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TECHNICAL NOTE

CRIMINALISTICS

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Analysis of Alprazolam by DART-TOF Mass Spectrometry in Counterfeit and Routine Drug Identification Cases

ABSTRACT: The high prevalence of alprazolam abuse translates to an increased workload for crime laboratories in characterizing seized tablets. These tablets may originate as diverted pharmaceuticals or counterfeited mimics, so efficient analytical techniques should provide confirmatory data while minimizing destruction of evidence. We offer the first report of a validated forensic method for confirming alprazolam tablets by direct analysis in real time–time of flight (DART-TOF) mass spectrometric analysis. This technique provides rapid identification of target analytes with minimal sample preparation, allowing direct analysis in the atmospheric sample gap. Selectivity is achieved through high resolution and mass accuracy, unique ion fragments, and chlorine isotopic ratios. This method utilizes fragmentation in two separate voltage functions to observe the alprazolam pseudo molecular ion at 309.09070 using 40 V and major ion fragments of 281.07197 and 205.07657 at 120 V. These parameters allow our laboratory to confirm alprazolam tablets efficiently, without compromising quality forensic standards.

KEYWORDS: forensic science, controlled substances, alprazolam, direct analysis in real time, confirmation, counterfeit

The high rate of use and abuse of the controlled benzodiazepine alprazolam (Xanax) has a significant effect on submissions to crime laboratories, specifically in drug identification and toxicology sections. According to the 2008 survey from the National Forensic Laboratory Information System (NFLIS), the Harris County Institute of Forensic Sciences in Houston, Texas has a very high occurrence of alprazolam tablet submissions—7% of all exhibits—compared to the national average of 2% (1). This figure does not include suspected alprazolam exhibits for which no analyses were performed. This high prevalence is not surprising as alprazolam, along with hydrocodone/acetaminophen (Vicodin) and carisoprodol (Soma), comprise what is known as the "Houston Cocktail," reflecting the frequency with which the combination of these substances is encountered by both physical tablet submissions for drug identification and in postmortem samples submitted for toxicological analysis.

While clandestinely produced tablets containing designer phenethylamines and related compounds are common in the forensic laboratory, they are easily distinguishable from legitimate pharmaceutical tablets on the basis of visual observation. However, there has been a marked increase in recent years of clandestinely produced, counterfeit pharmaceutical tablets. A recent review of the DEA *Microgram Bulletin* revealed many accounts of counterfeit pharmaceutical tablets containing alternative, primarily noncontrolled, active ingredients. Oftentimes, the appearance of the counterfeit tablets is strikingly similar to, or visually indistinguishable from the authentic pharmaceutical product. Of specific interest are published reports of mimic alprazolam tablets with the logo "GG249" actually containing melatonin in New York (2) and Texas (3), in addition to tablets reported to contain 5-(4-chlorophenyl)-7-bromo-1,4-benzodiazepin-2-one, a noncontrolled benzodiazepine, in Florida (4). The Institute of Forensic Sciences recently received their first two separate cases containing visually similar mimic alprazolam tablets (white, rectangular, triple-scored tablet bearing the logo "GG249") in which melatonin was the confirmed ingredient. Because the abundance of counterfeit tablets is likely to eventually cross into the legitimate tablet population, leading to frequent mixed submissions of suspected alprazolam tablets, it may be desired to sample a greater number of tablets from a single exhibit on a regular basis. Presented herein is a rapid confirmatory instrumental method using direct analysis in real time (DART)–time of flight (TOF) mass spectrometry which makes this task significantly more efficient than traditional analytical methods, while still producing high quality data suitable for confirmatory analysis.

