

Introduction of Mass Spectrometry and Ambient Ionization Techniques

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1.1 Evolution of Analytical Chemistry and Its Challenges in the Twenty-First Century

The Chemical Revolution began in the eighteenth century, with the work of French chemist Antoine Lavoisier (1743–1794) representing a fundamental watershed that separated the “modern chemistry” era from the “protochemistry” era (Figure 1.1). However, analytical chemistry, a subdiscipline of chemistry, is an ancient science and its metrological tools, basic applications, and analytical processes can be dated back to early recorded history [1]. In chronological spans covering ancient times, the middle ages, the era of the nineteenth century, and the three chemical revolutionary periods, analytical chemistry has successfully evolved from the verge of the nineteenth century to modern and contemporary times, characterized by its versatile traits and unprecedented challenges in the twenty-first century.

Historically, analytical chemistry can be termed as the mother of chemistry, as the nature and the composition of materials are always needed to be identified first for specific utilizations subsequently; therefore, the development of analytical chemistry has always been ahead of general chemistry [2]. During pre-Hellenistic times when chemistry did not exist as a science, various analytical processes, for example, qualitative touchstone method and quantitative fire-assay or cupellation scheme have been in existence as routine quality control measures for the purpose of noble goods authentication and anti-counterfeiting practices. Because of the unavailability of archeological clues for origin tracing, the chemical balance and the weights, as stated in the earliest documents ever found, was supposed to have been used only by the Gods [3].

During the middle ages (fifth to fifteenth century), alchemists began to assemble scattered knowledge that later became chemistry. Wet chemistry using mineral acids with noble metals symbolized the beginning of analytical chemistry as we know it today, and the evolution continued during the Age of Medicinal Chemistry (AD 1500–1650) as well as during the phlogiston era.



Figure 1.1 Portrait of Antoine-Laurent Lavoisier and his wife by Jacques-Louis David, about 1788.

The phlogiston theory was developed by J.J. Becher (1635–1682) late in the seventeenth century and was extended and popularized by G.E. Stahl (1659–1734). Some classical analytical methods had been developed since the seventeenth century: gravimetric analysis was invented by Friedrich Hoffmann (1660–1742), titrimetric analysis using nature dye indicators was widely practiced in 1874. Guy-Lussac (1778–1850) developed a titrimetric method for silver and got remarkable accuracy better than 0.05%, and Antoine Lavoisier who used balance to confute the phlogiston theory, demonstrated the law of mass conservation, which earned him the title “father of quantitative analysis.”

In 1826, Jean-Baptiste Dumas (1800–1884) devised a method for the quantitative determination of nitrogen in chemical substances. In 1860, the first instrumental analysis, namely, flame emissive spectrometry was developed by Robert Bunsen and Gustav Kirchhoff (Figure 1.2) who discovered rubidium (Rb) and caesium (Cs), and up to the latter half of the nineteenth century, about 90 elements were successfully discovered by the support of analytical chemistry, from which organic chemistry has benefited a lot. The periodic table of elements was created by Dmitri Mendeleev (1834–1907) in 1869. In 1876, the paper entitled “On the Equilibrium of Heterogeneous Substances” published by Willard Gibbs (1839–1903) introduced and developed systematic chemical concepts as cornerstones and fundamental principles for analytical chemistry.

The year 1894 was very significant when Wilhelm Ostwald (1853–1932) published an important and very influential text on the scientific fundamentals of analytical chemistry entitled “*Die Wissenschaftlichen Grundlagen der Analytischen Chemie*” (Figure 1.3). In addition, a series of chemical revolutions, that is, the first chemical revolution at the molar level from 1770–1790,

Figure 1.2 Photograph of Robert Bunsen (right) and Gustav Kirchhoff (left).



Figure 1.3 Wilhelm Ostwald (1853–1932). Recipient of the 1909 Nobel Prize for Chemistry “in recognition of his work on catalysis and for his investigations into the fundamental principles governing chemical equilibria and rates of reaction.”



the second chemical revolution at the molecular level from 1855–1875, and the third chemical revolution at the electrical level from 1904–1924, were chronologically implemented, which greatly facilitated the emergence and bloom of modern analytical chemistry, via which instrumental analysis became prevalent to address assorted analytical needs [4].

A prototype of mass spectrometer for ion separation and identification was invented by English physicist and 1906 Nobel Laureate in Physics Joseph John Thomson (1856–1940) at the beginning of the twentieth century, and in 1922, Francis William Aston (1877–1945) at the Cavendish laboratory in the University of Cambridge won the Nobel Prize for Chemistry for his investigation of isotopes and atomic weights using developed mass spectrometer with improved mass resolving power and mass accuracy. The spectrometer was developed in 1941, and self-recording Infrared, direct-reading, and self-recording emission spectrophotometers appeared in 1951. Gas chromatographs (GC) and nuclear magnetic resonance (NMR) spectrometers were produced in 1953, and the 1959 Nobel Prize for Chemistry was awarded to Heyrovsky for the invention of polarography. Around 1960, atomic absorption spectroscopy (AAS) was developed and GC coupled with mass spectrometry (MS) was applied for the identification of organic compounds. Later in the 1970s, high performance liquid chromatography (HPLC), with the merits of linking to MS with established analyte ionization strategies, emerged as a powerful tool to meet analytical challenges especially for natural product and biomedical researches.

Classical and modern chemistry with intellectual separation, identification, and quantitation strategies have been well studied and utilized to meet scientific, technical, and sometimes engineering needs; however, in the twenty-first century, due to rapid urbanization, mass industrialization, and business globalization, there are many serious problems, for example, resource shortage, climate change, and environment deterioration, facing the world, and therefore contemporary analytical chemistry needs to go further to deal with assorted eco-environmental, social public, macro-economic, or even individual ethical needs accordingly. Nowadays, micro-morphological imaging, visual identification, nontargeted profiling or multianalyte analysis, and ultra-sensitive, superior selective, high-throughput, *in situ* nondestructive and rapid cost-effective assay schemes are frequently needed for numerous analytical purposes, which are, to name a few, characterization of advanced materials, researches of noncovalent conjugates, discovery of therapeutic drugs, prognosis of new contagious diseases, surveillance of process or product quality, safeguarding food security and safety, management of consumer complaints, preservation of ecosystem, criminal investigations and forensic science, anti-terrorism practices, archeological excavations, and explorations of deep earth/sea and space missions. Therefore, to fulfill these challenging analytical assignments, contemporary analytical chemistry needs to interact intensively with its sister disciplines, for example, physics, electromechanics, biology, mathematics, and information science.

Probably the most challenging task in contemporary analytical chemistry lies in unveiling vital phenomena and life dynamics systematically using analytical tools developed for proteomics, metabolomics, and lipidomics researches. In addition, for analytes at the single molecular level or near zero concentrations where quantized nature of the matter dominates in its natural or complicated matrices, characterization of analysis capability and assurance of result fidelity continue to remain formidable tasks. As exemplified by the detection of persistent organic pollutant dioxins and polychlorinated biphenyls (PCBs) at part-per-trillion or part-per-quadrillion level, for geographical identification,

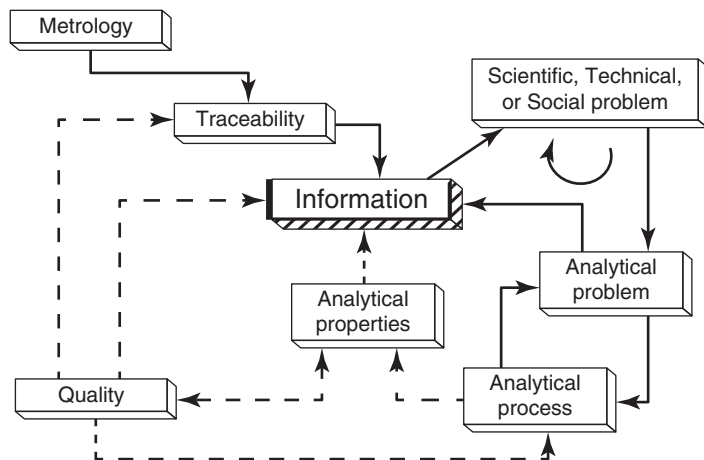


Figure 1.4 Essence and elemental relationships of contemporary analytical chemistry. (Adapted from Ref. [5], with permission from Elsevier.)

or for botanical/zoological authentication of olive oils and honeys, where sophisticated sample pretreatment steps and advanced instrumentations with chemometrics or bioinformatics packages are usually needed to acquire large volume analytical information for further data mining and model prediction.

