ARTICLE

Drug tablets instant analysis by desorption-electrospray ionisation mass spectrometry

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Key questions to analytical chemists today remain: "What's in there?" and "How much?" Indeed, both qualitative and quantitative aspects are important; they depend on the context in which the analysis is made, or the length of time available to provide a result! In some cases, just knowing that an analyte of interest is present or not, is sufficient. In other cases, quantitation is essential—*different questions, different answers, different tools*.

Interest has grown in the past few years around ambient desorption ionisation techniques coupled to mass spectrometers. As mass spectrometry (MS) instruments are often the tools of choice in terms of specificity, sensitivity and speed; desorption techniques allow direct surface analysis and imaging. Different ways are used to desorb and ionise analytes, sometimes with the help of a matrix added onto the surface, usually under a vacuum interface. It is only recently that ambient desorption ionisation techniques appeared, allowing analysis at atmospheric pressure, which is a considerable advantage in terms of ease of implementation and simplicity. The sample is brought directly to the mass spectrometer and analysed in its original intact form.

A new application in this field is the use of desorption-electrospray ionisation (DESI) for the rapid analysis of drug tablets either commercially produced, illicit or unknown. DESI is an atmospheric pressure ionisation method, where charged liquid droplets are directed towards the surface to be analysed with the help of a gas jet consisting generally of nitrogen.[1] A hydro-organic solution is typically sprayed at a flow rate of a few microlitres per minute by applying a voltage of a few kilovolts. A small amount of acidic (i.e. formic, acetic acid) or alkaline (i.e. aqueous ammonia) modifier might be added to the solvent when acquiring spectra in the positive or negative mode, respectively. The gas is co-axially brought to the spraying needle and helps to accelerate liquid droplets on the surface. Desorption and ionisation (or vice versa, depending on the mechanisms involved) occur and ions are sampled by the mass spectrometer. Instrumentation, mechanisms and applications of DESI have been reviewed recently.[2]

For the analysis of tablets, instead of grinding up selected tablets, extracting them with an appropriate solvent, filtering non-soluble excipients and diluting before analysis by a conventional analytical technique such as gas chromatography/electron impact mass spectrometry (GC-EI-MS) or liquid chromatography tandem mass spectrometry (LC-MS/MS), tablets are analysed by DESI-MS without pretreatment, in their original solid form (Figure 1). The spot or the surface to be desorbed is positioned typically a few millimetres from both the sprayer tip and the ion sampling tube of the mass spectrometer. A few reports presenting the coupling of a DESI source with different kinds of mass spectrometers have been published with drug tablets being used as the samples of choice.[3–5] The reports have demonstrated the feasibility of these different couplings, but a wider range of examples was needed to show a more general application for the rapid qualitative analysis of tablets.

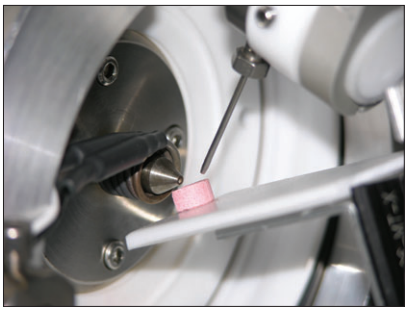

Figure 1. Direct ambient analysis of an illicit Ecstasy tablet by DESI-MS. The tablet is simply positioned in front of the mass spectrometer and the desorption occurs with the help of the inclined sprayer. Mass spectra of analytes on the surface are obtained in a few seconds.

A recent report by us has shown that different classes of compounds and contents can be desorbed from a larger variety of tablets.[6] A score of commercial tablets have been investigated: analgesic, benzodiazepine, antidepressant, hypnotic or antiepileptic—to name just few. The deprotonated or protonated pseudo-molecular ion of the main analyte was almost always the predominant ion (Figure 2), this observation was corroborated by other groups.[3,5,7] Drug contents ranging from 0.8% to more than 70% have been analysed with positive identification in our laboratory, but even lower amounts have been reported elsewhere.[3] Even when present as minor components, active ingredients can give a positive signal, although spatial distri-

