# II.2.7 3,4-Methylenedioxyamphetamines

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## Introduction

3,4-Methylenedioxyamphetamines (MDAs), which were described as a new drug class "entactogens" [a] by Nichols [1], are being abused to enhance mutual understanding, communicativeness and empathy together with their hallucinogenic effects [1–3]. They are known as a group of designer drugs, and include 3,4-methylenedioxyamphetamine(MDA), 3,4-methylenedioxymethamphetamine(MDMA), 3,4-methylenedioxyethylamphetamine (MDEA) and *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine(MBDB) (*Fig. 7.1*). Of the MDAs, MDA, MDMA and MDEA are strictly controlled by laws [b].

These drugs are being usually sold in tablet forms in black markets. The tablets are often imprinted with various kinds of graphic designs and commercial logos, including the 3-diamond ("Mitsubishi" mark), birds, animals and other characters on their faces. Some GC/MS and LC/MS studies have revealed that they contain various amounts of MDAs (in most cases ranging from 50 to 150 mg per tablet) as the primary ingredient, sometimes smaller amounts of amphetamines and/or other pharmaceutical agents, such as caffeine and ketamine [4, 5].

**Figure 7.1**

$NH_2$, $CH_3$
3,4-methylenedioxyamphetamine (MDA)

$NHCH_3$, $CH_3$
3,4-methylenedioxymethamphetamine (MDMA)

$NHC_2H_5$, $CH_3$
3,4-methylenedioxyethylamphetamine (MDEA)

$NHCH_3$, $C_2H_5$
N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine (MBDB)

$CH_3$, $NHCH_3$
N-methyl-1-(3,4-methylenedioxyphenyl)-3-butanamine (HMDMA)

**Structures of MDA and its analogues.**

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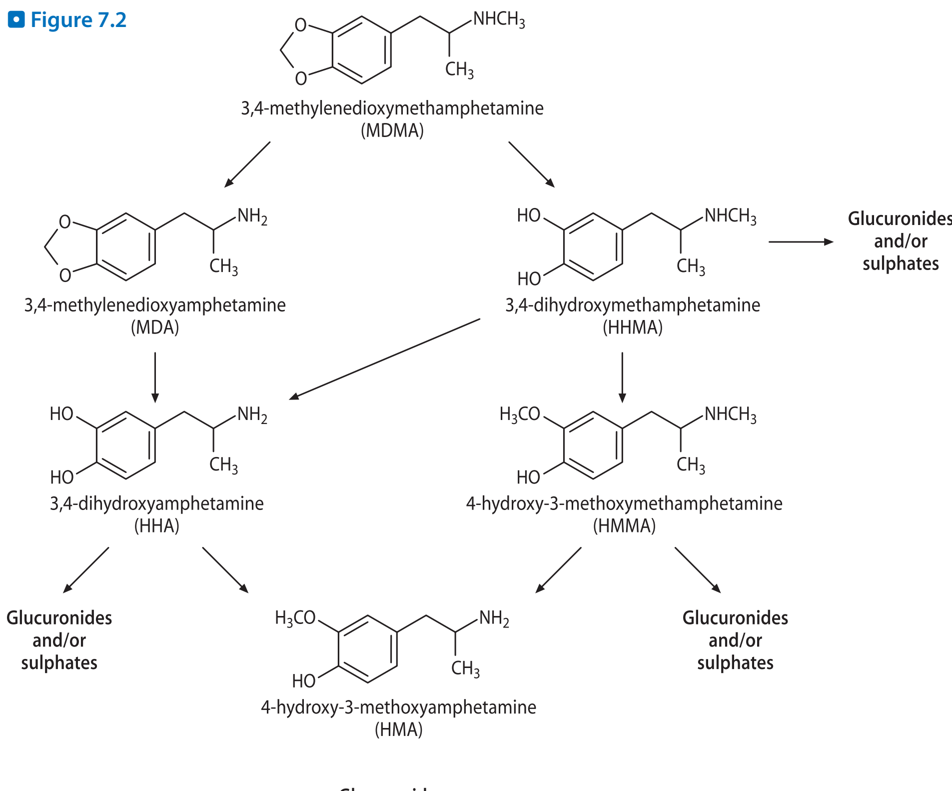
**Figure 7.2**




