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Separating the wheat from the chaff: Observations on the analysis of lysergamides LSD, MIPLA, and LAMPA

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Abstract

Lysergic acid diethylamide (LSD) is a potent psychoactive substance that has attracted great interest in clinical research. As the pharmacological exploration of LSD analogs continues to grow, some of those analogs have appeared on the street market. Given that LSD analogs are uncontrolled in many jurisdictions, it is important that these analogs be differentiated from LSD. This report presents the analysis of blotters found to contain the *N*-methyl-*N*-isopropyl isomer of LSD (MIPLA), and techniques to differentiate it from LSD and the *N*-methyl-*N*-propyl isomer (LAMPA) under routine conditions. Gas chromatography (GC)-solid phase infrared spectroscopy was particularly helpful. GC-electron ionization-tandem mass spectrometry of the *m/z* 72 iminium ion also provided sufficient information to distinguish the three isomers on mass spectral grounds alone, where chromatographic separation proved challenging. Derivatization with 2,2,2-trifluoro-*N,N*-bis (trimethylsilyl)acetamide (BSTFA) also led to improved GC separation. Liquid chromatography single quadrupole mass spectrometry (LC-Q-MS) and in-source collision-induced dissociation allowed for the differentiation between MIPLA and LAMPA based on distinct *m/z* 239 ion ratios when co-eluting. An alternative LC-MS/MS method improved the separation between all three lysergamides, but LSD was found to co-elute with iso-LSD. However, a comparison of ion ratios recorded for transitions at *m/z* 324.2 > 223.2 and *m/z* 324.2 > 208.2 facilitated their differentiation. The analysis of two blotters by LC-Q-MS revealed the presence of 180 and 186 µg MIPLA per blotter. These procedures may be used to avoid inadvertent misidentification of MIPLA or LAMPA as LSD.

KEYWORDS

forensic chemistry, isomers, LSD, new psychoactive substances, psychedelics

1 | INTRODUCTION

Lysergic acid diethylamide (LSD) (Figure 1) is one of the prototypical serotonergic hallucinogens capable of inducing significant changes in cognition, mood, and perception.^{1–3} Within the recreational context, one of the most common dosage forms of LSD is the perforated paper square called blotter. Amounts of 20–100 µg per blotter are common though drug testing services in Europe have occasionally reported blotters containing 200 µg LSD or more.⁴

Because LSD is listed in the United Nations Convention on Psychotropic Substances of 1971 (Schedule 1), it is a controlled substance around the world. However, isomers of LSD—*N*-methyl-*N*-isopropyllysergamide (MIPLA) and *N*-methyl-*N*-propyllysergamide (LAMPA) (Figure 1)—are not controlled in all UN Member States. The syntheses of these two lysergamides were disclosed by Eli Lilly and Company in 1961⁵ with analytical data recorded from LAMPA beginning to emerge in the early 1970s.^{6,7} The first electron ionization (EI) mass spectra and chromatographic data obtained from MIPLA and the *n*-butyl, isobutyl, *sec*-butyl, and *tert*-butyl isomers were published in 1989.⁸

From a forensic perspective it is crucial to distinguish between a controlled substance and one that is not controlled. Thus, various analytical approaches have historically been applied to differentiate between LSD and LAMPA. This line of investigation may have arisen from attempts to use LAMPA as a “legal decoy against LSD prosecutions,”⁹ spurring implementations of many analytical methods.

These involved high-performance liquid chromatography (HPLC),^{8,10–17} gas chromatography (GC),^{8,14–16,18–25} infrared spectroscopy (IR) (with or without coupling to a separation device),^{7,11,15,21,24,26,27} nuclear magnetic resonance spectroscopy (NMR),^{6,13,15} and other methods of separation, such as thin-layer chromatography (TLC),^{7,8,18} and capillary electrophoresis.^{28–32} Furthermore, a variety of bioanalytical methods used for the detection of LSD included the use of LAMPA as an internal standard.^{33–44} Compared to LSD and LAMPA, analytical studies involving the investigation of MIPLA are scarce.^{8,45} Recently, the detection of MIPLA in blotters seized in Japan was reported which involved the use of GC-mass spectrometry (GC-MS), liquid chromatography (LC)-MS, and NMR analyses.⁴⁵

The present investigation was prompted by the analysis of a blotter thought to contain MIPLA, followed by GC-MS and LC-MS-based

approaches to differentiate between the three isomers LSD, MIPLA and LAMPA. In a forensic laboratory, high sample throughput and the implementation of routine methods of analysis are preferred. It was found that the combination of GC-solid phase IR and GC-EI tandem MS (MS/MS) proved sufficient to prevent a misidentification of either MIPLA or LAMPA as LSD. Further GC-MS analysis of the three lysergamides was conducted after derivatization with 2,2,2-trifluoro-*N*, *N*-bis (trimethylsilyl)acetamide (BSTFA). An LC-MS-based quantitative estimation of MIPLA extracted from blotters has also been included.

2 | EXPERIMENTAL

2.1 | Materials

Acetonitrile (LC-MS grade) was obtained from VWR International (Darmstadt, Germany); ammonium bicarbonate (LC-MS grade) and methanol (LC-MS grade) were from Sigma Aldrich (Steinheim, Germany) and isopropanol (Rotisolv[®], ≥ 99.95%, LC-MS grade) was purchased from Carl Roth (Karlsruhe, Germany). Deionized water was prepared using a Medica[®] Pro single high-flow purification system from ELGA LabWater (Celle, Germany). Ammonia (25%, p.a.) was obtained from Merck (Darmstadt, Germany). All remaining chemicals used were analytical or HPLC grade and were obtained from Rathburn Chemicals Ltd (Walkerburn, Scotland, UK), Fisher Scientific (Dublin, Ireland) or Aldrich (Dorset, UK). MIPLA and LAMPA base were provided by Lipomed AG (Arlesheim, Switzerland). LSD was available from previous work. Blotters alleged to contain MIPLA were obtained from an online retailer.

2.2 | Instrumentation

2.2.1 | GC-MS

GC-MS/MS method 1

For EI mass spectrometry (EI-MS and EI-MS/MS), a Finnigan TSQ 8000 Evo triple stage quadrupole mass spectrometer coupled to a gas chromatograph (Trace GC 1310, Thermo Electron, Dreieich, Germany) and for chemical ionization MS (CI-MS) a Finnigan TSQ 7000 triple stage quadrupole mass spectrometer coupled to a gas chromatograph (Trace GC Ultra, Thermo Electron, Dreieich, Germany) was used. A Triplus RSH (Thermo Scientific for TSQ 8000 Evo) and a CTC CombiPAL (CTC Analytics, Zwingen, Switzerland for TSQ 7000) auto-sampler was employed for sample introduction. Mass spectra were recorded at 70 eV EI energy. The ion source temperature was set at 175°C and the emission current was 50 µA (TSQ 8000 Evo) and 400 µA (TSQ 7000). For recording of EI-MS the scan time was 1 s spanning a scan range between *m/z* 29 and 600, and samples were injected in splitless mode. For CI, the reagent gas was methane and the source pressure was 1.5 mTorr (0.2 Pa). The scan time was 0.5 s and the scan range was *m/z* 50–600. Samples were injected in splitless mode.

