Forensic Chemistry 27 (2022) 100382

Contents lists available at ScienceDirect

Forensic Chemistry

journal homepage: www.sciencedirect.com/journal/forensic-chemistry

DART-HRMS as a triage approach for the rapid analysis of cannabinoid-infused edible matrices, personal-care products and *Cannabis sativa* hemp plant material

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ARTICLE INFO

Keywords:
Cannabinoid-infused edible matrices
Direct analysis in real time – High-resolution mass spectrometry
Hemp plant material
Cannabinoid detection
Personal-care products

ABSTRACT

Forensic laboratories use traditional methods such LC-MS and GC–MS for determining if evidence is derived from *Cannabis sativa* or infused with cannabinoids. These approaches require sample pretreatment steps to render samples into a form suitable for analysis by these techniques, which can be time-consuming and resource-intensive, particularly for complex matrices such as edibles. Furthermore, there is no universal method for the analysis and quantification of cannabinoids in edibles, which is in part due to the ever-evolving range of products into which cannabinoids are infused. In this study, the ambient ionization technique direct analysis in real time – high-resolution mass spectrometry (DART-HRMS) was used for the rapid detection of cannabinoids in complex matrices. A variety of cannabinoid-infused samples were analyzed, including hemp (the non-psychoactive variety of *C. sativa*), commercial personal-care products, edible certified reference materials (CRMs), and edibles prepared in-house using cannabinoid analytical standards (i.e., THC and CBD). The absence or presence of cannabinoids within these samples, which are challenging to analyze by traditional methods, was determined within a matter of seconds by simply presenting bulk material to the DART gas stream for analysis. With no sample pretreatment or lengthy data processing, this approach provides a method that complements confirmatory testing for the rapid triage of complex plant materials, personal-care products, and edible matrices for cannabinoids prior to launching confirmatory tests, saving crime laboratories time and resources. This method accommodates a broad range of materials, and it is demonstrated that cannabinoids can be readily detected regardless of the matrix type.

Introduction

In its 2019 Report to Congress, the U.S. National Institute of Justice (NIJ) drew attention to multiple challenges that confront forensic laboratories, medical examiners, and coroner offices, several of which were related to drug detection and analysis. With specific regard to *Cannabis sativa* (i.e., marijuana and hemp) testing, two points were raised: (1) "the legalization and decriminalization of marijuana and the permitted production of hemp" may bring about challenges, such as an increase in casework, that demand implementation of new/alternative testing strategies [1]; and (2) new methods must be developed to analyze THC in a variety of complex matrices, including plant-based materials, edible marijuana products and extracts [1].

Although few literature reports focused on the effect that these challenges have had on the criminal justice system have appeared, many crime labs have expressed concerns about the impacts that have been imposed by: (1) the quantification experiments required to differentiate marijuana, a Schedule I controlled substance in the U.S., and hemp, which was declared an agricultural commodity in the Agriculture Improvement Act of 2018 (2018 Farm Bill) [1,2]; (2) the increased complexity of the nuanced methods associated with analysis of edibles using conventional forensic laboratory approaches; and (3) the increase in controlled substance testing backlogs. For many crime laboratories, the transition from simply analyzing seized materials to confirm the presence of THC, versus the requirement to quantify it, has had dramatic negative impacts on workload, imposed burdensome and time-consuming sample analysis steps, and in some cases has required the purchase of new instrumentation and the hiring of additional staff.

There is no universal method for the comprehensive analysis and quantification of cannabinoids in edibles, which is in part due to the

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https://doi.org/10.1016/j.forc.2021.100382
Received 23 June 2021; Received in revised form 11 November 2021; Accepted 17 November 2021
Available online 23 November 2021

myriad of complex edibles matrices commercially available, in addition to those prepared by consumers [3]. Furthermore, current confirmatory methods used in forensic crime laboratories for the analysis and quantification of THC, CBD, and other cannabinoids present in Cannabis can be extremely time-consuming and resource-intensive. The rise in popularity of cannabinoid-infused edibles and personal-care products, such as oils and cosmetics, further complicates the analysis of evidence; the preparation of these samples is typically a multi-step process that varies for each material type, and a decrease in sample throughput often results from the increased complexity [4]. These steps could include, but are not limited to, multiple extractions, sonication, centrifugation, filtrations, and dilutions. Lastly, the indiscriminate application of these protocols to seized evidence as a means to confirm the presence of cannabinoids is exceedingly wasteful, particularly in cases where the analyzed material does not contain them. For example, analysis of evidence in the form of a baked good (e.g., a brownie) for the presence of cannabinoids may involve extraction, sonication, filtration with or without using specialized cartridges, solvent evaporation or other steps, as well as instrument analysis and data processing time. If the material does not contain cannabinoids, then the time, human and material resources directed to the effort of detecting the compounds of interest is all for naught, and simply serves to further increase sample analysis backlogs. Therefore, the implementation of a screening technique to rapidly determine if a sample likely contains cannabinoids could dramatically enhance the efficiency of forensic laboratory workflows.

Plant material, as well as liquids, oils, and solids of various kinds are general categories of product-types that can contain cannabinoids. Complex matrices within these categories include, but are not limited to, concentrates, distillates, waxes, beverages, and an unlimited number of edible products (e.g., candies, chocolates, baked goods, popcorn, etc.). Non-edibles consist of a range of personal-care products, including lotions, creams, balms, soaps and cosmetics. Because of the diversity of the matrices of which these materials are comprised, different pretreatment approaches are often required before sample interrogation. Even though qualitative analysis may require less sample preparation than quantitative analysis experiments, conventional methods such as gas chromatography (GC) and liquid chromatography (LC) still require that samples be rendered into a form that can be injected into the system. Furthermore, the chemical components of many personal-care products, as well as plant and food materials, wreak havoc on the functioning of analytical instruments over time by adhering to columns, clogging syringes and contaminating subsequent runs, all of which contribute to a significant amount of instrument downtime.

Direct analysis in real time – high-resolution mass spectrometry (DART-HRMS), which operates through ambient ionization, has proven advantageous as a high-throughput screening technique by offering real-time information, sampling versatility and improved selectivity [5]. The added benefit of minimal to no sample pretreatment further promotes its use for the screening of complex samples prior to the performance of confirmatory tests. It can be applied to the analysis of seized drugs and plant-based evidence in a fashion that circumvents sample pretreatment. Noteworthy examples include the rapid detection of: (1) synthetic cannabinoids in 'Spice' products [6]; (2) psychoactive natural products in complex plant matrices and mixtures [7–9]; and (3) pesticides in food and environmental samples [10].

