

Rapid analysis of ecstasy and related phenethylamines in seized tablets by Raman spectroscopy

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Received 8th October 1999, Accepted 7th January 1999

Published on the Web 14th February 2000

Raman spectroscopy with far-red excitation has been used to study seized, tableted samples of MDMA (*N*-methyl-3,4-methylenedioxyamphetamine) and related compounds (MDA, MDEA, MBDB, 2C-B and amphetamine sulfate), as well as pure standards of these drugs. We have found that by using far-red (785 nm) excitation the level of fluorescence background even in untreated seized samples is sufficiently low that there is little difficulty in obtaining good quality data with moderate 2 min data accumulation times. The spectra can be used to distinguish between even chemically-similar substances, such as the geometrical isomers MDEA and MBDB, and between different polymorphic/hydrated forms of the same drug. Moreover, these differences can be found even in directly recorded spectra of seized samples which have been bulked with other materials, giving a rapid and non-destructive method for drug identification. The spectra can be processed to give unambiguous identification of both drug and excipients (even when more than one compound has been used as the bulking agent) and the relative intensities of drug and excipient bands can be used for quantitative or at least semi-quantitative analysis. Finally, the simple nature of the measurements lends itself to automatic sample handling so that sample throughputs of 20 samples per hour can be achieved with no real difficulty.

Introduction

Identification of prohibited substances, particularly MDMA (*N*-methyl-3,4-methylenedioxyamphetamine) and its near analogues, collectively known as 'ecstasy', can be achieved in a number of ways, ranging from simple colorimetric kits through to NMR spectroscopy¹ and gas chromatography-mass spectrometry (GC-MS), which is currently the method of choice for criminal prosecutions.² However, all the available methods suffer from either poor selectivity (colorimetric tests) or from high cost (both in capital equipment and in technician time needed to run each analysis) so that there is currently no rapid, non-destructive method for routine screening of these substances. There is, however, a significant need for such a method, since the number of suspected samples of this type being seized is constantly increasing. Vibrational spectroscopy, because it provides fingerprint spectra which are unique to each different chemical compound, is an excellent method for substance identification. Of the various vibrational spectroscopies available, Raman spectroscopy should be the method of first choice because of the information-richness of the spectra it produces and the fact that it needs virtually no sample preparation, which makes it ideal for analysis of tablets, powders and liquids.³

The main obstacles to the widespread adoption of the Raman spectroscopy for routine analysis have been the cost of the equipment required to make the measurements and the high running costs of the instrumentation. In many cases this has been exacerbated by the problem of high levels of background fluorescence which often occur when unpurified or inherently luminescent samples are used. A large number of strategies for overcoming the fluorescence problem have been followed but the most generally successful to date has been the use of long (> 700 nm)⁴ or short (244 nm)⁵ wavelength excitation at which the absorbance of the sample is diminished and/or the fluorescence is well-separated from the Raman signal. Long-wavelength excitation has been the norm in Fourier-transform Raman instruments since they were first developed.⁶ There have been several reports in the literature covering the use of

Fourier transform (FT) Raman spectroscopy to identify prohibited substances which demonstrated that the method could be used to identify both the prohibited substances and some of the diluents commonly used to prepare street-grade samples.^{7–10} More recently, the use of UV excitation to identify heroin and cocaine mixed with possible cutting agents has been reported but, like FT-Raman, UV Raman is an inherently costly technique; it also suffers from the additional problem of possible sample decomposition caused by the focused UV Raman excitation laser.⁵

Here we report the use of conventional, dispersive Raman spectroscopy with far-red excitation to study seized samples of MDMA and related compounds: MDA (3,4-methylenedioxyamphetamine), MDEA (*N*-ethyl-3,4-methylenedioxyamphetamine), MBDB (*N*-methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine), 2C-B (4-bromo-2,5-dimethoxyphenethylamine) and amphetamine; see Scheme 1 for structures). Far-red (785 nm) excitation was chosen because of the well-known reduction in interfering background luminescence which is often found when excitation is shifted from the visible region to longer wavelengths. In addition, use of this excitation wavelength gives the possibility of moving the technique into non-specialist laboratories using the new generation of compact, very low-cost Raman spectrometers, which are dispersive instruments operating with far-red excitation. There are two aspects to the work described here; the first is to demonstrate that the Raman spectra of even chemically-similar ring-substituted phenethylamines and related compounds can be distinguished readily, the second is to show that the spectra can also be used to identify the excipients or bulking agents used to prepare the tablets, giving a useful composition profile which will be very valuable for drug supply intelligence work.