In practice, analytical chemistry is inherently a metrological science with conventional separation, identification, and quantitation procedures. In order to tackle all sorts of scientific, technical, and social problems, contemporary analytical chemistry has been evolved nowadays as an autonomous scientific discipline that develops and applies methods, instruments, and strategies to obtain information on the composition and nature of matter in space and time [5] (Figure 1.4).

In the twenty-first century, much effort will be needed to make the analysis more objective and highly reproducible. Utilization of novel analytical schemes or frontier technologies, for example, ambient ionization MS, ultra-performance liquid chromatography (UPLC), surface enhanced Raman spectrometry (SERS), lab on a chip or micro total analysis systems (μ TAS), as well as profound researches on error propagation, uncertainty evaluation, and measurand traceability using certified reference materials and third-party proficiency tests or other relevant quality assurance measures are always needed to meet diverse fundamental, industrial, or regulatory requirements.

1.2 Historical Overview of Mass Spectrometry and Its Role in Contemporary Analytical Chemistry

Mass spectrometry (MS) is the study and recognition of matter through the determination of the abundance and the mass-to-charge ratio (m/z) of ions in gaseous state. The history of MS dates back to the early 1900s, when English physicist and 1906 Nobel Laureate in Physics Sir Joseph John Thomson

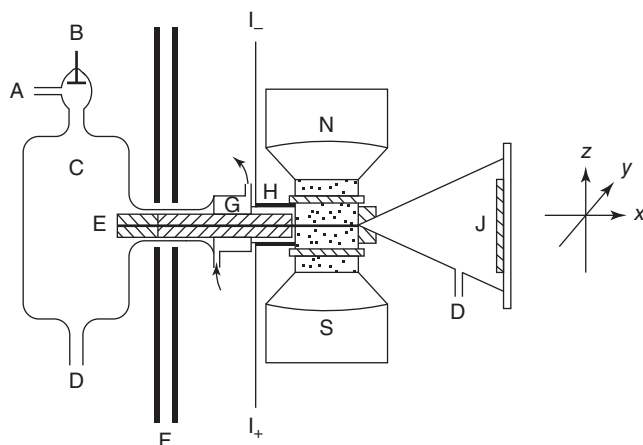


Figure 1.5 Schematic representation of the parabola mass spectrograph. A, the gas inlet; B, the anode; C, the discharge tube; D, the port to the vacuum system; E, the cathode; F, the magnetic shields; G, the water jacket for cooling; H, the insulators; and J, the photographic plate used to detect the ions. (Adapted from Ref. [6], with permission from Wiley.)

(1856–1940) developed a parabola mass spectrograph as the first prototype of mass spectrometer to separate different ions by their characteristic parabolic trajectories in electromagnetic fields and to identify these ions using a photographic plate (Figure 1.5). In 1913, authored by Thomson, the first book on MS, *Rays of Positive Electricity and Their Application to Chemical Analyses*, was published heralding the advent of MS research for precise characterizations in all fields of contemporary analytical chemistry [7].

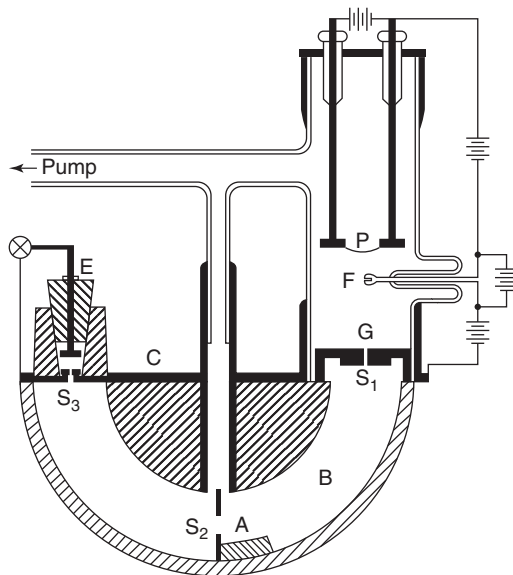
In order to improve MS resolving power to study isotopes, around 1911, Thomson's protégé, Francis William Aston (1877–1945) at the Cavendish laboratory in the University of Cambridge devised a velocity-focusing sector-based mass spectrometer to provide accurate m/z values and published in 1921 the famous paper "The Constitution of Atmospheric Neon," [8] which was considered to be the first paper in applied MS. In 1922, Aston won the Nobel Prize for Chemistry for his discovery of isotopes in a large number of nonradioactive elements by means of MS and the enunciation of whole number rule.

During the same period, the Canadian American physicist Arthur Jeffery Dempster (1886–1950) in the University of Chicago developed a direction-focusing sector-based mass spectrometer to provide accurate ion abundance values (Figure 1.6). In the late 1920s, Dempster proposed the combination of direction focusing and velocity focusing to further improve MS resolution along with Bartky [9] and around 1934 developed the first dual focusing mass spectrometer.

The pioneer works of Thomson, Aston, and Dempster were so profound for theoretical research, instrumental development, and technological evolution of MS as a competent tool in contemporary analytical chemistry that they are usually considered to be the founding fathers of modern MS [10].

With the aid of electronic ionization (EI) facilities and early magnet sector-based mass spectrometers, MS became an indispensable tool for fundamental

Figure 1.6 Schematic representation of Dempster's direction-focusing mass spectrometer that includes E, the ion-detection device; G, the glass ion-source housing containing the filament F that was heated to produce electrons that bombarded the platinum sample holder P; and B, the analyzer section surrounded by the magnet. A potential difference between the sample holder and the first slit (S_1) provided the ion acceleration and collecting with intermediate slit (S_2) and collector slit (S_3). (Adapted from Ref. [6], with permission from Wiley.)



particle profiling, isotope characterization, and elemental analysis and was mainly utilized for the researches of physicists, inorganic chemists, and geochemists prior to the 1940s. Worthy of note also is the utilization of preparative MS to separate uranium-235 from uranium-238 for the development of the atomic bomb during World War II.

While early mass spectrometric research was inherently focused on inorganic analysis, as complaints of detected ions from organic impurities rather than analytes were documented the potential of MS for organic analysis became noted by scientists and, accordingly, the 1940s saw the birth of organic MS, and early commercial mass spectrometers became available in the market especially for industrial oil or petroleum analysis, where volatile and thermally stable organic chemicals were frequently needed to be characterized. However, because gaseous ions had to be formed prior to separation and identification in early MS instrumentation, only limited organic compounds were suitable for mass spectral analysis.

Many research efforts and achievements on MS instrumentations had been acquired to enhance the analytical capability of mass spectrometers till the end of the 1950s. In 1946, William E. Stephens of the University of Pennsylvania proposed the concept of time-of-flight (TOF) MS, in which ions could be separated by differences in their straightforward drifting velocities toward the collector. The merit of the TOF mass analyzer lies in its superior resolving capability, high accuracy, virtually unlimited mass range, and rapid analyses at the milliseconds level for a full ionic scan [11]. Nowadays, due to efficient ionization facilities, for example, electrospray and matrix assisted laser desorption/ionization (MALDI), TOF mass analyzers have become routine research tools of choice for conducting research on both small organic molecules and large biomolecules.