The study presented here focuses on the rapid detection of cannabinoids in a variety of plant and food matrices, as well as personal-care products, by DART-HRMS. Through detection of high-resolution masses of protonated or deprotonated precursor molecules, this method rapidly interrogates samples for the presence of cannabinoids, while differentiating them from samples that do not. Since DART-HRMS cannot distinguish between cannabinoid isomers under soft ionization conditions without sample pretreatment (i.e., derivatization), the high-resolution masses and product details (i.e., *C. sativa* varieties and ingredients) were taken into consideration when assigning cannabinoids to the peaks detected. While the approach cannot be a replacement for confirmatory tests, it provides a complementary method for the rapid triage of complex plant materials, personal-care products and edible matrices for cannabinoids prior to launching confirmatory tests, thereby accomplishing time and resource savings, and enabling the more efficient deployment of laboratory instrumentation for performance of confirmatory analysis testing. This single approach accommodates analysis of a broad range of materials, and it is demonstrated that cannabinoid detection can be readily accomplished regardless of matrix type, including those containing sugars, lipids, fats and waxes.

Materials and methods

Chemical standards

Cannabidiol (CBD), Δ^9-tetrahydrocannabinol (THC), cannabinol (CBN), cannabigerol (CBG), Δ^9-tetrahydrocannabinolic acid (THCA), cannabidiolic acid (CBDA), and cannabigerolic acid (CBGA) analytical standards were purchased from Cayman Chemical (Ann Arbor, MI, USA). Polyethylene glycol (PEG 600) and Fomblin Y were purchased from Sigma Aldrich (St. Louis, MO, USA). Ultra-high purity helium gas was purchased from Airgas (Albany, NY, USA).

Cannabinoid-infused materials

Cannabis sativa plant material – Hemp variety

Two samples of *C. sativa* plant material of the hemp variety were purchased online from CBD Hemp Direct (Las Vega, NV, USA): (1) GSC CBD Hemp Flower; and (2) Jazzy CBG Hemp Flower. Hemp Bud certified reference material (CRM) (10 g) was purchased from Emerald Scientific (San Luis Obispo, CA, USA).

Cannabinoid-infused mock edibles prepared In-house

Baking ingredients (chocolate chips, sugar, eggs, flour, baking soda, baking powder, butter, popcorn, flavored and unflavored gelatin, chocolate and aluminum foil) were purchased from a local grocery store. Cotton tea bags were purchased from Amazon (http://amazon.com, USA). GSC CBD Hemp Flower purchased from CBD Hemp Direct (Las Vegas, NV, USA) was used to prepare hemp butter, as well as hemp cookies. Mainstays 4 Slice Black Toaster Ovens were purchased from Walmart (Albany, NY, USA).

Edible certified reference materials

Chocolate Matrix Blank, Hardy Candy Blank, Gummy Matrix Blank, Hemp Oil from Flower, CBD in Chocolate, and 5 Cannabinoids in Hard Candy Matrix CRMs were purchased from Emerald Scientific (San Luis Obispo, CA, USA). A Cannabinoids in Gummy Matrix Practice Proficiency Test was also purchased from Emerald Scientific. This test came with a sealed envelope containing information about the concentrations of cannabinoids present in the gummy matrix. This product was not purchased with the intent to test/validate a method. Rather, it was utilized as a resource to test the detection of cannabinoids in a gummy matrix that was not prepared in-house.

Commercial personal-care products

Sleep Body Cream (Full Spectrum Hemp Extract 200 mg), Relief Body Cream (Full Spectrum Hemp Extract 50 and 200 mg), Unicorn Body Cream, Chaga Bar Soap, Project H – Hemp Bar Soap and Unicorn Bar Soap were purchased from Rad Soap Co. (Albany, NY, USA). Three Organic CBD Balms (2500 mg) were purchased from Beak & Skiff (Lafayette, NY, USA) in the following scent combinations: (1) Menthol and Arnica Muscle Rub – "Rescue"; (2) Bergamot, Citrus and Sandalwood – "Revive"; and (3) Lavender, Rosemary and Eucalyptus – "Restore".

Sample preparation

Chemical standards

For acquisition of DART-HRMS profiles, cannabinoid analytical standards were analyzed at their CRM concentration of 1000 μg/mL (1 mg/mL). For investigations into the instrument detection limit, or IDL, (i.e., the level at which a signal is distinguishable from the noise), a stock solution of 100 μg/mL was prepared by diluting 50 μL of a 1000 μg/mL CRM with 450 μL methanol, for both THC and CBD. In ten separate microcentrifuge tubes, ten solutions at a concentration of 10 μg/mL and final volume of 200 μL were prepared from the 100 μg/mL stock solutions of THC and CBD.

Plant material, edible CRMs, and commercial products

C. sativa plant material, certified reference materials (CRMs) and commercial products were analyzed in their native forms without any sample pretreatment steps prior to interrogation by DART-HRMS. All samples were photographed in their original packaging prior to DART-HRMS analysis.

Mock edibles prepared in-house

GSC hemp flower (2 g) was ground in a mortar and pestle and spread on a small baking sheet covered in aluminum foil. The hemp flower was heated at 110 °C in a toaster oven for 40 min. Butter (11 tbsps.) was melted in a glass bowl on a hotplate in 1 c water. Once the butter was melted, the decarboxylated, ground hemp was added to the bowl and the contents were allowed to simmer for 1 h. The hemp/butter/water mixture was strained through a cotton tea bag into another glass bowl, which was then refrigerated for 2 h. Once hardened, the butter was separated from the water layer and stored in a glass bottle in the refrigerator.

The following baking ingredients were combined: 2 tbsps. chocolate chips; 2 tbsps. brown sugar; 1 tbsp. white sugar; 1 egg yolk; 1/3 c flour; 1/8 tsp. baking soda; 1/8 tsp. baking powder; 1/8 tsp. salt; and approximately 1 tbsp. water. The mixture was split in half, with 2 tbsps. plain butter added to half of the mixture (control cookie) and 2 tbsps. hemp butter added to the other half (mock hemp cookie mixture). Approximately 1 tbsp. of each mixture was placed on separate small baking sheets lined with aluminum foil and inserted into separate toaster ovens. The cookies were baked at 162.8 °C for 5 min, after which they were removed from the toaster ovens, cooled and refrigerated until analysis.

The hemp butter was also used to make mock hemp popcorn. This was accomplished by simply tossing a few pieces of popped popcorn in ~ 1 tbsp melted hemp butter. Control popcorn was also prepared by tossing the popcorn pieces in ~ 1 tbsp melted plain butter.

A mock CBD-infused gummy was prepared to test the IDL for CBD. This gummy was prepared by combining 1 CBD CRM (1 mg/mL in methanol), 2/3 oz. unflavored gelatin, 2 oz. lemon flavored gelatin, 64 mL water, and 15 mL methanol. In a glass jar, the mixture was sonicated with heat until the gelatin materials were completely dissolved, and stored in the refrigerator to solidify.