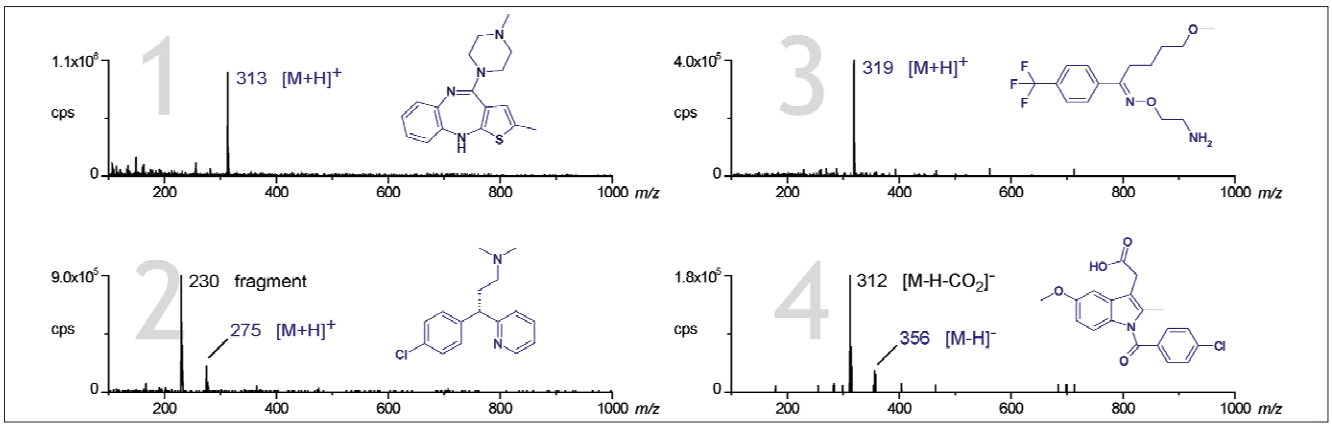

Figure 2. Typical DESI-EMS spectra of drug tablets, without background subtraction. (1) Zyprexa® tablet, containing 2.3% (w/w) of olanzapine (MW=312 Da), in positive mode. (2) Polaramine® tablet, containing 2.4% (w/w) of dexchlorpheniramine (MW=274 Da), in positive mode. (3) Floxyfral® tablet, containing 18% (w/w) of fluvoxamine (MW=318 Da), in positive mode. (4) Indocid® tablet, containing 11% (w/w) of indometacine (MW=357 Da), in negative mode.

bution starts to play an important role when dealing with contents in the few percent range, as microcrystals of the active ingredient are not uniformly distributed on the surface of the tablet. These results show a possible use of this technique as a simple preliminary screening test in emergency toxicology.

Another case where tablets would have to be rapidly and qualitatively analysed is that of illicit tablets. We investigated by DESI-MS some illicit tablets sold as "Ecstasy", seized on the local drug market. As shown in Figure 3 and Table 1, interestingly not all of them contained 3,4-methylene-dioxymethamphetamine (MDMA), the active ingredient of Ecstasy tablets. One tablet contained only caffeine, and others contained amphetamine or derivates (methamphetamine and methyl-thioamphetamine). GC-MS and LC-MS/MS analysis were performed in parallel to confirm the results obtained by DESI-MS. Another recent report also presented the analysis of Ecstasy tablets by DESI-MS, showing the identification of MDMA and methamphetamine, and also real-time sampling of *cannabis* plant material.[7] Colorimetric tests are currently used for on-site analysis, but they lack selectivity. With the help of smaller-sized MS instruments, this kind of ambient analysis could bring the selectivity of MS to new sites of analysis.

Total analysis time by DESI-MS is reduced to a minimum, as there is no sample preparation and no separation. Just a few seconds can give enough data to assess the presence of a specific compound in the tablet, with at least two MS/MS diagnostic fragments. This can be automatically obtained by an information-dependent acquisition strategy, where a first full scan of what is desorbed from the surface is recorded (i.e. the "survey scan" for precursor ions selection). The software then selects the most intense ions and sequentially performs MS/MS experiments (i.e. "dependent scans") on each of them to induce fragmentation for structure identification. Current software and instrumentation developments allow one to obtain data-rich spectra without having to optimise the compound-dependent fragmentation energy.

GC-MS and LC-MS/MS are currently well automated through the use of autosampler devices. However, depending on the GC parameters, individual analysis of an illicit tablet can routinely take around 5 min.[7] New fast- and ultrafast-GC as well as ultra-performance liquid chromatography (UPLC) will reduce sepa-