Experimental

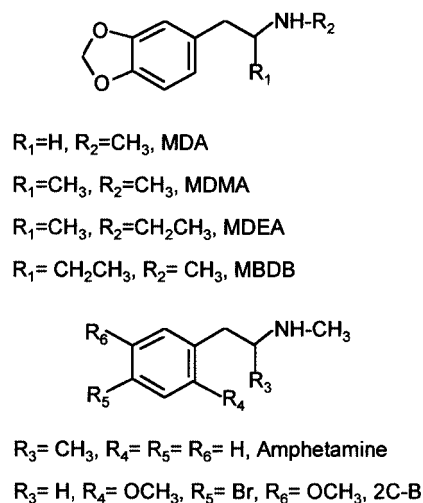
Raman spectra were recorded using 785 nm excitation (Spectra-Physics Inc (Mountain View, CA) Ti:sapphire laser pumped by

a Spectra-Physics 2020 Ar⁺ laser, typically 100 mw at sample) using a 180° backscattering geometry. The laser was line focused (<100 μm × 10 mm) onto the sample using a cylindrical lens. For this application, line focusing is superior to spot (typically <100 μm diameter) focus since it reduces the laser irradiance at the sample by <1/100, reducing the possibility of sample damage. Moreover, it overcomes a problem associated with spot focus, which is that because the spot can only probe a small area of the sample it can give unrepresentative spectra of badly-produced tablets which have poor drug homogeneity. Scattered light was collected, passed through a Kaiser Optical Systems Inc. (Ann Arbor, MI) (Stanmore, Middlesex) holographic notch filter and then dispersed by a Jobin-Yvon HR640 single stage spectrograph (600 grooves mm⁻¹ grating) onto a Princeton Instruments (Roper Scientific, Marlow, Buckinghamshire) LN 1152 liquid N₂ CCD detector. Spectra were typically accumulated for 120 s and were exported to the "LabCalc" spectral manipulation package¹¹ for processing and presentation. Due to the nature of the samples all the spectra were superimposed on a smooth background of stray light which rose smoothly to the low cm⁻¹ end of the spectrum. This background was removed from all the spectra shown herein by digitally subtracting a similar stray light signal which was generated by placing a rough aluminium plate or a piece of normal blackboard chalk in the sample position. The spectrometer was calibrated using a standard 50/50 mixture of toluene and acetonitrile.¹² The positions of strong, sharp bands are accurate to ±2 pixel (*ca.* 3 cm⁻¹).

Pure samples of MDMA, MDEA, MDA, MBDB and 2C-B were obtained from Sigma-Aldrich Ltd. (Poole, Dorset) as their hydrochloride salts and were used as received, as was the standard sample of amphetamine sulfate.

Results

Fig. 1 shows the Raman spectra of the commercial standard drugs. The spectra display pronounced differences over the entire cm⁻¹ range shown but the strongest bands lie in the range 700–1100 cm⁻¹ and Fig. 2 shows the data in this region in more detail. It is clear that although there are strong similarities between the spectra of some of the compounds (MDMA, MDEA, MDA and MBDB) there are also sufficiently large differences to allow the compounds to be distinguished from each other, even if only this smaller range is studied. Even MDEA and MBDB, which are simply geometrical isomers, give significantly different spectra.



Scheme 1 The structures and abbreviations used for the drugs in this study.

Fig. 3 shows the spectra of a series of seized samples (all previously determined on the basis of GC-mass spectrometry to contain MDMA) along with the spectrum of pure standard

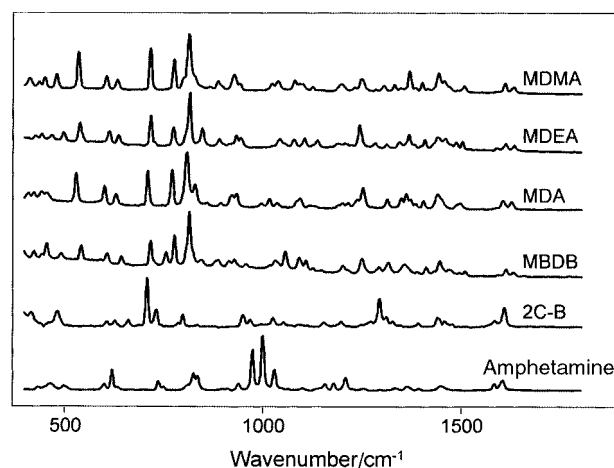


Fig. 1 Raman spectra of commercial standard samples of MDMA, MDEA, MDA, MBDB, 2C-B and amphetamine over the range 400–1700 cm⁻¹.