The DART ion source coupled with a TOF mass spectrometer is a powerful analytical tool which allows for the rapid identification of target analytes. DART is a unique, open-air ionization source that requires little-to-no preparation as samples can be introduced in their native forms, whether solid, liquid, or gas (5). Sampling of solids occurs through high sensitivity surface analysis, but can be used to detect internal components given the appropriate matrix and instrumental conditions. High resolution mass spectra are obtained almost instantaneously by the coupled TOF detector. While the surface ionization mechanism of DART is still not completely elucidated, it is believed to involve an ionizing beam of heated, metastable helium ions generated by a needle electrode with a potential of several kilovolts. In positive mode, metastable

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helium ions interact with atmospheric water molecules to generate hydronium clusters, which in turn transfers one or more protons to the sample molecule, generating a "pseudo molecular" ion. In negative mode, the dominant ion formation involves reactions between the metastable helium ions and oxygen–water clusters, which then form the corresponding adducts (5,6).

The TOF detector provides rapid identification based on high mass accuracy (5 mmu) and resolution (6000), along with isotopic patterns and fragmentation (7,8). The function voltage differential between Orifice 1 (O1) and Orifice 2 (O2) inside the TOF detector creates molecular strain leading to fragmentation of the generated pseudo molecular ion. This fragmentation can be negligible, minimal, or extensive depending on the chosen function voltage. Additionally, a function-switching mechanism allows for various voltage differentials to be applied sequentially, yet in near-real time, providing fragmentation information under different sets of conditions. This assists in distinguishing compounds which may share the same monoisotopic mass but have distinct fragments.

DART-TOF is an appealing tool in forensic chemistry as neither time-consuming chromatographic separation nor significant sample preparation is required prior to detection, thus use of this technique can improve case turn-around time and reduce laboratory backlog. A review of forensic literature reveals that this technique has been used primarily in a presumptive analytical capacity (9–13) and no validation has been published addressing confirmation of analytes for forensic laboratory casework.

TOF mass spectrometry is a technique generally coupled with a variety of ionization sources, such as matrix-assisted laser desorption/ionization (MALDI) or electrospray ionization (ESI). Consequently, TOF is commonly used to analyze large molecules and biomolecules including peptides and nucleic acid sequences. Unfortunately, little manufacturer information is available regarding mass accuracy in the molecular weight range applicable to the majority of forensic drug samples. For example, the JEOL AccuTOF™ performance certification is based upon analysis of compounds of a higher molecular weight than those commonly encountered in the forensic laboratory and states ±5 ppm mass accuracy for m/z 437–789. Testing, however, has shown that it is very difficult to routinely achieve this level of accuracy for the majority of analytes routinely analyzed including cocaine (m/z = 303), methamphetamine (m/z = 149), and alprazolam (m/z = 308). Additionally, the AccuTOF™ sensitivity measurements were also determined using an ESI source, but to our knowledge, no sensitivity data is yet publicly available utilizing the DART ion source.

In an effort to reduce case backlog and maintain efficient turn-around-time, DART-TOF analysis was investigated for the rapid confirmation of alprazolam. After performing an in-depth laboratory validation of the DART-TOF instrumentation, a systematic study to define the sample acceptance criteria and validate the instrument for the confirmatory analysis of alprazolam was performed. The acquisition parameters and validation results are presented herein.

Materials and Methods

Chemicals

Analytical standards of alprazolam (1 mg/mL; Alltech, Nicholasville, KY) and phenylbutazone (5 mg/mL; Sigma–Aldrich, St. Louis, MO), were prepared from solid in our laboratory using high-purity methanol (Burdick & Jackson, Muskegon, MI or equivalent). The mass calibration standard was polyethylene glycol PEG-600 (JEOL Ltd., Tokyo, Japan) diluted with methanol. Additionally, samples of suspected alprazolam tablets of different logos were collected from numerous laboratory cases for this study.

