Multimodal imaging of hallucinogens 25C- and 25I-NBOMe on blotter papers

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Abstract
Due to the much lower production costs but similar effects to lysergic acid diethylamide (LSD), phenethylamine derivatives are sold as a cheaper replacement or deceptively as LSD itself. These potent hallucinogenic substances can lead to severe intoxication, thus a more profound understanding of their use is required. This includes the elucidation of the manufacturing processes for the commonly used blotter papers and the assessment of the risk of overdosing because of a heterogeneous distribution on the blotter papers. Besides the rapid detection of the analytes, the manufacturing process was elucidated by three different imaging techniques and liquid chromatography-mass spectrometry (LC–MS). A blotter paper sample, containing the two hallucinogenic phenethylamine derivatives 25I-NBOMe and 25C-NBOMe, was analyzed by complementary techniques such as micro x-ray fluorescence (μXRF), laser ablation (LA)-inductively coupled plasma-optical emission spectroscopy (ICP-OES), matrix assisted laser desorption ionization (MALDI)-MS, and with LC–MS after extraction. Using the signal from chlorine and iodine within the compounds, μXRF proved to be the fastest, cheapest and easiest method for identification, requiring no sample preparation at all. LA-ICP-OES provided three-dimensional information of the elements in the blotter paper. Whereas μXRF and LA-ICP-OES detected signals for chlorine and iodine, MALDI-MS-imaging showed the molecular distribution of both analytes. LC–MS analyses as a complementary method support the imaging results. Quantitative results for different drug hotspots revealed a heterogeneous distribution of the drugs on the blotter paper implying an inherent risk of overdosing for consumers.

KEYWORDS
blotter paper, imaging, LA-ICP-OES, MALDI-MS, NBOMe

Received: 23 September 2019 Revised: 12 December 2019 Accepted: 13 December 2019
DOI: 10.1002/dta.2751
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Drug Test Anal. 2020;12:465–471.
1 | INTRODUCTION

Originally, phenethylamines and their derivatives, such as 2-(4-iodo-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethylamine (25i-NBOMe), were developed for pharmacological studies on the 5-HT\textsubscript{2A} receptor and for positron emission tomography (PET) imaging, respectively.\textsuperscript{1-3} Their rising popularity since 2010 as designer drugs of abuse can be traced back to the much lower costs of synthesis but similar effects compared with the better known hallucinogenic compound lysergic acid diethylamide (LSD).\textsuperscript{5-6} LSD and NBOMe derivatives as well, are highly potent ligands and partial agonists at the 5-HT\textsubscript{2A} receptor, which induces the typical and desired effects of these drugs.\textsuperscript{7-9} For NBOMe compounds, effects such as stimulation, euphoria, changes in consciousness and hallucinations are described.\textsuperscript{10-13} Hence, drug producers and dealers sell them as a replacement for LSD, or misleadingly as LSD itself.\textsuperscript{14-16}

Because of the similar effects and the low effective doses of LSD and NBOMes, unintentional effects of NBOMes by consumers may occur. Besides the reported clinical effects such as tachycardia, hypertension, agitation, and aggression, toxicological issues have to be considered as well.\textsuperscript{17} Maurer et al. showed an extensive metabolism of 25i-NBOMe, nevertheless, they claim a lack of systematic studies on the metabolism of NBOMe derivatives.\textsuperscript{18,19}

As already described in many cases, NBOMe consumption may lead to severe health problems or even death, caused by an overdose.\textsuperscript{20-23} To assess the risk of overdose incidents, blotter papers have to be investigated in more detail. NBOMes often are sold on perforated blotter sheets, from which small rectangles, the so-called “trips”, can be torn off. One common manufacturing process is the immersion of empty blotter paper into a drug solution and subsequent dry hanging. The amount of NBOMes on a single trip ranges from approximately 500 to 1500 µg, while the single effective dose for an inexperienced user is around 100 µg.\textsuperscript{24} Coelho et al. used direct ATR-FTIR spectroscopy for rapid detection of NBOMEs on blotter papers, which required no sample preparation and was directly applied on blotter papers. The data indicated a heterogeneous distribution of the NBOMes.\textsuperscript{25} Furthermore, the infrared spectra showed the presence of a plastic polymer on the front side of the blotter papers.

