Historical development and principles of dart biology essay

Science, Biology

1. 1Introduction

The analysis of sample without sample preparation is an ultimate goal in analytical chemistry. The analysis of sample before the introduction of ambient mass spectrometry like DART-MS had to do with the use of chromatography e. g. liquid chromatography for the analysis of samples in the pharmaceutical industry. This took a long time to get the chromatogram and also require sample preparation. Various ionisation sources have been used successfully with mass spectrometer; some require proper sample preparation and the introduction of samples into a high vacuum system. This include electron ionisation (EI), chemical ionisation (CI), field desorption/ field ionisation (FD/FI). These ionisation sources requires samples to be introduced into a high vacuum for analysis, which had a great disadvantage such as vacuum failure and/or contamination of the ionisation source if too much sample is introduced. These were only suitable for gas-phase ionisation. 1 The problem of a high vacuum system was overcome by the introduction of atmospheric pressure ionisation sources such as atmospheric pressure chemical ionisation (APCI), electrospray ionisation (ESI)2, atmospheric pressure photoionisation (APPI)3 and matrix-assisted laser desorption ionisation (MALDI). The atmospheric pressure ionisation sources increased the range of compounds that can be analysed by mass spectrometry but required the samples to be exposed to an elevated temperature and electrical potentials, ultraviolet irradiation, laser radiation or a high velocity gas stream which must be fully enclosed to protect the operator from danger. 4Ambient ionization technique shows a number of different characteristics from the atmospheric chemical ionisation like the

direct analysis of untreated samples or objects in the open environment, maintaining its original condition and existing properties of the sample. 5 Desorption electrospray ionisation (DESI) is an ambient ionisation which has been developed and it analysis samples on the surface but with an electrically charged aqueous mist spray on the analyte. 6 DESI analysis solids samples including complex biological samples which cannot be done by MALDI. DESI has the features of ESI but samples to be analyses by DESI don’t require in most cases any sample preparation. No matrix is needed to perform the experiment compared to MALDI that require a matrix to be added. This is similar to laser desorption from porous silicon surfaces. 7The ambient mass spectrometry has overcome the limitation of sample preparation or chromatographic separation of components of the sample, introduction of sample into high vacuum system and the exposure of samples to elevated temperatures and electrical potentials. 8 These ambient ionisation sources like DESI and DART has a distinctive feature compared to other ionisation sources because it ionises low molecular mass (weight) compounds present on the surface of solids or liquids in a gas stream without sample preparation or chromatographic separation. 9

1. 2Aim

The aimed to this review is to provide findings on the development, current trend of application and future use of DART an ambient ionisation source in analytical science.

2. 0HISTORICAL DEVELOPMENT AND PRINCIPLES OF DART

2. 1The History of DART

A direct analysis in real time (DART) source patent in September 2005 and 2006 (US Patent 6, 949, 741 and 7, 112, 785)10, 11 and the first DART-MS study was also done and published by Cody and Laramee in the same year. 12 This grew out of discussion at JEOL USA, Incorporated between the two authors about developing an atmospheric pressure thermal electron source to replace the radioactive sources used in hand-held detectors for chemical weapons agents (CWAs), drugs and explosives. 13 They discovered that DART could be used for positive ion and negative ion non-contact detection of materials on surface as well as for the detection of gases and liquid and this led to the development of a commercial product by JOEL which enables real-time non-destructive detection and identification of trace amounts of organic matter at ordinary temperature and atmospheric pressure. The DART was commercially introduced in February 2005 for the JEOL AccuTOF™ mass spectrometer and became a commercial product by March 2005. 14

