i>et al.</i> (2010) ^[32]
7.	AP, MA, MDA, MDMA and NK	>0.024 to 0.08 ng/mg for each analyte	Toenails	GC-MS	Kim JY <i>et al.</i> (2012) ^[33]
8.	AP and MDA	40 to 572,865 pg/mg	Fingernails and toenails	LC-MS/MS	Irene shu <i>et al.</i> (2015) ^[34]
9.	MDA	4.4 to 108 pg/mg for R- and S-MDA	Nail Clippings and Nail Scrapping	LC-MS	Madry <i>et al.</i> (2016) ^[35]
10.	MDA and MDMA	0.110 to 0.365 ng/mg in 8-11 mm nail segments for MDA 1.41 and 3.81 ng/mg in 0-8 mm nail segments for MDMA	Nail clippings	UPLC-MS/MS	Krumbiegel F <i>et al.</i> (2016) ^[36]

AP = amphetamine; MA = methamphetamine; MDA = 3,4-methylenedioxyamphetamine; MDMA = 3,4-methylenedioxymethamphetamine; THC = Δ^9 -tetrahydrocannabinol; THCCOOH = 11-nor- Δ^9 -tetrahydrocannabinol-9-carboxylic acid; NK= norketamine; FN- fingernail; TN- toenail.



and toenail clippings. From 1984 to 2010, only GC-MS was the preferred method for the detection of various amphetamine types of drugs. Very few studies used LC-MS analysis for detecting drug abuse.^[34-36]

In the present study, six samples of MDA abusers were examined, and results indicated the presence of MDA and concentration ranges of 0.105 ng/mg in fingernails and 0.08 ng/mg in toenails after 90 days of drug consumption. Samples were not tested for MDMA compounds and further metabolites such as HMMA and HMA in this study. Because the drug abusers have a history of MDA drug consumption instead of MDMA. Table 8 indicates the concentration of the detected drugs by previous workers and by the present authors. The developed analytical method for the estimation of MDA from nails using LC-MS is found to be sensitive, rapid, and precise. From a forensic perspective, the analytical methodology will be helpful for forensic toxicologists as well as the various law-enforcing agencies, to a great extent, in supporting the criminal justice system by adopting the same method in routine casework related to the same analyte. Nail clippings are an alternative biological matrix for analysis and have been proven to be useful tools to identify the analyte when conventional matrices such as blood and urine are unable to establish the presence of drugs. The developed method was found to be capable of detecting the MDA drug in nail clippings even after 90 days of drug consumption.

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ETHICAL APPROVAL

Necessary ethical approval was obtained from the Shri Vaishnav Vidyapeeth Ethics Committee with the reference code: FDSR/2023/312 and written consent was also obtained from the participants admitted in rehabilitation centre.

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