Additional mock THC- and CBD-infused chocolate candies were prepared by spiking melted semi-sweet, dark and white chocolate with 400 μg THC and CBD (in 400 μL methanol) and resolidifying the chocolate. Mock THC- and CBD-infused lime and raspberry gummies were prepared by spiking gummy mixes (gelatin, flavored gelatin, and water) with 400 μg THC and CBD (in methanol).

DART-HRMS mass spectral data acquisition and data analysis

Collection of mass spectral data was achieved through use of direct analysis in real time – high-resolution mass spectrometry (DART-HRMS). A DART-SVP ion source from IonSense (Saugus, MA, USA) was coupled to a JEOL AccuTOF high-resolution time-of-flight (TOF) mass spectrometer (Peabody, MA, USA) with a resolving power of 6000 FWHM and mass accuracy of 5 millimass units (mmu). Data collected in positive-ion mode was obtained at a DART ion source grid voltage of 250 V, with the following mass spectrometer settings: ring lens voltage, 5 V; orifice 1 voltage, 20 V; orifice 2 voltage, 5 V; peak voltage, 600 V; and detector voltage, 2000 V. Data collected in negative-ion mode was obtained at a DART ion source grid voltage of −250 V, with the following mass spectrometer settings: ring lens, −5 V; orifice 1, −20 V; orifice 2 voltage, −5 V; peak voltage, 600 V; and detector voltage, 2000 V. All data were collected at a DART gas temperature of 350 °C using ultra-high purity helium gas at a flow rate of 2 L min^{-1}. Mass spectral data were collected at a rate of 1 spectrum per s over a mass range of *m/z* 60–1000. TSSPro 3.0 software from Shrader Software Solutions (Grosse Pointe MI, USA) was used for the calibration, spectral averaging, background subtraction and peak centroiding of mass spectral data. Polyethylene glycol (PEG 600) was used as a mass calibrant in positive-ion mode. Fomblin Y was found to be a suitable mass calibrant for analyses conducted in negative-ion mode [11]. Processing of all mass spectral data was performed with the Mass Mountaineer software suite from RBC Software (Portsmouth, NH, USA).

Results

Cannabinoid standards

Several cannabinoid analytical standards (1000 μg/mL) were purchased and analyzed by DART-HRMS to confirm that the high-resolution masses associated with protonated and deprotonated cannabinoids in positive- and negative-ion modes respectively, could be readily detected. The seven major cannabinoids analyzed in this study were cannabidiol (CBD), Δ^9-tetrahydrocannabinol (THC), cannabinol (CBN), cannabigerol (CBG), Δ^9-tetrahydrocannabinolic acid (THCA), cannabidiolic acid (CBDA) and cannabigerolic acid (CBGA). The DART-HRMS spectra of these cannabinoids obtained in positive-ion mode are shown in Fig. 1, along with the structures, protonated $[M+H]^+$ and deprotonated $[M-H]^-$ molecular formulas and calculated masses. The spectra collected in negative-ion mode by DART-HRMS are shown in Supplementary Fig. S1. When analyzed in positive- and negative-ion modes, the cannabinoids were all detected within 5 mmu of their theoretical protonated and deprotonated masses. Protonated and deprotonated CBN ($C_{21}H_{26}O_2$) appeared at *m/z* 311.201 and 309.185, respectively. Both CBD and THC ($C_{21}H_{30}O_2$) appeared at *m/z* 315.232 when protonated and *m/z* 313.217 when deprotonated respectively. With the addition of a carboxyl group to the molecular framework of CBD and THC, the protonated and deprotonated masses of CBDA and THCA ($C_{22}H_{30}O_4$) appeared at *m/z* 359.222 and 357.207, respectively. CBG ($C_{21}H_{32}O_2$) appeared at *m/z* 317.248 when protonated and *m/z* 315.232 when deprotonated. The acid CBGA appeared at *m/z* 361.238 in positive-ion mode and *m/z* 359.222 in negative-ion mode. Although results acquired in both positive- and negative-ion modes are presented in this study, this was done to demonstrate that the detection of cannabinoids can be accomplished by either, and either would be acceptable for cannabinoid screening.

Instrument detection limit

Because detection of THC and CBD was the primary focus, investigations into determining the instrument detection limit (IDL) with the DART-HRMS instrument used in this study were conducted using THC and CBD analytical standards. Within one DART-HRMS acquisition, each of the 10 solutions (10 μg/mL) for the respective cannabinoid were analyzed by dipping the closed end of a glass melting point capillary tube, in triplicate, into the solution and holding the coated surface in the DART gas stream for approximately 5 s. This was done to determine the average peak intensity and relative intensity at nominal *m/z* 315 for each of the 10 solutions. The average peak intensity, standard deviation, relative standard deviation (RSD), sample concentration, and the

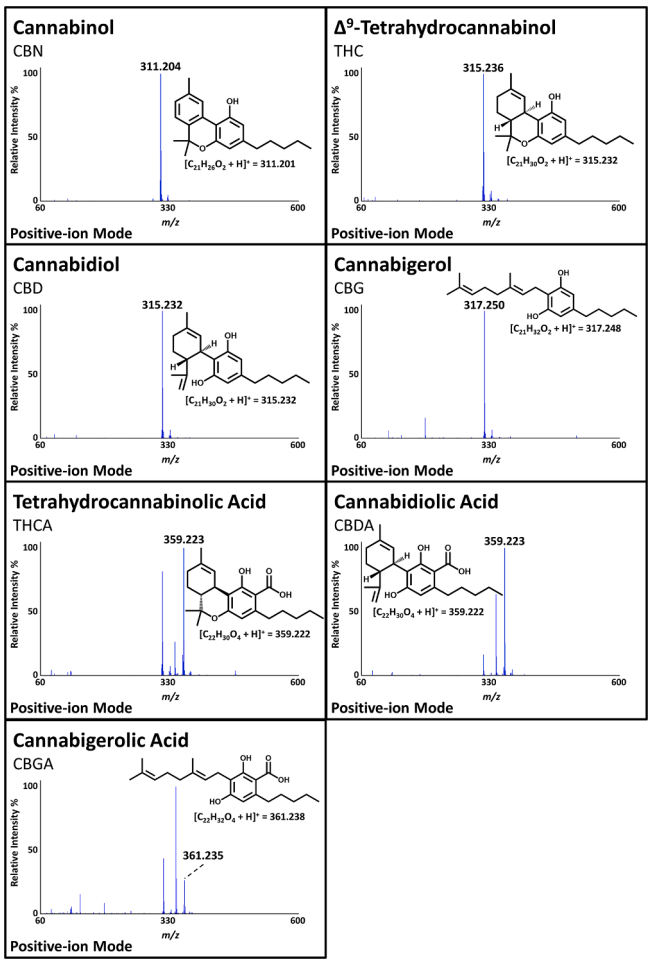

Fig. 1. DART-HR mass spectra (collected in positive-ion mode), structures and $[M+H]^+$ chemical formulas. Masses of peaks corresponding to the indicated cannabinoids are highlighted.

