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DART–MS in-source collision induced dissociation and high mass accuracy for new psychoactive substance determinations

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ABSTRACT

The influx of new psychoactive substances is a problem that is challenging the analytical capabilities of enforcement agencies. Cathinone designer drugs are less likely to be included in routine drug screens and typical drug formulations are commonly mixtures with continually shifting components. Ambient ionization mass spectrometry employs relatively mild conditions to desorb and ionize solid samples, imparting much less energy than that associated with conventional mass spectrometry methods. Direct analysis in real time mass spectrometry (DART–MS) is an ambient ionization method that was employed to rapidly screen cathinones, alone and in mixtures, readily enabling differentiation of the active drug(s) from various cutting agents. Accurate mass determinations provided preliminary identification of the various components of drug mixtures. The data generated in forensic mass spectrometry can be used for both elemental composition formulations and isotope abundance calculations for determination of unknown psychoactive substances, and we demonstrate how this data could be applied to the presence of new drugs as the active components shift in response to regulations. Isotope abundance calculations were used to develop a candidate pool of possible molecular formulas associated with cathinones as a specific class of designer drugs. Together, the combination of a time-of-flight (TOF) mass analyzer along with in-source collision-induced dissociation (CID) spectra were used to drastically narrow the pool of candidates to a single molecular formula. The $[M+H]^+$ and product ion peaks provided data for presumptive analysis of various substituted synthetic cathinones in a manner that is complementary to conventional GC–MS analysis of new psychoactive substances.

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1. Introduction

A series of new psychoactive substances are now being manufactured and sold as alternatives to compounds such as ecstasy, methamphetamine, and marijuana [1–6]. One class of these designer drugs is cathinone "bath salts", which have a core β-ketophenethylamine structure upon which various substituents are appended to create novel variants purposefully designed to circumvent legal restrictions, while retaining psychoactive properties. Slight chemical modifications in the core structure take advantage of the vagueness of current controlled substance analog laws, which leads to the "marketing" of these compounds as legal alternatives to banned substances. These new substances are now widely available for sale on the Internet and have been linked to an increase in poison control center calls, emergency room visits, and fatalities. Recent research assessing the effects of a particular cathinone derivative methylenedioxypyrovalerone (MDPV), suggest that it has significantly greater potency than methamphetamine, poses a higher risk of abuse, and is more likely to have long-term toxicity effects or be fatal [7]. Contributing to the incidence of overdoses is that these substances are oftentimes found as mixtures of multiple cathinones, with ever changing formulations of the active ingredients [8–12]. The shifting of active component formulations, their varying concentration and purity, and the continual emergence of new variants all contribute to this problem. Although legislation has been continually modified to address the constant influx of new cathinone variants, controlling the access and abuse of these drugs remains a difficult challenge.

Current rapid, preliminary testing methods for cathinones are limited, with conventional color tests or immunoassays not fully

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developed or with limited effectiveness across this structural class of molecules, analogs, and emerging variants [8,13–16]. Furthermore, confirmatory testing techniques employed for detecting cathinones center around conventional GC–MS, which also can be problematic for a number of reasons [8,13,16]. Specifically, mass spectral fragmentation patterns of cathinones from GC–MS are of limited utility for the purposes of molecular characterization, as they often exhibit extensive fragmentation with weak or even absent parent peaks [10,17–19]. Generally, this extensive fragmentation means that mass spectra across this class of compounds are similar enough to impede the ability to distinguish between cathinones. Ultimately, the limitations associated with conventional methods for cathinone testing and analysis, the inclusion of multiple cathinones or adulterants in a single product, and the constantly changing ingredient profiles, all contribute to the sample testing backlogs that are a growing problem for U.S. crime labs and enforcement agencies [18,20]. With the continual expanding and changing field of designer drug abuse, high throughput, informative methods are needed to keep pace with ever increasing casework.

Advanced mass spectrometry techniques, specifically those employing higher resolution and high mass accuracy measurements, have recently gained traction in part because of their potential to help identify new psychoactive substances for which no reference standards are available, as well as their ability to compensate for some of the limitations associated with more conventional analytical techniques [21–23]. High mass accuracy measurements can be used to drastically narrow the list of potential candidate formulas used in drug class determination or identification of an unknown. In the analysis of suspected designer drug samples, the data provided by these high resolution methods can be searched against NIST or the Scientific Working Group for the Analysis of Seized Drugs (SWGDRUG) libraries to further narrow the candidate pools or confirm an unknown substance's potential place within a drug class [24]. Once this preliminary information is established, it allows for further, more directed confirmatory analyses. An added advantage of these methods is that the information they yield is more detailed and/or complementary to that provided by conventional GC–MS methods. As compared to techniques such as immunoassay screening which provide information about the general chemical class of a drug that is present, methods such as high resolution DART–TOF–MS, when used as a preliminary screening tool, are not only just as rapid, but also provide high resolution $[M + H]^+$ and fragment ion information that is often not obtainable by the routine GC–MS protocols most often employed in crime labs.

