APPLICATION NOTE

Quantification of MDMA in Ecstasy Tablets – a Benchtop qNMR Method

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Introduction

The distribution of designer drugs has been an extreme challenge for law enforcement and other authorities. Both, identification and quantification of new drugs are important tasks in forensic laboratories. GC or LC coupled with MS have been employed as the standard analytical technique in qualitative and quantitative forensic analysis. However, these methods require certified reference material of the same compound that is investigated, which is a huge problem when analyzing new designer drugs. With NMR being an inherently quantitative technique, the internal calibrant used in quantitative NMR (qNMR) measurements can be a completely different substance, as long as it is of known purity and the signals of interest of the calibrant and the analyte do not overlap.[1] Despite these advantages, the high initial costs and maintenance aspects of traditional high-field NMR instruments have prevented this powerful analytical technique from being widely adopted in forensic analysis so far, where modern benchtop NMR is an accessible and attractive alternative.

While MDMA was only responsible for 1.8% of drug related deaths in 2020 in the UK, it is a very common drug in nightlife and music festival settings and its use is getting more common in teenagers. It is estimated that 3.9% of 15-year-olds have used MDMA in England.[2,3] Between 2009 and 2019 the concentration (mass of MDMA per ecstasy tablet) has increase by 149% in the European Union, which increases the risk of overdosing.[4] Thus, reliable, fast and easy methods for the quantification of MDMA are not only important for law enforcement and customs laboratories, but also for monitoring the potency of drugs by the healthcare system and prevention services.

In this application note we present a 60 MHz benchtop NMR method for the quantification of MDMA in ecstasy tablets collected at music festivals in the UK employing ethylene carbonate (EC) as internal calibrant. The work presented here is based on a paper that we recently published in collaboration with TICTAC Communications.[5] The 60 MHz NMR spectrum of an MDMA crystal sample mixed with EC is depicted in **Figure 1**.

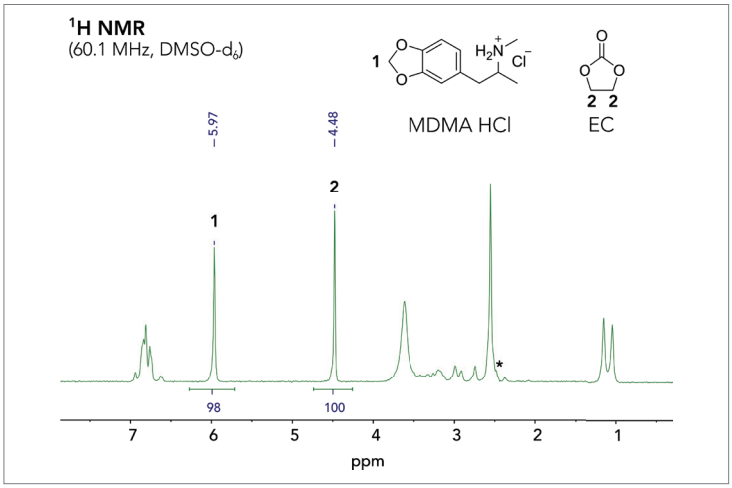

Figure 1. *¹H 60 MHz NMR spectrum of a crystal MDMA HCl sample and ethylene carbonate (EC) as internal calibrant.[5]*

General procedure for the qNMR analysis of ecstasy tablets

50 mg of the powder of an entirely crushed and ground ecstasy tablet was accurately weighed employing an analytical balance and transferred to a 1.5 mL micro-centrifuge Eppendorf tube with 1 mL of DMSO-d_6. The mixture was vortexed for 5 minutes and centrifuged for 1 minute. Then, 600 µL of the supernatant solution was transferred to a standard 5 mm NMR tube and 100 µL (equals 3.36 mg EC per aliquot) of an EC stock solution (0.382M) and 40 µL D2O (for the removal of labile proton signals in the NMR spectrum) were added. The sample was run in triplicates. From the observed NMR spectrum, the MDMA content of the ecstasy tablet was calculated by Equation (1).

$$MDMA\ (wt\%) = \frac{I_{MDMA}}{N_{MDMA}} \cdot \frac{N_{EC}}{I_{EC}} \cdot \frac{3.36\ mg}{MW_{EC}} \cdot \frac{MW_{MDMA}}{0.6\ m_{MDMA}} \cdot P_{EC} \cdot 100 \qquad (1)$$

Where: *MDMA* = 3,4-methylendioxymethamphetamine; *EC* = ethylene carbonate (internal calibrant); *I* = integration area; *N* = number of protons associated with the integrated signals; *m* = mass obtained from analytical balance; *MW* = molecular weight; *P* = purity.

Method Validation

Based on the UNODC guidelines[6] the method was successfully validated on a Nanalysis 60 benchtop NMR spectrometer. Please see our publication[5] and supporting information for the detailed method validation results. As NMR analysis is inherently quantitative, certified standard materials are not required as internal calibrants and an available crystal MDMA HCl sample of 89.94 wt% purity (determined via benchtop and high-field NMR) was employed for the validation. The benchtop NMR method was compared to LC-MS data from an external laboratory of ten randomly selected street samples (Table 1). Low deviations confirmed accurate quantification of MDMA via benchtop qNMR over a practically full concentration range for ecstasy tablets (2 – 60 wt% MDMA free base).