A blotter sheet, seized by the German police, containing approximately 20 “trips”, was analyzed by three different imaging techniques. These 2D analyses will reveal a possible heterogeneous appearance of NBOMes in some areas of the blotter paper, which could lead to overdose incidents if these hotspots are torn off. First, rapid and non-destructive analysis of the elemental distribution was performed by means of micro-X-ray fluorescence (µXRF) spectroscoopy and was subsequently supported by matrix assisted laser desorption ionization (MALDI)-mass spectrometry (MS) for molecular imaging. Additionally, imaging utilizing laser ablation (LA)-inductively coupled plasma (ICP)-optical emission spectroscopy (OES) was performed for 3D analysis since LA enables the acquisition of a depth profile. The obtained imaging results were then confirmed via high performance liquid chromatography (HPLC)-MS as a complementary technique.

2 | METHODS

The MALDI sample matrix compound 2.5-dihydroxybenzoic acid (DHB; 98%) and trifluoroacetic acid (TFA; 99%) were purchased from Sigma-Aldrich Co. (St Louis, Missouri, USA). Methanol (99.9%; LC-MS grade) was purchased from VWR Chemicals (Radnor, Pennsylvania, USA) and formic acid (FA, 99–100% p.a.) from Th. Geyer GmbH & Co. KG (Renningen, Germany).

Standard solutions of 25i-NBOMe hydrochloride (10\textsuperscript{-4} M) and 25C-NBOMe hydrochloride (10\textsuperscript{-4} M) for external calibration as well as a blotter sheet from a police seizure were provided by the Criminal Police Office (BKA), Forensic Science Institute, KT-45, Wiesbaden, Germany.

2.1 | Bench-top µXRF

Initial imaging analyses were realized by a laboratory bench-top µXRF (M4 Tornado, Bruker Nano GmbH, Berlin, Germany). Experiments were carried out in a sample chamber at a reduced pressure of 20 mbar, with a data acquisition time of 5 ms per spot, six consecutive measurement cycles and a spot-size of 25 µm. The incorporated Rh-anode micro-focus X-ray tube was set at a voltage of 50 kV and an anode current of 600 µA was applied. For the detection of the emitted X-ray fluorescence, a silicon drift detector (SDD, XFlash 5030, Bruker Nano GmbH) was utilized. Data evaluation was done using the integrated software ESPRIT HyperMap (M4 Tornado, Bruker Nano GmbH, Berlin, Germany). All images were created with an in-house developed software by Robin Schmid.

2.2 | MALDI-MS

Matrix application was done using an airbrush (Infinity, Harder und Steenbeck GmbH und Co. KG, Norderstedt, Germany). A total amount of 600 µL of DHB (0.1 M; 0.1% TFA) was sprayed onto the blotter paper (7 × 7 mm) by applying 100 µL stepwise from an approximate distance of 10 cm. The subsequent analysis of the molecular distribution experiments was carried out, using MALDI-MS imaging (iMScope TRIO, Shimadzu Corp., Kyoto, Japan) with a mass resolution of R = 10,000 and a mass accuracy better than 5 ppm (calculated with external calibration). With a spot size and pitch of 50 µm, accumulations were set to 1 time/pixel, the sample voltage was 3.50 kV and the detector voltage was set to 1.90 kV. The acquired m/z range was 200–500. The parameters of the 355 nm Nd:YAG laser such as the number of shots were set to 100 AU, the repetition rate was 1000 Hz and the laser intensity was set to 61.5 AU. Images were created using the instrument controlling software Imaging MS Solution, version 1.20.14 (Shimadzu Corp., Kyoto, Japan).
2.3 | LA-ICP-OES