2. 2The Principles of DART

DART is based on the atmospheric pressure interaction of long lived electronic excited stated atoms or vibronic excited state molecules with the samples and atmospheric gases. This is an ionisation method where the sample is ionised by a corona discharge within a He atmosphere. A gas (typically helium or nitrogen) flows through the chamber of the DART ion source where and electrical discharge produces ions, electrons, and excited-

state (metastable) atoms and molecules. Most of the charged particles are removed as the gas passes through the perforated lenses or girds and only the neutral gas molecules including the metastable species remain. The lens or gird at the exit of the DART prevents ion-ion and ion-electron recombination and also acts as a source of electrons by surface Penning ionisation and as an electrode to promote ion drift towards the orifice of the mass spectrometer’s atmospheric pressure interface. 13Figure 1: DART source showing the main parts. Taken from reference 12Several ionisation mechanism are possible depending on the polarity and reaction gas, the proton affinity and ionisation potential of the analyte and the presence of addictives or dopants. Penning ionisation is the dominant reaction mechanism when nitrogen or neon is used in DART source. Nitrogen or neon ions are effectively removed by the electrostatic lenses and are never observed in the DART background mass spectrum. The polarity of the DART ion source can be switch from positive mode to negative move by changing the polarity of the disk and gird electrode only. Positive ions are produced when helium is use and this involves the formation of ionised water cluster followed by proton transfer reactions. 12This is shown below: He (23S) + H2O H2O+■+ He (11S) + electron-H2O+■ + H2O H3O+ + OH■H3O+ + nH2O [(H2O)nH]+[(H2O)nH]+ + M MH+ + nH2OWhere M is the analyte of interestThe energy state of helium 23S state is 19. 8eV which is higher than the ionization energies of atmospheric gases and organic molecules which are usually lower than 19. 8eV and it has an efficient reaction with water with an estimated reaction cross section at 100Å2. This extraordinary high cross section helps in the perfect performance of DART without it being

affected by humidity. 9Negative ions are produced by a different method which involve the production of electron by Penning ionisation or surface Penning ionisation and are rapidly thermalized by collision with atmospheric pressure gases and undergo electron capture by atmospheric oxygen producing O2- which react with the analyte to generate sample anions. 12 This is shown belowM* + surface M + surface + electron- (Penning / surface Penning ionization)e-fast + gas e-slow (Thermalized by collision with gas)e-slow + O2 O2- (Electron capture by atmospheric oxygen)Nitrogen, neon and helium gas have virtually identical negative reagent mass spectra but nitrogen has the highest sensitivity and helium is least sensitve for the production of negative ion in DART. This is due to the effliciency in the formation of electrons by Penning or surface Penning ionisation as the internal energy of the metastable species increases. 15Ions can also be formed in DART by other reactions. E. g. dopants such as ammonium (from ammonium hydroxide headspace vapour) or chloride (from methylene chloride vapour) can be modify the chemistry to allow chemist to tail the experiment for a specific analyses. 12The mass spetra produced or observed in DART are characterised by M+• and/or [M+H]+ in the positive ion mode and M-• or [M-H]- in negative ion mode. Fragment ions are also observed depending on the sample and the source conditions. The degree of fragmentation can be adjusted by the gas temperature or the Mass Spectromter orifice potentials. Unlike electrospray (ESI) and desorption electrospray ionisation (DESI), alkali metal ion attachment (e. g. [M+K]+) or doubly charged ions (e. g. [M+H]2+) are not observed under DART. 13

3. 0APPLICATIONS OF DART

Direct analysis in real time (DART) mass spectrometry is a recently developed innovative technology, which has shown broad applications for fast and convenient analysis of complex samples. It is an ion source that permits rapid mass spectrometric detection of solids, liquids and gases in open air under ambient conditions. 12 The DART ion source has found a wide application in the analyze of extremely wide range of analytes16 including drugs (tablets, formulations etc), metabolites in body fluids, skin surface, flavors and fragrances, explosives, forensics, chemical weapon agents(CWA), synthetic organic and organometallic compounds, pesticides, toxic industrial materials, inks, dyes, foods, spices, beverages, fatty acids in bacteria and also materials on surfaces such as glass, concrete, paper or currency directly. DART ion source can also be use in the analysis of nonpolar compounds. 16DART technology can eliminate or reduce sample preparation and complements existing LC or GC analytical techniques. DART is unique in that samples are analysed in open air, using no radioactive components, solvent sprays, exposed high voltage, or vacuum to alter the sample state. Since its introduction, DART has gained wide acceptance for forensics, pharmaceuticals, and homeland security applications. Presently, DART-MS studies are rapidly progressing and the number of publications on the subject and corresponding analytical applications increases continuously since its innovation.

