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A Review of Recent Advances in Impurity Profiling of Illicit MDMA Samples

ABSTRACT: Profiling illicit ecstasy tablets has the potential to become an invaluable tool in the crackdown on drug trafficking, but that potential has yet to be fully realized. The impurity profile of an ecstasy tablet can be used to determine the method employed to synthesize the actual controlled substance, which in most cases, is 3,4-methylenedioxymethamphetamine (MDMA). Tablets can then be linked to a common synthetic route, potentially to a common manufacturer, and possibly even to a common manufacturing batch, based on the impurities present. Current methods for profiling MDMA tablets typically involve extracting the organic impurities for analysis by gas chromatography-mass spectrometry. The potential of profiling the trace metals present in tablets has begun to be investigated while more robust statistical and chemometric procedures are being applied to compare and link tablets. This article reviews the recent advances in MDMA impurity profiling from 2002 up to the end of 2006.

KEYWORDS: forensic science, MDMA, organic impurity profiling, trace metal impurity profiling, chemometric procedures

Initially synthesized by Merck (Whitehouse Station, NJ) in an attempt to develop new synthetic routes for blood clotting agents, 3,4-methylenedioxymethamphetamine (MDMA) has never actually been marketed (1). Today, MDMA has no legitimate medical use and is probably best known as the controlled substance in the club drug "ecstasy." A report published by the United Nations Office on Drugs and Crime indicated that regional differences in tablet composition were apparent: in East/South/South-East Asia, the term "ecstasy" is used to refer to any drug tablet, irrespective of the presence of MDMA, while in Europe and North America, there is a trend toward high purity ecstasy tablets containing only MDMA (2). Several authors have also reported trends in the composition of ecstasy tablets, in Europe, Asia, and North America (3–7). In almost all cases, MDMA was reported as the principal active ingredient, although other controlled substances may be present, for example 3,4-methylenedioxymethamphetamine (MDA), methamphetamine, ketamine, or amphetamine (7,8).

According to the 2005 midyear report published by the National Forensic Laboratory Information System, the number of MDMA exhibits seized in the United States decreased significantly between 2001 and the second quarter of 2005 (9). However, through January to June 2005, MDMA was the most commonly encountered club drug across all regions of the United States, constituting 88% of club drugs in the West, 86% in the South, 84% in the Midwest, and 64% in the Northeast (9). With this in mind, the need to crackdown on manufacturers to eliminate production and trafficking, both at the local and national levels, is apparent.

In the past, profiling of illicit tablets to identify a common source was based on a physical description of the tablet (10). However, physical characterization is limited as tablets with the same physical characteristics, such as dimension, mass, color, and motif, do not necessarily have the same chemical composition (3). Hence, profiling has moved toward chemical characterization of tablets, based on the impurities and by-products present as a result of the synthetic method (e.g., (3,11–14)). Likely sources of organic impurities include products from side reactions, poor chemical handling during synthesis, inadequate purification procedures, and contamination, which may be from contaminated reactants and materials, as well as effects from packaging, handling, and storage. Some impurities are specific to a particular synthetic route and are used as markers for profiling purposes. Tablets containing controlled substance produced in the same manufacturing batch are expected to contain similar levels of the same impurities and hence will have similar impurity profiles (13). Batches produced using different synthetic methods and/or in different laboratories are expected to yield significantly different impurity profiles (13). Organic impurity profiling of illicit ecstasy tablets in this way has proven successful in differentiating routes used to synthesize the MDMA, in both laboratory synthesized and seized samples (12,13,15,16).

More recently, the potential of identifying links among illicit drug seizures based on trace metal impurities has been investigated (17–26). While the initial potential of this method has been demonstrated, more thorough research is required to fully develop its potential. With optimization and validation of appropriate methodologies, routine trace metal profiling of illicit MDMA tablets is not out of reach.

A recent paper reviewed the analytical and chemometric methods used to profile illicit drug seizures up to and including 2002 (27). This paper does not intend to repeat the previously reported literature; rather, it is intended to make the reader aware of the most current research in this field, while also making recommendations as to the future direction for MDMA profiling.

Organic Impurity Profiling

Organic impurity profiling has mainly been based on liquid–liquid extractions of the impurities, followed by gas chromatography-mass spectrometry (GC-MS) analysis. While early profiling attempts identified potential synthetic route markers, today's researchers are going further, identifying precursors, intermediates, by-products, and excipients, thereby generating a "chemical fingerprint" of the sample (3,11,13–16,28–30). Different synthetic routes and variations of the same route have been studied, aiming to

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identify differences in the profiles generated (14,30). Attempts have also been made to identify the source of the precursor from the profile of the final MDMA product (16).

Palhol et al. extracted impurities from 52 ecstasy tablets using methylene chloride under basic conditions (13). Extracts were analyzed by GC with flame ionization detection (FID) and the identity of 29 precursors, intermediates, and by-products was confirmed by GC-MS. Nearly three quarters of the tablets analyzed contained 3,4-methylenedioxyphenyl-2-propanone (MDP2P), confirming its importance as the precursor of choice in the clandestine manufacture of MDMA. Impurities consistent with both the reductive amination synthesis, the most common in Europe, and the Leuckart synthesis were also identified. Palmitic and stearic acid were identified in 90% of tablets, presumably added as lubricants for direct compression of tablets. Two seizures of ecstasy tablets with different physical characteristics had similar chemical impurity profiles, potentially indicating a common synthetic batch. Furthermore, four seizures of tablets confiscated from different regions in Northern France between September 1999 and March 2000 had similar impurity profiles, indicating a common production laboratory.

Cheng et al. characterized the controlled substance, minor ingredients, and contaminants in a selection of MDMA tablets seized in Hong Kong during 2000–2001 (3). A plethora of analytical techniques were employed; infrared spectroscopy, high performance liquid chromatography (HPLC), and liquid chromatography-electrospray ionization-mass spectrometry (LC-ESI-MS), in addition to GC-MS. The most common impurities were identified as MDP2P, 3,4-methylenedioxyphenyl-2-propanol (MDP), 3,4-methylenedioxy-*N*-methylbenzylamine (MDB), piperonal, and *N*-formyl MDMA. Ketamine was present as an adulterant, presumably added to enhance the stimulating effects of MDMA (3). The presence of MDP2P was attributed to its use as a precursor for the popular Leuckart and reductive amination syntheses, while MDP was more likely to originate from the direct reduction of MDP2P with excess reducing agent. The presence of MDB was thought to be due to two possible sources: either as an intermediate from a less common synthesis involving the reaction of *N*-methylbenzylamine, MDP2P, and sodium cyanoborohydride, or as an impurity in the synthesis of MDP2P from piperonal.