**Metabolic pathways for MDMA and MDA.**

MDMA, which is well known by the street name of "Ecstasy", is now the most popular recreational drug in the world. It emerged in Europe in the 1980s and has generally been being used at all night techno dance parties (Raves). It is also becoming more popular in the United States and even in Japan.

Several studies have shown that MDMA is metabolized mainly by demethylenation, *O*-methylation, *N*-demethylation and conjugation as shown in *Fig. 7.2* [6–10]. For the proof of MDMA use, detection of MDMA and its metabolite MDA is being generally performed for urine specimens.

In this chapter, the procedures for GC/MS and LC/MS analyses of MDAs in the forms of tablets and those for GC/MS analysis of MDAs and their main metabolites 4-hydroxy-3-methoxymethamphetamine (HMMA) and 4-hydroxy-3-methoxyamphetamine (HMA) in urine specimens are presented.

## Reagents and their preparation

- MDA, MDMA and MDEA can be purchased from Sigma (St. Louis, MO, USA) with appropriate legal procedures. They can be also synthesized by reductive amination of piperonyl methyl ketone (Tokyo Kasei Kogyo Co., Ltd., Tokyo, Japan) using ammonium acetate or appropriate amines (Sigma and other manufacturers) and sodium cyanoborohydride (Aldrich, Milwaukee, WI, USA); every synthesized standard compound is purified as their hydrochloride. The standard stock solutions are prepared in distilled water (1 mg/mL), and diluted to appropriate concentrations with drug-free urine.
- Acetonitrile is of HPLC grade, and other chemicals used are of analytical grade.
- Samprep-LCR unit, a 0.2 µm plastic membrane filter, is purchased from Millipore (Bedford, MA, USA).
- HMMA is synthesized by the reaction of methylamine hydrochloride and sodium cyanoborohydride with 4-hydroxy-3-methoxyphenylacetone (Aldrich) [11]. HMA is synthesized by the reduction of 4-hydroxy-3-methoxyphenyl- 2-nitropropene, which has been prepared by reaction of 4-hydroxy-3-methoxybenzaldehyde (Aldrich) with nitroethane (Aldrich) [11]. Every synthesized standard was purified as each hydrochloride. The standard stock solutions are prepared with distilled water (1 mg/mL), and diluted to appropriate concentrations with drug-free urine.
- Diphenylmethane (DPM, obtainable from many manufacturers) solution is prepared by dissolving 1 mg DPM in 100 mL ethyl acetate, and used as internal standard (IS) solution for quantitation.
- Carbonate buffer solution (pH 10) is prepared by dissolving 2.1 g of $NaHCO_3$ and 7.9 g of anhydrous $Na_2CO_3$ in 100 mL distilled water.
- β-Glucuronidase (from *E. coli*, type IX-A) used for hydrolysis is purchased from Sigma.
- Bond Elut SCX (100 mg) cation-exchange cartridges used for solid-phase extraction are purchased from Varian (Harbor City, CA, USA).

## Instrumental conditions

### a) GC/MS

Instrument: Shimadzu GCMS-QP2010 (Shimadzu, Kyoto, Japan); columns: DB-1 and DB-17 MS fused-silica medium-bore capillary columns (both 30 m × 0.32 mm i. d., film thickness 0.25 µm, J&W Scientific, Folsom, CA, USA); injection mode: splitless; injection temperature: 250 °C; column temperature: 70 °C (1 min)→15 °C/min→300 °C (5 min); temperatures of the interface and the ion source: 250 and 200 °C, respectively; carrier gas: He; its flow rate: 3 mL/min; EI electron energy: 70 eV; multiplier gain, 1.2; scan range: *m/z* 40–400; scan rate: 0.5 s/scan.

