The historical development and principles of dart biology essay

Science, Biology

1. 1Introduction

The analysis of a sample without sample preparation is the major goal of analytical science. The analysis of a 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 industries. This took a long time to get the chromatogram and also require sample preparation. The earlier ionisation sources used successfully with mass spectrometer like electron ionisation (EI), chemical ionisation (CI), field desorption/ field ionisation (FD/FI) required proper sample preparation and the introduction samples into a high vacuum for analysis. These had a great disadvantage such as failure in the vacuum and/or introduction of impurities into the ionisation source if excess sample is introduced at a time. These sources were only suitable for gas-phase ionisation. 1 The problem of a high vacuum system1 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 number of compounds that could be determine by mass spectrometry, but required samples to be introduced to an elevated temperature and electrical potentials, ultraviolet irradiation, laser radiation or a high velocity gas stream which must be in a vacuum, to protect the analyst from danger. 4Ambient ionization technique shows a number of different characteristics from the atmospheric chemical ionisation like the direct analysis of samples or objects with less or no sample preparation in an

open environment, 5 maintaining its original condition and existing properties of the sample. 5 Desorption electrospray ionisation (DESI) is another type of ambient ionisation invented, 6 and analyses samples on the surface, but with an electrically charged aqueous mist spray on the analyte. 6 DESI analyses 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 do require less or no any sample preparation in most cases. No matrix is needed to perform the experiment7 compared to MALDI that requires 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, the introduction of a sample into a high vacuum system and the exposure of samples to elevated electrical potentials and temperatures. 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 available on the surface of solids or liquids in a gas phase with less or no 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

Direct analysis in real time (DART) source was 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 came out from a discussion at JEOL USA, Incorporated between the two authors suggesting the invention of an atmospheric pressure thermal electron source which could take the place of other ionisation sources like the electron emitting radiation sources used in hand-held detectors for drugs, explosives and chemical weapon agents (CWAs). 13 They discovered that DART could be used for positive ion and negative ion non-contact detection of materials on the surface and also for the detection of gases and liquids and this gave rise to the introduction 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. 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 centred on the influence of long lived electronic excited state atoms or vibronic excited state molecules with samples and atmospheric pressure gases. 13 This is an ionisation method where the sample is ionised by a corona discharge within a helium or nitrogen gas environment. Gas usually

use (helium or nitrogen) flows through the chamber of the DART ion source and it is electrical discharge to produce ions, electrons, and excited-state (metastable) atoms and molecules. Most of the particles (charged) are eliminated as the gas reaches the perforated lenses or girds and only the neutral gas molecules including the metastable species remain. The lens or gird at the exit of DART helps to reduce ion-ion and ion-electron mixing up again and it is also use as a source of electrons for surface Penning ionisation and as an electrode to enhance the ion drift towards the orifice of the mass spectrometer’s atmospheric pressure interface. 13Figure 1: DART source showing the main parts. Taken from reference 12Various ionisation mechanism are possible depending on factors like polarity of the reaction gas, the proton affinity and ionisation potential of the sample and the presence of addictives or dopants. 12 Penning ionisation process is the main reaction used when nitrogen or neon is used in DART source. 12 Nitrogen or neon ions are effectively eliminated by the electrostatic lenses and are cannot be detected in the DART background mass spectrum. 12 The polarity of the DART ion source can be adjusted from positive mode to negative move by changing the polarity of the disk and gird electrode only. 12 Positive ions are produced when helium is use and this involves the formation of an ionised water cluster followed by proton transfer reactions. 12This is shown below 12He (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 section9 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 an electron by Penning ionisation or surface Penning ionisation and are immediately thermalized by contact with atmospheric pressure gases and the electron combines with atmospheric oxygen give O2- which connect with the analyte of interest to form sample anions. 12 This is shown below12M* + 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. Fragmentation is possible depending on the sample and the source conditions. 12 Adjustment of the gas temperature or the Mass Spectromter orifice potentials determine the rate of fragmentation. 13 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

DART-MS is a newly invented technique, which has already shown wide applications for quick and safe analysis of complicated samples. 16 As a result of its capability to detect solids, liquids and gases in open air under ambient conditions using mass spectrometry, 12 it has found a wide application in they analyze of highly wide range16 of analytes 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. 16 DART ion source can also be use in the analysis of nonpolar compounds. 16DART can be done with less or no sample preparation and supplement existing LC or GC analytical techniques. DART is an exceptional technique that analyses sample in an open air, and this does not require any radioactive components, electrospray solvent, exposure to high voltage, or vacuum to change the analytes properties. Since its invention, DART-MS studies are increasing rapidly with the number of publications on the mechanism and its wide analytical applications.

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

Drug (tablets) analysis of 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 drugs17 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 pharmaceuticals18 by DART-MS was for the first carried out by studying an antimalarial products which contain Artesunate as an active ingredient 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 spectra 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 the 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 but determination of the quantity with DART-MS is very complex due to its low reproducibility. Quantitative analysis can be achieved only for liquid samples require a calibration curve and the use of reference samples to accurately determine the analyte concentrations but cannot be done for gas or solid samples. 20 a few study have been carried out on the quantitative analysis of solid samples like the semi-quantitative measurements of solid samples using 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 extra vacuum interface, the effect of doping agents and also the capabilities of DART-MS to analyse low concentration impurities when of the large amount of a major component are present. 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 a valuable 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 DART24 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 DART27 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 fast qualitative and quantitative analysis of various components in different kinds of food matrix 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 analysis 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 strobilurin residues with an internal standard (prochloraz)29 showed a good accuracy of DART-TOF MS based results, compared to the conventional analytical method like LC-MS/MS. 29 Further example of an effective 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 process reduces long sample preparation techniques and allows for fast sample analysis. 16The DART ion source coupled to time-of-flight mass spectrometry (TOF MS) for the determination 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 an 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

other compounds, including antimicrobial preservatives, artificial sweeteners, acidulants and saccharides, without any sample preparation and chromatographic separation in soft drinks, 33 coffee and tea infusions, 16 Analysis of multiple mycotoxins in cereals under ambient conditions using direct analysis in real time (DART) ionization coupled to high resolution mass spectrometry, 16 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 analysis of chemical warfare agents in 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 the original sample. Nilles et al. 35 used the DART technique for quantitative analysis of chemical warfare agents. This study showed a great result compared to conventional 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

DART and DESI are the two major ambient ionisation technique created. DESI is a new ionisation source that permits the use of mass spectrometry to get spectra of either solid or liquid phase of a material (condensed-phase) under atmospheric conditions. 44 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 need electrospray of liquid solvent as used by DESI as shown in figure 3 below. Studies of both ionisation sources show that the both gives a high throughput result on the analysis of the 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 raw 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 Preparat-ion

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. YesSample introduced to an elevated temperature and electrical potentialNoLiquid samples onlyMALDIMostly singly charged molecular ions but with few multiply charged onesYesThe rapid photo-volatilization of a sampleembedded in UV-absorbing matrixYesSolid samples only

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

DART-MS is a fast and easy analytical method that is used to analyse complicated samples at atmospheric pressure to gives a good result 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’s 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.