Impurities in ecstasy tablets seized in Hong Kong between 2002 and early 2004 were later studied by Cheng et al. using a liquid–liquid extraction procedure with subsequent analysis by GC-MS (11). The 89 ecstasy seizures considered mostly contained MDMA as the single controlled substance. However, some tablets contained a mixture of MDMA, MDA, and methamphetamine. Ketamine was present in 80% of the tablets, although mostly as an impurity rather than an active ingredient. Nineteen impurities were identified as "prominent markers" in the impurity profiles obtained from GC-MS analysis, and used as markers for subsequent classification of tablets using hierarchical cluster analysis (HCA). Four groups of tablets were identified by HCA and, in each group, impurities consistent with a specific synthetic route could be identified. For example, in one group, the prominent impurities included MDA- and MDMA-dimers, which previous studies reported were indicative of the Leuckart synthesis. Three substituted pyridines were also prominent and were attributed to by-products of the Leuckart reaction, resulting from the condensation of one molecule of formamide with two molecules of MDP2P.

More recently, Gimeno et al. investigated impurities not only in the final MDMA product but also in the reaction intermediates for samples produced using reductive amination routes (15). MDP2P was synthesized from isosafrole, *via* the intermediate isosafrole glycol, and from piperonal, *via* the nitrostyrene route. MDMA was then synthesized from MDP2P by the reductive amination route, using different reducing agents: $NaBH_4$, $NaBH_3CN$, and Al–Hg amalgam. Differentiation of the precursor synthetic route proved difficult as the route-specific impurities, isosafrole glycol and 1-(3,4-methylenedioxyphenyl)-2-propanone oxime, were rarely detected in the final MDMA product due to their low levels and poor chromatographic resolution (15). However, differentiation of the routes was possible based on the presence of the impurities *p*-methoxymethamphetamine and *N*-methyl-1-[1,2-dimethoxy-4-(2-aminopropyl)]benzene. It was not possible to differentiate among the reducing agents used in the reductive amination synthesis as common impurities were present independent of reducing agent. The authors conceded that differences in profiles due to precursor differences disappear during MDMA synthesis although proposed that $^{15}N/^{14}N$ isotopic ratios of the MDMA may allow differentiation of precursor synthesis.

Świst et al. also synthesized MDP2P *via* isosafrole oxidation and the nitrostyrene route and identified route-specific impurities by GC-MS (16). For the isosafrole oxidation, characteristic impurities were identified as 1-(3,4-methylenedioxyphenyl)-1-propanone, 1-methoxy-1-(3,4-methylenedioxyphenyl)-2-propanone, and 2,2,4-trimethyl-5-(3,4-methylenedioxyphenyl)-[1,3]dioxolane. *N*-cyclohexylacetamide and 3-methyl-6,7-methylenedioxyisoquinoline-1,4-dione were considered characteristic of the nitrostyrene synthesis. MDMA was then synthesized from MDP2P following the reductive amination route, using $NaBH_4$ as the reducing agent (16). The previously identified route-specific impurities were present in the MDMA profiles, allowing not only the identification of MDP2P as a precursor, but also the method by which the precursor was synthesized.

Świst et al. continued their work in this area, extracting basic and neutral impurities from synthesized MDMA and MDP2P samples and comparing the resultant profiles (30). MDP2P was synthesized as described in their previous paper (16), while MDMA was synthesized *via* the Leuckart, bromosafrole, and reductive amination routes. Impurities were extracted under neutral and alkaline conditions, with the latter proving more effective as the majority of impurities produced during the syntheses are basic in nature. However, some exceptions were highlighted. The route-specific impurity in the bromosafrole route, 3,4-methylendioxyphenyl-2-bromopropane, was completely converted to isosafrole under basic conditions. In the reductive amination route using MDP2P synthesized from piperonal, the route-specific impurity 3-methyl-6,7-methylenedioxyisoquinoline-1,4-dione was extracted more efficiently under neutral conditions. In addition, the authors reported that none of the route-specific impurities identified in this work were directly from the starting materials; rather, such impurities were by-products formed from impurities in the starting materials or were formed in side reactions to the principal reaction (30).

Similar methods were used to prepare samples of MDMA and MDP2P although this time, Świst et al. concentrated their efforts on profiling the basic impurities extracted using a carbonate buffer of pH 10 (14). Each route was repeated in triplicate and the qualitative composition of impurities generally did not change among different batches produced by the same synthetic route. This is thought to be the first time that a qualitative approach has been used to determine synthetic route. Some impurities were common to different routes, indicating the necessity of using groups of impurities rather than a single impurity to determine synthetic route. It was also possible to distinguish reductive amination routes that used different reducing agents, based on the impurities present, for example 2-(dimethylamino)-2-methyl-3-(3,4-methylenedioxyphenyl)-propanenitrile was found to be indicative of a sodium cyanoborohydride reducing agent. This observation conflicts with

observations by Gimeno et al. who reported that distinction of the reducing agents was not possible as common impurities were observed independent of reducing agent (15).

While GC-MS is undoubtedly the technique of choice for impurity profiling, GC-isotope ratio mass spectrometry (GC-IRMS) has the potential to add an extra dimension of discrimination. Several papers have highlighted the potential of isotopic characteristics for differentiation of ecstasy tablets, either according to synthetic route or batch (28,29,31–33).

Carter et al. extracted MDMA from four different ecstasy tablets, which was followed by oxidation of the MDMA to MDP2P and piperonal (32). $\delta^{13}C$ values for the MDMA and corresponding oxidation products were determined by GC-IRMS. For one of the four samples, the $\delta^{13}C$ value was significantly more concentrated in piperonal compared with MDP2P, suggesting the final MDMA product was synthesized from piperonal rather than from safrole/isosafrole (32). Based on the $\delta^{13}C$, $\delta^{2}H$, and $\delta^{15}N$ values of MDMA in ecstasy tablets from five different batches, Carter et al. demonstrated batch differences among the tablets (33). While the tablets visually appeared similar, three batches were isotopically distinct based on $\delta^{13}C$ values, and four of the five batches were isotopically distinct based on $\delta^{2}H$ values. Complete distinction of the batches was possible by considering the combined $\delta^{13}C$, $\delta^{2}H$, and $\delta^{15}N$ values for each batch (33).