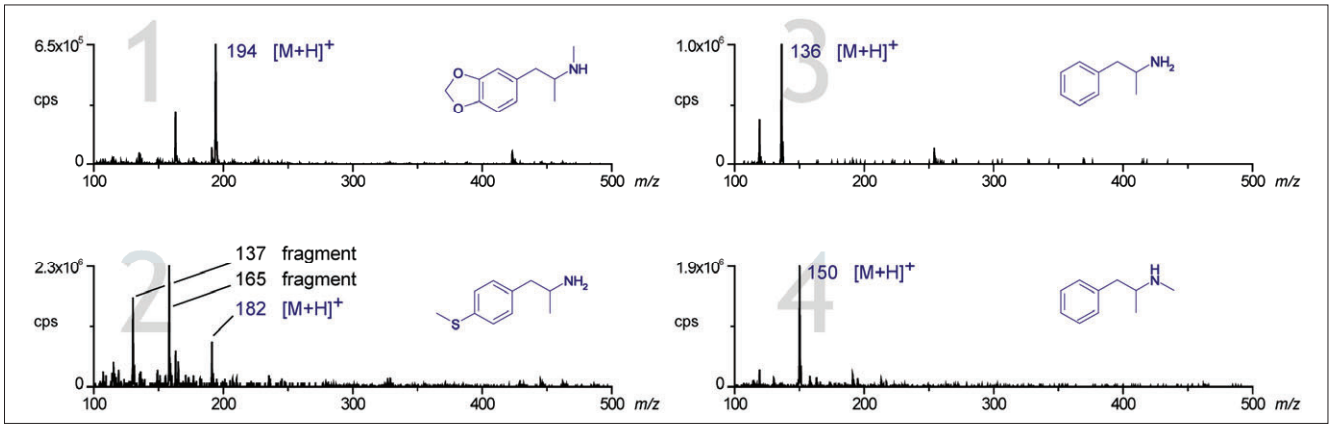

Figure 3. Full scan spectra of different illicit Ecstasy tablets analysed by DESI-MS, showing different analytes. (1) Tablet T8 contains Ecstasy (MDMA MW=193 Da), (2) T5 4-methylthioamphetamine (4-MTA, MW=181 Da), (3) T3 amphetamine (MW=135 Da) and (4) T7 methamphetamine (MW=149 Da). Spectra are shown without background subtraction.

Table 1. Comparison of analytes identified by DESI-MS, GC-MS and LC-MS/MS in a set of different Ecstasy tablets seized from the local drug market. Analytes in parenthesis correspond to minor components. MDMA: 3,4-methylene-dioxymethamphetamine; MDE: 3,4-methylene-dioxyethamphetamine; MTA: methyl-thioamphetamine.

Ecstasy tablet identifier	Analytes identified by DESI-MS	Analytes identified by GC-MS	Analytes identified by LC-MS/MS
T1	MDMA	MDMA	MDMA
T2	MDMA	MDMA, (MDE)	MDMA
T3	Amphetamine	Amphetamine Caffeine	Amphetamine (Caffeine)
T4	No desorption	MTA	MTA
T5	MTA	MTA	MTA
T6	Caffeine	Caffeine	Caffeine
T7	Metamphetamine	Metamphetamine Caffeine	Metamphetamine Caffeine
T8	MDMA	MDMA	MDMA

ration time, but not the time required for sample preparation. As they remain techniques of choice for quantitation, the simpler DESI-MS can be used first as a rapid qualitative screening tool, before complementary analyses is undertaken, if needed. It must be pointed out that a consequence of "rapid" can be, as shown in Table 1, that no desorption occurs or it can cause lower content analytes to be missed. A longer desorption is in some cases required to perform what could be called an "exhaustive desorption".

To increase throughput, moving belts with identical tablets placed on them have been developed, which allow a sampling rate as high as three samples per second.[3] The drawback of this approach is the difficulty of correct positioning for tablets of different sizes, especially different thicknesses. The distance between the spot desorbed and the sprayer tip or the ion-sampling orifice varies too much from one tablet to another when analysing a heterogeneous batch. An alternative is to use a robotised arm. Current robotised arms can transport a tablet and position it with regard to its size (a laser sensor has determined its height), scan the surface for some seconds and deposit the tablet back to where it was originally, within a cycle time of less than 10 s and a sufficient repeatability in positioning (20 µm are achievable).

The interesting feature of these desorption techniques is that solubilisation of the sample is no longer mandatory. Instead of physically changing the sample, from solid to liquid, it is analysed untouched. Spatial information remains high, contents of analytes on some areas of the surface are not averaged by the solubilisation, and chemical imaging is possible. Although DESI-MS does not have the resolving power of some more established desorption ionisation techniques like matrix-assisted laser desorption ionisation imaging (MALDI-IMS) or time-of-flight secondary ion mass spectrometry (ToF-SIMS), which have resolutions around 50 µm and 1 µm, respectively, DESI-MS has the great advantage of performing ambient analysis in air, without the need for a high-vacuum interface and without any matrix addition. Thus, the sample remains accessible while it is analysed. It means that experiments could even be performed on the sample during analysis, while its "chemical response" is monitored.

The very new DESI-MS technique complements the analytical toolbox, especially with its power to instantly question surfaces in ambient air, without requiring any matrix addition. As this source is simple in terms of construction and operation at atmospheric pressure it could well fit smaller sizes of mass spectrometers. There is no doubt that desorption techniques are an alternative to solution-based ones. Gaining more experience on DESI-MS as well as related ambient analysis techniques will help bring the power of mass spectrometry to answer new "ambient questions".

Acknowledgements

The authors would like to thank Jean-François Mandscheff (University of Geneva), Marc Fathi (Geneva University Hospital), Christian Giroud and Marc Augsburger (Institute of Legal Medicine, University of Lausanne) for valuable help in this project, as well as Linda Allen for editorial suggestions.

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