In the 1950s, Wolfgang Paul, a German experimental physicist of the University of Bonn, successfully developed both quadrupole (Figure 1.7) and ion trap, the

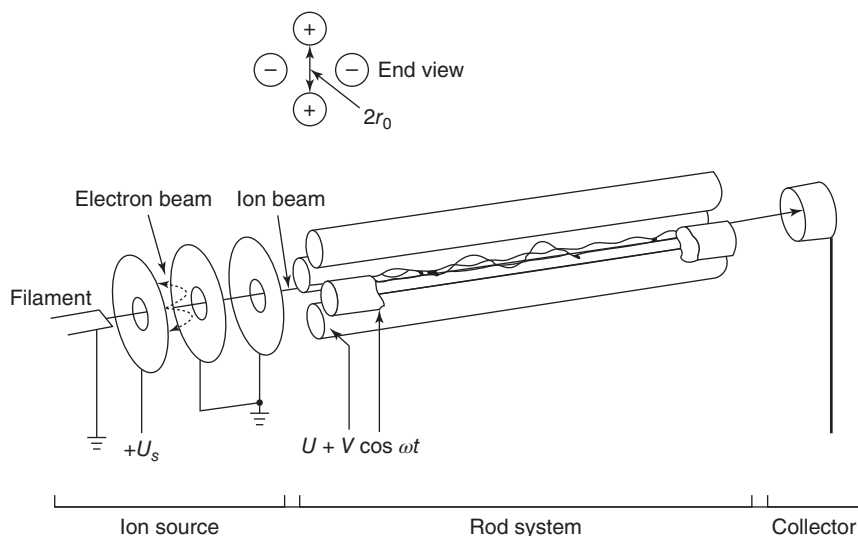


Figure 1.7 Schematic view of the quadrupole mass spectrometer or mass filter. (Reproduced with kind permission of Wolfgang Paul [12], The Nobel Foundation 1989.)

two most-used nonmagnetic mass analyzers. Compared with highly precise and accurate double focusing mass spectrometers, cost-effective quadrupole and ion trap mass spectrometers can furnish excellent dynamic range, spectral stability, and the facileness to perform tandem MS, which are deemed to be ideally suited for the development of frontier analytical instrument and method; for instance, Ouyang and Cooks at Purdue University had developed a handheld mass spectrometer for future field assays with a miniaturized ion trap mass analyzer operating at several milli Torr and maintaining sufficient ion capacity [13].

Thanks to the aforementioned mass analyzers and the application of desktop computers for data acquirement/analysis, the GC, developed around 1952 by A.T. James and A.J.P. Martin was coupled with the mass spectrometer in the 1960s, and gas chromatography mass spectrometry (GC-MS) became one of the most widely used analytical instruments for organic analysis or reaction mechanism interpretation in the 1970s, when high performance liquid chromatography mass spectrometry (HPLC-MS) emerged but was initially not as successful as GC-MS, because the ionization of analytes coeluting with HPLC mobile phases was not always possible.

In 1974, Melvin B. Comisarow and Alan G. Marshall of the University of British Columbia developed Fourier transform ion cyclotron resonance mass spectrometry (FT-ICR-MS) [14], which determines simultaneously the mass-to-charge ratio (m/z) of ions based on the cyclotron frequency of the ions in a fixed magnetic field. It can provide superior resolving power and accuracy as the ultimate solution for high-resolution MS analysis, as exemplified by Bruker's Solarix XR FT-ICR-MS system for metabolomics, proteomics, environmental, petroleum and energy researches, and an incredible resolving power of 10 million can be achieved using superconductive, refrigerated, and ultrashielded magnets. Theoretically, in FT-ICR-MS, the excited ions, when trapped in a

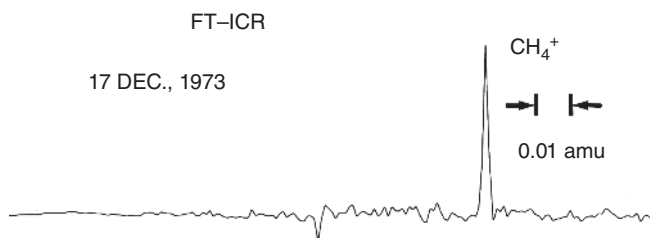


Figure 1.8 First FT-ICR mass spectrum. (Adapted from Ref. [11], with permission from Prof. Alan G. Marshall.)

Penning trap and rotating at their cyclotron frequency as ion packets, can induce an image current on electrodes as the packets of ions approach the electrodes, and mass spectrum can be extracted subsequently by Fourier transforming from the resulting signal called free induction decay (FID) (Figure 1.8).

Other than EI, a series of novel ionization schemes, for example, electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), and MALDI were successively developed from the 1960s to the 1980s, which gave birth to the technical maturing and commercial prosperity of HPLC coupled with the competency of various mass analyzers for the analysis of small organic compounds and large biomolecules. In addition, inductively coupled plasma (ICP) ionization was successfully combined with mass analyzer for inorganic analysis with unparalleled sensitivity and broad applicability.

At the end of the twentieth century, by virtue of the development of various mass analyzers and ionization strategies, MS had been chronologically utilized for numerous applications of chemical and biochemical researches: peptide mapping was investigated in 1990 with electrospray ionization mass spectrometry (ESI-MS) [15], noncovalent interactions were studied with ESI in 1991 [16], oligonucleotide ladder sequencing and protein identification were reported in 1993 [17, 18], MALDI ion imaging was developed in 1994 [19], intact virus analysis was implemented in 1996 [20], and the year 1999 saw quantitative proteomics and metabolomics with isotope labels [21].

In the twenty-first century, new mass analyzing technology as exemplified by Orbitrap™ was further developed together with many fascinating ambient ionization schemes, for example, desorption electrospray ionization (DESI), direct analysis in real time (DART), and paper spray ionization (PSI). For challenging explorations, MS was being extensively used in researches of shotgun lipidomics [22] and human proteome map drafting (Figure 1.9) [23].

Accompanying with the development of MS throughout the years, the role of MS in contemporary analytical chemistry is obvious and irreplaceable, and the uniqueness of MS stems from its physical simplicity, outstanding resolving power, superior mass accuracy, and facile and high-throughput analytical capability for ionic molecules or fragments. In the twenty-first century, in order to meet rigorous eco-environmental, social public, macro-economic, or even individual ethical demands, and to deal with assorted scientific, technical, or civil engineering needs, MS, with its perfectionism achieved by MS researchers in the world, is undoubtedly deemed to be the ultimate solution for contemporary analytical chemistry (Table 1.1).