Palhol et al. also described ^{15}N isotopic analysis for the comparison of illicit ecstasy seizures, using GC-IRMS to determine the $^{15}N/^{14}N$ ratios (28,29). For the initial 43 samples considered, significant variation in the $\delta^{15}N$ values was correlated with the tablet logo or composition, potentially indicating a common manufacturing source (29). In their more detailed study, Palhol's group determined $\delta^{15}N$ values for the major nitrogenous precursors (28). The range in values for the precursors was significantly less than the range in $\delta^{15}N$ values for MDMA, which was attributed to isotopic fractionation during synthesis. The samples were classified into five groups according to $\delta^{15}N$ value and, with an assessment of the impurities present, each group represented a different synthetic route. Principal component analysis (PCA) indicated that the $\delta^{15}N$ value and the MDMA content of the tablets were the two most important parameters, accounting for the majority of the variation in the data set. Further statistical analysis using HCA indicated that correct classification of similar tablets was enhanced with the inclusion of the $^{15}N/^{14}N$ isotopic ratios rather than simply the physical parameters and MDMA content of the tablets (28).

Composition Profiling

Bell et al. have been prolific in their application of Raman spectroscopy for profiling ecstasy tablets (34,35), based on compositional differences. Their previous studies showed that distinction of tablets from different seizures was possible based on the identity of the excipient present, the drug:excipient ratio, and the degree of hydration of the illicit substance, which in most cases was MDMA (34,35). In 2003, the group carried out what is believed to be the largest study yet conducted to investigate the feasibility of compositional profiling (36). A total of 1500 ecstasy tablets from different seizures were considered and again significant differences in Raman spectra allowed differentiation of all but two sets of tablets. The authors reported that differences in spectra were sufficiently significant to preclude matching of tablets by random chance. Furthermore, differences in spectra of tablet batches taken from the same seizure were sufficiently small and could be attributed to random variations in the manufacturing method.

Ryder applied PCA to classify solid mixtures of cocaine, heroin, and MDMA based on the corresponding Raman spectra (37). Mixtures of the illicit substance and various common excipients were prepared, which for MDMA included $MgSO_4$, baby milk formula, maltose, lactose, $NaHCO_3$, and flour, in varying proportions. By taking the first derivative of the spectra and applying PCA, differentiation of the samples was possible. In addition, by restricting the spectral variables used in the data analysis, the computational time was substantially reduced. While offering promise for a rapid profiling technique based on the excipients present in lab prepared samples, the technique must be applied to seized samples to properly assess its full potential.

A slightly different approach to compositional profiling was adopted by Goldmann et al., in which the dyes present in illicit tablets were analyzed (38). A solid-phase extraction (SPE) method, followed by thin layer chromatography (TLC) and capillary zone electrophoresis with a diode-array detector (CZE-DAD) allowed separation, identification, and quantification of 14 hydrosoluble, acidic, synthetic food dyes. Although TLC and CZE-DAD allowed complete separation with no co-elution of dyes, losses in the extraction procedure were reported. The authors proposed that the additional information provided by their method could play a significant role in drug intelligence, presumably by building up a more complete characterization of a seized tablet for comparative purposes to determine common production sources.

Near infrared (NIR) spectroscopy has also been reported for the quantification of MDMA and 3, 4-methylenedioxyethylamphetamine (MDEA) present in seized ecstasy tablets (39). Tablets were analyzed *via* transmittance and diffuse reflectance modes, using whole tablets. The transmittance mode proved to offer more accurate quantification than diffuse reflectance when determined concentrations were compared with HPLC quantification (39). Poor homogeneity in illicit tablets was overcome by powdering the tablet, allowing a "pseudo" nondestructive sample analysis.

Baer et al. focused their study on differentiating the different chemical forms of the two most common excipients in ecstasy tablets, cellulose and lactose, also using NIR spectroscopy (40). Pure standards of each excipient form were distinguished based on NIR spectra after data preprocessing. Similarly, in mixtures of excipient and varying concentrations of amphetamine, NIR spectral data allowed identification of both the excipient and the controlled substance, with the spectra also reflecting the variation in amphetamine concentration. NIR spectra of seized ecstasy tablets containing more than one excipient were more complex as a result of absorbance contributions from each. As a result, excipient identification was not possible for some of tablets.

Trace Metal Profiling

Trace metal impurities can be present in illicit ecstasy tablets as a result of leaching metal from reaction vessels used during synthesis, residues of catalysts and reducing agents, components of dyes used to color tablets, and contamination in the adulterants and diluents added during tablet preparation. Hence, trace metal impurities in illicit ecstasy tablets can provide evidence to support the likely route used to synthesize the MDMA, as identified from the organic impurities. Furthermore, trace metal impurities yield additional information on the tablet production process, in terms of the dyes and tablet presses used.

Thus far, research has mainly focused on identifying trace metals in heroin and cocaine seizures, with few papers reporting elemental analysis to profile fully synthetic drugs. Muratsu et al. investigated the potential of synchrotron radiation total reflection X-ray

fluorescence for the determination of trace metals in a variety of controlled substances, including four different seized tablets containing MDMA in the hydrochloride salt form (22). Spectra for all four tablets were considered sufficiently distinct to allow discrimination of the tablets, mainly based on the likely salt form of MDMA present in the tablet (22).

Spectroscopic techniques such as flame atomic absorption spectroscopy (FAAS), electrothermal atomic absorption spectroscopy (ET-AAS), inductively coupled plasma-atomic emission spectroscopy (ICP-AES), and ICP-MS have been more routinely applied for trace metal determinations in amphetamine type samples (18,20,21,24). Marumo et al. reported the use of ICP-MS, FAAS, and ET-AAS for the determination of trace metals in methamphetamine samples (21), Comment et al. compared ICP-AES and ICP-MS for trace metal determinations in ecstasy samples (18), and Waddell et al. classified tablets from 12 different ecstasy seizures based on the trace metal profiles generated by ICP-MS (24).

