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Direct Analysis in Real Time Mass Spectrometry: a Powerful Tool for Fast Analysis

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Abstract: Direct analysis in real time mass spectrometry (DART-MS) is one of the variants of ambient mass spectrometry. The ionization process of DART-MS is in open environment and only takes few seconds, so it is suitable for fast analysis. Actually, since its introduction in 2005, more and more attentions have been drawn to its various applications due to its excellent properties, e.g., fast analysis, and no or less sample preparation, high salt tolerance and so on. This review summarized the promising features of DART-MS, including its ionization mechanism, equipment modification, wide applications, coupling techniques and extraction strategies before analysis.

Key words: DART-MS, fast analysis, coupling techniques

Introduction

The appearance of ambient mass spectrometry (AMS) is undoubtedly a millstone in the field of mass spectrometry. It allows for the direct analysis of ordinary objects in the open atmosphere of laboratory or in their native environment. In this way, complicated sample preparation or time-consuming chromatographic separation is not necessary to some extent. Since the pioneer work of Cooks and coworkers,[1] many variants of ambient ion sources have been developed.[2] Among all, desorption electrospray ionization (DESI) and direct analysis in real time (DART) are the two most popular and representative techniques. Considering the primary ionization mechanism, DESI is based on electrospray (ESI) mechanisms, while DART belongs to atmospheric pressure chemical ionization (APCI) mechanisms that thermal desorption with gas transport is used in all cases.[2] Most ion source of AMS are self-built for research use, and only few is commercially available. DART was the first commercialized ambient ion source. Moreover, DART showes many advantages over other ion sources: 1) high speed and throughput, 2) clear spectrometry without multi charge ions, 3) soft ionization almost without fragmentation, 5) molecular ion without alkali metal adducts, 6) no memory effects or sample carryover, 7) high salt tolerance. In this review, we will summarize the promising features of DART-MS and its applications for fast analysis. In addition, the equipment modification and coupling techniques will be briefly discussed.

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Ionization mechanism and instrument improvement of DART

DART was first introduced by Cody *et al*. in 2005,[3] and was one of the most widely used ion sources in AMS nowadays. From the cutaway view of the DART source in Figure 1, there are four successive chambers: corona discharge chamber, perforated electrode chamber, heater chamber and grid electrode chamber. The discharge chamber is the key part where the work gas is converted to plasma by high voltage. In the second chamber, needless ions are removed from the plasma. Then the plasma is heated to a high temperature in the third chamber because energy is necessary to evaporate target molecules. Next, the gird electrode repels the unnecessary ions in case of signal lose. At last, the follow-out gas (excited-state helium or nitrogen) is directly used to ionize gaseous, liquid, or solid samples.

The ionization process is based on the reactions of electronic or vibronic excited-state species with target

molecules, which is named Penning ionization.[4] The excited helium(2^3S) atom had an energy of 19.8 eV, which is higher than the ionization energies of common atmospheric gas and organic molecules. In the positive ionization process, the atmospheric water molecules are ionized to form ionized water clusters. By the proton transfer, water clusters ionize the target molecules. Similarly in the negative ionization process, negative-ion clusters is produced by the reaction between excited helium and water/oxygen.

In ambient condition, because the molecules in air are much more than metastable helium in quantitative terms, most of the excited helium is quenched half-way. Low ionization efficiency is a common problem for all ambient sources. Since its introduction, great efforts have been made by scientists to improve its performance and four generations of DART have been put into market: DART®, DART®-ET, DART®-SVP and ID-CUBE®. Many changes have improved the ionization efficiency remarkably: the maximum heater temperature was increased from 250°C to 550°C; adjustable source holder was added to change the angle between DART and MS; various sample loading modes were developed for various morphology of samples, like dip-it sampler, transmission mode, open spot sample card and so on; a membrane pump was added to the vapor interface to maintain proper vacuum condition and suck more targets into the MS; new design of appearance shortened the distance of ion transfer.