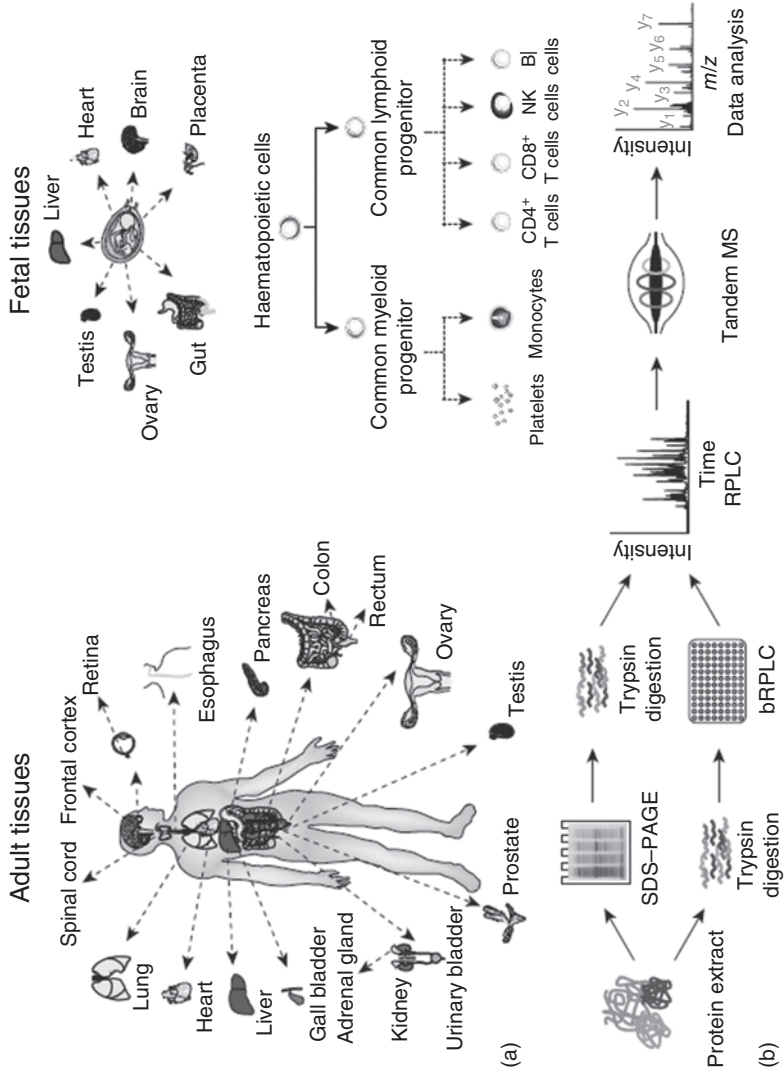


Figure 1.9 Overview of the workflow of MS for human proteome map drafting. (a) The adult/fetal tissues and hematopoietic cell types that were analyzed to generate a draft map of the normal human proteome. (b) The samples were fractionated, digested, and analyzed on the high-resolution and high-accuracy Orbitrap mass analyzer. (Adapted from Ref. [23] by permission from Macmillan Publishers Ltd: Nature, copyright 2014.)

Table 1.1 Historical developments in mass spectrometry.

Year	Contribution	Investigator(s)	Remarks
1899–1911	First mass spectrometer	J.J. Thomson	1906 Nobel Laureate in Physics
1918	Electron ionization and magnetic focusing	Dempster	
1919	Atomic weights using MS	Aston	1922 Nobel Laureate in Chemistry
1934	Double focusing instruments	Mattauch and Herzog	
1946	Time-of-flight mass analysis	Stephens	
1949	Ion cyclotron resonance	Hipple, Sommer and Thomas	
1953	Reverse geometry double focusing instruments	Johnson and Nier	
1953	Quadrupole analyzers	Paul and Steinwedel	1989 Nobel Laureate in Physics (Wolfgang Paul)
1956	High-resolution MS	Beynon	
1959–1963	GC/MS	McLafferty and Ryahe	
1966	Peptide sequencing	Biemann, Cone, Webster, and Arsenault	
1966	Chemical ionization	Munson % field	
1968	Electrospray ionization	Dole	
1969	Field desorption-MS of organic molecules	Beckey	
1974	Plasma desorption-MS	MacFarlane and Torgerson	
1974	FT-ICR-MS	Comisarow and Marshall	
1978	Triple quadrupole MS	Yost and Enke	
1981	Fast atom bombardment (FAB)	Barber	
1984	ESI on biomolecules	Fenn	2002 Nobel Laureate in Chemistry
1985–1988	Matrix facilitated laser desorption/ionization	Tanaka, Karas, and Hillenkamp	2002 Nobel Laureate in Chemistry (Tanaka)
1990	Protein conformational changes with ESI-MS	Chowdhury, Katta, and Chait	
1991	Noncovalent complexes with ESI-MS	Ganem, Li, Henion, Chait, and Katta	
1993	Oligonucleotide ladder sequencing	Pieles, Zurcher, Schar, and Moser	
1993	Protein mass mapping	Henzel, Billeci, Stults, Wong, Grimley, and Watanabe	

(Continued)

Table 1.1 (Continued)

Year	Contribution	Investigator(s)	Remarks
1996–2001	Intact viral analysis	Benner, Siuzdak, Bothner, and Fuerstenau	
1998	Electron capture dissociation (ECD)	Zubarev, Kelleher, and McLafferty	
1999	Nanostructure desorption/ionization	Wei, Buriak, and Siuzdak	
1999	Quantitative proteomics and metabolomics with isotope labels	Tong, Want, Smith, Shen, Tsao, Meng, Brandon, Webb, Siuzdak, Gygi, Rist, Gerber, Turecek, Gelb, and Aebersold.	
2000	Orbitrap	Makarov	
2003	Shotgun lipidomics	Han and Gross	
2004	Desorption electrospray ionization (DESI)	Takats, Wiseman, Gologan, and Cooks	
2004	Electron transfer dissociation (ETD)	Syka, Coon, Schroeder, Shabanowitz, and Hunt	
2005	Direct analysis in real time (DART)	Cody, Laramée, and Durst	
2013	Surgical “intelligent knife” (iKnife)	Balog, Sasi-Szabo, Kinross, Lewis, Muirhead, Veselkov, Mirnezami, Dezso, Damjanovich, Darzi, Nicholson, and Takatz	
2014	Draft of the human proteome	Kim, Pinto, Wilhelm, Schlegl <i>et al.</i>	

1.3 Desorption/Ionization in Mass Spectrometry

MS is the application of science and art to identify matters in their ionic forms with magnet sector or nonmagnet sector based mass analyzers, and analyte ionization is the most crucial procedure for MS. As shown in Figure 1.10, instrumental configuration of a mass spectrometer for MS characterization normally comprises a sample inlet, an ionization source, a mass analyzer/filter and an ion detector. The sample was first introduced into the spectrometer through a sample inlet, ionized by the ionization source and propelled into the mass analyzer/filter where sample ions were separated by their characteristic m/z , and eventually identified by the ion detector.

Small molecules with low boiling points and most inorganic compounds can be easily ionized with a specific ionization source for successful mass spectrometric analysis without any desorption or ablation procedures, as evidenced by ubiquitous applications of EI source prior to the 1960s. However, for nonvolatile, thermal labile compounds, and polymer or large biomolecules,

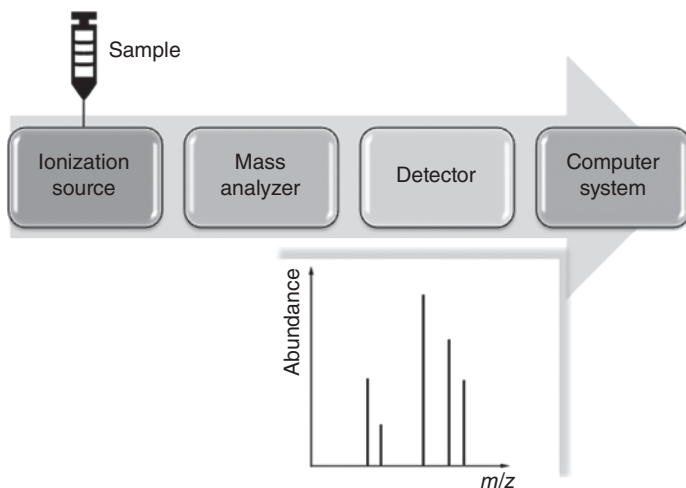


Figure 1.10 A schematic view of a mass spectrometer.

efficient desorption and/or ionization strategies are the *sine qua non* for routine mass spectrometric analysis.