More recently, Koper et al. analyzed the trace metals present in MDMA tablets and powders using ICP-AES and ICP-MS (20). Based on the elements present, the synthetic route was identified for 91% of the MDMA tablets and 84% of the powders. Elemental analysis indicated that reductive amination using a Pt catalyst was by far the most common synthetic route employed. Pearson correlation coefficients (R) were calculated to assess similarity among tablets from different batches (20). Potential links among 13 of the 97 tablets ($R > 0.9$) were identified and, through comparison with the organic impurity profile, ten such links were confirmed.

Although ICP-MS offers rapid and sensitive multi-element analysis, sample preparation procedures typically involve an acid digestion of the sample, which can be a lengthy and time-consuming procedure. Sample digestion also poses additional problems; elements such as Hg, Se, Zn, Cd, and As may be lost through volatilization, elements such as Zr, Ta, Ti, U, and Th may be chemically inert, resulting in either no or incomplete dissolution, and the stability of elements in the final solution varies greatly (25,41).

Laser ablation (LA)-ICP-MS offers a possible solution to such problems, allowing direct analysis of the solid sample. Hence, sample preparation is minimized and perhaps more importantly, so too is the risk of sample contamination, which is critical in trace analyses (42). The ablation process typically produces a crater 100 μm in diameter and 100 μm deep, such that sample consumption is minimal, generally on the order of 500 ng, also an important consideration in forensic cases where subsequent analyses may be necessary (43,44). LA-ICP-MS has been applied in the analysis of forensic samples, particularly glass and paint, where typically only small samples are available and sample integrity must be maintained (41,42,44,45).

In terms of LA-ICP-MS applications for drug profiling, Watling reported a LA-ICP-MS methodology in which trace elements in cannabis crops were determined (25). Limitations of the technique include variation in analyte signals between ablation events and the lack of quantitative information available. Analyte signal variation is a result of variations in coupling and transport efficiency, the number of shots, and the color and morphology of the substrate. Collecting quantitative information is limited by a lack of matrix-matched standards. However, Watling's methodology overcame such limitations. Rather than comparing absolute elemental concentrations, Watling compared the associations of elements among samples. Despite variation in analyte signals, discrimination among samples was still possible using ternary diagrams that showed the association among three elements in samples being compared. Four bulk cannabis samples seized in a single police raid were likely from different sources as a result of differences in the elemental associations of ^{64}Zn:^{86}Sr:^{98}Mo, ^{64}Zn:^{85}Rb:^{60}Ni, and ^{232}Th:^{238}U:^{182}W. In comparison, it was not possible to distinguish a second set of four bulk samples, again seized in a single raid, based on the elemental associations of ^{137}Ba:^{86}Sr:^{51}V, ^{64}Zn:^{85}Rb:^{60}Ni, and ^{232}Th:^{238}U:^{182}W, implying that these four samples originated from a common source.

Despite these initial indications of the potential for trace metal profiling, a search of the recent literature (2002–current) failed to find any subsequent papers published in this area. The exact reasons for this will probably remain unclear although reasonable assumptions include the limited availability of ICP-MS and LA-ICP-MS, presumably due to the initial expense of the instrumentation and the associated high running costs.

Current International Efforts in Impurity Profiling

Between 1999 and 2003, the European Commission and the Federal Office of Education and Science of Switzerland funded a pan-European project to develop a harmonized procedure for profiling amphetamine samples (46–51). The project aimed to develop a standardized procedure for the extraction and analysis of impurities from such samples, and the transfer of data at the local, regional, and international levels. By transferring electronic data, not only are difficulties in transferring samples among laboratories avoided but also, impurity profiles generated in different laboratories can be compared directly. The success of the project led to the initiation of the CHEDDAR (Collaborative Harmonized European Database Determination of Amphetamine Relations) project, for which the main objective was to create and develop a central database where all laboratories implementing the harmonized profiling procedure could transfer and store profiles (52).

The more recent CHAMP (Collaborative Harmonization of Methods for Profiling Amphetamine Type Stimulants) project builds upon the CHEDDAR project, developing a harmonized procedure for the analysis and comparison of amphetamine type stimulants, principally methamphetamine and MDMA (53). The project involves numerous partner crime laboratories throughout Europe as well as the Drug Enforcement Administration. The CHAMP project was scheduled to end in September 2006; as yet, no information was readily available detailing the success of the project.

Future Directions for Profiling Ecstasy

While the CHAMP project is undoubtedly significant in terms of MDMA profiling, numerous avenues remain open to further consideration, namely alternative methods for organic impurity extraction and analysis, trace metal impurity profiling, and chemometric procedures to link tablets based on the combined organic and trace metal impurity profiles.

Organic Impurity Profiling

Solid-phase microextraction (SPME) has found numerous applications in forensic science, presumably due to its speed, improved detection limits as a result of concentrating analytes on the fiber, and elimination of solvent extraction steps, hence reducing sample preparation times and increasing sample throughput. Headspace (HS)-SPME offers potential by further reducing sample preparation steps and the use of excessive solvents. Forensic applications of SPME include, although are certainly not limited to, the analysis of fire debris (54), explosives (55–57), and toxicological samples for drugs of abuse (58,59).

More recent applications of SPME are in the extraction of organic impurities from illicit drugs for profiling purposes. Impurities were extracted from illicitly produced 4-methoxyamphetamine and methamphetamine using SPME, in both cases identifying the likely synthetic route based on the impurities and by-products detected (60,61). Kuwayama et al. optimized HS-SPME parameters for the extraction of impurities from methamphetamine samples, analyzing the extracts by GC-MS (62). Optimum discrimination and classification of samples was achieved using a logarithmic conversion of peak area and the cosine distance as an indicator of similarity.

To the best of the author's knowledge, only one paper has been published that applies SPME for the extraction of organic impurities from illicit MDMA samples. Using a polydimethylsiloxane-divinylbenzene fiber, Kongshaug et al. developed a HS-SPME method for the efficient extraction of both polar and nonpolar impurities from ecstasy tablets (63). A liquid–liquid extraction was also performed to allow comparison between the two methods. In addition to significantly reducing the sample preparation time and eliminating solvent use, HS-SPME also offered preferential extraction of impurities over the illicit substance and concentration of impurities on the fiber. The repeatability of the HS-SPME extractions ranged from 2.2–12.6% for the six impurities considered, which was comparable to the repeatability of the liquid–liquid extractions. The authors illustrated the potential of this method for profiling purposes, showing distinctly different impurity profiles obtained from four different ecstasy tablets extracted using the HS-SPME method.