### b) LC/MS

Instrument: Shimadzu LCMS-QP2010; column: CAPCELL PAK SCX (150 × 1.5 mm i. d., Shiseido, Tokyo, Japan)[c]; mobile phase: acetonitrile/10 mM ammonium acetate (70:30, v/v, pH 5.5); flow rate: 150 µL/min; interface: electrospray ionization (ESI); capillary voltage:

+ 3.5 kV; probe voltage: 2.5 kV; CDL voltage: –20 V; CDL temperature: 230 °C; deflector voltage: 40 V; multiplier voltage: 650 V; quantitative analysis: by the absolute calibration curve method employing the protonated molecule of each analyte in the selected ion monitoring (SIM) mode[d].

## Procedures

### a) Tablet specimens

#### i. For GC/MS analysis

i. A sample tablet is ground into fine powder. A 10-mg aliquot of it is dissolved in 10 mL of distilled water.
ii. The solution is extracted with 20 mL of ethyl acetate under ammonia-alkaline conditions (pH 9).
iii. The organic layer is dried with anhydrous sodium sulfate, and evaporated to dryness under a stream of nitrogen after adding 10 μL of 2.5 M HCl solution.
iv. To the residue is added 0.2 mL of trifluoroacetic anhydride and 0.2 mL of ethyl acetate, and the mixture is heated at 60 °C for 30 min[e].
v. The reaction mixture is evaporated to dryness under a gentle stream of nitrogen and reconstituted in 100 μL of DPM (IS) solution. A 1-μL aliquot of it is injected into GC/MS.

#### ii. For LC/MS analysis

i. A sample tablet is ground and dissolved in distilled water as described above.
ii. The aqueous solution is further diluted to appropriate concentrations with distilled water. The resulting sample aqueous solution is passed through a Samprep-LCR unit, a 0.2 μm plastic membrane filter[f].
iii. A 5-μL aliquot of the filtrate is injected into LC/MS.

### b) Urine specimens for MDAs and their metabolites

#### i. Hydrolysis

Enzymatic hydrolysis:
To 2 mL of urine is added 0.4 mL of 75 mM phosphate buffer (pH 6.8), containing 2000 Fishman units/mL urine of β-glucuronidase[g]. The mixture is incubated at 37 °C for 3 h. After centrifugation, the supernatant solution is subjected to the below extraction procedure.
Acid hydrolysis[h]:
To 2 mL of urine is added 0.5 mL of conc. HCl, and the mixture is heated at 100 °C for 1 h. After cooling to room temperature, the mixture is neutralized with solid $Na_2CO_3$. The solution is subjected to the below extraction procedure.

#### ii. Extraction

Liquid-liquid extraction:
i. The above hydrolyzed solution is mixed with 2 mL of carbonate buffer solution (pH 10)[i] and extracted with 5 mL of chloroform/isopropanol (3:1, v/v).

ii. After centrifugation, the organic layer is separated and dried with anhydrous sodium sulfate.
iii. It is transferred to a screw-capped Pyrex tube and evaporated to dryness under a stream of nitrogen after adding 10 µL of 2.5 M HCl solution. The residue is subjected to the below trifluoroacetyl (TFA)-derivatization.

Solid-phase extraction [6]:

i. A Bond Elut SCX cartridge is successively preconditioned with 2 mL of methanol, 1 mL of distilled water and 1 mL of 25 mM $KH_2PO_4$ solution.
ii. The hydrolyzed urine sample is mixed with 1 mL of 75 mM $KH_2PO_4$ solution and loaded on the preconditioned cartridge.
iii. The cartridge is washed with 1.5 mL of 25 mM $KH_2PO_4$ and then 1 mL of methanol.
iv. Target compounds are eluted with 2 mL of methanol/2.5 M HCl solution (97.5:2.5, v/v).
v. The eluate is transferred to a screw-capped Pyrex tube and evaporated to dryness under a stream of nitrogen. The residue is subjected to the below TFA-derivatization.