Instrumentation

An IonSense (Saugus, MA) DART-100 Direct Analysis in Real Time source coupled with a JEOL (Peabody, MA) AccuTOF™ JMS-T100LC time of flight mass spectrometer (DART-TOF) was utilized for analysis. Instrument operation was performed by DART Control software, v2.11 and Mass Center System software, v1.3.6e, both provided by JEOL. Pseudo molecular and fragment exact mass predictions were calculated by JEOL Elcomp software, v3.0. Data acquisition was performed in profile mode from m/z 60 to 600 for all experiments and subsequently converted to centroid mode, an average calculated for points in the upper 50% of the peak. DART ionization was performed in positive mode. Solid standards were dissolved in methanol and applied to a borosilicate melting point tube (Kimble Glass Inc., Vineland, NJ), followed by manual introduction into the sample gap of the DART source. Suspected alprazolam tablets were directly introduced into the sample gap, unless otherwise indicated.

Instrument Parameters

Because there have been no published reports of the confirmation of controlled substances utilizing DART-TOF, the Harris County Institute of Forensic Sciences performed an in-depth instrument validation prior to analyte-specific validations in order to optimize the many parameters and acceptance criteria necessary to produce reliable spectra for sample confirmation. Specific instrument parameters utilized are listed in Table 1 and were determined from the repeated analysis of multiple controlled substance standards. Areas investigated in the instrument validation include background profile, sensitivity, resolution, mass accuracy, reproducibility, and mass calibration. A procedure was developed to include daily system verification utilizing a 10 ng alprazolam sample with lower limits defined with regards to signal-to-noise ratio and peak resolution. Mass accuracy was required to be ±5 milli-atomic mass unit (mmu) from the calculated value of each pseudo molecular or fragment ion. Additionally, criteria were established for the mass calibration curve residual ($1 - R^* < 1 \times 10^{-10}$) and standard error values (<0.002). All parameters were determined after repeated analysis utilizing both analytical standards and case samples.

Analytical Procedure

Prior to each sample introduction, a methanol blank was introduced and analyzed to ensure a clean system. Following sample

TABLE 1—*DART-TOF instrument and acquisition parameters.*

DART needle voltage	+3500 V
Grid electrode voltage	+150 V
Discharge electrode voltage	+250 V
DART temperature	300°C
Helium flow	3.5 L/min
Orifice 1 voltage	40 V for function 1 120 V for function 2
Orifice 1 temperature	100°C
Ion guide peak voltage	300 V
Detector voltage	2300 V
Acquisition range	m/z from 60 to 600
Spectrum record interval	0.25 s

introduction, PEG-600 calibration standard was introduced and a multi-point internal mass calibration was performed for the current sample acquisition.

Exact Mass Analysis

For determining experimental exact mass, 30 previously analyzed alprazolam tablet case samples were subjected to analysis by DART-TOF. Presumptive examination was performed by logo match against an approved literature reference, or UV–Vis spectrophotometry in instances when a full logo was not visible. DART-TOF confirmation was considered successful upon the presence of the alprazolam pseudo molecular ion and two selected fragment ions. This data was compared with the conventional GC–MS or FT-IR analytical results. The exact mass of the pseudo molecular ion was observed with Function 1 (F1) at 40 V, and the exact mass of the two fragment ions was obtained from Function 2 (F2) with O1 at 120 V. These voltages were determined through repeated introduction of an alprazolam standard (1 mg/mL in methanol) to optimize the abundance of the pseudo molecular and fragment ions in the respective functions.

Homogeneity Study

A homogeneity study was conducted to investigate the effect of the sample form on the result, and if different introduction methods could lead to exact masses outside the defined mass window. A full tablet from three different cases was chosen and broken in half. Three areas of the first half tablet were introduced: the flat surface, the tablet edge, and the broken surface. The second half tablet was crushed into powder and divided into two parts. The first portion was introduced in powder form by dipping a melting point tube into powder and then placing it into the sample gap of the DART source. The second portion was dissolved into 1 mL methanol, vortexed, and introduced using a melting point tube. This was performed to determine if different methods of sample preparation and introduction affected the exact mass result and overall sensitivity.