Number of Publication

Yearhttp://charts. webofknowledge. com/ChartServer/draw? SessionID= X22A@GGDNpcdD8G8l84&Product= UA&GraphID= PI_BarChart_30Figure 2. Number of publications per year from Web of Science search of the topic: " Direct Analysis in Real Time Mass spectrometry" (Timespan 2005-2013)

3. 1Pharmaceutical Application of DART

Analysis of drug tablets is one application where direct analysis is of extreme importance. Drugs can also be sampled in pill form by wiping or placing the pill in front of the DART source and analyte ions are detected in few seconds. 16 The study on the detection of illicit drugs on the surface using direct analysis in real time (DART) time-of-flight mass spectrometry has been carried out and it shows a high sensitivity, speed and precision for the detection of drugs on surface. It also encourages the detection of smoked drugs from surface and spilled drugs from carpet, mostly for drug with structure that contain non-aromatic N-atoms. 17Counterfeit drugs are not just iilegal but dengerous to the health and some may not contain the active ingredient of a particular drug but a different ingredient which may be potentially toxic to the body. 18, 19 Rapid detection of counterfeit pharmaceuticals by DART-MS was for the first time demonstrated by study of an artesunate containing antimalarial products and a counterfeit drug which had no active ingredient of the antimalarial product. 18 The mass spectra of the artesunate containing antimalarial products show the active ingredient of the drug but the speatra of the counterfeit drug had no active ingredient but had a pharmacologically inactive substance stearate anions (calcium

stearate is a common pharmaceutical inactive ingredient). 18 The DART-MS source was not only able to detect the counterfeit drug but it also reveals the inactive ingredient in the counterfeit drug. DART-MS can be use to authenticate between a good drug and counterfeit drug. 18Qualitative studies of pharmaceutical product using DART-MS is very effective because it is rarely affected by major parameter. 20 Quantitation with DART-MS is much more complex than identification. Relatively accurate measurement results can be achieved only for liquid samples due to the need for calibration and thus reference samples with accurate analyte concentrations, which cannot be done for solid samples. 20 However, there was one publication where semi-quantitative measurements of solid samples were made with DART-MS. 21 The quantitative study of pharmaceutical product using DART-MS is still under development to ascertain the best parameters that will make it a labelled standard. It sensitivity depends on parameters like the kind of sample analyte, the absence or presence of an additional vacuum interface, the influence of different doping agent and also the capabilities of DART-MS to determine the low concentration impurities in the presence of the large amount of a major component. Further studies on the quantitation of pharmaceutical product using DART are still under development. 17DART-MS is replacing the LC/UV/ESI-MS in the monitoring of drug discovery. 19 Monitoring the simple organic transformation with few by-product is more effective with compared to LC/UV/ESI-MS. Also the rapid confirmation of molecular weight of the final product is faster using DART-MS. 19 Pharmaceutical bioanalysis is also possible using DART and this shows a comparative result to the conventional LC/MS/MS. 22

3. 2Forensic Application of DART

Forensic analysis is an important area of application of DART-MS because it does not require sample preparation thereby altering the original sample. Forensic studies using DART has shown high-resolution mass detection of samples. Validation DART source has been study23 and it shows a great result for screening drugs and this has encourage the forensic science department in Virginia to approve the use of this technique for the detection of solid dosage form of drug abuse. Other areas of forensic application like the detection of gamma-Hydroxybutyric acid in various drink matrices using DART is very efficient and show high sensitivity and it is more reliable with less time and can be detected at lower limit in variety of drink matrices. 24 The sensitivity and selectivity ability of the DART source was study by combining it with TLC for the analysis of forensic drugs and this gave a more favourably result compared to the GC-MS which took longer time to identified the drugs. 25 Other areas of forensic application include the differentiation of writing inks using DART-MS26 and detection of bank dye and pepper spray using DART which has become a valid method use for screening bank dye and pepper spray by Virginia’s department of forensic science laboratories. 27