While impurity profiles are most commonly generated by GC-MS, the technique is limited for the analysis of nonvolatile impurities and components (64). However, the sensitivity and definitive identification capabilities offered by MS warrant further research in this area, potentially using different methods of sample introduction, for example desorption ionization on porous silicon (DIOS) and desorption electrospray ionization (DESI) (64,65).

In 2006, Kraj et al. synthesized MDMA by four different synthetic routes (reductive amination with two different reducing agents, bromosafrole, and Leuckart routes) and analyzed the final product using DIOS-MS (64). The ionization method is similar to matrix-assisted laser desorption ionization (MALDI) except that DIOS does not require a matrix. Hence, resultant spectra are not overwhelmed with matrix fragments, which can limit MALDI-MS, particularly in the spectral region below m/z 500 (64). Using DIOS, ions were identified that were specific to each of the synthetic routes investigated, for example, the presence of a fragment ion at m/z 149.1 was due to α-cleavage of piperonal, indicating this aldehyde as a precursor for the synthesis. Although numerous ions were found to be common to different impurities, significant differences in spectra in the range m/z 300–550 were sufficient for distinction of the synthetic route (64). While the potential of this technique is not in doubt, the authors did not apply DIOS-MS to the analysis of illicitly produced ecstasy tablets and hence, further investigation is necessary.

Desorption electrospray ionization, an ionization method first developed by Cooks and co-workers, has immense potential in the analysis of forensic samples of interest (66–68). Charged solvent droplets are sprayed onto the sample surface under ambient conditions, forming singly and multiply charged species, which are subsequently separated and detected by MS. Samples can be analyzed directly, hence increasing sample throughput, and molecular weight and structural determinations are possible by MS, allowing definitive sample identification. Rodriguez-Cruz demonstrated rapid, real-time analysis of five MDMA tablets using DESI-MS, with no cross-contamination from previously run samples and no interferences from tablet constituents (65). In all tablets, the major component was observed at m/z 194, corresponding to protonated MDMA. Peaks at m/z 150 were also observed, indicative of methamphetamine, which was later confirmed by independent analyses. The study was successful in its intended purpose; rapid analysis of illicit tablets to determine the controlled substance present. However, the potential of profiling the impurities in illicit tablets using DESI-MS was not approached. While DESI may only be in its infancy, there again appears to be no reason why its potential for impurity profiling should not be studied more fully.

Trace Metal Impurity Profiling

While the significance of trace metal impurity profiling in illicit drug seizures has begun to be realized, its true potential has yet to be fully explored (18,20,21,24,25). ICP-MS would be the technique of choice due to its multi-elemental capabilities when compared with FAAS and ET-AAS and enhanced sensitivity compared with ICP-AES. LA-ICP-MS offers further advantages in minimizing sample preparation and elemental losses. In the past, expensive instrumentation may have limited the routine use of ICP-MS in forensic laboratories but decreasing prices in the past 5 years may make this technique more accessible in the future (69).

Watling applied LA-ICP-MS for elemental determinations in cannabis samples and concluded that such an approach could "possibly point the way for similar systems for the control of other 'harder' drugs such as cocaine and heroin" (25). However, as far as this author is aware, no further studies have been published applying LA-ICP-MS to drug profiling since Watling's paper appeared in 1998. Perhaps the perceived limitations of the technique, principally lack of quantitative information and variation in analyte signals, have discouraged researchers, yet Watling successfully based his comparisons on elemental associations (i.e., patterns of elements) rather than absolute elemental concentrations. LA-ICP-MS would appear to be a logical step in advancing drug profiling. The technique requires little, if any, sample preparation, has low sample consumption, and allows for rapid and sensitive multi-elemental analysis. However, the technique may be limited due to poor homogeneity of illicitly produced tablets.

Statistical and Chemometric Procedures for Comparison of Profiles

The application of mathematical procedures to compare profiles allows a nonsubjective comparison, removing the subjectivity associated with visual assessment of chromatograms and spectra, strengthening proposed links among tablets. Chemometric procedures, such as PCA and HCA, are used to identify natural groupings of similar samples in data sets. Both procedures are unsupervised pattern recognition methods, requiring no prior knowledge of sample origin, and tend to be considered as exploratory methods of data analysis rather than strict classification procedures (70). A previous review of analytical and chemometric procedures for drug profiling has already outlined the applications of PCA, HCA, and linear discriminant analysis (LDA) to identify links among drug seizures and tablets (27).

Ternary plots are used extensively in geochemistry and mineralogy, displaying associations among elements in order to compare similar samples (71,72). In terms of forensic samples, ternary plots offer a simple representation of similarities among samples and are ideal for presentation to a jury. Watling has already illustrated the application of ternary plots for the elemental profiling of cannabis

samples (25), but again, this is an area that deserves further consideration and investigation.

Artificial neural network (ANN) algorithms are more robust methods that can be used to classify samples according to source. ANN algorithms are nonparametric methods, making no prior assumptions concerning the distribution of the data, hence providing a means to discriminate complex samples of different origin without requiring a normally distributed data set. Esseiva et al. applied ANN algorithms for the classification of heroin seizures according to chemical class (73). Following GC-FID analysis, PCA was applied to identify natural groupings of samples based on the chromatographic profile of six alkaloids. Of 1000 samples analyzed, 498 were classed into one of 20 groups identified by PCA. The ANN algorithms were trained based on these samples for which chemical class was known. The optimized algorithm successfully classified 96.6% of samples, with a false positive rate less than 4% (73). The authors concluded that ANN algorithms should "be increasingly used in situations involving profile comparisons and classifications" (73).

Gosav et al. developed two separate ANN algorithms for the classification of 159 amphetamine and non-amphetamine samples based on GC-Fourier transform infrared spectroscopy data (74). The first algorithm contained two outputs to differentiate the amphetamine samples from the non-amphetamines, while the second algorithm contained three outputs, further classifying the amphetamine samples as stimulants or hallucinogens. The three output algorithm proved to be the more selective algorithm, correctly classifying 85.7% of samples compared with 83.4% using the two output algorithm. For both algorithms, false positives were relatively high; 18.7% and 16.7% for the two output and three output algorithms, respectively. However, the authors conceded that the training set used to develop the algorithms was not fully optimized (74). Even with such preliminary results, the power of ANN algorithms was apparent and optimization of the training set would be expected to decrease the rate of false positives and increase the correct classification rate.