Interference and Selectivity Studies

The original instrument validation indicated that mass accuracy is reliable ±5 mmu. To give additional safety in the identification of potential interfering substances, a survey of compounds ±10 mmu of the alprazolam mass was performed utilizing the NIST Chemistry Webbook (14). Potential interfering compounds were identified and investigated.

Results

Exact Mass Analysis

JEOL Elcomp elemental composition software calculated the exact monoisotopic masses of the pseudo molecular ion to be 309.09070 ($C_{17}H_{13}ClN_4 + H^+$), detected in F1 (40 V), and the major fragment ions to be 281.07197 ($C_{16}H_{12}ClN_3$) and 205.07657 ($C_{14}H_9N_2$), detected in F2 (120 V) shown in Fig. 1. Under the moderate F1 voltage, virtually no fragmentation was observed, leaving the pseudo molecular ion dominant. Sequential acquisition in F2 indicates a distinct decrease in abundance of the pseudo molecular ion and the presence of two fragment ions, supporting a likely parent/daughter ion relationship. Comparison to MS/MS spectral information supports a transition from the pseudo molecular ion to the *m/z* 281 fragment and additional fragmentation from *m/z* 281 to 205; however, additional investigation is needed to definitively assign these transitions. One notable spectral feature of the F1 spectrum is a 3:1 isotopic ratio of the M:M+2 ion peaks. This is due to the presence of a single chlorine atom, having stable isotopes of ^{35}Cl (75.77% abundance) and ^{37}Cl (24.23% abundance).

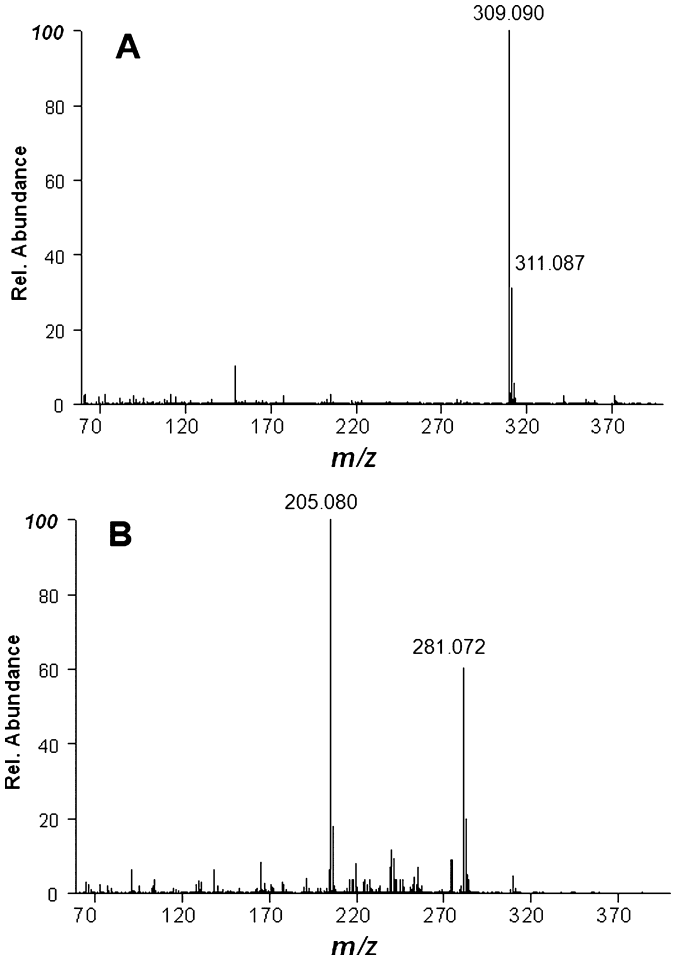

FIG. 1—*DART-TOF spectra of alprazolam fragmented in Function 1 at 40 V (A) and in Function 2 at 120 V (B). The approximate 3:1 ratio of m/z 309 to 311 peaks in (A) is indicative of the presence of a chlorine atom.*

In all 30 case samples analyzed, alprazolam was able to be positively identified by its pseudo molecular ion and two fragment ions within ±5 mmu mass accuracy (Fig. 2). No deviation greater than 3 mmu was observed for any ion or fragment ion in this study. The chlorine isotopic pattern of M:M+2 at approximately 3:1 ratio was also verified on the pseudo molecular ion spectra, providing further criteria for confirmation. These positive results are in agreement with the previous confirmatory results obtained by GC–MS or FT-IR methods.