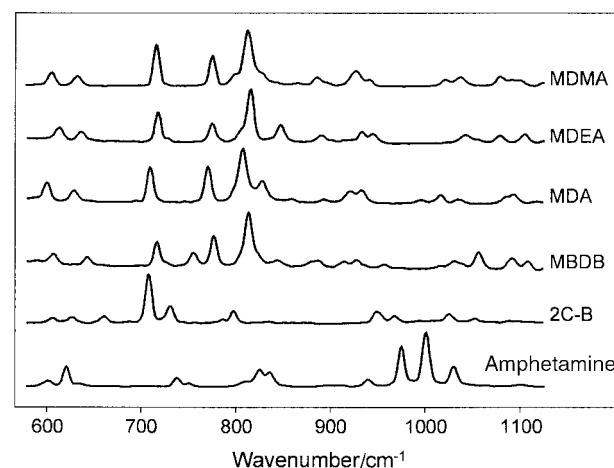


Fig. 2 Raman spectra of the same commercial standard samples of MDMA, MDEA, MDA and MBDB, 2C-B and amphetamine as were shown in Fig. 1 expanded to show the 600–1100 cm⁻¹ region in more detail.

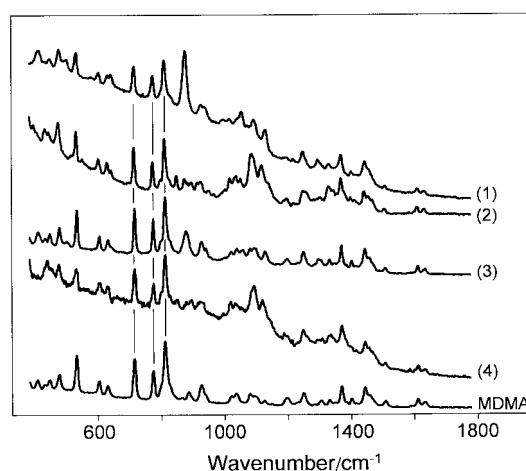


Fig. 3 The Raman spectra of a series of seized tablets (labelled 1–4), all of which were previously determined by GC-MS to contain MDMA, along with the spectrum of pure standard MDMA. All the spectra of the seized samples contain strong bands characteristic of the MDMA content, although there are clearly additional features due to the excipients that have been used to bulk the tablets.

MDMA. It is clear that 785 nm excitation gives spectra in which the fluorescence backgrounds are sufficiently low so as not to cause difficulties with the analysis.

All the spectra of the seized samples contain strong bands characteristic of the MDMA content, although there are clearly additional features due to the excipients that have been used to bulk the tablets. Unambiguous identification and full spectral fingerprinting is most readily achieved by digitally subtracting the bands due to the excipients from the spectra of the tablets to leave residual peaks which should match those of the active compound. Here we show the results of this subtraction process for two different MDMA-containing seized samples.

Fig. 4 shows the spectrum of an MDMA tablet which has been bulked with sorbitol. The MDMA and sorbitol both give distinct sets of Raman bands and there is little interference between the bands from either compound so that even before excipient subtraction the MDMA bands are readily identified. Subtracting the spectrum of sorbitol from that of the tablet removes any uncertainty in assignment since the resulting spectrum is identical to that of pure MDMA. Similarly, Fig. 5

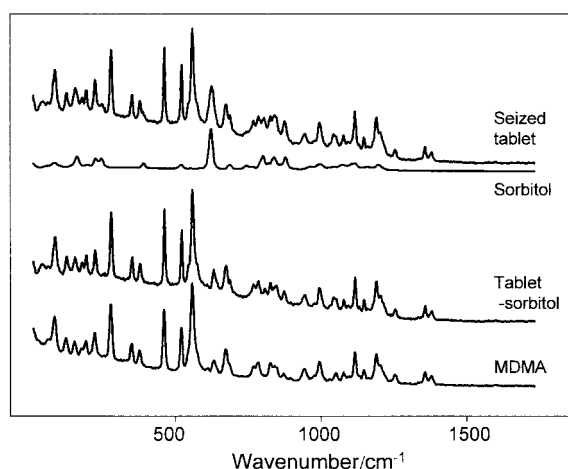


Fig. 4 An illustration of digital subtraction of excipient bands to leave the Raman spectrum of the active component. The top two spectra are those of an MDMA-containing seized tablet and a sample of pure sorbitol. Since MDMA and sorbitol both give distinct sets of Raman bands there is little interference between the bands from either compound. Subtracting the spectrum of sorbitol from that of the tablet gives a spectrum (shown in the figure) which is identical to that of pure MDMA, which is shown as the bottom trace.