The application of ANN algorithms to classify or differentiate samples based on trace metal content is widely reported in the literature (75–79). However, as far as the author is aware, only one paper has been published that applies ANN algorithms for the classification of MDMA tablets based on the trace metal profile (24).

Combining Organic and Trace Metal Impurity Profiles

No literature is currently available which explores the potential of profiling illicit ecstasy tablets based on a combination of both the organic and trace metal impurities. Combining the organic and trace metal profiles would provide a more definitive "fingerprint" of the tablet, potentially characterizing both the synthetic route used to manufacture the illicit substance and the subsequent manufacturing and tabletting processes. Mathematical procedures for comparison of profiles remove subjectivity associated with visual comparisons. ANN algorithms have further advantages as no prior assumptions are made concerning the distribution of the data. The combined organic and trace metal impurity profiles with ANN algorithms for classification could enhance the significance of links identified among tablets, with more confidence in the linkage.

Conclusion

From 2002 to the end of 2006, significant research has been conducted in impurity profiling of MDMA. Different synthetic routes and variations of the same route have been studied, identifying differences in the impurity profiles generated by GC-MS. Successful discrimination of tablets according to route or batch based on isotopic composition has also been demonstrated using GC-IRMS, adding an additional dimension to the discrimination. Raman spectroscopy and NIR spectroscopy have been reported for the determination of the controlled substance and excipients present in ecstasy tablets containing MDMA; however, both techniques require further investigation for specific applications in impurity profiling. MS with different ionization methods (e.g., DIOS and DESI) has been demonstrated for profiling organic impurities in MDMA synthesized by different routes. DESI is certainly worthy of further research in this area due to its capability to ionize samples under ambient conditions.

Studies investigating trace metal impurities specifically in ecstasy tablets are certainly limited, perhaps due to lack of available instrumentation. However, with the decreasing cost of ICP-MS instruments, the use of this multi-element, sensitive, and rapid technique may become more common. LA-ICP-MS does offer a means to analyze tablets directly; however, poor homogeneity of illicitly produced tablets may be a limiting factor in the applications of this technique.

Statistical and chemometric procedures to assess links among profiles and ultimately classify samples according to source are widely applied by numerous researchers, although not specifically for MDMA profiling. ANN algorithms are becoming more prominent in forensic science research and it is surely only a matter of time before such procedures are routinely applied for sample classification.

Finally, the importance of impurity profiling has gained prominence with European Union funded projects such as CHEDDAR and CHAMP. Given the success of these projects, it is hoped that funding for impurity profiling continues, allowing researchers to concentrate their efforts in this area.

References

1. Freudenmann RW, Öxler F, Bernschneider-Reif S. The origin of MDMA (ecstasy) revisited: the true story reconstructed from the original documents. Addiction 2006;101:1241–5.
2. United Nations. Ecstasy and amphetamines. Global survey 2003. New York: Office on Drugs and Crime, 2003.
3. Cheng W-C, Poon N-L, Chan M-F. Chemical profiling of 3,4-methylenedioxymethamphetamine (MDMA) tablets seized in Hong Kong. J Forensic Sci 2003;48:1249–59.
4. Cole JC, Bailey M, Sumnall HR, Wagstaff GF, King LA. The content of ecstasy tablets: implications for the study of their long-term effects. Addiction 2002;97:1531–6.
5. Parrott AC. Is ecstasy MDMA? A review of the proportion of ecstasy tablets containing MDMA, their dosage levels, and the changing perceptions of purity. Psychopharmacology 2004;173:234–41.
6. Tanner-Smith EE. Pharmacological content of tablets sold as "ecstasy": results from an online testing service. Drug Alcohol Depend 2006;83:247–54.
7. Makino Y, Kurobane S, Miyasaka K, Nagano K. Profiling of ecstasy tablets seized in Japan. Microgram J 2003;1:169–76.
8. US Department of Justice Drug Enforcement Administration Office of Diversion Control. Drugs and chemicals of concern; 3,4-methylenedioxymethamphetamine. Available at http://www.deadiversion.usdoj.gov/drugs_concern/mdma/mdma.htm. (Accessed April 2007).
9. National Forensic Laboratory Information System, Drug Enforcement Administration, Office of Diversion Control, Midyear report 2005. Available at http://www.deadiversion.usdoj.gov/nflis/2005midyear.pdf. (Accessed April 2007).
10. Gomm PJ, Humphreys IJ, Armstrong NA. Physical methods for the comparison of illicitly produced tablets. J For Sci Soc 1976;16:283–93.
11. Cheng JYK, Chan MF, Chan TW, Hung MY. Impurity profiling of ecstasy tablets seized in Hong Kong by gas chromatography-mass spectrometry. Forensic Sci Int 2006;162:87–94.