Homogeneity Study

The case samples analyzed for exact mass analysis were in tablet form. However, suspected alprazolam samples are occasionally submitted in crushed or powder form. To our knowledge, no data has been published with regard to the effect of tablet edge orientation within the sample gap. Subsequently, a homogeneity study was conducted to investigate the effect of the sample form as described in the "Materials and Methods" section. Table 2 displays the

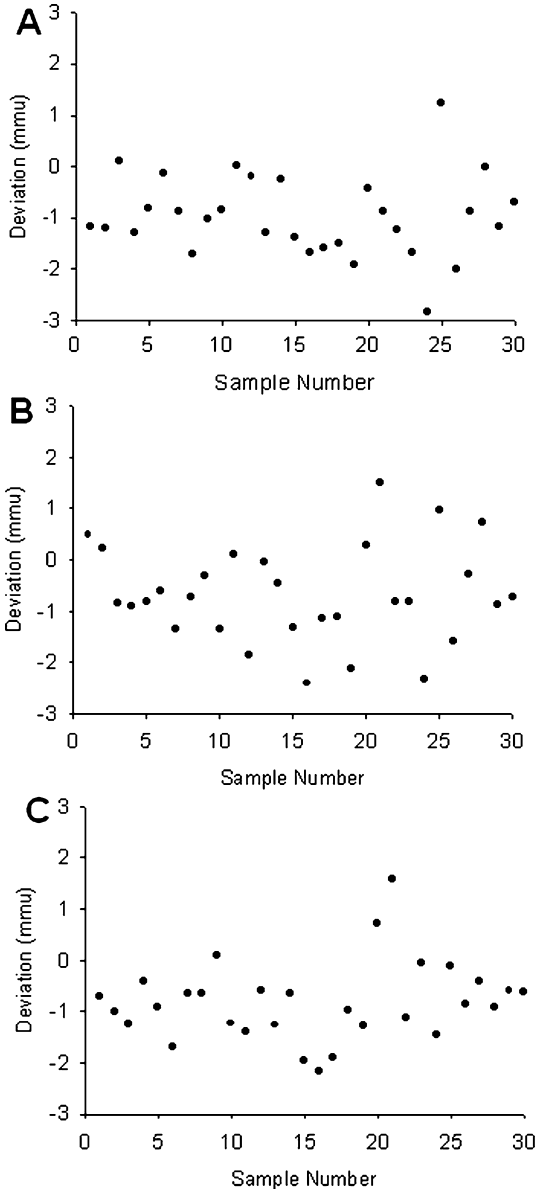

FIG. 2—*Thirty alprazolam case sample tablets were analyzed via DART-TOF and data were examined for deviation from the computed exact mass of the m/z 309 ion (A), m/z 281 fragment ion (B), and the m/z 205 fragment ion (C). All introductions were well within the defined 5 mmu window.*

results of the three case samples tested in each of five sample forms. It was determined that there was no significant difference with regard to the orientation of sample introduction. Due to the manual nature of sample introduction into the sample gap, the position was unable to be standardized across all samples, thus it was difficult to separate the effects of sample preparation versus sample gap position. Nonetheless, ion signals were sufficiently abundant for all sample types, regardless of these variables.