Chronologically, desorption and ionization can happen concurrently or subsequently, and the pathway of ionization was by electron ejection, electron capture, protonation, cationization, deprotonation, or transferring a charged molecule from a condensed phase to a gaseous phase. In order to interpret complicated MS ionization mechanisms, various desorption/ionization schemes with relevant facilities were outlined as follows.

1.3.1 Electronic Ionization (EI)

Retrospectively, EI, formerly known as electron impact ionization and electron bombardment ionization, was the first and one of the most important ionization methods developed for MS. In 1918, Canadian American Physicist Sir Arthur J. Dempster first described EI in the article “*A new method of positive ray analysis*” [24]. In 1929, Bleakney began to apply a focused monoenergetic beam of electrons for ionization of gas phase atoms and molecules [25].

The mechanism of EI is rather straightforward as shown in Figure 1.11. Parent analyte molecules as precursors in gaseous samples thermally and vacuum desorbed from a probe or eluted from a capillary column were introduced into the ion source in a perpendicular orientation to impact with the electron beam via which electrons are produced through thermionic emission by heating a wire filament with electric current running through it. The electron beam has an accelerated 70 eV kinetic energy, because the energy of the bombarding electrons is higher than most ionization energies of analyte molecules. Both dissociative and nondissociative fragment ions will be formed by electron ejection, from which molecular or quasi-molecular ions, neutral fragments, and charged fragments can be produced for subsequent mass spectrum interpretation and molecular identification.

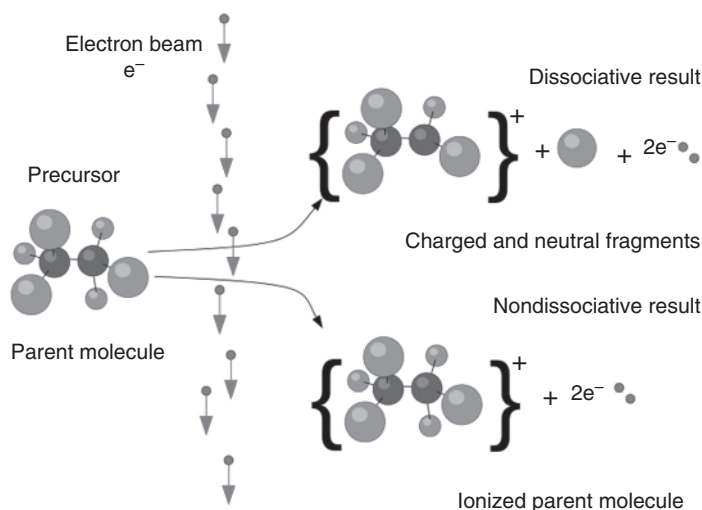


Figure 1.11 A schematic view of an electron ionization mechanism. (https://upload.wikimedia.org/wikipedia/commons/thumb/0/0c/Electron_ionization.svg/800px-Electron_ionization.svg.png. Licensed under CC BY SA 4.0.)

EI is frequently deemed to be a “hard” ionization method because of the facile production of many fragment ions, and EI is inherently suitable for the identification of small nonthermal-labile molecules, for EI-MS analysis, with a typical mass range reaching 600 Da. The merits of EI lie in its mechanistic simplicity, good sensitivity of picomole level, convenient procurement of standardized spectrum, that is, National Institute of Standards and Technology (NIST) database (>1 00 000 compounds) for easy fragment comparison and molecular identification. On the other hand, the demerits of EI are its poor amenability for liquid chromatography (LC)/MS, limited mass range due to its desorptive ionization requirement, and circumscribed practicability for biomolecular analysis.

1.3.2 Chemical Ionization (CI)

Compared to EI, chemical ionization (CI) is a lower energy ionization technique, which usually yields less fragmentation and a simpler mass spectrum for analyte identification and successive structural interpretation. For chemical ionization, ions are normally produced through the collision of the analyte with primary or secondary reagent gas ions, such as methane, ammonia, and isobutene, which are typical reagent gases used.

In principle, because the reagent gas molecules is present in large numbers compared to that of the analyte inside the ion source, electrons entering the source will bombard and ionize the reagent gas preferentially, and an ionization plasma will be created; both positive and negative molecular ions will be formed by the reaction of the analyte with the plasma [26].

In order to improve analyte ionization selectivity and applicability, APCI and atmospheric pressure photoionization (APPI) began to emerge as two important variants of chemical ionization strategies. An atmospheric pressure corona

discharge was introduced to APCI to ionize the analytes in gas or liquid spray eluted from high liquid chromatography, and a single photon or multiple photons with sufficient excitation energy in APPI can overcome the ionization potentials of atoms and molecules and ionize the analytes accordingly.

Both APCI and APPI have shown good amenability to LC/MS and have been successfully used for the analysis of hydrophobic materials with high femtomole sensitivity and no obvious matrix interference. However, these chemical ionization strategies have low salt tolerance at the millimole level, are inherently suitable for small molecular analysis, and have a typical mass range of about 1200 Da (Figure 1.12).

1.3.3 Fast Atom/Ion Bombardment Ionization (FAB)

Developed by Michael Barber at the University of Manchester [27], fast atom/ion bombardment ionization (FAB) is similar to chemical ionization and is a relatively low fragmentation ionization technique producing primarily intact protonated and deprotonated molecules. As shown in Figure 1.13, a beam of primary high-energy atoms or ions with about 4000–10 000 eV first strike the surface of the sample probe that is directly inserted into the mass spectrometer, then the analyte in the sample is mixed with a nonvolatile matrix compound to be desorbed and charged into the gas phase as secondary ions, and these are extracted, and aligned and propelled electrostatically to the mass analyzer for molecular characterization.

The atoms and ions used in FAB are typically from an inert gas such as argon or xenon and cesium ions, respectively. Common matrices include glycerol, thioglycerol, *m*-nitrobenzyl alcohol (NBA), 18-crown-6 ether, 2-nitrophenyloctylether, sulfolane, diethanolamine, and triethanolamine, which are frequently used to facilitate the replenishment of the probe surface with a new sample for efficient analyte desorption and ionization under atom/ion bombardment. In addition, these matrix compounds can absorb most of the energy of an incident atom/ion beam and prevent sample degradation from the beam effectively.

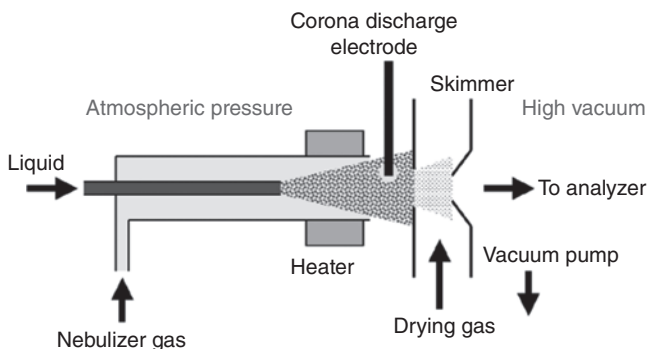


Figure 1.12 A schematic view of atmospheric pressure chemical ionization mechanism. (<https://upload.wikimedia.org/wikipedia/commons/c/c4/Apci.png>. Licensed under CC BY SA 3.0.)