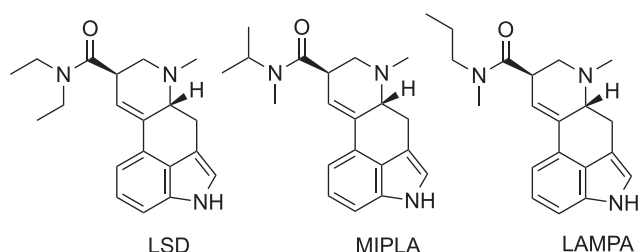


FIGURE 1 Chemical structures of three isomeric lysergamides: LSD, MIPLA, and LAMPA

In the EI-MS/MS product ion mode, under the same conditions described above, the scan range started at m/z 10 and ended about 10 mass units above the ion under examination. The collision gas was argon. The collision energy was approximately 20 eV, and the collision gas pressure was approximately 1.5 mTorr (0.2 Pa). The exact target thickness was set using *n*-butylbenzene in EI-MS mode and adjusting intensity ratios m/z 92/91 to 0.2 and m/z 65/91 to 0.02 by variation of collision energy and collision gas pressure. This method ensured reproducibility of the product ion mass spectra and the use of a product ion mass spectra library for the identification of the structures of the product ions.^{46,47}

Separation was achieved using a fused silica capillary DB-1 column (30 m \times 0.25 mm, film thickness 0.25 μ m). The temperature program consisted of an initial temperature of 80°C, held for 2 min, followed by a ramp to 280°C at 15°C/min. The final temperature was held for 20 min. The injector temperature was 280°C (TSQ 8000) and 220°C (TSQ 7000), respectively. The transfer line temperature was set at 280°C and the carrier gas was helium in constant flow mode at a flow rate of 1.2 ml/min. For analysis, 1 μ l of the blotter extract or of a standardized, free base lysergamides was injected into the GC-MS system. Retention indices are given as Kovats indices calculated from measurement of an *n*-alkane mixture analyzed with the above mentioned temperature program.

GC-MS method 2

Samples were analyzed on an Agilent 6890 N gas chromatograph coupled to a 5975 inert MSD. A Restek Rxi[®]-5Sil MS column (30 m \times 0.25 mm \times 0.25 μ m; Thames Restek, High Wycombe, UK) was used in splitless mode with helium carrier gas at a constant flow of 0.8 ml/min. The injection port and transfer line temperatures were set at 295°C. The initial oven temperature was 200°C, held for 2 min, ramped at 25°C/min to 295°C, and held at 295°C for 19.2 min (total run time 25 min). The ionization energy was set at 70 eV, the quadrupole at 150°C, the ion source at 230°C and the mass range was set at m/z 40–600. The sample injection volume was 2 μ l. Standards were run at 200 μ g/ml.

2.2.2 | GC-solid phase infrared analysis

All samples were analyzed using a GC-solid phase infrared analysis (GC-sIR) system that consisted of an Agilent GC 7890B (Waldbronn, Germany) with probe sampler Agilent G4567A and a DiscovIR-GC[™] (Spectra Analysis, Marlborough, MA, USA). The column eluent was cryogenically accumulated on a spirally rotating ZnSe disk cooled by liquid nitrogen. IR spectra were recorded through the IR-transparent ZnSe disk using a nitrogen-cooled MCT (mercury cadmium telluride) detector. GC parameters: injection in splitless mode with an injection port temperature set at 240°C and a DB-1 fused silica capillary column (30 m \times 0.32 mm i.d., 0.25 μ m film thickness). The carrier gas was helium with a flow rate of 2.5 ml/min and the oven temperature program was as follows: 80°C for 2 min, ramped to 290°C at 20°C/min, and held at for 20 min. The transfer line was heated at 280°C.

Infrared conditions: oven temperature, restrictor temperature, disc temperature, and Dewar cap temperatures were 280°C, 280°C, –40°C, and 35°C, respectively. The vacuum was 0.2 mTorr, disc speed 3 mm/s, spiral separation was 1 mm, wavelength resolution 4 cm^{-1} and IR range 650–4000 cm^{-1} . Acquisition time was 0.6 s/file with 64 scans/spectrum. Data were processed using GRAMS/AI Ver. 9.1 (Grams Spectroscopy Software Suite, Thermo Fischer Scientific, Dreieich, Germany) followed by implementation of the OMNIC Software, Ver. 7.4.127 (Thermo Electron Corporation, Dreieich, Germany).

2.2.3 | LC-electrospray ionization single quadrupole MS

LC-MS was performed on Agilent 1100 LC system using a Kinetex[®] F5 column (2.6 μ m, 100 Å; 100 \times 2.1 mm) (Phenomenex, Macclesfield, Cheshire, UK) with mobile phase A being acetonitrile containing 0.1% formic acid and mobile phase B being water containing 0.1% formic acid. The elution program was 2% A (0–1 min) followed by a linear gradient up to 30% A at 35 min, followed by a linear gradient down to 2% A at 37 min and 5% A for 18 min. The flow rate was 200 μ l/min and the injection volume was 1 μ l (5 μ g/ml for selected ion monitoring (SIM)) and 10 μ l (100 μ g/ml for full scan mode (TIC)). The LC system was coupled to a Hewlett Packard/Agilent 1100 MSD (Santa Clara, CA, USA) using the following conditions: electrospray ionization (ESI) mode (positive with a fragmentor voltage of 150 V for in-source collision-induced dissociation (CID)); TIC, m/z 50–500; SIM, m/z 324 and m/z 239), capillary voltage 3500 V, drying gas (N_2) 12 L/min at 350°C and nebulizer (N_2) pressure 50 psig. The mass spectrometer was tuned according to the manufacturer's instructions using ESI Tuning Mix G2421A (Agilent Technologies).

2.2.4 | LC-electrospray ionization-tandem MS

The HPLC-MS/MS system consisted of a Nexera X2 UHPLC system composed of three LC-30 AD pumps, a DGU-30A3 degasser, a SIL-30 AC autosampler (set to 10°C, injection volume: 10 μ l), a CTO-30 AC column oven, and a CBM-20A controller. Separation was performed using a LUX[®] 3 μ m AMP column (150 \times 3 mm, 3 μ m particle size, Phenomenex, Aschaffenburg, Germany) equipped with a corresponding guard column (SecurityGuard[™] ULTRA cartridge, Phenomenex, Aschaffenburg, Germany). The HPLC system was coupled to a QTRAP[®] 5500 triple quadrupole linear ion trap mass spectrometer equipped with a TurbolonSpray[®] Interface (Sciex, Darmstadt, Germany), operated in positive ESI mode. Data acquisition was performed in multiple reaction monitoring (MRM) mode using Analyst[®] software (version 1.6.2) monitoring two transitions: m/z 324.2 > 223.2 (DP 50 V, EP 10 V, CE 32 V, CXP 13 V); m/z 324.2 > 208.2 (DP 50 V, EP 10 V, CE 50 V, CXP 11 V). Ion source temperature and ion source voltage were set to 500°C and +5500 V, respectively. Dwell time was 30 ms for every MRM transition. Curtain gas (N_2) pressure was 20 psi, ion source gas 1 and 2 (compressed air) pressure were both 60 psi and

collision gas (N_2) pressure was set to 'medium'. Mobile phase A consisted of ammonium bicarbonate (5 mM) adjusted to pH 11 with ammonium hydroxide and acetonitrile was as mobile phase B. The analysis was carried out under isocratic conditions at 50% B for 10 min at 40°C. The flow rate was 0.4 ml/min.