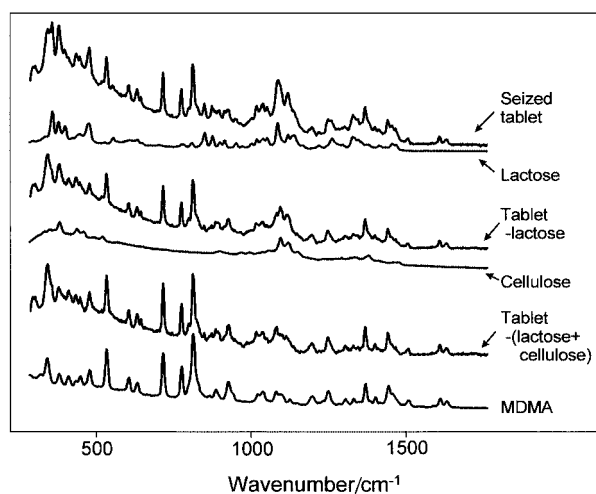


Fig. 5 An illustration of digital subtraction of excipient bands from a seized MDMA-containing containing tablet both cellulose and lactose. As in Fig. 4, the Raman spectrum of the seized tablet and spectra of the excipients are shown along with the final subtracted spectrum, which can be compared with that of the standard MDMA sample.

shows an MDMA tablet which has been bulked with a mixture of cellulose and lactose. The spectrum of this sample is extremely complex since there is more overlap between the bands of the drug and excipients but the strongest MDMA bands are still clearly visible in the raw data. The assignment is confirmed by subtraction of the bands due to lactose and then cellulose (see Fig. 5), which again results in a spectrum near-identical to that of pure MDMA.

Three component samples provide a greater challenge than simple samples made from a drug plus a single excipient but they can be analysed without excessive effort. To demonstrate this point and to show that the method is not confined to a single drug-excipient mixture we show here just one (for the sake of brevity) further example, which is a seized MBDB (from GC-MS) tablet. Fig. 6 compares the spectrum of the seized sample with that obtained by subtraction of the major excipient (lactose) and that of a pure MBDB sample. As was the case for the MDMA samples, the spectrum of the seized sample becomes very similar to that of the pure drug after subtraction of the major excipient. The only noticeable difference is the marginally high intensity of the group of bands around 1100 cm^{-1} , which is due to a small quantity of cellulose also present in the seized sample. For clarity of presentation this minor excipient contribution has not been subtracted from the spectrum in the figure.

In most cases the spectra of the seized sample after excipient subtraction is indistinguishable from the pure standards and, in addition to the MDMA and MBDB examples shown above, we have also found this to be the case for MDA and MDEA. However, two seized, known MDMA samples had clearly distinguishable strong bands whose positions were close to those of the pure MDMA standard but whose relative intensities were very different. Fig. 7 compares the unprocessed spectrum of one of these samples with the more common MDMA sample and the difference is clear even before excipient subtraction. The existence of differently hydrated/polymorphic forms of MDMA has been reported in studies of the pure drug¹³ and in seized samples.¹⁴ To test the hypothesis that the differences in the anomalous seized MDMA samples were due to a hydrated form of the drug we crystallised a small quantity of the initially anhydrous pure standard by evaporating the solvent from a small quantity of an aqueous solution of the complex placed on a metallic surface. The solid produced by this procedure formed small domains of crystalline aggregates. The spectra of the larger proportion of these aggregates were indistinguishable from that of the anhydrous standard but one of the domains gave a distinctly different spectrum (see Fig. 7) whose relative band

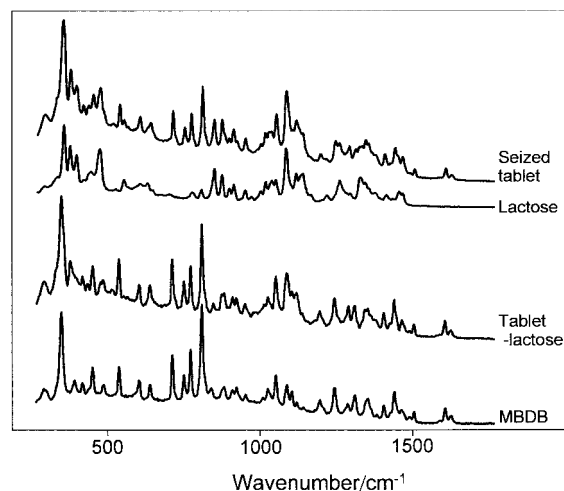


Fig. 6 An illustration of excipient subtraction in the Raman spectrum of an MBDB-containing, seized sample. The spectrum of the seized sample after subtraction of the major excipient (lactose) is very similar to that of the pure MBDB.

intensities mirrored those of the anomalous seized MDMA samples. Further characterisation of the hydrated form(s) of MDMA and their Raman spectra is now in progress.