Interference Study

The traditional approach to GC–MS interference studies would examine the co-elution/spectral similarities between alprazolam and other benzodiazepines due to the possibility of co-elution between analytes of similar structure. Because DART-TOF does not utilize chromatography, the only concern is compounds of similar mass. No known benzodiazepines have a monoisotopic mass near that of alprazolam, therefore a compound search was performed. Widening the exact mass parameter by a safety factor of 2, a NIST Webbook survey of compounds with monoisotopic masses ±10 mmu of alprazolam results in nine possible interfering compounds (Table 3). The presence of the 3:1 M:M+2 ratio alone excludes compounds not containing chlorine, leaving three remaining possible interfering compounds from the original list: liarozole [CAS# 145858-50-0], (*p*-chlorobenzyl)(*m*-tolylazo)-malononitrile [CAS# 3701-16-4], and (*p*-chlorobenzyl)(*p*-tolylazo)-malononitrile [CAS# 3701-17-5].

At the time of validation, liarozole was being investigated as an anti-cancer agent and was not commercially available. Minimal information was available for the malononitrile derivatives, categorized only as drugs/therapeutic agents, and they were not commercially available. Thus, this study resulted in an exclusion of all reasonable interfering compounds within the molecular weight tolerance range of alprazolam. Whereas all available compounds ±10 mmu of alprazolam were eliminated on the criteria above, the noncontrolled analgesic phenylbutazone was chosen for the selectivity study by nature of being a pharmaceutical tablet preparation with the same nominal mass as alprazolam and a monoisotopic mass of 309.16030.

Selectivity Study

Utilizing the alprazolam acquisition method, 10 sample introductions of phenylbutazone were obtained and analyzed (Fig. 3). Spectra were carefully examined for the presence of the characteristic alprazolam fragments. The pseudo molecular ion ranged from 68.42 to 71.76 mmu away from that of alprazolam, significantly

TABLE 2—*Homogeneity study.*

ID (Logo)	Sample Form	$[M+H]^+$ Mass	Diff. (mmu)	Frag. 1 Mass	Diff. (mmu)	Frag. 2 Mass	Diff. (mmu)
A (G3722)	Flat surface	309.08933	−1.37	281.07089	−1.08	205.07520	−1.37
	Edge	309.09028	−0.42	281.07238	0.41	205.07803	1.46
	Broken surface	309.09085	0.15	281.07266	0.69	205.07660	0.03
	Dry powder	309.08961	−1.09	281.07208	0.11	205.07757	1.00
	Powder in MeOH	309.09011	−0.59	281.07171	−0.26	205.07580	−0.77
B (R039)	Flat surface	309.08816	−2.54	281.06993	−2.04	205.07656	−0.01
	Edge	309.08882	−1.88	281.07051	−1.46	205.07514	−1.43
	Broken surface	309.09036	−0.34	281.07192	−0.05	205.07695	0.38
	Dry powder	309.09047	−0.23	281.07208	0.11	205.07736	0.79
	Powder in MeOH	309.09107	0.37	281.07209	0.12	205.07590	−0.67
C (GG249)	Flat surface	309.09127	0.57	281.07186	−0.11	205.07498	−1.59
	Edge	309.09068	−0.02	281.07221	0.24	205.07614	−0.43
	Broken surface	309.08936	−1.34	281.07138	−0.59	205.07727	0.70
	Dry powder	309.09018	−0.52	281.07221	0.24	205.07710	0.53
	Powder in MeOH	309.08976	−0.94	281.07117	−0.80	205.07546	−1.11

TABLE 3—*Potential alprazolam interference compounds.*

	Compound Name	Nominal Mass (protonated monoisotopic mass)	mmu Difference	Cl
1	Cyclotetrasiloxane, heptamethyl-,vinyl-	308.08 (309.08299)	7.71	0
2	Tris(1,2-ethanediamine-*N*,*N*′)nickel dichloride dehydrate	308.08 (309.08712)	3.58	0
3	1,2,3-Diphosphaarsirane, 1,2,3-tris(1,1-dimethylethyl)-	308.08 (309.08822)	2.48	0
4	Alprazolam	308.08 (309.09070)	–	1
5	Methane sulfonic acid, phenylcarbamoyl-, aniline salt	308.08 (309.09090)	0.20	0
6	6,13-Pentacenedione	308.08 (309.09155)	0.85	0
7	Liarozole	308.08 (309.09070)	0	1
8	Malononitrile, (*p*-chlorobenzyl)(*m*-tolylazo)-	308.08 (309.09070)	0	1
9	Malononitrile, (*p*-chlorobenzyl)(*p*-tolylazo)-	308.08 (309.09070)	0	1