Imaging data, as well as the depth profile data, were carried out using a laser ablation system with a 213 nm wavelength Nd:YAG-laser (LSX 213 G2+, CETAC Technologies, Omaha, NE, USA) hyphenated to an ICP-OES (Arcos, SPECTRO Analytical Instruments GmbH, Kleve, Germany). For the first image creation, a laser fluence of 5 J/cm² and 20 Hz laser shot frequency were chosen. For the following depth profile analyses, the laser energy was reduced by 50%, whereas the laser spot size (50 μm) and scan rate (100 μm/s) were maintained. Helium as carrier gas for the laser ablation cell was set to 0.8 mL/min. Plasma conditions such as rf power (1350 W), cool gas flow (14.5 L/min Ar), and auxiliary gas flow (1 L min⁻¹ Ar) were used with nebulizer gas (0.8 L/min Ar) as additional argon flow in order to stabilize the plasma (makeup gas), which can otherwise be affected by the helium coming from the ablation cell. Due to the high amounts of ablated material, a radial setup of the ICP was applied. Spectral lines for chlorine (I) detection were 133.573 nm, 135.165 nm, and 134.724 nm, which showed the most abundant signals. For iodine (I), the detected spectral lines were 183.038 nm and 178.276 nm, which showed the most abundant signals. The data acquisition rate was set to 2 Hz.

For data processing, Smart Analyzer Vision software, version 6.01.0945 (Spectro Analytical Instruments) was used. All images were again created with the same in-house developed software by Robin Schmid.

2.4 | HPLC-MS/MS

To extract both NBOMe compounds from certain regions with higher concentrations (hotspots) or regular areas, specific punch pliers were used to reproducibly cut out the same area (1 cm²). Afterward, these regions were extracted in 10 mL methanol (99.9%; LC-MS grade) in an ultrasound bath. For HPLC-MS/MS analyses, the extraction solutions had to be diluted by a factor of 1000 due to high concentrations.

For the HPLC-HESI-MS/MS analyses, a triple quadrupole mass spectrometer with UHPLC system (EVOQ Elite, Advance UHPLC, Bruker Corporation, Billerica MA, USA) was used. Both 25C-NBOMe and 25I-NBOMe were separated on a Restek Raptor Biphenyl 2.7 μm, 150 x 2.1 mm column (Bellefonte, PA, USA) and detected via multiple reaction monitoring mode (MRM). The mobile phase was A: bidistilled water containing 0.1% FA and B: methanol. With a flow rate of 200 μL/min, the gradient was ramped from 20% of B to 90% within 5 minutes, which was held constant until 12 minutes and decreased to 20% at 15 minutes, followed by an equilibration time of 5 minutes. The oven temperature was set to 50°C. The HESI spray voltage in positive ionization mode was set to 3.5 kV. The cone temperature and heated probe temperature was 350°C, while the cone and probe gas flow were set to 20 AU. The nebulizer gas was 60 AU.

Table 1 shows the HPLC-MS/MS separation parameters such as retention time, precursor ions, and corresponding product ions, the scan time and applied collision energy.

| Compound       | Rt/min | Prec. ion (m/z) | Prod. ion (m/z) | CE/AU |
|----------------|--------|----------------|-----------------|-------|
| 25I-NBOMe      | 6.3    | 428.1          | 121.1           | 18.0  |
|                |        |                | 91.2            | 31.0  |
|                |        |                | 93.2            | 27.0  |
| 25C-NBOMe      | 6.5    | 336.1          | 121.1           | 16.0  |
|                |        |                | 91.2            | 28.0  |
|                |        |                | 65.3            | 74.0  |

An independent two-tail t-test was applied to certify the significance of the statistical difference between the two areas.