In addition, high resolution data can be obtained using more recently developed ambient MS methods. Several ambient ionization methods, which include direct analysis in real time (DART), desorption electrospray ionization (DESI), and desorption atmospheric pressure photoionization (DAPPI), have demonstrated utility in forensic drug analysis applications, and have the added advantage that the analyses are instantaneous and performed directly on the solid or liquid sample [18,25–30]. In previous work, DART–MS was applied to cathinone analysis, demonstrating that DART–TOF–MS can be used to differentiate between structural isomers and closely related cathinone compounds [18]. However, although commercially available "street" samples can be found for sale as pure compounds, they are commonly observed to be combined with adulterants as binary mixtures or occasionally incorporated as mixtures of multiple cathinones [9,10,14]. Such street drugs are often "cut" with diluents to add bulk to the sample sold, thereby increasing profits for the drug dealer or manufacturer. Common cutting agents can include stimulants or anesthetics having their own central nervous system effects, such as benzocaine, lidocaine, and caffeine [10,20]. Indeed, work by Brandt and coworkers has shown that common cathinone mixture additives include these stimulants, among other compounds [9,10,14].

Herein, DART–TOF–MS was not only used to identify cathinones within mixtures containing common adulterants, but it was also demonstrated that this method can serve as a means to characterize the individual components within complex MS profiles of drug mixtures. In-source collision induced dissociation (CID) was employed to demonstrate that the high mass accuracy measurements of constituents of these mixtures can provide informative $[M + H]^+$ values and specific molecular formulas related to both $[M + H]^+$ and product ions. In this capacity, seized samples could be triaged using rapid high resolution DART–TOF–MS to provide definitive information on the presence of novel cathinone components as well as to indicate the presence of various cutting agents. Solid samples were ionized directly without solubilization, extraction, derivatization, or coupling to chromatographic methods, which greatly reduced analysis time while providing important information that cannot be gleaned from traditional preliminary or confirmatory screening methods. The rapidity of the method may serve not only as a means to manage the backlog of forensic drug cases, but may also promote more effective regulation and response to the rapidly evolving synthetic drug production and distribution pipeline.

2. Experimental

2.1. DART–MS sample ionization

A DART-SVP™ ion source (Ionsense, Saugus, MA, U.S.A.) was used for ionization, combined with an AccuTOF™ mass spectrometer (JEOL USA, Inc., Peabody, MA, U.S.A.) to acquire all mass spectra. Samples were tested as previously described. Briefly, solid materials were sampled directly by dipping the closed end of a capillary melting point tube in the solid material and holding the tube between the heated helium stream from the DART ion source and the inlet of the mass spectrometer [18]. Samples were either held in the correct position manually, or by the use of the Dipit-tubes™ system (Ionsense, Saugus, MA U.S.A.). The Dipit-tube system consists of a multi-sample rack that moves capillary tubes laterally while placing them in the optimal position for sampling [18,31]. The automated rack moves perpendicular to the flow of ionizing gas to enable optimal positioning of samples and permit analysis of multiple samples within a single assay. Dipit-tubes with cathinone samples were positioned 1.8 cm apart in the rack and transported laterally through the helium stream at a speed of 1.0 mm/s while acquiring spectra. DART–MS analysis is not susceptible to sample carryover or contamination between samples, and no carryover or contamination is observed in any of our spectra.

2.2. DART–MS parameters

An AccuTOF mass spectrometer was run in positive ion mode for all measurements, with a resolving power of 6000 (FWHM definition) as measured for protonated reserpine. Poly(ethylene glycol) (PEG; average MW 600; Sigma-Aldrich, St. Louis, MO, U.S.A.) was measured with each data acquisition as a reference standard for exact mass determinations. Orifice 1 was varied from 20, 30, 60, and 90 V, while orifice 2 was operated at 5 V, and the ring lens voltage was 3 V. The RF ion guide voltage was generally set to 600 V to allow detection of ions above m/z 60. The DART ion source was operated with helium gas (Ultra high purity; Airgas, Cambridge, MA, U.S.A.) at 300 °C, a flow rate of 2 L/min, and a grid voltage of 530 V. The mass range was 60–600 Da. TSSPro3 software (Shrader Analytical, Detroit, MI, U.S.A.) together with Mass Spec Tools (MSTools) programs (ChemSW Inc., Fairfield, CA, U.S.A.) were

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