2.3 | Extraction of MIPLA from blotters

2.3.1 | Extraction before analysis by GC-MS method 1

A blotter was extracted by ultrasound in 0.5 ml methanol for 15 min. The solution (1 μ l) was then subjected to GC analysis without dilution.

2.3.2 | Extraction from blotters before analysis by LC single quadrupole MS

Two blotters were extracted with acetonitrile/water/formic acid (50/50/0.1) (AWFA) (4 \times 2 ml, rolling for 5 min). The extracts were

combined and made up to 10 ml with AWFA. This solution (200 μ l) was diluted with (800 μ l) AWFA and analyzed by LC single quadrupole MS (LC-Q-MS). The blotter was then extracted with another portion of AWFA (1 ml, rolling for 5 min) to exclude the presence of any remaining MIPLA. Extracts and MIPLA standards (20, 10, 5, 2.5, 1.25, 0.625, and 0.3125 μ g/ml in AWFA) were analyzed by the LC-Q-MS method by a modified method (Supporting Information) aimed at reducing run time compared to the method above designed to maximize separation between analytes. Each sample injection was carried out in duplicate.

2.4 | Derivatizations for analysis by GC-MS method 2

A blotter was extracted with 200 μ l methanol and an aliquot of this extract (40 μ l) was evaporated to dryness. The trimethylsilyl (TMS) derivatization agent (acetonitrile/BSTFA/trimethylsilyl chloride; 10/9/1) (100 μ l) was added and heated at 90°C for 30 min. This was allowed to cool to room temperature and then analyzed by GC-MS method 2. Derivatizations of LSD, MIPLA, and LAMPA followed the same derivatization procedure.

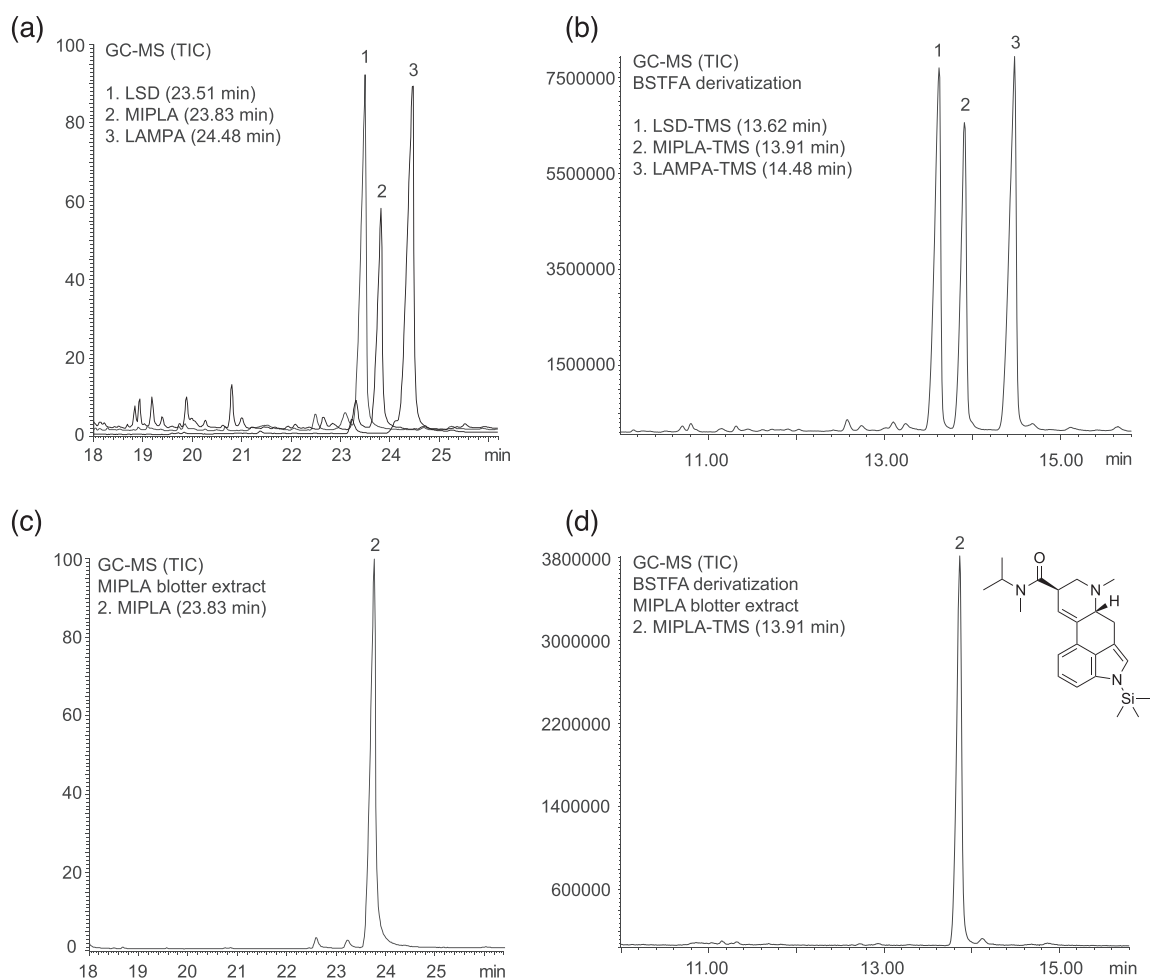


FIGURE 2 Exploration of two GC-MS methods. (a) GC-MS separation of underivatized LSD, MIPLA, and LAMPA standards using GC-MS method 1. (b) GC-MS separation of BSTFA-derivatized LSD, MIPLA, and LAMPA standards using GC-MS method 2. (c) Identification of MIPLA in a blotter extract using GC-MS method 1. (d) Identification of MIPLA in a blotter extract following BSTFA derivatization using GC-MS method 2

3 | RESULTS AND DISCUSSION

Though LSD is used recreationally around the world, there is little evidence to suggest that LAMPA is available on the market. However, it has been demonstrated that both LAMPA and MIPLA show LSD-like properties, though with lower potency.⁴⁸ The interest in the pharmacology of LSD is in probing the interaction of such ligands with the 5-HT_{2A} receptor thought to mediate the psychoactive effects of serotonergic hallucinogens in humans.^{3,49} Clinical research into the potential use of serotonergic hallucinogens for a number of psychiatric conditions has re-emerged in recent years.^{2,3,50} This suggests the investigation of novel LSD analogs will continue.⁴⁸