respective t-value (2.821) were used to calculate the predicted IDL for both THC and CBD. It was determined that when using the capillary tube sampling technique, the IDL for THC and CBD was 1.09 and 1.29 ug/mL, respectively. Therefore, the average peak intensity of THC and CBD at a 1 μg/mL was used to determine the cutoff for a positive identification screen to minimize the potential for false positives. Moving forward throughout this study, a peak intensity of greater than 100 was considered a positive identification of the presence of either THC and/or CBD in each complex matrix analyzed; this value does not refer to the relative intensity of a peak, but rather the to the ion counts associated with the relevant *m/z* value. Translating this to real-world applications, any sample that produced an ion count greater than 100 would be subjected to confirmatory testing. Furthermore, because this cutoff pertains only to THC and CBD molecules, the presence of other cannabinoids was determined based on detection, in positive- or negative-ion mode, of high-resolution masses consistent with their calculated masses.

Subsequent to the IDL experiments, a mock CBD-infused lemon gummy candy was prepared using 1 mg CBD in 152 g of gummy matrix. When analyzed by DART-HRMS using the capillary tube sampling technique in triplicate, a peak at *m/z* 315.235 was detected at a peak intensity of 280. Therefore, the method described herein was able to detect a concentration of 6.58 μg/g (ppm) CBD in a gummy.

Cannabis sativa hemp plant material

Initial investigations into *Cannabis sativa* plant material focused on detecting cannabinoids by DART-HRMS in hemp, the non-psychoactive variety of *C. sativa*. A total of three hemp samples were purchased from two vendors: 1 CBD hemp flower, 1 CBG hemp flower, and 1 hemp bud CRM. These plant samples could be analyzed by either presenting whole flower buds to the DART gas stream via tweezers, or by inserting the closed end of a glass melting point capillary tube into the flower and then presenting the coated surface into the DART gas stream. The DART-HRMS spectra of these three hemp flower samples collected in positive- and negative-ion modes are shown in Fig. 2. Fig. 2 Panels A, B, and C show three DART-HRMS spectra acquired from analysis of these hemp flower samples in positive-ion mode, and Panels D, E, and F show the results obtained in negative-ion mode. Peaks consistent with major cannabinoids are labeled, color-coded and accompanied by the respective cannabinoid molecular structure. In the GSC CBD hemp flower, the protonated masses of CBD and CBDA were detected at *m/z* 315.231 and 359.219 in positive-ion mode, while deprotonated masses of CBD and CBDA were detected at *m/z* 313.214 and 357.208 in negative-ion mode, respectively. These cannabinoid peaks were readily detectable in both ionization modes. In the Jazzy CBG hemp flower, *m/z* 317.246 and 361.236 (positive-ion mode) and *m/z* 315.227 and 359.216 (negative-ion mode), were prominent peaks detected, and are consistent with the presence of CBG and CBGA, respectively. The Hemp Bud CRM was reported to contain cannabinoids at the following concentrations: 73,725.32 μg/g CBDA; 173.52 μg/g CBG; 4,349.07 μg/g CBD; 52.88 μg/g CBN; 523.98 μg/g THC; and 1,912.71 μg/g THCA. In positive-ion mode, peaks consistent with the protonated masses of CBN, THC/CBD, CBG, and THCA/CBDA were detected at *m/z* 311.210, 315.227, 317.240, and 359.221, respectively. When analyzed in negative-ion mode, THC/CBD, CBG, and THCA/CBDA were detected at *m/z* 313.214, 315.227, and 357.202, respectively.

Cannabinoid-infused edibles

Mock edibles prepared in-house

The control and hemp butter samples were analyzed by the capillary tube sampling technique. The resulting mass spectra from analysis in positive-ion mode by DART-HRMS revealed similar mass spectral profiles reflective of the fact that they were derived from the same butter sample. They differed primarily in that the hemp butter exhibited a prominent peak at *m/z* 315.230, consistent with the anticipated presence of protonated CBD. A peak at *m/z* 317.247, which is consistent with protonated CBG, was also present. It should be noted that although CBDA is one of the major cannabinoids typically observed in hemp plant material, no peak consistent with its presence (at nominal *m/z* 359) was detected. This observation indicates that the controlled heating of the hemp plant material that was performed in order to cause the decarboxylation of CBDA to form CBD was successful. When analyzed in negative-ion mode, the presence of CBD and CBG was observed again, this time at *m/z* 313.217 and 315.231, respectively, in the hemp butter. The control butter did not contain either of these peaks.

The mock control and hemp cookies revealed similar results, which was anticipated given that, with the exception of the use of hemp butter in the hemp cookies, both treats were prepared using the same ingredients. Representative spectra of these two samples collected in positive-ion mode, rendered as a head-to-tail plot for ease of comparison, are shown in Fig. 3 Panels A and B, with the data obtained in negative-ion mode shown in Supplementary Fig. S2 Panels A and B. Peaks consistent with protonated CBD at *m/z* 315.231 (positive-ion mode) and deprotonated CBD at *m/z* 313.212 (negative-ion mode) respectively were detected by DART-HRMS only in the hemp cookie. This illustrates the ease with which samples containing cannabinoids can be identified. This is further exemplified by the ease of sampling; the cookies were analyzed by simply holding them in the DART gas stream between the ion source and mass spectrometer inlet, with no sample preparation required, as demonstrated in Fig. 4 Panel A. *This is crucial because it demonstrates not only how capable this DART-HRMS method is for analyzing extremely complex food products, but also how the detection of*