### iii. Derivatization

i. To the extract residue are added 0.2 mL of trifluoroacetic anhydride [j] (TFAA) and 0.2 mL of ethyl acetate, and the mixture is heated at 60 °C for 30 min.
ii. The reaction mixture is evaporated to dryness under a gentle stream of nitrogen and reconstituted in 0.1 mL of DPM (IS) solution. A 1-µL aliquot of it is injected into the GC/MS system with a DB-17MS system[k].

## Assessment of the methods

EI mass spectra of TFA derivatives[l] of MDA, MDMA and MDEA, obtained from clandestine tablets, are shown in *Fig. 7.3*. The MDAs produce EI mass spectra characterized by intense ions resulting from the α-cleavage of the amines and some less intense fragment ions.

Recently, MBDB and an MDMA homologue, *N*-methyl-1-(3,4-methylenedioxyphemyl)-3-butanamine (HMDMA) (*Fig. 7.1*), have appeared as components of clandestine drug samples even in Japan. MBDB and HMDMA are regioisomers of MDEA [9]; MBDB yields a very similar EI mass spectrum to that of MDEA. The discrimination of these isomers can be accomplished by proton nuclear magnetic resonance spectrometry, but it is useless for small amounts of the compounds in a tablet mixture. As an alternative technique for such isomer discrimination, TFA derivatization followed by GC/MS is applicable (*Fig. 7.3*).

The quantitative analysis data for MDAs in many kinds of clandestine tablets encountered in Japan are summarized in *Table 7.1* [4, 5]. For simple and rapid quantitation, the LC/MS technique without any derivatization would be more recommendable.

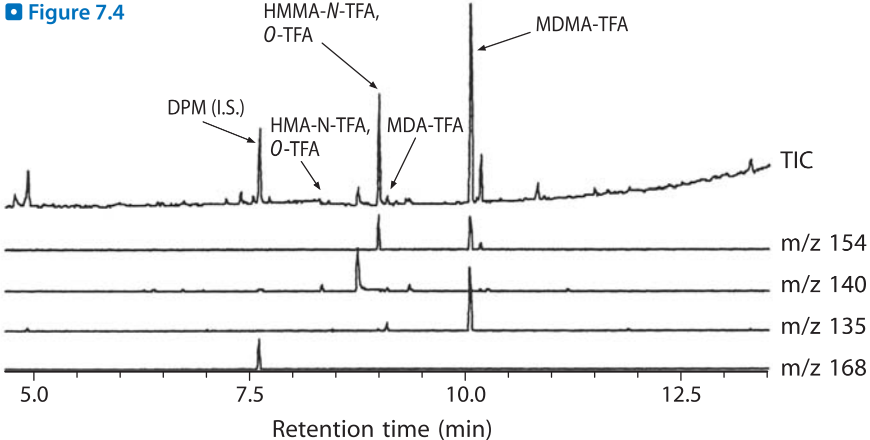
A total ion chromatogram and mass chromatograms obtained from an MDMA addict's urine by the GC/MS technique after the liquid-liquid extraction are shown in *Fig. 7.4*. Not only MDMA and its metabolite MDA, but also their metabolites with open methylenedioxy rings, HMMA and HMA, were detected in the urine sample (HHMA not monitored). The mass spectra of TFA derivatives of MDMA and its three metabolites obtained from the urine specimen are shown in *Fig. 7.5*.