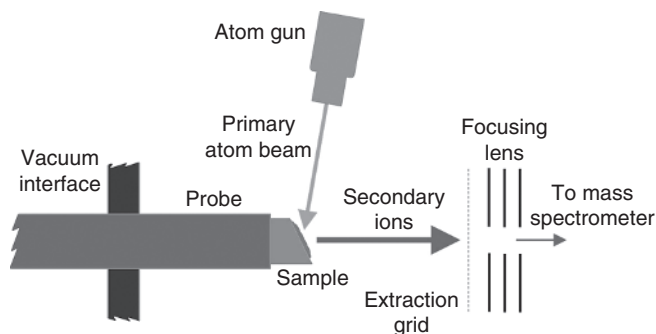


Figure 1.13 A schematic view of fast atom bombardment ionization mechanism. (https://upload.wikimedia.org/wikipedia/commons/thumb/a/ad/FAB_Schematic.jpg/1280px-FAB_Schematic.jpg. Licensed under CC BY SA 4.0.)

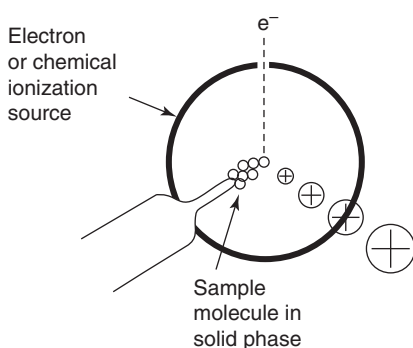


Figure 1.14 A schematic view of the direct exposure ionization method for DEI or DCI. (Adapted from Ref. [28], Copyright 1980, The American Chemical Society.)

FAB is relatively a soft insensitive ionization technique, and has very limited amenability to LC/MS. The sensitivity of FAB is usually at a nanomole level and has a typical mass range of 7000 Da for mass characterization of most target molecules.

For molecules with relatively no volatility and lability, two desorption ionization techniques other than FAB, namely, desorption electron ionization (DEI) and desorption chemical ionization (DCI) were successfully developed in the 1980s [28]. As shown in Figure 1.14, in this technique, the solid sample molecules coated onto the surface of an inert probe tip protrude directly into the ionization region of the ion source, and the analyte molecules on the probe are desorbed without decomposition by an apparent volatility enhancement process and ionized either by electron ionization or by chemical ionization consequently. In 1989, FAB, DEI, and DCI were comparatively utilized for mass spectrographic analysis of peripherally substituted synthetic porphyrins [29].

1.3.4 Electrospray Ionization (ESI)

ESI is a technique used in MS to produce ions using an electrospray in which a high voltage is applied to a static or continuous liquid flow to create charged droplets. Thanks to the relevant theoretical base of charged droplet and electrospray prior to the 1940s, the first use of ESI with MS was reported by Dole

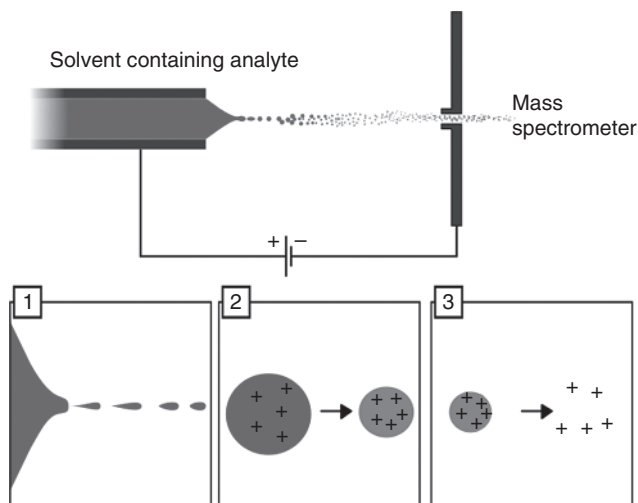


Figure 1.15 A schematic view of electro spray ionization mechanism. (https://upload.wikimedia.org/wikipedia/commons/thumb/b/b4/Electrospray_Ionization_Spectroscopy.svg/662px-Electrospray_Ionization_Spectroscopy.svg.png. Licensed under CC BY SA 4.0.)

et al. [30] John Bennett Fenn was awarded the 2002 Nobel Prize for Chemistry for the development of ESI MS in the late 1980s [31].

The mechanism of ESI is schematically shown in Figure 1.15. First, under the high voltage applied to the nozzle (or needle), the analyte-containing fluid was forced to emerge from the nozzle (or needle) as a Taylor Cone and emitted a jet of liquid droplets. Secondly, the solvent from the droplets were progressively evaporated, leaving the droplets more and more charged. Thirdly, when the charge exceeded the Rayleigh limit where the surface tension and electrostatic repulsion were equal, the droplets became attracted to the entrance of the mass analyzer and were explosively dissociated into numerous smaller droplets, leaving a stream of charged analyte ions.

For a low-flow scenario on nanoliters per minute order, for example, microfluidic MS, nanoelectrospray ionization (nanoESI) was developed accordingly to acquire better ionization efficiency and mass sensitivity, while the introduced sample volume can be remarkably reduced through the very small spray needle or nozzle made by metallized glass or fused silica. In addition, better tolerance of salts and other impurities can be expected because of the less evaporation needed for ionization of small droplets.

ESI or nanoESI are still the mainstream ionization techniques for chemical or biochemical analysis nowadays. They are usually deemed to be soft ionization methods as well because of the little fragmentations observed. The multiple charging capability of ESI or nanoESI is especially applicable for mass characterization of large biomolecules; normally, ESI or nanoESI is amenable to LC/MS and the typical mass range can reach 70 000 Da. However, for complicated mixtures, significant suppression might be an obstacle when employing ESI or nanoESI. In addition, little structural information can be directly gained from ESI-MS or nanoESI-MS, where tandem MS or other ionization schemes will be needed.

1.3.5 Matrix Assisted Laser Desorption/Ionization (MALDI)

Similar to ESI, MALDI is a soft ionization method developed by Karas *et al.* [32]. The 2002 Nobel laureate in Chemistry, Tanaka *et al.* [33], utilizes a combination of pulsed laser and assisted matrix compound for intact analyte ionization with high sensitivity, which became the dominant ionization strategy for accurate mass characterization of biomolecules and large organic molecules, such as peptides, proteins, oligonucleotides, carbohydrates, polymers, dendrimers, and lipids.

In practice, MALDI is usually considered to be a three-step process. As shown in Figure 1.16, the analyte in the sample applied to a metal plate is first co-crystallized with a large molar excess of a matrix material. Secondly, a pulsed UV laser irradiates the sample, triggering ablation and vaporization of the sample and matrix material, in which the analyte molecules were carried. Finally, the analyte molecules are ionized by protonation or deprotonation in the hot plume of ablated gases, and can then be accelerated into the mass analyzer for further mass characterization [34].

The energy transfer and desorption behavior are rather complicated during a typical MALDI process, and the mechanism of MALDI is still unveiled, although some theories, for example, thermal-spike model and pressure pulse theory, can partially interpret the ionization induced by MALDI. In terms of matrix material, UV-absorbing weak organic acids, such as 2,5-dihydroxy benzoic acid (DHB), 3,5-dimethoxy-4-hydroxycinnamic acid (sinapinic acid), and α -cyano-4-hydroxycinnamic acid (α -cyano or HCCA), were frequently used for various applications. Worthy of note is that MALDI can be performed on matrix-free plates, where porous silicon or silicon nanowires with large specific surface area and obvious UV-absorbing capabilities can be successfully applied for mass spectrometric analysis of organic analyte molecules, which led to the terminology of MALDI to be superseded by desorption/ionization on silicon (DIOS).