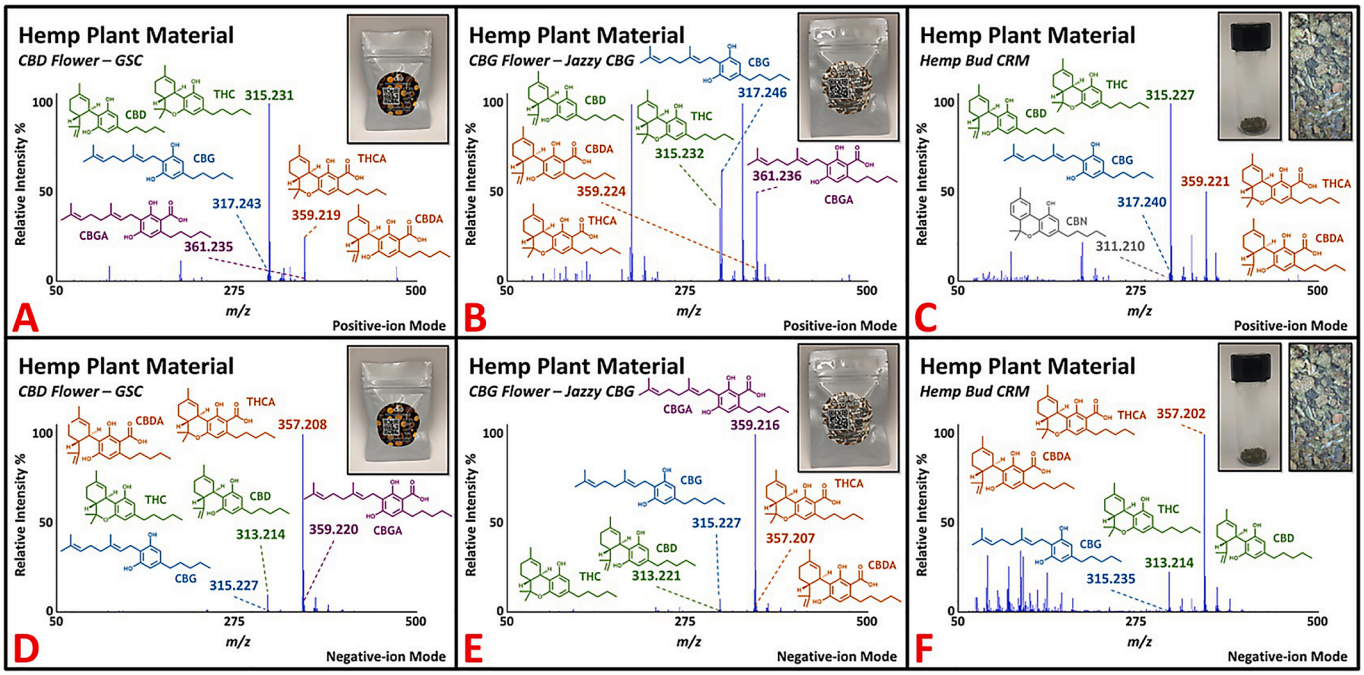

Fig. 2. DART-HR mass spectra of hemp flower products analyzed in positive- (top) and negative-ion (bottom) modes (20 V/-20 V). Peaks consistent with protonated/deprotonated cannabinoids are labeled, color-coded, and accompanied by the respective cannabinoid molecular structure. Hemp samples include CBD flower (Panels A and D), CBG flower (Panels B and E) and Hemp Bud CRM (Panels C and F). Images of the corresponding products/plant materials are shown in the insets.

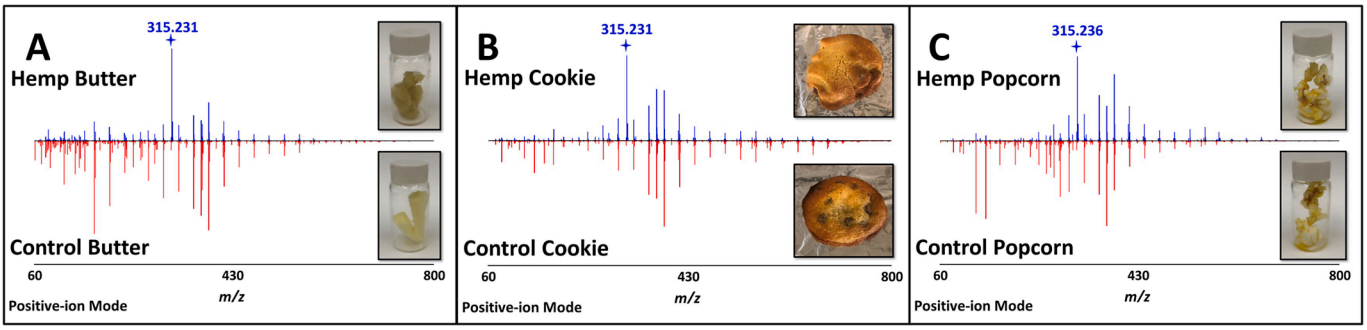

Fig. 3. Head-to-tail plot renderings of DART-HR mass spectral data acquired when analyzing control (red) and hemp (blue) edibles prepared in-house. Edibles shown include butter (Panel A), cookies (Panel B) and popcorn (Panel C). Analyses were performed under soft ionization conditions (20 V) in positive-ion mode. For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.

relevant and diagnostic masses is unencumbered by the inherent complexities of the material matrix. The revelation of such information using conventional methods would require extensive sample pretreatment to render the product to a form compatible with analysis by GC–MS, HPLC, etc.

The DART-HRMS results from analyzing the mock popcorn samples further emphasize this point. By simply holding a piece of popcorn in the DART gas stream for a few seconds, as illustrated in Fig. 4 Panel B, the plain butter versus hemp butter coated popcorn were readily distinguished based on the detection of peaks consistent with the presence of various cannabinoids. CBD was detected at *m/z* 315.236 (positive-ion mode) and *m/z* 313.213 (negative-ion mode), respectively, as indicated by Fig. 3 Panel C and Supplementary Fig. S2 Panel C, respectively.

The mock gummy and chocolate candy samples could be analyzed by DART-HRMS using either the capillary tube technique or by suspending them using tweezers in the open-air gap between the ion source and mass spectrometer inlet, as is demonstrated in Fig. 4 Panel C. In positive-ion mode, DART-HRMS analysis of the plain candies revealed no peaks consistent with cannabinoids, while the spectra of the mock THC- and CBD-infused gummies and chocolates all produced a peak at *m/z* 315, which is consistent with the protonated mass of THC and CBD. These matrices, which are very troublesome to analyze by conventional methods, did not interfere with the rapid detection of cannabinoids by DART-HRMS. This is revealed by the observed spectra, collected in positive-ion mode, presented in Supplementary Fig. S3.

Certified reference materials

Three blank certified reference materials (CRMs) were analyzed by immersing the closed end of a melting point capillary tube into the sample and presenting the coated surface of the tube to the DART gas stream. As anticipated, no cannabinoids were detected in these blank samples in either positive- or negative-ion modes.