For the proof of the use of MDMA, detection of MDA along with MDMA itself is being usually performed [12–14]. However, the main metabolic pathway of MDMA in humans is the

**Figure 7.3**

**Mass spectra of TFA derivatives of MDA, MDMA, MDEA, MBDB and HMDMA obtained by GC/MS.**

**Figure 7.4**




**Total ion chromatogram and mass chromatograms for TFA derivatives obtained from an MDMA addict's urine. Detailed GC/MS conditions are described in the text.**

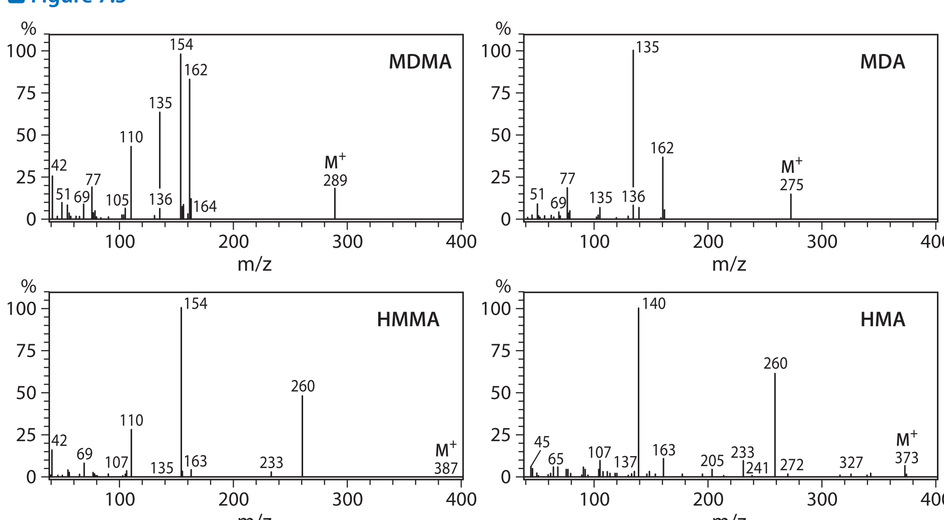
**Table 7.1**

**Clandestine MDMA or MDA tablets encountered in Osaka**

| Logo | Color | Diameter (mm) | Weight (mg) | Active ingredients (mg)* |
|---|---|---|---|---|
| Y2K | off white | 9.2 | 290 | MDMA 73, AP 4.4 |
| Y2K | light green, blue mottled | 9.2 | 230 | MDMA 87, MA 30 |
| RN | off-white | 8.4 | 250 | MDMA 83, AP 9.3 |
| RN | light green | 9.2 | 300 | MDMA 120 |
| JB | light blue and purple mottled | 8.4 | 290 | MDMA 62 |
| [smiling sun] | off-white | 9.3 | 290 | MDMA 160 |
| SKY | green mottled | 8.1 | 310 | MDMA 100 |
| ["KAPPA" logo] | light green | 9.3 | 320 | MDMA 81 |
| [pac man] | light yellow | 8.2 | 350 | MDMA 120, caffein |
| [fort] | yellow | 8.2 | 330 | MDMA 180, caffein |
| [none] | light brown mottled | 8.4 | 320 | MDMA 120 |
| [none] | off-white | 7.2 | 290 | MDMA 88 |
| [none] | red mottled | 6.9 | 140 | MDMA 64 |
| [none] | light green, blue, yellow mottled | 8.1 | 300 | MDMA 95, MA 25, ketamine |
| [none] | blue mottled | 8.4 | 330 | MDMA 110, MA 1.7, ketamine |
| ["Mitsubishi" logo] | off-white | 9.1 | 340 | MDMA 130 |
| ["Mitsubishi" logo] | off-white | 8.1 | 340 | MDMA 65 |
| ["Mitsubishi" logo] | off-white | 8.2 | 340 | MDMA 98 |
| ["Mitsubishi" logo] | red mottled | 9.1 | 300 | MDMA 160 |
| O | off-white | 8.2 | 270 | MDMA 93 |
| O | light green mottled | 8.2 | 270 | MDMA 90 |
| M3 | yellow | 8.1 | 310 | MDMA 130 |
| B | yellow | 7.1 | 200 | MDMA 140 |
| B | bluish purple | 7.3 | 160 | MDMA 52 |
| ["Channel" logo] | pink | 8.2 | 250 | MDMA 89, MA 1.0, AP 6.9, ketamine, caffeine |
| [Ying Yang] | off-white | 8.1 | 270 | MDMA 60 |
| [crown] | off-white | 8.2 | 270 | MDMA 98 |
| [sparrow] | off-white | 9.1 | 270 | MDMA 28, MDEA 49 |
| [monster face]/ ["Mitsubishi" logo] | off-white | 8.3 | 250 | MDA 86 |
| [diamond] | orange | 8.1 | 190 | MDA 110 |
| ["Mitsubishi" logo]/[lips] | light brown mottled | 8.2 | 250 | MDA 94 |
| ["Mitsubishi" logo] (both sides) | light brown mottled | 8.3 | 250 | MDA 100 |