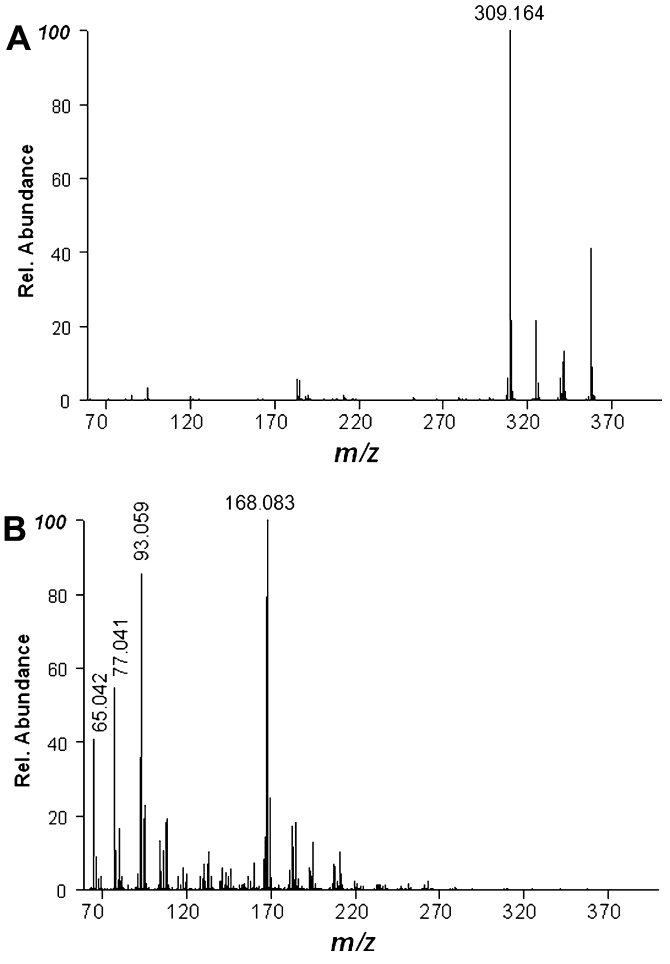

FIG. 3—*DART-TOF spectra of phenylbutazone fragmented in Function 1 at 40V (A) and in Function 2 at 120V (B) utilizing the same acquisition method as alprazolam. No similar fragments to those of alprazolam appear in Function 2.*

outside the ±5 mmu window required for alprazolam confirmation. Additionally, F2 generated fragment ions substantially differ from those of alprazolam. The isotopic pattern of M:M+2 at approximately 3:1 ratio was not observed for phenylbutazone, further differentiating it from alprazolam. The interference and selectivity studies provide additional confidence that all reasonable compounds that could be misidentified as alprazolam have been researched and excluded with a high degree of confidence.

Discussion

Maintaining a minimal case backlog and reducing turn-around-time is of paramount interest to all crime laboratories. This can be facilitated in several ways, the most direct of which is to reduce analytical time by more rapid instrumental methods. Being one of the most common types of evidence submitted to the Institute of Forensic Science for drug analysis, alprazolam tablets were targeted to be the first compound for analysis via DART-TOF, and the method utilized has been presented herein.