3.1 | GC-MS

The result from applying the GC-triple quadrupole-MS approach (method 1) to the analysis of underivatized LSD (RI = 3140, 23.51 min, DB-1), MIPLA (RI = 3157, 23.78 min, DB-1) and LAMPA (RI = 3183, 24.48 min, DB-1) is shown in Figure 2a where it can be seen that the separation between LSD and LAMPA was considered satisfactory based on the retention time difference of about 1 min. This was in agreement with many other investigators who also demonstrated a successful separation under GC conditions^{8,14,19,20,22,24,25} in addition to those GC-based studies that used LAMPA as an internal standard.^{33,40,41,43} Even though the differentiation between LSD and LAMPA was straightforward, the inclusion of MIPLA revealed that it eluted between LSD and LAMPA under these conditions. The differentiation from LAMPA was feasible but the gas chromatographic trace showed some overlap between MIPLA and LSD (Figure 2a). In such situations, the addition of a standard spike is recommended. Derivatization of all three analytes with BSTFA followed by GC-single quadrupole-MS (LC-Q-MS, method 2) led to an improved separation between the three isomers (Figure 2b). GC-MS analysis of blotter extracts confirmed that the retention times of the resulting peaks (23.83 and 13.91 min) were consistent with MIPLA (Figure 2c,d). Methods for separating derivatized LSD and LAMPA successfully on a GC column were reported some decades ago,^{18,34,38,51} though GC separation involving all three derivatized lysergamides could not be identified in the literature. The elution order remained unchanged when subjecting the three analytes to derivatization with BSTFA (Figure 2a,b).

As shown in Figure 3, a comparison of the three EI mass spectra revealed only minor differences, as expected. Some general trends could be observed. EI mass spectrum of LSD: m/z 44 > m/z 43; ratio m/z 58 vs. m/z 72 negligible with an increasing relative abundance trend observed for ions at m/z 235, 249 and 265. EI mass spectrum of MIPLA: m/z 44 < m/z 43; ratio m/z 58 vs. m/z 72 larger than the ratio seen in LSD with an decreasing relative abundance trend observed for ions at m/z 237, 249 and 265. EI mass spectrum of LAMPA: m/z 44 < m/z 43; ratio m/z 58 vs. m/z 72 larger than the ratio seen in LSD, and an increasing relative abundance trend observed for ions at m/z 237, 249 and 265. Another differentiating

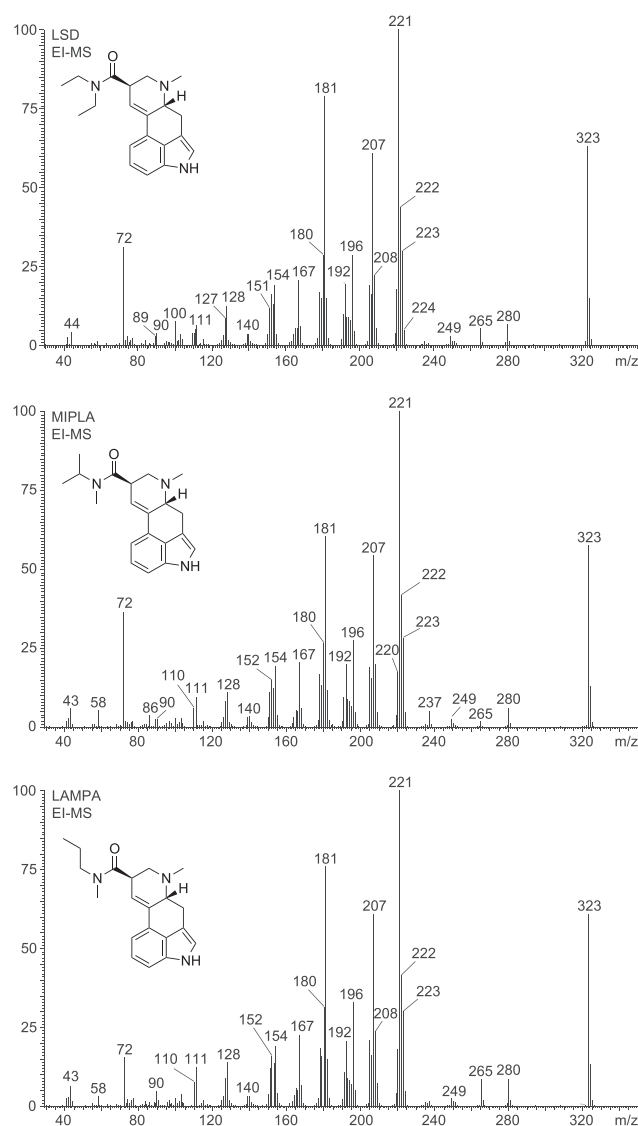


FIGURE 3 Electron ionization mass spectra of LSD, MIPLA, and LAMPA

feature noticed in the EI mass spectrum of LSD compared to the other two lysergamides (MIPLA and LAMPA) was that the relative abundance values of m/z 100 and m/z 111 were comparable (~8%). In the cases of MIPLA and LAMPA however, the relative abundance of m/z 100 dropped to about 3%. However, relying on such relative comparisons alone as the sole method for differentiation between the three isomers cannot be considered definitive and may fail critical examination; it is recommended to run all three standards at the same time under identical conditions when attempting a comparison with a sample obtained from casework.

One observation in the mass spectrum of MIPLA included the detection of m/z 86 that was detected at a relatively low abundance though it was not detectable to any significant extent in the two other mass spectra. Suggested fragmentations that might account for the detection of m/z 86 are shown in the Supporting Information. A comparison of the EI mass spectra recorded in the present study with

those reported in the literature confirmed that the results were consistent. As far as LAMPA was concerned, previously reported LAMPA spectra however differed to some extent in terms of the recorded (or presented) scan ranges since one additional difference found in the spectrum of LSD was the m/z 29 carbenium ion that cannot be formed from MIPLA and LAMPA under EI conditions. A comparison of the low mass ranges which includes the m/z 29 ion for LSD can be found in Figure 4a. It is recommended to consider increasing the scan

range to capture this ion. Recorded (or displayed) scan ranges reported for LAMPA spectra previously included m/z 150–350,⁷ m/z 50–330,¹⁹ m/z 50–330,²⁰ m/z 40–340,⁸ m/z 25–400,²² m/z 40–360,¹⁵ m/z 20–336,²⁴ m/z 40–330,²⁷ and m/z 29–600.²⁵ As suggested previously by other authors, inclusion of lower masses into the scan range requires particular attention to cleanliness of the instrumentation to minimize appearance of low mass impurities.⁸ The EI mass spectrum of MIPLA recorded in the present study was