3 | RESULTS AND DISCUSSION

3.1 | μXRF-imaging

The aim of the project, to obtain two-dimensional as well as three-dimensional information required the use of complementary analytical techniques. First, analyses were carried out using the non-destructive μXRF technique, which allows two-dimensional mapping of elemental distributions and does not require any form of sample preparation. In this case, chlorine for 25C-NBOMe was detected using its K-α-line (2.6 keV) and iodine, for 25I-NBOMe, necessarily via its L-β-line (3.9 keV), due to interference of L-α-lines from calcium and iodine. The L-β-line delivers a much less intense signal than the K-α-line of chlorine, which results in a less explicit image (see Figure 1B). However, iodine and chlorine (Figure 1B and 1C) exhibit heterogeneous distributions on the blotter paper with hotspots of both elements, respectively. Outlines of the sun on the blotter paper can be slightly observed in the chlorine and iodine distributions in Figures 2B and 2C. This could be caused by a heterogeneous distribution, but more likely because of different X-ray interaction behavior of the blotter paper matrix. Additionally, the elemental signals show that 25C-NBOMe and 25I-NBOMe have the same distribution since both patterns are identical. This leads to the hypothesis that the compounds were transferred to the blotter paper from a single solution. Furthermore, the presence of hotspots indicates an application from above, via a spray device or similar. Some of the hotspots fit the darker spots, which can already be recognized in the photograph of the blotter paper (Figure 1A).

FIGURE 1 Structural formula of 25X-NBOMe, whereas X = Cl or I
3.2 MALDI-MS-imaging

In order to validate that the chlorine and iodine signals observed in μXRF measurements also represent the molecular distribution of both NBOMe compounds, and are not caused by salt precipitations or due to the corresponding anion of the original hydrochloride solution, MALDI-HRMS imaging experiments were carried out subsequently. Figure 3 shows the distribution of the [M + K]$^+$ of both analytes since it showed higher signal intensities than the corresponding [M + H]$^+$. The hotspot pattern obtained via MALDI imaging is identical to the pattern observed via μXRF and therefore confirms that the detected iodine and chlorine signals belong to 25I-NBOMe and 25C-NBOMe.

A particular effect, which hardly occurred in μXRF-images, is the appearance of the picture motifs such as the sunbeams or the two lines of the mountains. It has to be pointed out that only picture motifs that are printed in black ink appear in the MALDI images. This effect can be traced back to stronger absorption of the MALDI laser beam. This was further investigated by measuring a blank blotter paper with a spiked amount of the analyte 25C-NBOMe via LDI (laser assisted desorption ionization). The analyte was applied
homogeneously onto the blank blotter paper. Nevertheless, regions with black ink showed higher signal intensities for 25C-NBOMe (Figure S2).

This effect reduces the visibility of the hotspots in the MALDI-MS images since the scale in these images is normalized and signal intensities are highest in regions with black ink.

3.3 | LA-ICP-OES imaging and depth profile

Although MALDI is considered as a semi-destructive method, enough material was left over, so that further analyses could be carried out via LA-ICP-OES. At first, a certain area on the blotter sheet was analyzed (red rectangle, Figure 1B, 1C and Figure 2B, 2C and 3). The resulting images (Figure 4A and 4B) of the iodine and chlorine distributions correlated to both the µXRF and MALDI-MS results. Using LA-ICP-OES and therefore an ablation-based technique with a pulsed 213 nm laser, no signs of different absorption effects were observed, thus only hotspots and no picture motifs were visible. Besides the detection of chlorine via OES, this method shows the advantage of higher matrix tolerance.

Afterward, a small area (small red rectangle, Figure 4B) that contained a hotspot was ablated six times consecutively. The obtained data provide three-dimensional information of the compounds on blotter paper. Figure 4C shows the depth profile of chlorine via LA-ICP-OES, where the second to sixth images have the same scale bar dimension. The hotspot of chlorine from 25C-NBOMe almost completely disappeared after the sixth ablation, which supports the hypothesis of an application on the front side via a spray device or similar.

3.4 | HPLC-MS/MS

With the obtained LA-ICP-OES data, a depth profile could be created which indicates a decreasing analyte concentration in the third dimension. Nonetheless, it is possible that hotspots only seem to have a higher amount of drugs per cm² due to less diffusion in the third dimension. This hypothesis was further investigated via HPLC-MS/MS after corresponding sample preparation. Therefore, five hotspot regions as well as five regular areas, which did not contain a hotspot, were cut out manually using punch pliers. Afterwards, the analytes were extracted and then analyzed via LC-MS. A recovery rate of 101% was determined using self-produced trips with known concentrations of 25C-NBOMe.