Discussion

This is the first report on the Raman spectroscopy of the current most widespread class of drugs of abuse in the UK and at the outset it is important to emphasise that the data show that it is easy to distinguish between the drugs investigated, despite the similarity in chemical structure of some of them. Moreover, these differences are readily apparent even in unprocessed spectra of seized samples which have been bulked with other materials. The level of fluorescence background in the seized samples is sufficiently low that there is little difficulty in obtaining sufficiently high quality data with moderate 2 min data accumulation times while the fact that the technique is non-destructive (no sign of sample degradation was observed in any of the pure or seized samples) means that repeated measurements or more extensive signal accumulation should be possible if required.

Our original intention was to explore the possibility of using Raman spectroscopy to screen for these drugs in seized samples without the need for any preparation of the samples and with reasonably short data collection times. It is clear from this preliminary study that this approach is completely viable. The rationale behind the choice of the 785 nm excitation wavelength was that low-cost compact Raman instruments based on diode lasers are already commercially available and have a much greater chance of widespread use than, for example, ultra-violet excitation Raman systems or FT Raman systems, which are currently more expensive and physically larger than dispersive diode laser-based systems and are likely to remain so for the foreseeable future. The combination of simple data collection coupled with automated spectral database searching software should allow high throughput, completely automated sample screening to be realised in the near future.

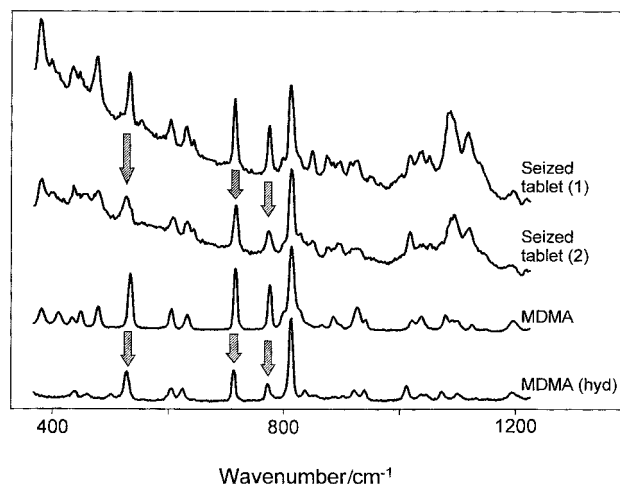


Fig. 7 The Raman spectra of two seized, known MDMA, samples (1 and 2), both of which have clearly distinguishable strong bands in positions close to those of the pure MDMA standard but which have different relative band intensities. The most obvious differences are marked by arrows. The lower pair of spectra are of an anhydrous sample of pure MDMA and a hydrated form prepared as described in the text. Again both spectra have strong bands in very similar positions but have differences in relative intensity which match those found in the seized samples.

However, the richness of the spectral information available from the Raman measurements will also allow more sophisticated analysis to be carried out. In particular, the ability to identify excipients as well as the drug content in a single measurement should give much greater ability to profile the drug supply available at street level. This ability to distinguish between different batches of samples on the basis of the excipients used is enhanced by the fact that the relative band intensities of drug and excipients vary with the relative dilution of the drug in the solid samples. Indeed, there is no reason why the technique should not be made at least semi-quantitative, for example the spectra of Figs. 3 (1) and (3), which are both MDMA–sorbitol mixtures, show very pronounced differences in the relative MDMA and sorbitol bands (814 and 877 cm^{-1} , respectively). In addition, the observation of differently hydrated forms of MDMA in seized samples with similar excipients gives another parameter by which apparently similar seized samples can be distinguished. The existence of polymorphic or hydrated forms of drugs of abuse in seized samples has not been considered in previous Raman studies but it clearly has implications not only for increasing traceability but also for construction of libraries of drug Raman spectra.

In conclusion, Raman spectroscopy of seized samples of ecstasy and related substances is a rapid and non-destructive method for the identification and characterisation of both the drug and the excipients present. The spectra can be used to distinguish between even chemically similar substances, such as MDEA and MBDB, and between differently hydrated forms of the same drug. The spectra can be processed to allow unambiguous identification of both drug and excipients (even when more than one compound has been used as the bulking agent) and the relative intensities of drug and excipient bands could be used for quantitative or at least semi-quantitative analysis. Finally, the simple nature of the measurements lends itself to automated sample handling so that instruments with throughputs of 20 samples per hour can be constructed using readily-available technology.

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Paper a908091k