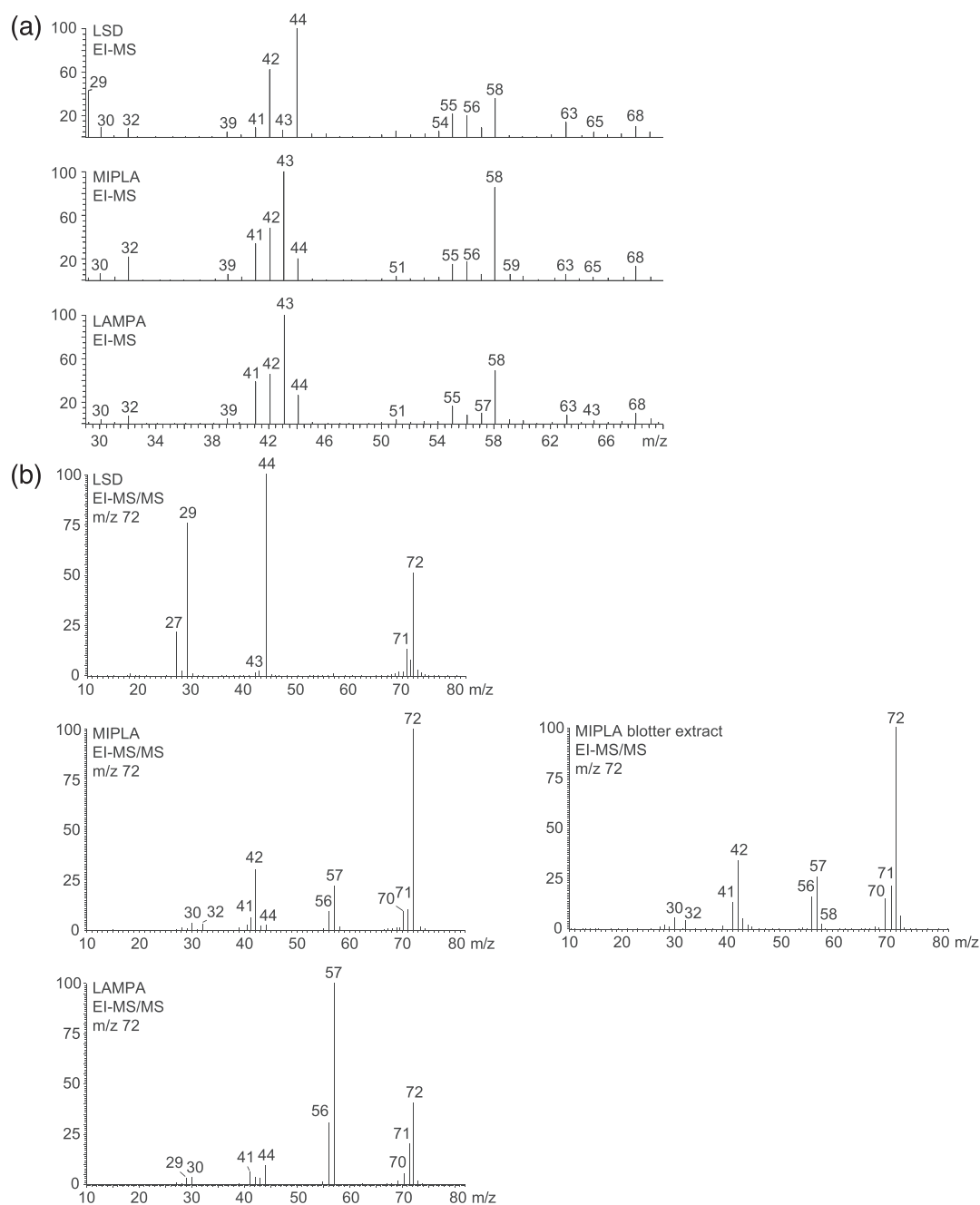


FIGURE 4 (a) Partial electron ionization (EI) mass spectra of LSD, MIPLA, and LAMPA showing the lower mass ranges (full spectra in Figure 3). (b) EI tandem mass spectra obtained from collision-induced dissociation of the m/z 72 iminium ion. The m/z 72 ion was detectable in all three EI mass spectra (Figure 3) and investigated further for the purpose of differentiation. The EI-MS/MS data of the blotter extract confirmed the detection of MIPLA

comparable to those reported previously^{8,45} and proposed EI fragmentation pathways for a range of closely lysergamides have been reported elsewhere.^{52–58} The EI mass spectra recorded for the TMS derivatives of LSD, MIPLA, and LAMPA are shown as Supporting Information and were comparable but also with minor differences in relative abundance. For example, the MIPLA-TMS spectrum showed similar relative abundances for m/z 309, 337, and 352 whereas LSD-TMS and LAMPA-TMS displayed an increased relative abundance of m/z 337 compared to the other two. Suggested fragmentation pathways for MIPLA-TMS are shown as Supporting Information. The LSD-TMS and LAMPA-TMS spectra were in agreement with those reported earlier^{34,51,59} though in one example, the scan range shown for the EI mass spectrum of LSD-TMS commenced at m/z 100.⁵¹ GC-MS spectra for LSD, MIPLA, and LAMPA were identical (data not shown) which did not aid the differentiation process.

One of the fragment ions common to the EI mass spectra of LSD, MIPLA, and LAMPA was the iminium species at m/z 72 (Figure 3) which reflected the isomeric nature of these compounds. However, an effective approach to explore additional differentiating mass spectral features involved a tandem mass spectral experiment using GC-triple quadrupole-MS/MS method 1 where the m/z 72 ion was subjected to further CID analysis. This approach was previously implemented by Westphal and Junge²⁵ and in the present study this was extended to the analysis of LSD, MIPLA, as well as the blotter extract. Figure 4b shows the product ion spectra recorded from the three m/z 72 iminium precursor ions where it can be seen that all three tandem mass spectra were distinguishable on mass spectrometric grounds alone. It could also be confirmed from the MS/MS data that MIPLA was indeed the lysergamide detected in the blotter extract (Figure 4b) consistent with the data obtained from the gas chromatographic analysis described above. The distinct formation of product ions reflected the different alkylamide substituents. For example, in the case of LSD, the two most prominent product ions were detected at m/z 44 (base peak) and m/z 29 which were not detected to that extent in the tandem mass spectra of MIPLA and LAMPA. In case of MIPLA, the precursor ion (m/z 72) emerged as the base peak with m/z 57 and m/z 42 representing two product ions of moderate abundance. On the other hand, the tandem mass spectrum obtained for LAMPA revealed the m/z 57 ion to be the base peak species including some other ions of relatively low abundance (Figure 4b). A proposal for the differences in fragmentation is shown in Figure 5. As shown in the Supporting Information section, GC-MS analysis of the blotter extract also revealed the additional detection of three minor peaks with retention times of 22.61 (RI = 3102), 23.24 (RI = 3135), and 27.06 min (RI = 3304). The corresponding mass spectra confirmed a molecular ion at m/z 323 in all cases. Analysis of the same extract by LC-Q-MS (see below and Supporting Information) did not reveal the detection of these isomeric analytes, suggesting that these might have been generated artificially under GC conditions. The EI mass spectrum of the peak at 22.61 min might have been consistent with a ring-opened imine species possibly formed in the injection port (Supporting Information). However, without the availability of standard reference material, the exact nature of these GC-induced