By employing MALDI, little to no fragmentation can be observed, and typical mass range can reach 3 00 000 Da. MALDI can acquire a femtomole level sensitivity and a good salt tolerance in millimolar concentrations as well, and

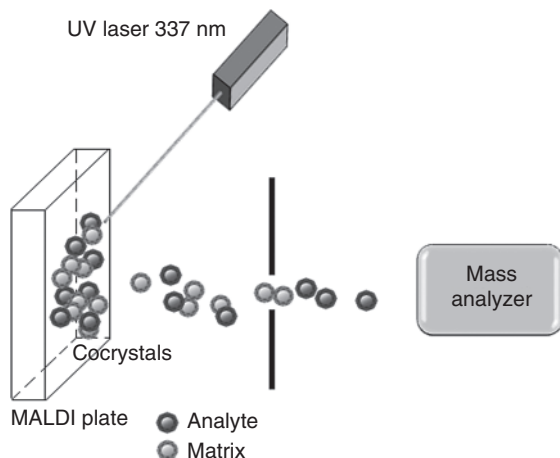


Figure 1.16 A schematic view of matrix assisted laser desorption/ionization mechanism.

the applicability of MALDI for the analysis of complex mixtures is exceptional. However, the demerits of MALDI are possible matrix background for low molecular weight analyte molecules, and photo-degradation induced by laser ablation/ionization.

1.3.6 Field Desorption (FD) or Field Ionization (FI)

Developed by R. Gomer at the university of Chicago in 1954 [35] and H.D. Beckey at the Institut für Physikalische Chemie der Universität Bonn in 1969 [36], field desorption (FD) or field ionization (FI) is an ionization method used in MS in which a high-potential electric field is applied to a solid emitter with a sharp surface or a tungsten filament with numerous field-enhancing graphite microneedles or whiskers. FD or FI has been successfully utilized for mass characterization of nonvolatile or thermally labile analytes since the 1960s.

Nevertheless, “field desorption” is considered by IUPAC to be an ambiguous term mechanistically because it implies that the electric field desorbs a material as an ion from some kind of emitter on which the material is deposited. There is growing evidence that some of the ions formed are due to thermal ionization and some to field ionization of vapor evaporating from the material on the emitter. Because there is generally little or no ionization unless the emitter is heated by an electric current, “field desorption” is a misnomer [37].

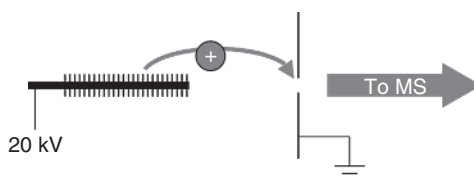
Compared with other highly energetic ionization strategies, FD or FI is a soft ionization method and has little or no fragmentation. The mass spectra are dominated by molecular radical cations $M^{+\bullet}$ for easy interpretation. Nowadays, because of the need of tedious filament preparation steps and delicate workloads, FD or FI is largely replaced by other facile ionization techniques such as FAB, DCI, MALDI, and ESI (Figure 1.17).

1.3.7 Plasma Desorption (PD) (ICP, LTP, DART)

Plasma refers to an ionized state of matter similar to a gas in physics and can function with helium, argon, nitrogen, and air flexibly. As utilized in fission fragment ionization (FFI), ICP, low temperature plasma (LTP), and DART for fast analysis with less sample consumption and deterioration, various plasma desorption (PD) methods have been consistently used as efficient ionization strategies for mass characterization or for identification of inorganic metal elements, organic chemicals, or biomolecules.

Developed by Ronald D. Macfarlane at the Texas A&M university, FFI involves the ionization of a material in a solid sample by bombarding with ions and/or neutral atoms resulted from the fission of a suitable nuclide, typically californium-252 (^{252}Cf) [38]. Although FFI heralded the genesis of bioanalytical

Figure 1.17 A schematic view of field desorption or field ionization. (https://upload.wikimedia.org/wikipedia/commons/5/56/Field_desorption.gif. Licensed under CC BY SA 3.0.)



MS for peptides, proteins, and oligonucleotides since the late 1970s, this PD ionization technique is no longer in use because the radioactive nature of the ionization source will always present a significant problem with regard to safety and disposal for a number of laboratories.

On the contrary, ICP, which is similar in principle to the well-known induction heating and encouraged by the thermal plasma studies in the 1960s, emerged as a very efficient ionization strategy in the 1980s and became popularized in the twenty-first century as a highly sensitive technique for inorganic elemental analysis when coupled with MS. Theoretically, G.I. Babat and T.B. Reed had investigated ICP on a stream of gas in 1947 [39] and 1961 [40], respectively. The core component of this ionization technique is an ICP torch as shown in Figure 1.18, which is essentially a copper coil of several turns subjected to an alternating current of radio frequency, through which cooling water is run to dissipate the heat produced during the operation. The coil wraps a coaxial quartz confinement tube, inside which the induction plasma is generated and maintained on a continuum gas flow.

LTP is an ionization technique developed in 2008 by R. Graham Cooks at Purdue University [41]. As illustrated in Figure 1.19, with the selection of discharge gas from helium, argon, nitrogen, or air, an AC power supply is utilized to induce a dielectric barrier discharge (DBD) through a grounded axially inserted electrode and a ring electrode outside the glass tube. An LTP as low as 30 °C is extracted

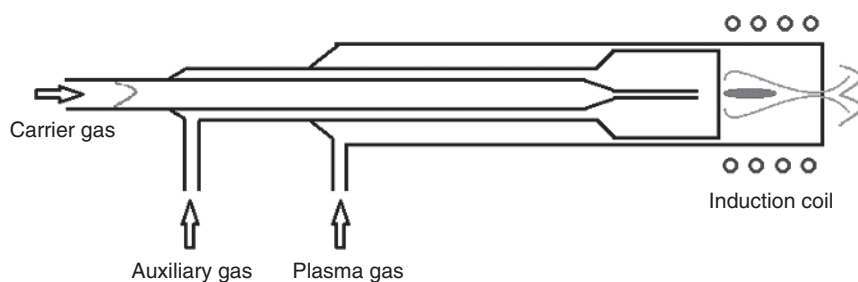


Figure 1.18 A schematic view of inductively coupled plasma torch.

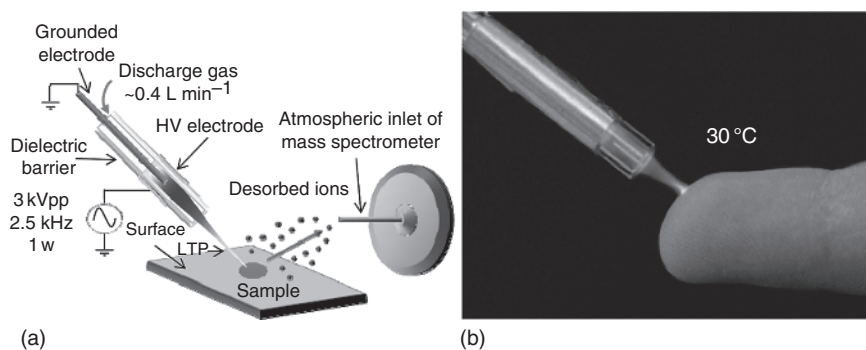


Figure 1.19 A schematic view of low-temperature plasma ionization for mass spectrometry. (Adapted from Ref. [41], Copyright 2008, The American Chemical Society.)

from the probe where it interacts directly with the sample being analyzed, desorbing, and ionizing the surface molecules in the open air environment, which allows subsequent MS analysis to be performed successfully for a wide variety of analytes from complex samples in their native conditions.

Although the mechanism of LTP still remains to be further understood, preliminary studies have indicated that the possible processes including thermal desorption, chemical sputtering, and surface reactions, could simultaneously occur during the desorption ionization process.

The configuration and implementation of an LTP probe for sampling analysis is relatively easy, and the relative positions of LTP probe, sample, and MS inlet for ionization softness adjusting are not critical, which are deemed to be remarkable contributions to the robustness of LTP-MS and for integration into miniaturized mass spectrometric system for field or onsite screening. Compared with ESI or APCI, LTP works well for both polar and nonpolar analytes; however, LTP does not work well for ionic analytes.

As a typical ambient ionization strategy, DART will be systematically described in Section 1.4.