Apart from the engineers' efforts in instrument design, researchers strived in sample loading. Haefliger and coworkers designed a new sample probe, which showed higher sensitivity and better reproducibility than the commercial dip-it sampler.[5] In detail, this sample probe was prepared by coiling twelve turns of 0.12 mm wide nickel chromium resistance wire around a syringe needle. The outer wire increased the contact surface area to the sample solution, so the sensitivity was elevated by more sample loading in deed, without use of solid-phase extraction. Moreover, the metal wire probe conducted the heat more efficiently than the glass dip-it sampler, which facilitated the sample evaporation. Because of its smaller size, this probe overcame the double-peak spectrogram that was common when dip-it sampler was used. DART could be used to analyze various samples, but diffusion loss was a serious problem for gaseous samples. Li placed a tee-shaped PEEK flow tube between the DART ion source outlet and the MS orifice for sample loading.[6] This interface efficiently controlled the sample loss and detection sensitivity was increased at least by two orders of magnitude. This interface was in a continuous flow mode, and therefore quantity analysis is hard to realize. Fernaìndez and coworkers designed a temperature-programmable sample holder named electro-thermal vaporizer,[7] which was constructed by two glass tubes and a nichrome ribbon as the key part for sample loading. By programmable power supply, the temperature of vaporizer increased concomitantly and the target solutes were sequentially volatilized and exposed to the DART source. This device was successfully applied to detect varous compounds including ethyl acetate, acetone, acetaldehyde, ethanol, ethylene glycol, dimethylsilanediol, formaldehyde, isopropanol, methanol, methylethyl ketone, methylsulfone, propylene glycol, and trimethylsilanol. Although DART is a soft ion source, it is still hard to get molecular ions for some labile compounds. Liu and coworkers solved this problem by introducing a makeup solvent device between DART and analyte.[8] In their design, the makeup solvent worked as a medium of energy transfer, so the analyte was ionized by metastable solvent molecules instead of the argon plasma. The usefulness of this device was demonstrated by analysis of methanol, alcohol, fluorobenzene, and acetone solvent was used for the analysis of nucleosides, alkaloids and glucose. DART showed good performance for nonpolar compound,[4] but low ionization efficiency for polar compounds was obtained because of their poor evaporation. Jang *et al*. developed an *in situ* methylation method for evaporation enhancement of hydrophilic glycosides,[9] in which, two microliters of tetramethylammonium hydroxide solution were added on dip-it sampler with raw powder sample for methylation. This simple method could improve sensitivity by at least four orders of magnitude.

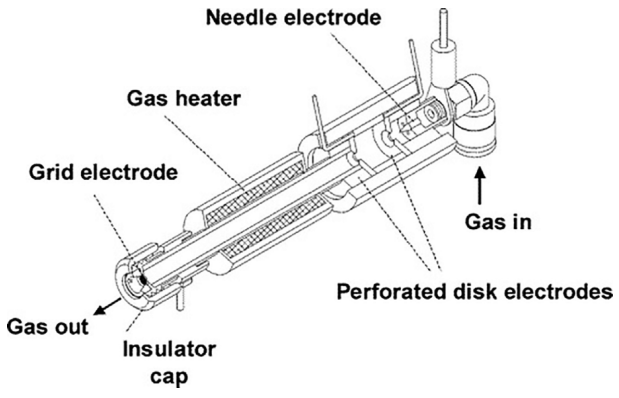

Figure 1. Cutaway view of the DART source. Reprinted from [3] with permission.

During the method development, many parameters need to be optimized to get the higher sensitivity, such as flow rate of gas,[10] grid voltage,[11] heating temperature,[12] sample loading mode and desorption angle.[13] Generally, helium is used as work gas more often than argon and nitrogen for its higher energy of excited state. But, Cody and coworkers used argon as work gas to realize selective ionization of melamine and avoid interference from 5-hydroxymethylfurfural.[14] It was hard to differentiate melamine from 5-hydroxymethylfurfural only by their molecular weight (calculated $\Delta m/z$ 0.0337). The excited argon had an energy of 11.55 eV for $^3P_2$ state and 11.72 eV for $^3P_0$ state, which were enough for ionization of melamine, but not for 5-hydroxymethylfur-

fural. Based on the mechanism of Penning ionization, water molecular was important in the whole process. But for ambient analysis, precise control of humidity of air was very hard and was often neglected. Research by Newsome *et al*. found that humidity greatly affected relative ion abundance of hexamethylene triperoxide diamine.[15] In low temperature, the relative ion abundance varied greatly among various humidity. The abundance of radical fragment ion at *m/z* 88 in 12.8 g/m^3 absolute humidity was observed less than 5% in 5.0 g/m^3 absolute humidity. In consequence, humidity control was necessary for quantity analysis.