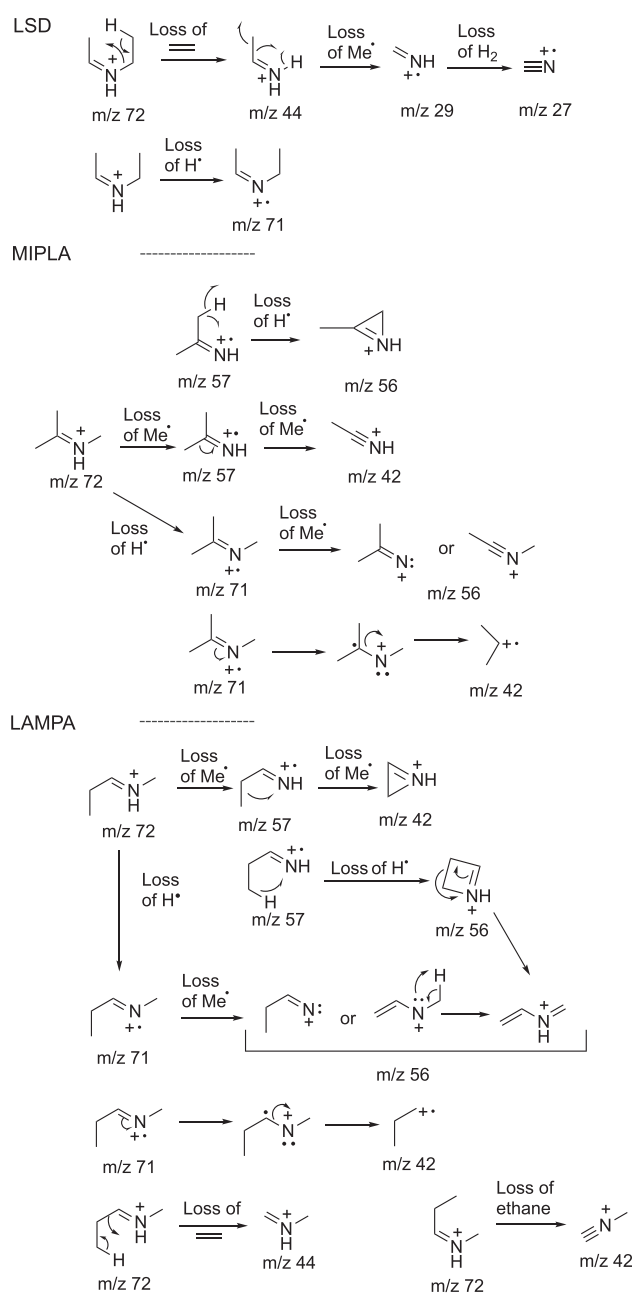


FIGURE 5 Proposed fragmentation pathways for the product ion formations of the m/z 72 iminium ions detected in the EI mass spectra of LSD, MIPLA, and LAMPA

compounds remains speculative. During previous work involving the lysergamide 1CP-LSD, an imine-type GC-induced artifact was also suggested to be formed.⁵⁷

3.2 | LC-MS

When implementing a single quadrupole LC-Q-MS method to the analysis of LSD, MIPLA, and LAMPA, it was found that LSD (29.95 min) could be conveniently separated from MIPLA and LAMPA

(30.52 min) but MIPLA and LAMPA could not be separated (Figure 6a) even after attempts to optimize the method and conditions further. LC-based separations between LSD and LAMPA have been reported in the literature.^{8,10,14,17,37,60} In some cases, the separation between LSD and LAMPA was unsuccessful under the conditions used¹⁶ whereas other reports showed a partial overlap still suitable for differentiation.^{11–13,15} Various other methods employing LAMPA as an

internal standard have also been reported^{36,42,61} with one method displaying partial overlap.⁴⁴ One study could be identified that reported an unsuccessful HPLC-based separation between LSD and MIPLA.⁸

The optimized LC-Q-MS method employed in the present study was ultimately unable to separate MIPLA from LAMPA (Figure 6a), which prompted further evaluations of the responses recorded by the mass spectrometer. In order to increase the formation of product ions

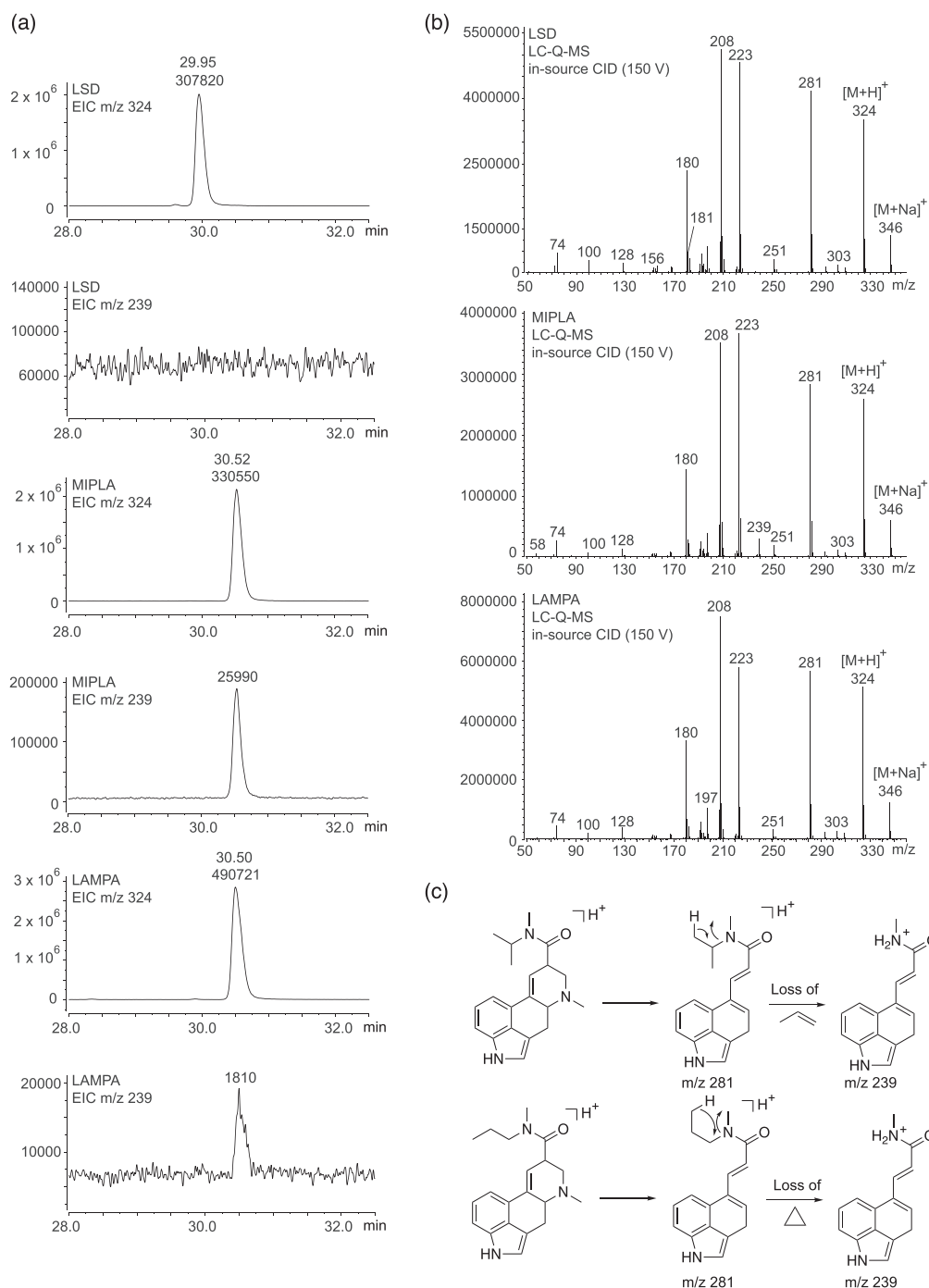


FIGURE 6 (a) Liquid chromatography-electrospray ionization single quadrupole mass spectrometry traces using increased fragmentor voltages to induced in-source collision-induced dissociation (CID). LSD was separated from MIPLA and LAMPA. MIPLA and LAMPA could be differentiated by distinct ion ratios involving the m/z 239 ions formed. (b) in-source CID mass spectra of LSD, MIPLA, and LAMPA. (c) Proposed fragmentation pathways for the detection of m/z 239 in the mass spectra of MIPLA and LAMPA