12. Gimeno P, Besacier F, Chaudron-Thozet H, Girard J, Lamotte A. A contribution to the chemical profiling of 3,4-methylenedioxymethamphetamine (MDMA) tablets. Forensic Sci Int 2002;127:1–44.
13. Palhol F, Boyer S, Naulet N, Chabrillat M. Impurity profiling of seized MDMA tablets by capillary gas chromatography. Anal Bioanal Chem 2002;374:274–81.
14. Świst M, Wilamowski J, Parczewski A. Determination of synthesis method of ecstasy based on the basic impurities. Forensic Sci Int 2005;152:175–84.
15. Gimeno P, Besacier F, Bottex M, Dujourdy L, Chaudron-Thozet H. A study of the impurities in intermediates and 3,4-methylenedioxyamphetamine (MDMA) samples produced via reductive amination routes. Forensic Sci Int 2005;155:141–57.
16. Świst M, Wilamowski J, Zuba D, Kochana J, Parczewski A. Determination of synthesis route of 1-(3,4-methylenedioxyphenyl)-2-propanone (MDP-2-P) based on impurity profiles of MDMA. Forensic Sci Int 2005;149:181–92.
17. Bora T, Merdivan M, Hamamci C. Levels of trace and major elements in illicit heroin. J Forensic Sci 2002;47:959–63.
18. Comment S, Lock E, Zingg C, Jakob A. The analysis of ecstasy tablets by ICP/MS and ICP/AES. Probl Forensic Sci 2001;66:131–46.
19. Infante F, Dominguez E, Trujillo D, Luna A. Metal contamination in illicit samples of heroin. J Forensic Sci 1999;44:110–3.
20. Koper C, van den Boom C, Wiarda W, Schrader M, de Joode P, van der Peijl G, et al. Elemental analysis of 3,4-methylenedioxymethamphetamine (MDMA): a tool to determine the synthesis method and trace links. Forensic Sci Int 2007;171:171–9.
21. Marumo Y, Inoue T, Seta S. Analysis of inorganic impurities in seized methamphetamine samples. Forensic Sci Int 1994;69:89–95.
22. Muratsu S, Ninomiya T, Kagoshima Y, Matsui J. Trace elemental analysis of drugs of abuse using synchrotron radiation Total Reflection X-Ray Fluorescence analysis (SR-TXRF). J Forensic Sci 2002;47:944–9.
23. Myors R, Wells RJ, Skopec SV, Crisp P, Iavetz R, Skopec Z, et al. Preliminary investigation of heroin fingerprinting using trace element concentrations. Anal Commun 1998;35:403–11.
24. Waddell RJH, NicDaéid N, Littlejohn D. Classification of ecstasy tablets using trace metal analysis with the application of chemometric procedures and artificial neural network algorithms. Analyst 2004;129:235–40.
25. Watling RJ. Sourcing the provenance of cannabis crops using inter-element association patterns 'fingerprinting' and laser ablation inductively coupled plasma mass spectrometry. J Anal At Spectrom 1998;13:917–26.
26. Wells RJ, Skopec SV, Iavetz R, Robertson J. Trace element analysis of heroin by ICP-MS. Chemistry in Australia 1995;62:14.
27. NicDaéid N, Waddell RJH. The analytical and chemometric procedures used to profile illicit drug seizures. Talanta 2005;67:280–5.
28. Palhol F, Lamoureux C, Chabrillat M, Naulet N. $^{15}N/^{14}N$ isotopic ratio and statistical analysis: an efficient way of linking seized Ecstasy tablets. Anal Chim Acta 2004;510:1–8.
29. Palhol F, Lamoureux C, Naulet N. ^{15}N isotopic analyses: a powerful tool to establish links between seized 3,4-methylenedioxymethamphetamine (MDMA) tablets. Anal Bioanal Chem 2003;376:486–90.
30. Świst M, Wilamowski J, Parczewski A. Basic and neutral route specific impurities in MDMA prepared by different synthesis methods. Comparison of impurity profiles. Forensic Sci Int 2005;155:100–11.
31. Carter JF, Sleeman R, Hill JC, Idoine F, Titterton EL. Isotope ratio mass spectrometry as a tool for forensic investigation (examples from recent studies). Sci Justice 2005;45:141–9.
32. Carter JF, Titterton EL, Grant H, Sleeman R. Isotopic changes during the synthesis of amphetamines. Chem Commun 2002;21:2590–1.
33. Carter JF, Titterton EL, Murray M, Sleeman R. Isotopic characterization of 3,4-methylenedioxyamphetamine and 3,4-methylenedioxymethamphetamine (ecstasy). Analyst 2002;127:830–3.
34. Bell SEJ, Thorburn Burns D, Dennis AC, Speers SJ. Rapid analysis of ecstasy and related phenethylamines in seized tablets by Raman spectroscopy. Analyst 2000;125:541–4.
35. Bell SEJ, Thorburn Burns D, Dennis AC, Matchett LJ, Speers SJ. Composition profiling of seized ecstasy tablets by Raman spectroscopy. Analyst 2000;125:1811–5.
36. Bell S, Barrett L, Thorburn Burns D, Dennis A, Speers S. Tracking the distribution of ''ecstasy'' tablets by Raman composition profiling: a large scale feasibility study. Analyst 2003;128:1331–5.
37. Ryder AG. Classification of narcotics in solid mixtures using principal component analysis and Raman spectroscopy. J Forensic Sci 2002;47:275–84.
38. Goldmann T, Taroni F, Margot P. Analysis of dyes in illicit pills (amphetamines and derivatives). J Forensic Sci 2004;49:716–22.
39. Schneider RC, Kovar K-A. Analysis of ecstasy tablets: comparison of reflectance and transmittance near infrared spectroscopy. Forensic Sci Int 2003;134:187–95.
40. Baer I, Gurny R, Margot P. NIR analysis of cellulose and lactose—application to ecstasy tablet analysis. Forensic Sci Int 2007;167:234–41.
41. Watling RJ, Lynch BF, Herring D. Use of laser ablation inductively coupled plasma mass spectrometry for fingerprinting scene of crime evidence. J Anal At Spectrom 1997;12:195–203.
42. Trejos T, Montero S, Almirall JR. Analysis and comparison of glass fragments by laser ablation inductively coupled plasma mass spectrometry (LA-ICP-MS) and ICP-MS. Anal Bioanal Chem 2003;376:1255–64.
43. Aeschliman DB, Bajic SJ, Baldwin DP, Houk RS. Multivariate pattern matching of trace elements in solids by laser ablation inductively coupled plasma mass spectrometry: source attribution and preliminary diagnosis of fractionation. Anal Chem 2004;76:3119–25.
44. Hobbs A, Almirall JR. Trace elemental analysis of automotive paints by laser ablation inductively coupled plasma mass spectrometry. Anal Bioanal Chem 2003;376:1265–71.
45. Trejos T, Almirall JR. Effect of fractionation on the forensic elemental analysis of glass using laser ablation inductively coupled plasma mass spectrometry. Anal Chem 2004;76:1236–42.
46. Aalberg L, Andersson K, Bertler C, Borén H, Cole MD, Dahlen J, et al. Development of a harmonised method for the profiling of amphetamines I. Synthesis of standards and compilation of analytical data. Forensic Sci Int 2005;149:219–29.
47. Aalberg L, Andersson K, Bertler C, Cole MD, Finnon Y, Huizer H, et al. Development of a harmonised method for the profiling of amphetamines II. Stability of impurities in organic solvents. Forensic Sci Int 2005;149:231–41.
48. Andersson K, Jalava K, Lock E, Finnon Y, Huizer H, Kaa E, et al. Development of a harmonised method for the profiling of amphetamines III. Development of the gas chromatographic method. Forensic Sci Int 2007;169:50–63.
49. Andersson K, Jalava K, Lock E, Huizer H, Kaa E, Lopes A, et al. Development of a harmonised method for the profiling of amphetamines IV. Optimisation of sample preparation. Forensic Sci Int 2007;169:64–76.
50. Andersson K, Lock E, Jalava K, Huizer H, Jonson S, Kaa E, et al. Development of a harmonised method for the profiling of amphetamines VI. Evaluation of methods for comparison of amphetamine. Forensic Sci Int 2007;169:86–99.
51. Lock E, Aalberg L, Andersson K, Dahlén J, Cole MD, Finnon Y, et al. Development of a harmonised method for the profiling of amphetamines V. Determination of the variability of the optimized method. Forensic Sci Int 2007;169:77–85.
52. Efficient amphetamine profiling by use of a Harmonised Method and a Common Database. Available at http://www.enfsi.org/agenda/cheddar (Accessed April 2007).
53. European commission research scientific support to policies. CHAMP. Available at http://www.ec.europa.eu/research/fp6/ssp/champ_en.htm (Accessed April 2007).
54. Furton KG, Almirall JR, Bruna JC. A novel method for the analysis of gasoline from fire debris using headspace solid-phase microextraction. J Forensic Sci 1996;41:12–22.
55. Brown H, Kirkbride KP, Pigou PE, Walker GS. New developments in SPME part 2: analysis of ammonium nitrate-based explosives. J Forensic Sci 2004;49:1–7.
56. Furton KG, Almirall JR, Bi M, Wang J, Wu L. Application of solid-phase microextraction to the recovery of explosive and ignitable liquid residues from forensic specimens. J Chromatography A 2000;885:419–32.
57. Kirkbride KP, Klass G, Pigou PE. Application of solid-phase microextraction to the recovery of organic explosives. J Forensic Sci 1998;43:76–81.
58. Nagasawa N, Yashiki M, Iwasaki Y, Hara K, Kojima T. Rapid analysis of amphetamines in blood using headspace-solid phase microextraction and selected ion monitoring. Forensic Sci Int 1996;78:95–102.
59. Yashiki M, Kojima T, Miyazaki T, Nagasawa N, Iwasaki Y, Hara K. Detection of amphetamines in urine using headspace-solid phase microextraction and chemical ionization selected ion monitoring. Forensic Sci Int 1995;76:169–77.
60. Coumbaros JC, Kirkbride KP, Klass G. Application of solid-phase microextraction to the profiling of an illicit drug: manufacturing impurities in illicit 4-methoxyamphetamine. J Forensic Sci 1999;44:1237–42.