Applications of DART-MS

High throughput is one of the promising features of AMS because analysis is performed directly on sample surfaces in an open atmosphere. For DART, the total analysis time for each sample typically could be less than 5 s and 12 samples could be analyzed at a single run by automated dip-it sampler. So, researchers mainly focused attention on high-throughput screening of target compounds, and several reviews had summarized these advances.[16-19] Here we merely concentrate on new trends of DART-MS, like fingerprint, reaction monitor, imaging and so on.

Fingerprinting techniques are generally based on measurement of the material composition (*e.g.*, foodstuffs, extracts) in a non-selective or selective way.[16] By analyzing the MS data of complex samples, benchmark database could be built and characteristic compounds could be found. By statistical approach, like principal component analysis (PCA),[20] linear discriminant analysis (LDA),[21] artificial neural networks with multilayer perceptrons (ANN-MLP)[22] and so on, authenticity assessment is feasible. Qu and coworkers combined DART-MS with principal component analysis for rapid identification Danshen injections from five manufacturers.[23] At last, five compounds (fructose, glucose, sucrose, protocatechuic aldehyde and salvianolic acid A) were identified as potential markers. This method showed great potential in quality control of drugs. Li used DART-MS to analyze volatile organic compounds in exhaled breath.[24] By accurate mass measurements and isotopic distribution comparisons, a list of compounds was confirmed. This was an ideal and promising strategy for early noninvasive clinical diagnosis and therapy. The DART-MS could also be applied in metabolomics analysis. Xiao and coworkers applied DART-MS in non-targeted metabolomic analyses of an orange bud mutant and wild-type.[25] A total of 54 compounds were tentatively identified by DART-MS. Substantial metabolomic differences were revealed between mutant and wild-type. Because of the low sensitivity of DART, many trace compounds could not be detected, that would restrict the use of DART based fingerprinting techniques in some area.

Ascribed to the fast analysis of DART-MS, real time monitor was possible. Petucci and coworkers applied DART-MS to monitor two synthetic transformations reaction that include the N-methylation of an indole and a debenzylation reaction of heterocyclic compound.[26] When the ratios of reactant to product ion signal intensities reached constant, the reaction was finished. Additionally, the result from DART mass spectra was close enough to those of the diode array or the total ion chromatogram, which was frequently used for qualitative reaction monitoring. In addition to the purely monitor, this method could also find place in side reaction control and capture of unstable intermediate that was very important in mechanism explanation. DART-MS was also used to monitor solid phase synthesis by Linington and coworkers.[27] The developed method was used to directly analyze resin-bound peptides and products of Heck reaction without prior chemical cleavage. Recently, Kubec and coworkers used DART-MS to monitor biology process.[28] Before their work, there were several possible precursors of color change on wounded *Allium subg.* and *Melanocrommyum* detected by LC-MS method.[29] The complicated sample preparation process may provide false positive result, so direct evidence was of vital importance. By monitoring the content changes of various compounds, the whole process of color change was revealed: the formation of pigments was initiated by alliinase-catalyzed cleavage of *S*-substituted cysteine *S*-oxide precursors [*S*-(2-pyrrolyl) cysteine *S*-oxide and *S*-(*E*)-(1-propenyl) cysteine *S*-oxide (isoalliin), respectively] following wounding the bulbs. At the same time, this method denied a former hypothesis that *S*-(3-pyrrolyl)cysteine *S*-oxide was one precursor of the red pigment.

Mass spectrometry imaging (MSI) could provide molecular distribution information with high specificity. Feng and coworkers applied DART-based source (plasma assisted laser desorption ionization)[30] for imaging of traditional Chinese seal as illustrated in Figure 2 and some effective components in the herbal medicine *Radix Scutellariae*.[31] In this source, laser was focused on the sample surface and used to desorb the analytes. After desorption, DART was used to ionize the analytes. By the introduction of laser, resolution of 60 μm × 60 μm pixel size was achieved. This system could be used to study the distributions of active component in traditional Chinese medicines. However, the imaging process took too much time, and more improvement was needed.