under single quadrupole conditions, the fragmentor voltage was increased to induce in-source CID. The corresponding mass spectra are shown in Figure 6b and reflected similar mass spectral information also reported for a range of other lysergamides previously.^{52–58} A closer inspection however also revealed that the mass spectrum of MIPLA contained a fragment at m/z 239 that was undetectable in the spectrum of LSD and only detectable at very low abundance in the mass spectrum of LAMPA (Figure 6b). The difference in abundance of the m/z 239 ions across all three mass spectra facilitated the use of extracted ion chromatograms, reflecting significant differences in the peak areas associated with the m/z 239 ions. The LSD trace therefore did not yield any peak at all for this ion in that trace whereas MIPLA revealed a peak area ratio (protonated molecule at m/z 324 relative to m/z 239) of 12.72 for MIPLA compared to 271.12 recorded for the LAMPA trace. This indicated that this difference contributed to the differentiation even in the case of co-elution. A suggested rational for the formation of m/z 239 is shown in Figure 6c where the m/z 239 ion might have been formed from the *retro*-Diels-Alder fragment (m/z 281) by way of elimination of propylene and cyclopropane from the isopropyl (MIPLA) and *n*-propyl (LAMPA) group. The analysis of two blotters using the LC-Q-MS method revealed 180.0 ± 2.0 μg and 186.0 ± 0.8 μg MIPLA per blotter (for calibration curve and representative sample LC-Q-MS trace, see Supporting Information) which might be a reflection of the fact that MIPLA is thought to be less potent than LSD with typical doses of MIPLA suggested to be in the 180–300 μg range.⁴⁸ Mass spectral data recorded from LC-QTOF-MS/MS analyses are provided as Supporting Information.

Under LC-MS/MS conditions, a variety of HPLC gradient profiles, columns, temperatures, and mobile phases were also evaluated based on an in-house method developed previously for the separation of phenethylamine enantiomers.⁶² Though most results were considered insufficient (Supporting Information), it was observed that the implementation of an isocratic profile led to an improvement in the separation between all three lysergamides (Figure 7). Though LSD and iso-LSD were found to co-elute under these conditions, a comparison of ion ratios recorded for the transitions m/z 324.2 > 223.2 and m/z 324.2 > 208.2 confirmed that their differentiation was possible (Figure 7b,c).

3.3 | Spectroscopic features

IR provides an important support for the positive identification of unknown substances and aids in the differentiation process between isomers. IR spectra of LSD^{7,11,15,21,24,26,27,63–69} and LAMPA^{7,11,15,21,24,26,27} have been published previously. The extent to which a direct comparison between spectral data collected from lysergamide samples can be made depends on various factors such as the presence of salt or base forms (or mixtures), how the sample was prepared for the IR measurement, and how the data were recorded.

An advantage of coupling GC to a sIR device is that eluting peaks are deposited cryogenically onto a rotating disk, which then permits the recording of solid phase IR spectra. IR spectra may be obtained

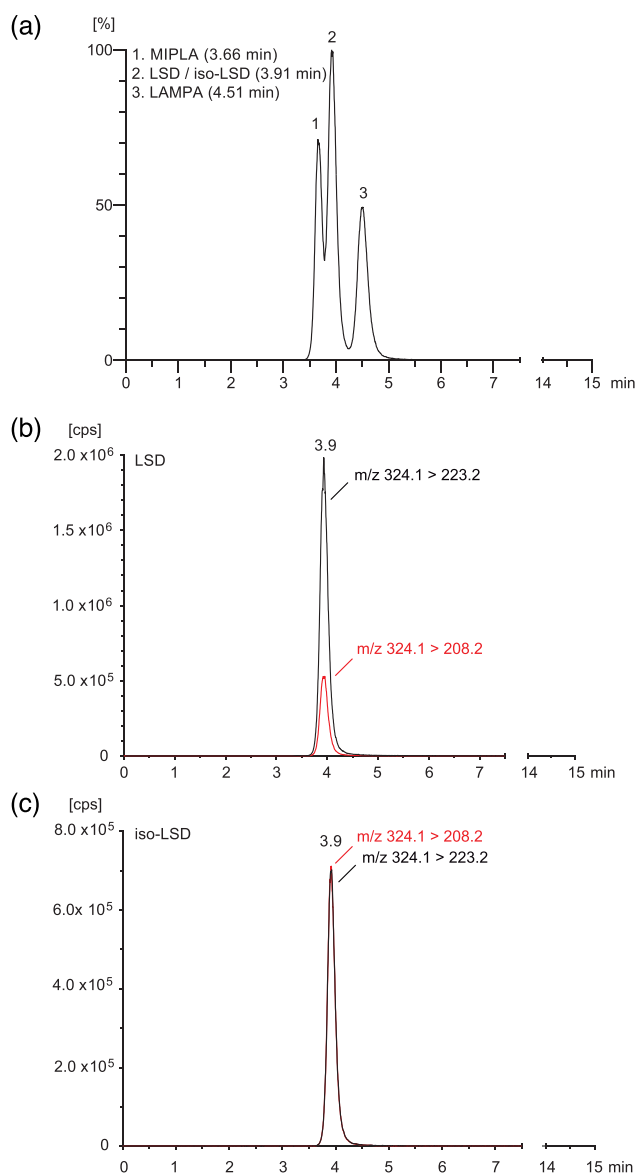


FIGURE 7 (a) Liquid chromatography-electrospray ionization-tandem mass spectrometry trace using isocratic elution. The resulting co-elution between LSD and iso-LSD could be mitigated by comparison of ion ratios. (b) LSD. (c) Iso-LSD [Colour figure can be viewed at wileyonlinelibrary.com]

from the main constituents detected in the chromatogram and the high sensitivity of the detector also allows for the collection of IR spectra from minor peaks such as impurities or lysergamides extracted from blotters. Spectra recorded under these conditions are comparable to those obtained from typical ATR-IR instruments (in freebase form) where spectra are typically recorded if sufficient amounts of sample material is available in high purity. A number of other lysergamides have been subjected to GC-sIR analysis previously.^{52–58} Earlier examples of spectral acquisition from LSD and LAMPA involving the coupling with GC have been reported though an example involving MIPLA could not be identified. For example, the IR spectra of LSD and LSD-TMS have been recorded following large volume

injections (10 μ l) into the GC followed by recovery of the eluting analytes on potassium bromide crystals.⁶⁶ GC vapor phase infrared spectra of LSD and LAMPA have been presented for visual comparison and differentiation^{21,24} though the GC-sIR data recorded in the present study showed a superior resolution compared to vapor phase spectra, which can be affected by molecular motion in the gas phase. The combination of preparative TLC followed by wick evaporation and IR analysis reportedly also allowed the differentiation between LSD and LAMPA.²⁶ Since then, the development of GC-sIR technology has improved spectral quality significantly.