* The values were calculated as the free base; MDMA=3,4-methylenedioxymethamphetamine; MDA=3,4-methylenedioxyamphetamine; MDEA=3,4-methylenedioxyethylamphetamine; MA=methamphetamine; AP=amphetamine.

**Figure 7.5**




**Mass spectra of TFA-derivatives of MDMA, MDA, HMMA and HMA extracted from an MDMA addict's urine. Detailed GC/MS conditions are described in the text.**

cleavage of the methylenedioxy bridge by *O*-dealkylation, followed by *O*-methylation and conjugation; HMMA is the major urinary metabolite of MDMA [6–9]. For more reliable and effective proof of the use of MDAs, their metabolites with the cleavage of methylenedioxy rings, such as HMMA, HMA and 4-hydroxy-3-methoxyethylamphetamine, are more useful than the unchanged drugs [m].

HMMA and HMA are excreted mainly as conjugates (glucuronides and/or sulfates) into urine [6, 7]; the hydrolysis of urine is, therefore, essential prior to extraction.

The confirmatory cutoff level for urinary MDAs recommended by the Substance Abuse and Mental Health Services Administration (SAMHSA) is 250 ng/mL.

## Symptoms, and toxic and fatal concentrations

MDMA causes increased catecholamine (including serotonin) release and blockade of reuptake resulting in cardiac and central nervous system effects [15]. The effects of MDMA vary depending on its doses, frequency and duration of use; not only acute effects but also chronic (long-term) effects have been studied [16]. Acute and chronic symptoms provoked by MDMA are summarized in *Table 7.2* [15]. The effects of chronic MDMA use have not been well studied, but appear to include both toxic hepatitis and damages of the serotoninergic neural pathways [17, 18]. The acute MDMA toxicities are similar to those noted with other amphetamines; they are tachycardia, hypertension, seizures, hyperthermia, rhabdomyolysis, acute renal failure, disseminated intravascular coagulation and death [19, 20]. A detailed review by Kalant [16] revealed that 87 MDAs-related fatalities were associated with hyperpyrexia, rhabdomyolysis, intravascular coagulopathy, hepatic necrosis, cardiac arrhythmias, cerebrovascular disorders, and drug-related accidents or suicides. The effects of other MDAs are similar to those of MDMA.