Table 2 and Table 3 show the results of the HPLC-MS/MS experiments for 25C-NBOMe and 25I-NBOMe, respectively. The mean amount of 25C-NBOMe in hotspots is significantly higher than in regular areas, which was proved using the independent two-tail t-test (n = 10; \( P = 0.999 \)). For 25I-NBOMe, a similar result is obtained. However, likely due to lower concentrations, it is less explicit but remains significant (t-test: \( n = 10; P = 0.980 \)). Using all the acquired data from Table 2 and Table 3, the mean amount of 25C-NBOMe in hotspots is significantly higher than in regular areas.

### Table 2

| Compound     | Mean amount/µg | SD/µg | RSD/% |
|--------------|----------------|-------|-------|
| Hotspots     | 207.9          | 16.2  | 7.8   |
| Regular areas| 153.2          | 14.1  | 9.2   |

**FIGURE 4** Obtained iodine and chlorine distribution of a certain area of the blotter paper (see red rectangle in Figure 1B, 1C and Figure 2B 2C and 3) of the blotter paper via LA-ICP-OES. Figure 3C shows a depth profile of the chlorine signal from a hotspot (small rectangle in Figure 4B), which was obtained by ablating the same area six times via LA-ICP-OES. Experiments were performed using a spot size of 50 µm and a scan rate of 100 µm/s [Colour figure can be viewed at wileyonlinelibrary.com]
the different techniques, the hypothesis of hotspots, which contain a significantly higher amount of drug compared with regular areas, was shown. Furthermore, a manufacturing process via a spray device could be confirmed.

Table 2 shows the results of the HPLC-MS/MS analyses for 25C-NBOMe of both extracted hotspots and regular areas. The mean amount of 25C-NBOMe in hotspots is significantly higher than in regular areas. A total number of five hotspots and five regular areas were used.

The results of the HPLC-MS/MS analyses for 25I-NBOMe of both extracted hotspots and regular areas are shown in Table 3.

Similar to the results of 25C-NBOMe, the mean amount of 25I-NBOMe in the hotspots is significantly higher than in the regular areas. A total number of five hotspots and five regular areas was used.

4 | CONCLUSIONS

In this proof-of-concept study, non-destructive μXRF was used as the first technique for a rapid elemental mapping of 25C-NBOMe and 25I-NBOMe. The results highlight the potential danger of an overdose as a consequence of NBOMe consumption since some trips did not contain a hotspot whereas others contained multiple hotspots on a single trip.

Subsequent analyses using MALDI-MS supported the results obtained by μXRF and showed that both are suitable techniques for NBOMe analysis on blotter sheets. The following analyses via LA-ICP-OES confirmed the results from both μXRF and MALDI-MS, but additionally enabled the acquisition of a depth profile and therefore delivered information of the compound distributions in a third dimension. The observed decreasing signal intensity in the third dimension elucidated the manufacturing process, where the compounds are sprayed onto the blotter sheets from one side, in contrast to the frequently applied manufacturing process of immersing the blotter paper in a solution of the active substance followed by air-drying. The occurrence of hotspots can be caused by a droplet formation during the spray process. Therefore, the complementary results of all three imaging techniques support the two major hypotheses, namely inhomogeneous distribution and manufacturing process.

As an approach that is independent of the imaging techniques, HPLC-MS/MS analyses and statistical evaluation were applied to confirm these results and to assess the potential risk of overdose because of heterogeneous distribution of the active substances on the investigated blotter paper. The HPLC-MS results did not show major differences referring to the consumption unit of single trips. This can be attributed to the manufacturing process by one-sided spraying, which seems to be less prone to cause inhomogeneous distribution on the paper surface compared with immersing and drying. The main source of heterogeneity found for the studied blotter papers was the hotspots caused by the spray process. These hotspots could contribute to an overdose incident if an unusually high number of them were located on a single trip, but their overall contribution to the total amount of active substance in a trip is less than originally expected.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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

How to cite this article: Lützen E, Holtkamp M, Stamme I, et al. Multimodal imaging of hallucinogens 25C- and 25I-NBOMe on blotter papers. Drug Test Anal. 2020;12:465-471. https://doi.org/10.1002/dta.2751