Three cannabinoid-infused CRMs were then similarly analyzed. The CBD chocolate CRM was reported to contain 100 mg/g CBD. Major peaks at *m/z* 315.232 in positive-ion mode and *m/z* 313.212 in negative-ion mode were consistent with its presence. The Hard Candy Matrix CRM was reported to contain 100 μg/g of the five cannabinoids: CBN, CBD, THC, THCA and CBDA. When analyzed by DART-HRMS, three peaks consistent with the presence of these cannabinoids were detected. A peak at *m/z* 311.200 was consistent with the high-resolution protonated mass of CBN, while peaks at *m/z* 315.229 and 359.222 were

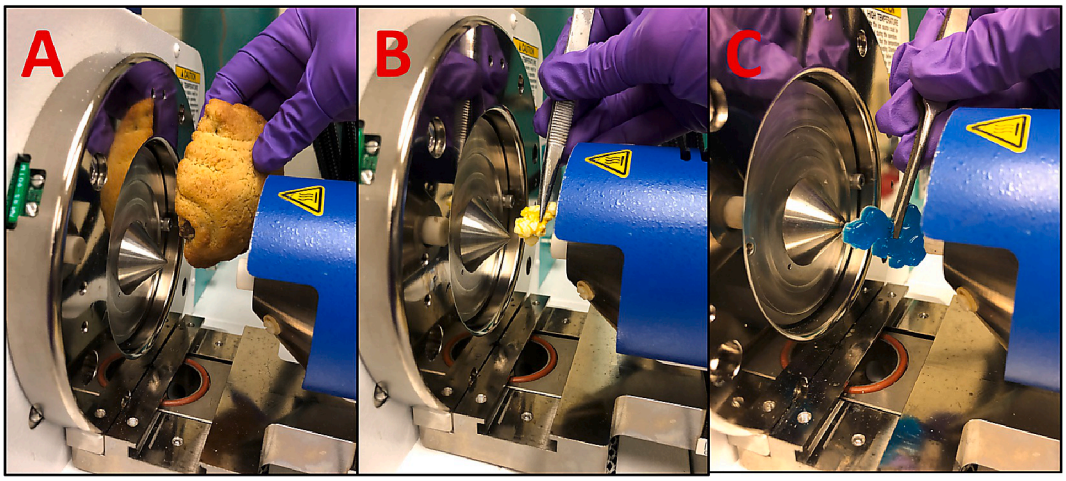

Fig. 4. Direct analysis of hemp-based products and mock edibles prepared in-house by DART-HRMS. The featured edibles include a cookie prepared with hemp butter (Panel A), popcorn coated with hemp butter (Panel B) and a cannabinoid-infused gummy candy (Panel C).

consistent with the protonated masses of THC/CBD and THCA/CBDA, respectively. DART-HRMS analysis performed in negative-ion mode indicated the detection of CBN, THC/CBD, and THCA/CBDA with peaks consistent with their respective deprotonated masses of *m/z* 309.181, 313.214, and 357.202. A head-to-tail plot featuring the DART mass spectra of the cannabinoid-infused hard candy CRM (blue) and the corresponding blank CRM (red) collected in positive-ion mode is shown in Fig. 5. The figure illustrates their highly similar spectra (which reflects their common candy matrix), but highlights the distinctions resulting from the additional compounds present in the cannabinoid-infused CRMs.

The final edible CRM analyzed in this study was a Cannabinoids in Gummy Matrix Practice Proficiency Test. The sealed envelope that accompanied this proficiency test declared the gummy to contain 679 μg/g CBD, 76.6 μg/g THC, 201 μg/g THCA, 0 μg/g CBN and 0 μg/g CBDA. DART-HRMS analysis of this gummy in positive-ion mode revealed two peaks at *m/z* 315.229 and 359.217, results which are consistent with the protonated masses of THC/CBD and THCA. Furthermore, DART-HRMS analysis of this candy in negative-ion mode revealed peaks at *m/z* 313.213 and 357.202, which is also consistent with the deprotonated masses of THC/CBD and THCA. Although differentiation between THC and CBD was not attempted in this triage method development, no peak was detected at nominal *m/z* 311, confirming that there was no CBN present in the gummy. DART mass spectra of the CRM gummy products are shown in Supplementary Fig. 4 rendered as a head-to-tail plot.

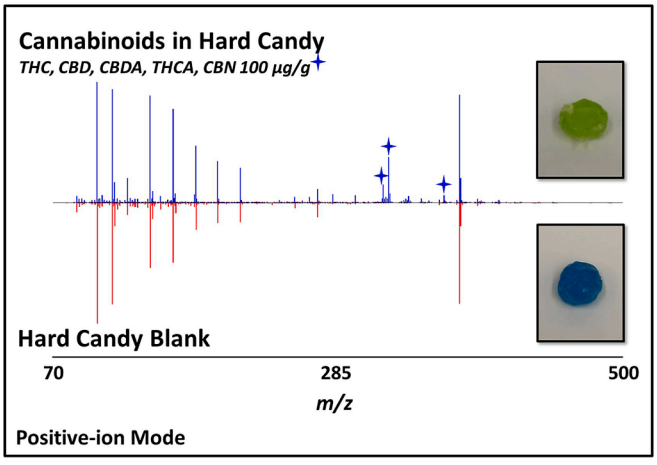

Fig. 5. Head-to-tail plot rendering of DART-HR mass spectral data obtained when analyzing blank (bottom) and cannabinoid-infused (top) hard candy matrices in positive ion-mode (20 V).

Commercial personal-care products

The range of cosmetics and personal-care products purchased for this project encompassed three types of commercially available materials: (1) those derived from hempseed oil; (2) those derived from hemp extracts/oils; and (3) those that were not derived from *C. sativa* at all. The capillary tube sampling method was used for the DART-HRMS analysis of all products due to their waxy or liquid consistency. The Unicorn Body Cream and Bar Soap represent the controls in this experiment, and serve as the third product type. When analyzed by DART-HRMS in positive- and negative-ion modes, no peaks consistent with known cannabinoids were detected. Furthermore, there were no peaks that would interfere with the detection of cannabinoids, if any had been present.

Hempseed oil is derived from hemp seeds, which do not contain cannabinoids [12]. However, contact with resins from other parts of the plant could contribute to miniscule amounts of cannabinoids present in products derived from hempseed oil [12]. Therefore, DART-HRMS analysis of hempseed oil is not generally expected to yield spectra with a peak consistent with the presence of CBD, although trace levels might be detectable as a consequence of cross contamination from exposure of the seeds to other plant parts during processing [12]. The Chaga Bar Soap and Project H – Hemp Bar Soap both list "unrefined hempseed oil" as an ingredient. When analyzed by DART-HRMS, no peak consistent with CBD was detected in either positive- or negative-ion modes when the Project – H Hemp Bar Soap was analyzed. However, a small peak at *m/z* 315.236 was detected when the Chaga Bar Soap was analyzed in positive-ion mode. DART-HRMS spectra of the control products and products derived from hempseed oil collected in positive-ion mode, are shown in Supplementary Fig. S5.