3. 3Food Application of DART

The introduction of direct analysis in real time mass spectrometry (DART-MS) has showed a simple and high-throughput qualitative and quantitative analysis of various components in different kinds of food matrices both major and minor (trace) components. 28 The analysis of food is one of the growing

areas of the application of DART-MS. Studies of the pesticides found in crops and their product have been carried out using DART. Schurek et al. 29 used a DART-TOF-MS technique for the determination of strobilurin fungicides (azoxystrobin, picoxystrobin, dimoxystrobin, kresoxim-methyl, pyraclostrobin, and trifloxystrobin) from wheat grains and an ethyl acetate extract was prepared for the quantitative analysis. Analysis of samples containing incurred strobilurin residues showed a good trueness of DART-TOF MS based results, comparable with that obtained by the conventional analytical approach employing LC-MS/MS. 29 Further example of successful qualitative analysis of pesticide residues in solid samples using DART was carried out on grapes, apples and orange peels. 30 A rapid detection of pesticides by DART has enhanced the conventional technique (LC/MS and GC/MS) for confirmatory and quantitative analysis and the surface swabbing method eliminates the lengthy sample preparation techniques and allows for rapid sampling. 16The DART ion source coupled to time-of-flight mass spectrometry (TOF MS) for analysis of melamine (MEL) and cyanuric acid (CYA) in milk powder and milk based products study31 has shown an excellent option for the determination of contaminate in pet food, infant formula and other milk product without any incubation steps required or chromatographic separation. This yields exact mass measurement and accurate isotope-peak intensities to detect and identify melamine and cyanuric acid in contaminated milk based food. Other areas in food which DART has been applied include16 the analysis of Lycopene in tomato skin, analysis of flavones and flavour components in Basil leaf chemotypes, analysis of deoxynivalenol in beer, 32 direct analysis of caffeine and the

presence of various compounds, including antimicrobial preservatives, artificial sweeteners, acidulants and saccharides, without any sample preparation and chromatographic separation in soft drinks, 33 coffee and tea infusions, Analysis of multiple mycotoxins in cereals under ambient conditions using direct analysis in real time (DART) ionization coupled to high resolution mass spectrometry, analysis of lipids in cooking oil and adulterated olive oil without sample preparation, 34 etc.

3. 4Analysis of Chemical Warfare Agents and Explosives (Homeland Security)

Studies have shown successful use of DART-MS for the detection of chemical warfare agents on a variety of militarily relevant surfaces. 35 High-quality mass spectra can be recorded with intensities and this is successful even in the field because the DART source does not require any vapour pressure, time-consuming sample extractions, spraying solvents, or other sample manipulations. It is non-destructive to original sample. Nilles et al. 35 used the DART technique for the quantitative analysis of chemical warfare agents. This study showed a great result compared to tried and true chromatographic techniques such as GC/MS and LC/MS. The DART technique shows a great advantage for the identification and quantification of chemical warfare agents (CWAs) because of its short time of analysis and accuracy. Explosive have also been detected using DART technique. Triacetone triperoxide (TATP) and hexamethylenetriperoxide diamine (HMTD) are explosive peroxide compounds that are difficult to be detected using conventional mass spectrometry techniques. Study shows that the DART technique can easily detect these explosive (like peroxides) without any

sample preparation36 and can be detected on different surface like clothes, fingertips, muddy water and boarder passes. 16Other areas of application of DART-MS in homeland security include the rapid detection of trace component of herbicides. 16