**Table 7.2**
**Acute and chronic effects of MDMA**

| Acute effect | Chronic effect |
|---|---|
| bruxism/trismus | memory impairment |
| nausea/vomiting | depression |
| irregular eye movements | sleep problems |
| tachydysrhythmias | anxiety |
| hypertension | paranoia |
| intracranial bleeding | liver disease |
| altered mental status | |
| altration in muscle tone/activity | |
| automatic instability | |
| hyperthermia | |
| diarrhea | |
| hyponatremia | |
| seizures | |
| rhabdomyolysis | |
| acute renal fairure | |
| disseminated intravascular coagulation | |
| death | |

The typical dose range of MDMA for "recreational" use varies from 50 to 150 mg, but its amount per tablet is different according to tablets [4, 5] as summarized in Table 7.1. MDMA is readily absorbed from the intestinal tract and reaches its peak concentration in plasma about 2 h after oral administration [21, 22]. The doses of 50, 75 and 125 mg in the usual "recreational" range for healthy human volunteers produced peak blood concentration of 106, 131 and 236 ng/mL, respectively. According to the review by Kalant [16], most of the cases with serious toxicity or fatality gave blood levels ranging from 0.5 to 10 µg/mL, which are up to 40 times higher than the usual recreational levels. However, some serious cases showed levels as low as 0.11–0.55 µg/mL, which overlap the "normal" range or a little above it. From such data, Kalant [16] mentioned that seriousness of its effects may be dependent also on environmental factors other than the blood drug concentrations.

## Notes

a) The created word "entactogen" is derived from the Greek and Latin origins; "en", "gen" and "tactus" mean "within", "produce" and "touch", respectively. Therefore, the word means "to produce a touching within" [1].
b) MDA, MDMA and MDEA are all classified as Schedule I drugs in the US, and as Class A drugs in the UK. However, MBDB is currently uncontrolled in both countries, as well as in Japan.
c) An ODS-type column is also applicable. However, the SCX column allows to use a much less polar mobile phase, leading to highly sensitive ESI-MS determination.
d) For the quantitation by LC/ESI-MS, no IS is required. In the SIM mode, the ions at $m/z$ 180, 194 and 208 should be selected for MDA, MDMA and MDEA, respectively.

e) For the TFA-derivatization, *N*-methylbis(trifluoroacetamide) (MBTFA) is also applicable as an on-column derivatization reagent [23, 24]; MBTFA is injected immediately after the sample injection. Upon applying to a high concentration of a sample, a part of the injected analytes, however, may be underivatized.
f) The filtration will avoid clogging and deterioration of the analytical column.
g) For the hydrolysis of conjugates, β-glucuronidases from several sources, such as *Helix pomatia*, *Escherichia coli* (*E. coli*), bovine liver and abalone entrails, are commercially available. The enzymatic activities greatly change depending on the properties of enzymes and substrates. Shima et al. [25] have shown that β-glucuronidase from *E. coli* is most preferable for the enzymatic hydrolysis of conjugates of the metabolites after cleavage of the methylenedioxy rings (HMMA and HMA).
h) The hydrolysis with hydrochloric acid is faster and more efficient than with β-glucuronidase [6, 23]. However, the hydrolysate with the acid, containing a large amount of $Na_2CO_3$, cannot be applied to the SCX cartridge directly.
i) A mixture at pH value higher than 10 gives lower recoveries of HMMA and HMA.
j) For derivatization, pentafluoropropionic anhydride (PFPA) and heptafluorobutylic anhydride (HFBA) are also applicable. However, for the TFA-derivatization of HMMA and HMA, on-column derivatization with MBTFA is not suitable.
k) The non-polar column, DB-1, does not give sufficient separation of MDA-TFA from HMMA-*N*,*O*-diTFA.
l) For the derivatization of MDAs, PFPA [10] and HFBA [6, 14] are also applicable.
m) In controlled experiments with six volunteers performed by Pizarro et al. [9], 44.7 % of the total dose was found to be eliminated into urine as MDMA (23.9 %), MDA (1.8 %), HMMA (17.1 %) and HMA (1.9 %) during the first 24 h after the administration of 100 mg MDMA.
n) Another study with 3 volunteers by Ensslin et al. [26] revealed that 19 % of the MDEA dose was eliminated into urine as an unchanged form, 31.6 % as 4-hydroxy-3-methoxyethylamphetamine and 2.8 % as MDA within 32 h after oral administration of 140 mg MDEA.

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