Hemp extracts and CBD oils are derived from parts of the plant (i.e., flowers, leaves, and the stalk) which contain CBD and other cannabinoids [12]. Therefore, in contrast to products manufactured with hempseed oils, products made from hemp extracts and CBD oils should contain levels of CBD that are readily detectable by DART-HRMS. All three Organic CBD Balms listed "CBD oil" on the product packaging, while the "sleep" and "relief" body creams listed "full spectrum hemp extract oil" on their ingredient lists. In positive-ion mode, all six products exhibited a peak consistent with the protonated mass of CBD at nominal *m/z* 315 when analyzed by DART-HRMS. These spectra are shown in Fig. 6, with the CBD content very prominent in the three CBD balms, which were indicated to contain 2500 mg of CBD each.

While the relative intensities of the peaks are not necessarily directly

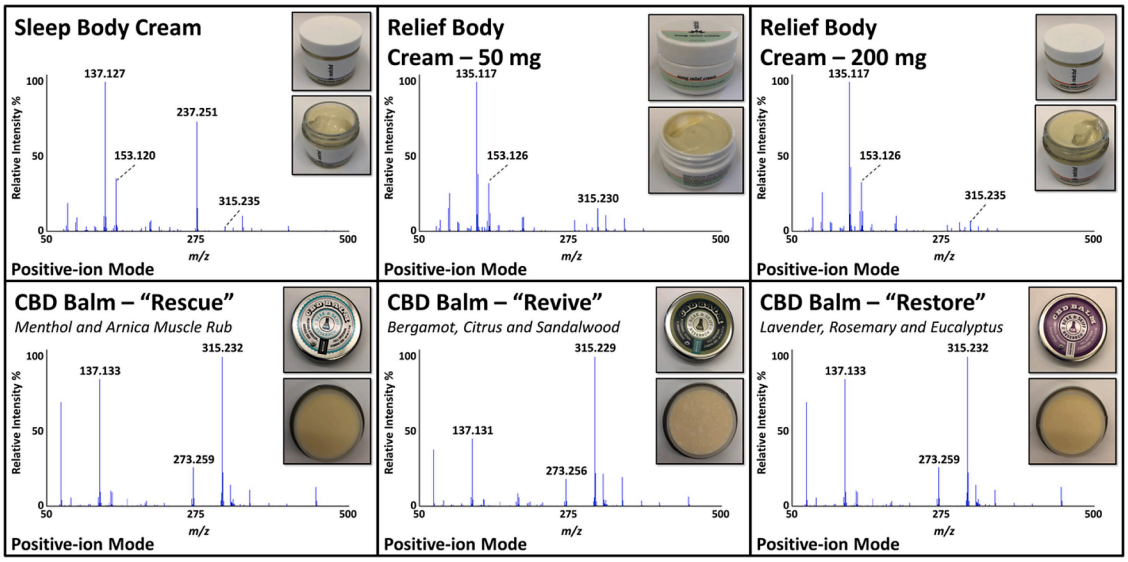

Fig. 6. DART-HR mass spectral analysis performed in positive-ion mode at 20 V of commercial cosmetics reported to contain hemp/CBD extract oil. Images of the corresponding cosmetics and their packaging are shown in the insets.

correlated with the relative concentrations of the compounds represented by the observed *m/z* values, the approach is nevertheless highly useful because of the advantages it confers in terms of simplicity of analysis, time savings, and avoidance of matrix-specific and nuanced sample preparation steps. Despite the complexity and diversity of the matrices sampled, no *m/z* values of interest were obscured by the immense number of additional peaks present.

Discussion

In the U.S., the ever-increasing number of jurisdictions that have legalized the recreational use of *C. sativa* has had a number of consequences both within society as a whole, and in the forensic science community in particular. Among members of the general population, it has resulted in greater popularity of edible marijuana products. One challenge associated with this trend is the increased opportunity for accidental ingestion, which is not just limited to children [13]; pets and the elderly are other groups at higher risk of accidentally consuming foods infused with cannabinoids. Additional challenges associated with the consumption of edibles include: (1) the delay (in comparison to smoking) in the onset of the initial "high" that results from oral consumption (30 to 90 min for eating versus 20 to 30 min for smoking) which often causes individuals to ingest larger and larger doses [14]; (2) longer lasting "highs" [14]; (3) the diversity of cannabinoids contained within a single product or package; and (4) cannabinoid content inconsistencies in batch product manufacture [15]. These factors can contribute to the accidental consumption and overconsumption of edibles, and undesirable or unexpected effects. Product serving sizes listed on edibles packaging is another factor. While the manufacturer may associate a given dosage with a particular serving size, consumers, for a variety of reasons, may unwittingly overdose on cannabinoids by consuming multiple serving sizes in one sitting. In this regard, it has been found that the enhanced understanding of dosage information that resulted from either unit-serving packaging or multi-dose packaging with servings partitioned as separate units [16], reduced the tendency of consumers to overdose on products. However, this approach to packaging has not been widely adopted, nor is packaging of Cannabis-infused edibles legislated [16].

Another facet of the legalization of various types of *C. sativa* products is the dramatic increase in *C. sativa* related materials submitted to crime labs, and the concomitant expansion in workload and drain on resources. Since the reassignment of hemp from the Schedule I controlled substance list to a legal agricultural commodity, crime laboratories and personnel have had to alter their entire approach to analysis of Cannabis evidence, depending on state legislation. This has included updating existing protocols (or in some cases, acquiring new instruments) and the development/validation of protocols. The latter also requires additional training for staff and delays in the accomplishment of casework. The DEA has offered some assistance with regard to analytical analysis of *C. sativa* plant material and food products [3]. However, there are few additional reports offering guidance for the analysis of edibles and personal-care products, and therefore there is little uniformity in the protocols used by crime laboratories for the analysis of such evidence.

Although approaches exist for the detection of cannabinoids in Cannabis plant materials, edibles and cosmetic matrices, many are encumbered by the need for extensive sample preparation prior to analysis. For example, numerous LC-based techniques have been reported for the analysis of marijuana plant material and hemp products such as distillates, concentrates (e.g., waxes and oils), cosmetics/creams, food products and the flower. These include LC-UV-MS/MS [17] and UHPLC-UV-MS/MS [18], as well as additional approaches for analysis of brownies and cookies from casework by UHPLC-MS [19], gummy bears and brownies by HPLC [20], brownie medibles (marijuana edibles) by UPLC-MS/MS [21], plant material and edible products by UPLC with PDA and MS [22], and commercial food, beverages, vapes and supplements by HPLC-DAD [23]. One study in particular utilized LC-MS/MS to simultaneously quantify 4 cannabinoids (CBD, CBDA, THC, and THCAA) in consumer products, including oils, plant materials, creams and cosmetics [24]. Another method utilized LC-DAD to quantify 11 cannabinoids in hemp-derived products such as tinctures/oils, powders, edibles (e.g., gummies, candies) and beverages [25]. LC methods including LC-UV and HPLC-PDA have also been used for the analysis of *C. sativa* hemp and marijuana plant material [26] and medical marijuana products, including hemp oil [27]. As is common with LC methods, including those referenced in this discussion, sample pretreatment steps including dilution, sonication, and filtration are generally required, which are time- and resource-intensive processes. Although several studies have tried to address this concern by using the QuEChERS extraction method for complex matrices including, but not limited to, Cannabis plant material and edibles such as candies, chews, chocolates, baked goods, oils, and beverages prior to HPLC analysis [28,29], or utilizing alternative extraction protocols, such as matrix-removal cartridges for the analysis of chocolate prior to HPLC analysis [30,31], these methods have not comprehensively resolved the challenges associated with the myriad of