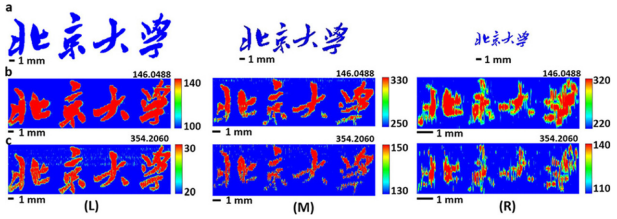

Figure 2. MSI of laser print blue Chinese characters. Reprinted from [31] with permission.

DART also find its place in forensic sciences, for example detection of synthetic cannabinoids,[32] psychoactive substance determinations,[33] sexual assault evidence[34] and so on. Fraser even used DART-MS for characterization of blood on an encrustation of an African Komo mask.[35] To confirm that blood was indeed present in the encrustation, an indirect method was developed for identifying the haem moiety from blood. By using *in situ* methylation and DART-MS detection, the permethylated haem ion (calculated *m/z* 644.208) from myoglobin, haemoglobin, fresh blood, and blood aged in the laboratory for 10 years was readily observed. Combining with XRF, IR and Raman spectroscopy, the presence of blood was eventually confirmed. Smoking is harm to health, and DART could be a sensitive tool for monitoring tobacco smoke and contamination transfer by using nicotine as an indicator.[36]

DART-MS is not only an analytical instrument, but a surface characterization tool as well, since it could provide the chemical composition of the interfacial region. Kpegba and coworkers analyzed the self-assembled monolayers of dodecanethiol on gold using DART-MS.[37] By putting the sample under the gas stream, signals of monomers, dimers, and trimers of the self-assembled monolayers molecules were observed. The content of monolayers could be figured out by relative peak heights. Follow the same strategy, Beek and coworkers analyzed a diverse set of monolayers having different chemistries (amides, esters, amines, acids, alcohols, alkanes, ethers, thioethers, polymers, sugars) on five kinds of substrates (Si, Si_3N_4, glass, Al_2O_3, Au).[38] The results showed that substrate did not play a major role in formation of hydrolysis products except gold, and fragmentation of monolayers of the same group followed a predictable manner. Wilson and coworkers used DART-MS to *in situ* analyze the chemical characterization of sub-micron organic aerosols.[39,40] Mass spectra were obtained just by introducing a stream of nanometer-sized aerosols into the ionization region and found that smaller diameter and more volatile aerosols yielded higher ion signals. From this work, DART-MS showed potential in studying interfacial chemistry of organic aerosols.

Coupling techniques

As well known, DART-MS showed distinctive advantages in various applications, especially for rapid *in situ* analysis, but one should be kept in mind that this approach could not recognize isomers that shared the same *m/z*. The direct analysis really saved the time for sample preparation and chromatographic separation in traditional methods, like GC-MS, LC-MS. This didn't mean DART was useless in these coupling techniques. On the contrary, it showed better performance in some aspects.

The first work about coupling DART-MS with GC was reported by Cody and coworkers.[4] The interface between GC and the mass spectrometer was a copper tubing: the column extended from the oven went through the copper tubing which was wrapped with heating tape and heated to 250°C. And, DART blew the outflow into the MS. Nonpolar compounds such as alkanes and cholesterol were successfully analyzed by this system. Compared to the traditional electron ionization, DART showed its advantages as follows: as a soft ionization, more abundant molecular ions with less fragmentation were achieved; charge-exchange reagent such as oxygen or fluorobenzene could be used outside to increase signal intensity; high vacuum was not needed in the ion source region.

Klampfl and coworkers did the original work of coupling DART-MS with LC.[41] The mobile phase was introduced to the ionization region of DART by a single PEEK transfer capillary. In their work, eluents were added with phosphate buffer from 20 mM to 120 mM and there was no significant influence for four pyrazine derivatives. The availability of LC eluents was greatly extended due to the DART's insusceptibility toward ion suppression. Based on the former work, the researchers moved on to investigate the effects of gradient elution and sample matrix on signal intensities,[42] showing that higher organic solvent decrease the ionization efficiency and a make-up liquid was necessary to provide acceptable sensitivity. Moreover, DART ionization showed a reduced tendency towards ion suppression effects compared to other widely employed ionization techniques like ESI and APCI. Chang and coworkers applied this LC-DART-MS system for chiral analysis.[43] They utilized normal phase LC to qualitative and quantitative analysis of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and jasmonic acid enantiomers. Good linearity and reproducibility were obtained by the proposed method. Compared with ESI and APCI, DART showed its advantages of low in-source thermal fragmentation.