3. 5Other Major Application Areas of DART

Analysis of flavour and fragrances is mainly carried out by GC/MS and LC/MS but study have been carried out using DART in the analysis of flavour and fragrances but result shows that it is a valuable method that can complement the convention methods. 37 Analysis of non-polar compounds is also possible using DART. 38 Another area of application of DART is for the rapid detection of serum metabolomics fingerprint, 39 organometallic compounds, 40 analysis of self-assembled monolayers on gold surfaces41 and the analysis of printing and writing papers. 42 DART-MS has also been use to determine different skin surface compounds. 43

4. 0APPRECIATION OF DART IN ANALYTICAL DEVELOPMENT

4. 1Comparison of DART with DESI, ESI and MALDI

These are the two major ambient ionisation technique created. DESI is new ionisation source that permit the use of mass spectrometry to get spectra of condensed-phase samples under ambient conditions. This source can be use with samples like solids, liquid, frozen solution and adsorbed gases. It is use for small and large organic molecules with high sensitivity and fast analysis of samples on the surface. 44DART is a new ionisation source which is also operated under ambient conditions. Samples analyse in it include solid, liquid

and gases. It is very sensitive for low molecular weight molecules with noncontact and fast analysis. 44 One main feature that distinguishes the two ambient ionisation sources is that the DART source exposes samples to excited gas and does not require electrospray of liquid solvent as require by DESI as shown in figure 3 below. Studies of both ionisation sources show that the both gives high throughput result on the analysis of surface of some common drugs and biological samples. Both ionisation sources have a limiting sensitivity due to ion suppression which could be a problem since there is no sample preparation. Figure 3. DESI (upper) and DART (lower) analyses for ambient high-throughput mass spectrometric analysis of unprepared samples (skin, bricks, urine spots, clothing, tissue, etc.). Taken from reference 44The table below shows the comparison of DART with DESI, ESI and MALDI showing some distinctive properties. Table 1: Comparison of DART with DESI, ESI and MALDI

Ionisation source

Ion produced

Sample Preparation

Basic principle

Surface Analysis (Imaging)

Sample Type

Key References

DARTSingly charged molecular ions. NoSample surface exposed to excited gas (He, N)NoSolid, liquid and gas19, 44, 45, 46, 47, 48DESISingly or

multiply charged molecular ions. NoSample surface exposed toelectrospray plumeYesSolids, liquid samples, frozen solutions, and to loosely surface-bound species like adsorbed gases. ESISingly or multiply charged molecular ions. YesNoLiquid samples onlyMALDIMostly singly charged molecular ions but with few multiply charged onesYesThe rapid photo-volatilization of a sampleembedded in a UV-absorbing matrixYesSolid samples only

4. 2Comparison of DART with Conventional Method like GC and LC MS

DART-MS is a rapid and simple analytical technique that is used to analyse complex materials at atmospheric pressure to give a high-resolution but with low reproducibility compared to conventional GC and LC MS. 49

4. 3Coupling of DART with Other Analytical Instruments

Recent studies show the coupling of DART with IMS for the detection of toxic chemicals and chemical warfare agent simulants. 50 This showed a get advantage compare to DART-MS because IMS does not require reduced or vacuum conditions and this reduce the complexity of the instrument making it portable. 50 Study of the coupling of HPLC to DART shows a perfect result for identification and qualitative purpose but the quantitative analysis have some demerit with dependence on the position of the HPLC plate to the ion source. 51

5. 0CONCLUSION

The recently developed ambient MS ionisation DART has shown a great application in many fields of analytical science and has a great advantage for the rapid and ease detection of analytes. Its reproducibility is yet to be

ascertained. It application in homeland security, food, pharmaceutical, chemical warfare detection and other areas have shown it efficiency in analytical science (qualitative analysis) but further study on the mechanism is needed to increase its ability in quantitative analysis. One of it disadvantage to educational laboratories is that it is expensive. The coupling of the DART source to IMS has shown a great future for t field ionization which could be employed by the government and military personnel with little or no training.