edible products that could enter a crime laboratory as evidence. One of the most exploited instrument techniques used in forensic crime labs is GC–MS. GC–MS/MS has been used to detect major cannabinoids on hair after application of hemp oil [32]. GC–MS methods have also been used to analyze cannabinoid content in hemp products, plant material [33], and edibles [34,35]. However, challenges that were encountered with LC methods (e.g., time-consuming sample preparation) were also encountered in many of these reports.

Through use of either of the sampling approaches described in this study (i.e., direct analysis or the capillary tube technique), anywhere between 20 and 30 samples could be screened, calibrated, and analyzed by DART-HRMS in 1 h, with minimal training needed to become proficient. LC and GC run-times reported for the detection and baseline separation of cannabinoids could take up to 25 min for each sample [17–20,23–30,32–35]. In combination with published extraction methods and sample preparation steps, which could take anywhere between 10 and 75 min per sample [17–20,22–26,29–30,32,34,36], the total analysis of one candy or one lotion could be up to 1.5 h. Within that time frame, one analyst could have screened 30 to 45 samples for cannabinoids by DART-HRMS. To analyze this volume of samples by conventional methods, whether or not they contain cannabinoids, would require hours or days. By using DART-HRMS to screen samples, substantial amounts of time can be saved, and samples that do not contain cannabinoids can be kept out of the confirmatory analysis testing rotation. Additional dividends include savings on solvent costs (since the analysis of the materials in their native forms circumvents the need for solvent extracts); reduction of instrument downtime through avoidance of contamination from analysis of sugar and/or lipid-rich complex matrices (which is minimized due to the detection limit of the instrument, and the miniscule sample size required to conduct DART-HRMS experiments); and reduced chromatography consumables costs. Furthermore, because the JEOL AccuTOF high-resolution mass spectrometer coupled to the DART ion source has nanogram detection limits, only a very small amount of sample is required for each analysis. For most analyses, the closed end of a glass capillary tube is inserted or dipped into a sample, and then presented to the open-air DART gas stream. The capillary tube is not smothered with sample; rather, a small amount of sample adheres to the surface of the capillary tube. For all DART-HRMS experiments, should a situation arise where the inlet appears to have residue on it, a cotton swab dipped into methanol can be used to remove it. In this work and with other studies, no carry-over issues resulting from the analysis of these sample types containing high concentrations of cannabinoids was observed. Cannabinoid chemical standards of 1000 μg/mL were frequently analyzed, as were edibles samples infused with up to 10 mg CBD. Commercial CBD balms with 2500 mg CBD did not result in carryover either. Even at these high concentrations, such a miniscule amount of sample is exposed to the DART gas stream that the potential for carry-over is minimal. These findings, coupled with the speed of analysis in contrast to conventional methods, make this a promising approach for adoption by forensic laboratories.

It is noted that LC and GC are not the only methods reported for cannabinoid analysis; ion mobility spectrometry (IMS) as a screening method to detect cannabinoids and other potential hazards in various commercial hemp products (e.g., salves, supplements, drops and oils) prior to confirmatory analysis by LC-MS also been reported [36]. Like DART-HRMS, IMS detects whole protonated molecules and cannot differentiate between cannabinoid isomers. In contrast to IMS however, DART-HRMS does not require pretreatment of the materials being analyzed. With IMS, samples must be extracted, filtered, and diluted prior to analysis [36].

Conclusions

The rise in popularity and use of marijuana edibles and personal-care products in recent years and the perpetual emergence of new product types within which *C. sativa* and its derived compounds are infused continues to create challenges for crime laboratories. The analysis of these products (predominantly edibles) by conventional methods can prove particularly troublesome. This is because the broad diversity of the food matrices that are encountered often requires nuanced and time-consuming method development simply to detect the presence of cannabinoids, and assess whether further confirmatory testing is warranted. However, as demonstrated here, DART mass spectrometry analysis of a broad range of plant materials, personal-care products and food matrices in their native forms, and in the absence of any sample pre-treatment steps, can rapidly register the presence of numerous cannabinoids, and the complexity of the matrix was not found to obscure the ability to detect the m/z values of relevant cannabinoids. Further, none of the masses detected that were native to the matrices themselves coincided with cannabinoid masses, thus reducing the possibility of false positives. The potential for false positives is extremely small due to the resolving power of the mass spectrometer. The risk of false positives can be minimized even further by coupling the DART ion source to a mass spectrometer with an even higher resolving power, or with MS/MS analysis capability. To date, no complex matrix has shown interference from peaks above the IDL threshold that have masses consistent with the protonated/deprotonated forms of those from cannabinoids. However, the potential for this to occur remains, in principle, which is the reason why the ever-evolving matrices into which cannabinoids are infused should be tested on a regular basis. While the approach is not confirmatory since it does not enable discrimination between isomeric cannabinoids, this limitation is offset by not only the sheer range of complex matrices that can analyzed without instrument contamination and compound carryover, but also by the speed of the triage analysis (several seconds per sample) and the elimination of the need for extraction and other sample pretreatment steps. Therefore, when implemented as an orthogonal method for preliminary screening of edibles, personal-care products and plant materials to detect cannabinoids, this approach has great potential to assist crime laboratories not only in the analysis of *C. sativa* evidence, but also through redeployment of laboratory equipment such as GC and LC instruments for other analyses that can be focused on structure confirmation, thereby reducing costs and increasing efficiency.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The funding support of the 2020 Northeastern Association of Forensic Scientists (NEAFS) Carol De Forest Research Grant to MIC; the National Institute of Justice (NIJ), Office of Justice program, US Department of Justice (DOJ) under Grant Nos. 2015-DN-BX-K057, 2017-R2-CX-0020 and 2019-BU-DX-0026 to RAM; and the U.S. National Science Foundation (NSF) under Grant No. 1429329 to RAM is gratefully acknowledged. The opinions, findings, and conclusions or recommendations expressed in this publication are those of the authors and do not necessarily reflect those of the DOJ and/or the NSF. Thanks are extended to Dr. Kirk Jensen at JEOL for assistance with IDL experiment design.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.forc.2021.100382.

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