Motivated by low ion suppression and low matrix effect in DART-MS, Chang and coworkers realized the online coupling of DART-MS with CE.[44] In this CE-DART-MS system, a commercial sheath liquid tip was used as the interface. A mixture of 4-aminoantipyrine, zolmitriptan, and quinine was separated and detected by capillary zone electrophoresis and micellar electrokinetic chromatography mode. Additionally, the signal intensity of the analytes remained constant even in buffer of 100 mM sodium borate containing 30 mM sodium dodecyl sulfate. This system showed higher tolerance of detergents and salts than traditional CE-ESI-MS.

Sample enrichment before DART-MS

DART was operated in ambient environment, so fast and real time analysis was possible. However, strong background greatly lowered its detection sensitivity, so some enrichment protocols were needed for trace compounds, like solid phase extraction, packed sorbent microextraction, liquid extraction,

stir bar sorptive extraction and so on.

Jagerdeo and coworkers tried four different packed sorbents for fast screening of drug abuse in urine samples.[45] Quantification of the analytes was realized by using a DART source with a deuterated reagent as internal standard. The manual operation and desorption process were not suitable for high throughput analysis. Haunschmidt and coworkers used the polydimethylsiloxane coated stir bars for enrichment of very low concentrations of UV filters.[46] After sufficient adsorption, the stir bars were directly analyzed by DART-MS without extra elution step. Bai and coworkers used single-drop liquid-liquid-liquid microextraction (SD-LLLME) strategy combined with DART-MS for the rapid analysis of six phytohormones in fruit juice.[11] A 10 μL flat-cut HPLC syringe was used to introduce and suspend the 6 μL microdroplet of diluted ammonia solution for the extraction. After extraction, the microdroplet was transferred to the surface of glass inserts and subjected to DART-MS analysis after drying in air. By integrating the high clean-up and enrichment abilities of SD-LLLME with the fast analytical speed of DART-MS, good extraction efficiencies and detection sensitivities were obtained. Pawliszyn and coworkers developed a C18-polyacrylonitrile thin-film solid-phase microextraction coating for reusable extraction of diazepam from whole blood.[47] After direct extractions for 30 times, this coating still showed reproducible extraction efficiency. Recently, Wang and coworkers developed the interface of online coupling of in-tube solid-phase microextraction (IT-SPME) with DART-MS, as shown in Figure 3,[48] in wihch the single-wall carbon nanotubes incorporated monolith showed high affinity for six triazine herbicides. With the online combination of IT-SPME with DART-MS, the analytes desorbed from the monolith were directly ionized by DART and transferred into MS for detection, thus rapid determination was achieved. Besides, Li and coworkers used a porous material MIL-101(Cr) as a solid-phase extraction packing material combined of DART-MS for the analysis of triazine herbicides.[49] Due to the enrichment step, DART-MS became a more powerful tool for the analysis of trace compounds, especially for fast screening of targets in complicated matrices.

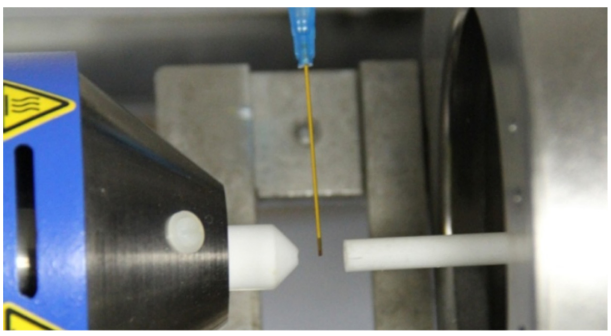

Figure 3. Schematic of the online coupling of IT-SPME with DART. Reprinted from [48] with permission.

Conclusions

After nearly ten years of development of DART-MS, great improvements have been made in various applications. Now, DART-MS is widely used in different areas, from fast screening to non-target fingerprinting, from quality control to forensic science, and from imaging to reaction monitoring. Great achievement is inspiring, but there are several problems remianed to be solved. First, its sensitivity is still not satisfactory due to the low ionization efficiency and ion quench during the air transfer. Second, the accessible mass range of DART-MS needs to be extended, so that macro biological molecules could be detected. Third, it is difficult to obtain quantitative data by DART-MS without the addition of proper internal standards. Nevertheless, DART-MS is still a promising tool, and will find more applications in various fields.

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