Table 1. *Comparison with external LC-MS analysis of ten ecstasy street sample tablets.[5]*

Tablet ID	MDMA content in wt%		Deviation in %
	NMR results	LC-MS results	
16152	47.52	46.0	3.3
18861	31.45	33.3	-5.6
20252	33.95	33.2	2.3
20284	20.06	20.0	0.3
20307LA	30.79	32.7	-5.8
22192/4	38.84	37.1	4.7
24803	2.20	2.25	-2.2
27099	12.92	12.8	0.9
28042	41.53	40.6	2.3
29596	60.69	59.8	1.5

Street Sample Analysis

Once the method was validated, we decided to apply it in the analysis of street samples. For the extensive study and discussion of the analysis of 100 ecstasy tablets, including low dose tablets, cut tablets, and collected tablets from 2019 and 2021 the reader is kindly asked to view our journal publication[5]. In the following within-batch variation experiment the consistency of the content of MDMA free base[7] in tablets of the same batch was studied.

Two different ecstasy tablet batches, seized in early 2020, were investigated in the within-batch variation study. One of the batches appears as rectangular shaped tablet with a "Red Bull" mark on one and a bull on the other side. The other batch of tablets are pressed in the shape of a trophy marked with "1" on one side (Figure 2). Signature shapes and motives of ecstasy tablets are common practice and are supposed to be appealing for the buyer. Here, the "Red Bull" tablet implies an energized feeling and the "trophy" tablet suggests a high MDMA content.

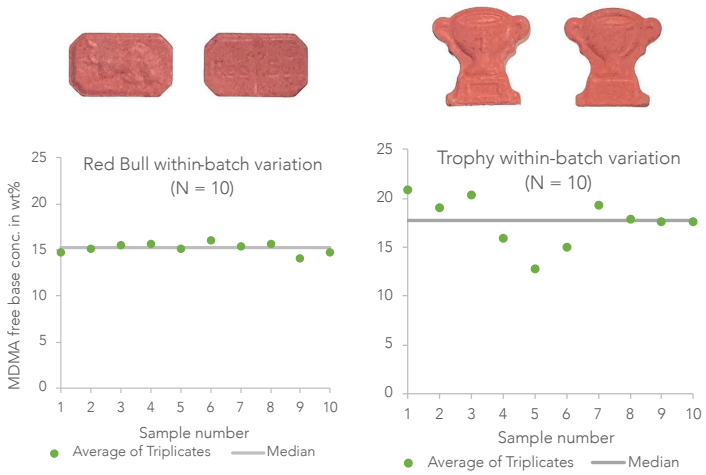

Figure 2. *Red Bull (left) and Trophy (right) tablets from early 2020 used for the within-batch variation analysis.*[5]

Interestingly, not only the median MDMA concentration of the "trophy" tablet is higher than the "Red Bull" (approx. 18 wt% vs. 15 wt%), but also the variation of the MDMA content of the ten "trophy" tablets was found to be much higher with a range from 72.58 mg to 119.07 mg of MDMA free base per tablet. For the 10 analyzed trophy tablets, the strongest tablet contained 1.6 times more MDMA than the lowest concentrated tablet of the same batch. The ten "Red Bull" tablets showed a smaller variation between 67.45 mg and 76.85 mg MDMA free base per tablet.

Conclusions

A 60 MHz qNMR method for the quantification of MDMA in ecstasy tablets employing ethylene carbonate as a well-suited internal calibrant was demonstrated. The successful method validation includes (amongst other) a comparison with an orthogonal (LC-MS) interlaboratory study. The within-batch variation of two batch seizures of 10 tablets each was presented here. The reader is highly encouraged to view our original publication[5] in the *Journal of Pharmaceutical and Biomedical Analysis* for more details. If you have any questions about forensic NMR analysis or qNMR, please don't hesitate to contract us via **sales@nanalysis.com**.

References

[1] https://www.nanalysis.com/nmready-blog/category/qNMR (accessed November 25, 2022).

[2] Office for National Statistics, Deaths related to drug poisoning in England and Wales: 2020 registrations. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsrelatedtodrugpoisoninginenglandandwales/2020 (accessed August 3, 2022).

[3] Pilgrim, J.L.; Gerostamoulos, D.; Drummer, O.H. *J. Anal. Toxicol.* **2011**, *35*, 219.

[4] UNODC, World Drug Report *2022* (United Nations publication, 2022).

[5] Frinculescu, A.; Maier, A. F. G.; Shine, T.; Ramsey, J.; Araneda, J. F.; Riegel, S. D.; Frascione, N.; Abbate, V. *J. Pharm. Biomed. Anal.* **2022**, 214. 114728.

[6] United Nations Office on Drugs and Crime, Validation of analytical methodology and calibration of equipment used for testing of illicit drugs in seized materials and biological specimens. https://www.unodc.org/documents/scientific/validation_E.pdf (accessed August 3, 2022).

[7] It should be noted that the free base content was calculated from the calculated MDMA HCl account assuming that all MDMA is present in its hydrochloride salt form; an NMR study on HBr and HCl salt analysis in drugs was recently published: Guillou, V.; Schönberger, T. *J. Pharm. Biomed. Anal.* **2022**, *213*, 114690.

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