Unlike an electron impact mass spectrometer, which yields complete fragmentation at 70 eV, the DART allows for the ionization and subsequent introduction of pseudo molecular ions into the TOF, where a voltage differential in one or more functions fragments the species due to molecular strain. Because GC–MS methods employ chromatographic separation in order to differentiate compounds of similar masses and/or fragmentation, it is also the most time consuming portion of the analysis. TOF mass spectrometry has a much higher resolution and mass accuracy than the quadrupole mass analyzer generally employed in GC–MS, giving significant formula information from the pseudo molecular ion itself. The addition of a subsequent second function to generate additional fragments from the pseudo molecular ion yields even more specificity to the data, despite the fact that in general, fewer fragments are produced compared to electron impact methods. As DART ionization is an open-atmosphere method, it should be noted that there may be instrument- and environment-dependent modifications in the voltages to achieve optimal ion balance.

Nonetheless, confirmation using currently validated methods is still subject to instrumental limitations, and caution must be exercised when interpreting results. An example is that the direct analysis of solids using DART-TOF is dependent on the temperature of the He gas stream; low temperatures only perform surface sampling of the item (including any potential contaminants and/or tablet binders), while a higher temperature stream additionally samples the active pharmaceutical ingredient/target analyte of the tablet. It is also dependent on the nature of the solid exhibit. Pharmaceuticals such as capsules or heavily coated tablets likely are not able to be analyzed due to the barrier around the target analyte. While potential surface contamination must always be considered (especially when handling multiple exhibits), additional, independent sampling for the presumptive examination can give more information regarding whether an identified analyte is a surface contaminant or a true ingredient in the substance. Exercising such caution, DART-TOF is currently validated on a compound-by-compound basis, including interference and selectivity studies.

The homogeneity study indicated that the developed method was sufficient to detect the pseudo molecular ion and selected fragments of alprazolam in a variety of sample preparations with mass accuracy within the specified range. While signal abundance was shown to vary somewhat depending on sample preparation (powder samples tended to produce stronger signals than solvated or solid samples), it was also influenced by the position of placement within the sample gap. Because the purpose of this method was qualitative identification, not quantification, no distinction was attempted to

separate abundance variability due to sample placement and sample preparation. It is believed that an automated sample introduction method would minimize the position effect, however no autosampling device existed at the time of this investigation.

Not all suspected controlled substances are directly distinguishable by the current DART-TOF methodology. For example, both Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are cannabinoid components in marihuana. The standard operating procedures at the Institute of Forensic Sciences require the presumptive and confirmatory analysis of THC, in addition to a positive microscopic examination, for confirming the presence of marihuana. As THC and CBD are structural isomers of each other, and that initial testing resulted in no observed unique fragments in F2, confirmation of marihuana is not performed using DART-TOF at the present time. Additionally, DART-TOF is currently utilized for positive confirmation only. If alprazolam is not detected in a suspected sample, traditional GC–MS analysis will be performed in an effort to further investigate the presence/absence of nonvalidated compounds. Further validations are currently underway in order to broaden the scope of analytes able to be confirmed by DART-TOF.

While confirmation by DART-TOF in the forensic laboratory is rare to date, the 5th Edition recommendations from the Scientific Working Group for the Analysis Seized Drugs—SWGDRUG (15) made no distinction between methods of mass spectrometry. All forms of mass spectrometry are considered a Category A technique unless "the mode of operation diminishes its discriminating power." An example would be a mass spectrometry technique which produces only molecular weight information. The DART-TOF method presented herein utilizes two distinct voltage functions, providing a high resolution pseudo molecular mass in F1 and two subsequent fragments in F2. To our knowledge, this is the first report of confirmation in the forensic laboratory using these criteria. Though this technique does not employ a chromatographic component, resulting high resolution mass data produces highly specific confirmatory data which is then compared to the parent and fragment ions of a known standard. Furthermore, periodic review of scientific and forensic literature should be performed to remain continually aware of other potential interfering compounds. Finally, the analyst must be able to adequately interpret and articulate the results achieved, including any known instrumental limitations.

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