A partial section (650–1900 cm^{-1}) of the GC-sIR spectra recorded for LSD, MIPLA, and LAMPA is shown in Figure 8 to allow for a spectral comparison (full spectra and overlaid spectra are supplied as Supporting

Information). The spectrum of LSD was consistent with others reported in the literature (e.g., Mills et al.²⁷) including signals typical for other lysergamides at 1627 ($\text{C}=\text{O}_{\text{str}}$), 1448 ($\text{C}-\text{N}_{\text{str}}$), and 779 and 749 cm^{-1} that might have been associated with C-H out of plane deformation vibrations in the indole part of the molecule.⁶⁷ A visual inspection of all three spectra in Figure 8 revealed distinct differences. For example, LSD did not show the band of medium intensity at 1407 (MIPLA) and 1409 cm^{-1} (LAMPA), which might have been related to C-H bending in the *N*-methyl amide group.⁷ LSD did also not display the bands at 1099 and 878 cm^{-1} that have been recorded for MIPLA. LSD also showed a band of small intensity at 908 cm^{-1} not detected in MIPLA. LAMPA could also be differentiated from LSD (Figure 8). For example, the band at 1400 cm^{-1} in LAMPA was absent in the spectrum of LSD whereas the band at 908 cm^{-1} not detected in MIPLA did also not appear in the spectrum of LAMPA. In contrast, a small intensity band at 878 cm^{-1} was not detected in the spectrum of LSD. A comparison between MIPLA and LAMPA also revealed some valuable differences. For example, a sharp band at 1232 cm^{-1} was detected for MIPLA where a broader band at 1222 cm^{-1} in LAMPA, whereas a sharp band was observed for LAMPA at 1164 cm^{-1} . LAMPA also displayed a sharp band at 1078 cm^{-1} whereas a sharp band at 1099 cm^{-1} was seen in MIPLA. The band at 878 cm^{-1} seen in MIPLA was also not detectable in the spectrum of LAMPA (Figure 8). In practice, a visual spectral comparison allows for an unambiguous identification of the corresponding isomer.

4 | CONCLUSION

LSD, MIPLA, and LAMPA are three lysergamide isomers that share some analytical features, which makes it important to avoid inadvertent misidentification given that LSD is a controlled substance whereas MIPLA and LAMPA are uncontrolled in many jurisdictions. This investigation reports on the exploration of distinguishing features that arose when investigating a blotter found to contain MIPLA. Two of the most powerful approaches taken were the use of GC-sIR and GC-QqQ-MS/MS analysis involving the m/z 72 iminium ion typically detected for these three lysergamides. The advantage of using these techniques is that an unambiguous identification can be made even in cases where gas chromatographic separations are not conclusively discriminating. An additional advantage is that every $\text{C}_4\text{H}_{10}\text{N}^+$ iminium ion (m/z 72) could be univocally distinguished with this method without the necessity to have all LSD-derivatives for comparison since only the MS/MS spectra of the ions m/z 72 is explored and all MS/MS spectra of these immonium ions are known.⁴⁷ However, derivatization of the lysergamides with BSTFA improved the separation, which might also help improve detection capability compared to underivatized analytes where adsorptive losses might occur without derivatization. The use of LC-Q-MS enabled the separation of LSD from MIPLA and LAMPA. Though MIPLA and LAMPA remained indistinguishable, differentiation was still achieved by exploring distinct ion ratios of the protonated molecule at m/z 324 relative to m/z 239. A quantitative analysis of two blotter samples by LC-ESI-Q-MS found 180 μg and 186 μg MIPLA per blotter. The implementation of

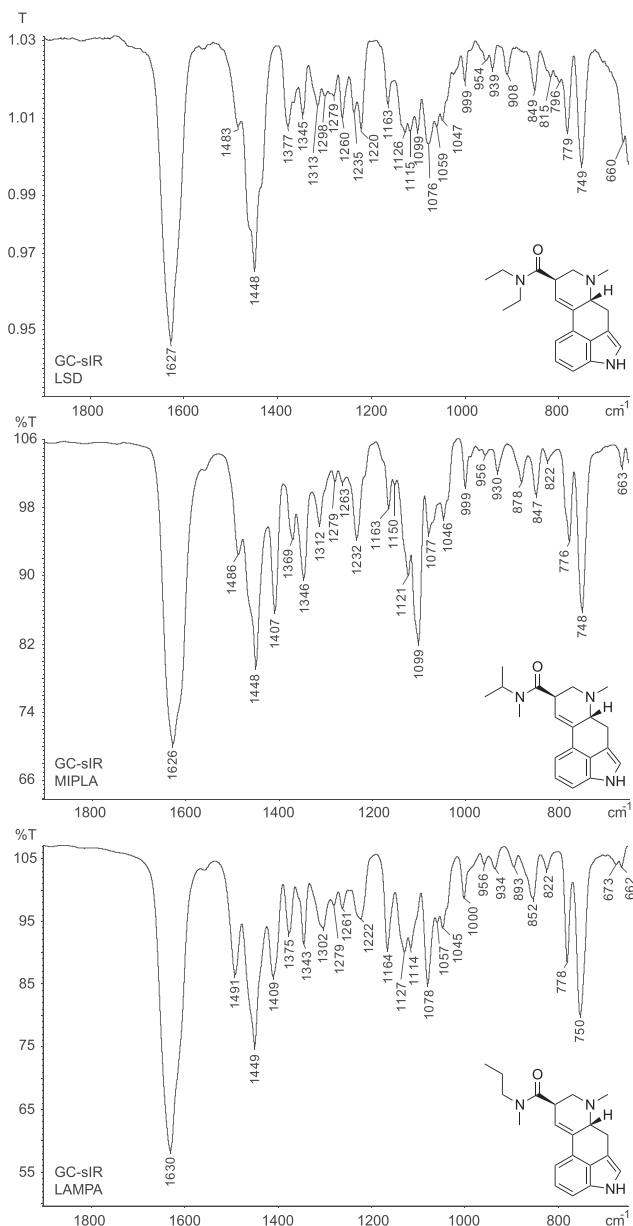


FIGURE 8 Partial solid phase infrared spectra of LSD, MIPLA, and LAMPA following analysis by gas chromatography (GC-sIR)

LC-MS/MS analysis under alkaline conditions facilitated the separation of all three lysergamides but also led to the co-elution of LSD/iso-LSD. However, both analytes could be differentiated when comparing the ion ratios recorded for transitions at m/z 324.2 > 223.2 and m/z 324.2 > 208.2.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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