61. Koester CJ, Andresen BD, Grant PM. Optimum methamphetamine profiling with sample preparation by solid-phase microextraction. J Forensic Sci 2002;47:1002–7.
62. Kuwayama K, Tsujikawa K, Miyaguchi H, Kanamori T, Iwata Y, Inoue H, et al. Identification of impurities and the statistical classification of methamphetamine using solid phase microextraction and gas chromatography-mass spectrometry. Forensic Sci Int 2006;160:44–52.
63. Kongshaug KE, Pedersen-Bjergaard S, Rasmussen KE, Krogh M. Solid-phase microextraction/capillary gas chromatography for the profiling of confiscated ecstasy and amphetamine. Chromatographia 1999;50:247–52.
64. Kraj A, Świst M, Strugăla A, Parczewski A, Silberring J. Fingerprinting of 3,4-methylenedioxymethamphetamine markers by desorption/ionization on porous silicon. Eur J Mass Spectrom 2006;12:253–9.
65. Rodriguez-Cruz SE. Rapid analysis of controlled substances using desorption electrospray ionization mass spectrometry. Rapid Commun Mass Spectrom 2005;20:53–60.
66. Chen H, Talaty NN, Takáts Z, Cooks RG. Desorption electrospray ionization mass spectrometry for high-throughput analysis of pharmaceutical samples in the ambient environment. Anal Chem 2005;77:6915–27.
67. Takáts Z, Cotte-Rodriguez I, Talaty N, Chen H, Cooks RG. Direct, trace level detection of explosives on ambient surfaces by desorption electrospray ionization mass spectrometry. Chem Commun 2005;15:1950–2.
68. Takáts Z, Wiseman JM, Gologan B, Cooks RG. Mass spectrometry sampling under ambient conditions with desorption electrospray ionization. Science 2004;306:471–3.
69. Cottingham K. ICPMS: it's elemental. Anal Chem 2004;76:35A–8A.
70. Adams MJ. Chemometrics in analytical spectroscopy. London: Royal Society of Chemistry, 1995.
71. Guillong M, Günther D. Quasi 'non-destructive' laser ablation-inductively coupled plasma mass spectrometry fingerprinting of sapphires. Spectrochim Acta Part B 2001;56:1219–31.
72. Resano M, Vanhaecke F, Hutsebaut D, De Corte K, Moens L. Possibilities of laser ablation-inductively coupled plasma-mass spectrometry for diamond fingerprinting. J Anal At Spectrom 2003;18:1238–42.
73. Esseiva P, Anglada F, Dujourdy L, Taroni F, Margot P, Du Pasquier E, et al. Chemical profiling and classification of illicit heroin by principal component analysis, calculation of inter sample correlation and artificial neural networks. Talanta 2005;67:360–7.
74. Gosav S, Praisler M, Van Bocxlaer J, De Leenheer AP, Massart DL. Class identity assignment for amphetamines using neural networks and GC-FTIR data. Spectrochim Acta Part A 2006;64:1110–7.
75. Alcazar A, Pablos F, Martin MJ, Gonzalez AG. Multivariate characterization of beers according to their mineral content. Talanta 2002;57:45–52.
76. Cameàn AM, Moreno I, López-Artíguez M, Repetto M, González AG. Differentiation of Spanish brandies according to their metal content. Talanta 2001;54:53–9.
77. Díaz C, Conde JE, Estévez D, Olivero SJP, Trujillo JPP. Application of multivariate analysis and artificial neural networks for the differentiation of red wines from the Canary Islands according to island of origin. J Agric Food Chem 2003;15:4303–7.
78. Hernandez-Caraballo EA, Avila-Gomez RM, Capote T, Rivas F, Perez AG. Classification of Venezuelan spirituous beverages by means of discriminant analysis and artificial neural networks based on their Zn, Cu, and Fe concentrations. Talanta 2003;60:1259–67.
79. Herrador MA, González AG. Pattern recognition procedures for differentiation of green, black, and Oolong teas according to their metal content from inductively coupled plasma atomic emission spectrometry. Talanta 2001;53:1249–57.

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