1.4 Ambient Ionization and Direct Analysis in Real Time

1.4.1 Ambient Ionization

With the evolution of contemporary analytical chemistry, and in order to get spatial or time-resolved information on the composition and nature of matter, the concept of open-air analysis under ambient conditions in MS was proposed and successfully proved its applicability in the first decade of the twenty-first century. Nowadays, abundant ambient ionization technologies have sprung up as novel potential analytical tools with short analysis time, minimum carryover, less ionization suppression, possessing fascinating analytical capabilities of direct analysis, surface profiling, tissue imaging, or other precise characterizations; hence, ambient ionization in MS can widely be utilized for disease diagnosis, authenticity identification, geographical tracing, and quality grading, which were definitely rather challenging tasks for conventional analytical chemistry prior to 2000.

In this chapter, characteristics and applications of some ambient ionization technologies are systematically summarized in Table 1.2 [42–107]. Among various ambient ionization techniques, two general categorizations based on the primary ionization mechanism are presented in Figure 1.20: APCI-related (panel (a)) and ESI-related (panel (b)). DART can be regarded as a member of APCI-related ionization techniques, and has a common feature with all the other techniques in this group in that it uses a stream of heated gas derived from atmospheric components for analyte ion generation [108]. The ionization process can be generated by electrical discharge or ion evaporation, while desorption mechanisms mostly combine thermal desorption with momentum desorption [109].

ESI-related ionization techniques belong to another category wherein the analyte molecules can be directly conducted from gas samples into the ESI plume for ionization, or desorbed/sampled from solid or liquid samples before being

Table 1.2 Ambient ionization (AI) techniques and analytical traits.

Acronyms	AI techniques	Characteristics of ambient ionization-mass spectrometry (AI-MS)	References
APCI-related			
ASAP	Ambient solid analysis probe	Rapidly analyzing volatile/semivolatile liquid or solid, no need for preparation	[42, 43]
DAPCI	Desorption atmospheric pressure chemical ionization	Good selectivity, higher resolution, no need for high pressure gas in analyzing medium/weak polar compounds only for low MW and volatile compound	[44–48]
DAPPI	Desorption atmospheric pressure photo ionization	Analysis of various polar especially middle/nonpolar compounds on surfaces	[49, 50]
DBDI	Dielectric discharge barrier ionization	Minimized matrix effects, high sensitivity in trace analysis. Simple structure, low carrier gas flow rate, easy operation, good repeatability, dispense with solvent poorer mass range, limit of detection (LOD), sensitivity	[51, 52]
LD-DBDI	Laser desorption dielectric barrier discharge ionization	Detection of nonvolatile chemicals on surfaces	[53]
ND-DBDI	Neutral desorption dielectric barrier discharge ionization	Fast identification of various complex viscous samples	[54]
LTP probe	Low-temperature plasma probe	Gentle ionization, capable of desorbing chemicals without matrix or laser, potential for large-area surface sampling; no need of solvents, simple structure, higher sensitivity, suitability in the surface with big area, lower power, atmosphere as discharge gas	[55–59]
LDTD	Laser diode thermal desorption	Rapid and high throughput	[60–62]
DCBI	Desorption corona beam ionization	Direct analysis of samples from surface	[63, 64]
ESI-related			
SESI	Secondary electrospray ionization	High ionization efficiency for small volatiles, nonradioactive for ion mobility spectrometry	[65, 66]
DESI	Desorption electrospray ionization	No need for preparation, direct analyzing multiple small molecule or large molecule analytes in different gas, liquid, and solid samples as well as the surface; gentle ionization. Solvent is needed resulting in contaminated samples. Difficulty in analyzing powder directly and VOCs in liquids accurately; poor sensitivity and selectivity; rigorous operating conditions especially for detecting <i>in vivo</i>	[57, 67–79]

Table 1.2 (Continued)

Acronyms	AI techniques	Characteristics of ambient ionization-mass spectrometry (AI-MS)	References
Nano-DESI	Nanospray desorption electrospray ionization	Analysis of organic and biological molecules on substrates	[80]
ELDI	Electrospray laser desorption/ionization	Rapid analysis of solid material, higher spatial resolution for molecular imaging without matrix in need. Need preparation	[81]
EESI	Extractive electrospray ionization	High matrix tolerance to omit preparation; rapid real-time on-line direct analysis of surfaces and various samples in the gas, liquid, and solid phases; gentle <i>in vivo</i> application to prevent samples from solvent pollution	[82–88]
ND-EESI	Neutral desorption extractive electrospray ionization	Real-time, online gentle profiling of highly viscous samples or surface, low ion suppression, <i>in vivo</i> poor stability and repeatability	[89]
EASI	Easy ambient sonicspray ionization	Simple, quick, and reliable analysis of medium/nonpolar compounds in lipid samples; gentle, concise mass spectrum, higher S/N, easy to assemble	[90–96]
TI-EASI	Thermal imprinting easy ambient sonicspray ionization	Simple, fast and eco-friendly in the analysis of lipid-based food	[97, 98]
PSI	Paper spray ionization	High-throughput analysis of complex mixtures due to its facile operation, low cost and simple separation; pneumatic assistance is not required; difficult to elute off polar compounds in a short time, to quantify/semiquantify compounds with low levels in biological samples	[99–104]
LESA	Liquid extraction surface analysis	Determination of surface chemical residues	[105]
LDSPI	Laser desorption spray post-ionization	Simplicity, flexibility and high throughput	[106]
LAESI	Laser ablation electrospray ionization	Suitability to analyze water-contained samples	[107]

transported into the mass spectrometer in evaporating charged solvent droplets [109, 110]. Either charge residue or ion evaporation may occur during the ionization process, while desorption mechanisms differ a lot between energy-sudden activation and momentum desorption [109].

As a representative of ESI-related ionization techniques, DESI was proposed by the R. Graham Cooks group in 2004 [111], and has found wide applications similar to DART. During the ionization process, the electrically charged aerosol is created when a pneumatically assisted electrospray needle hits the surface

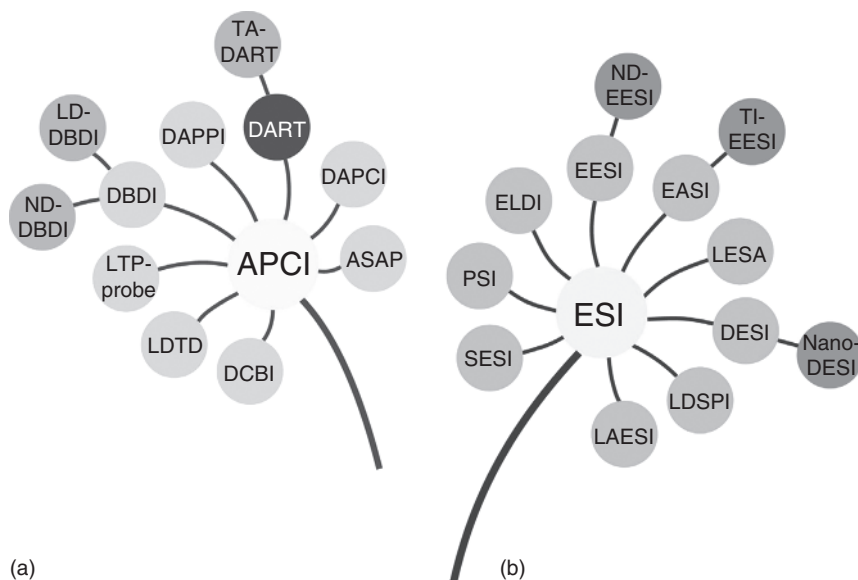


Figure 1.20 A pattern of flowers to summarize ambient ionization techniques.

of samples, and desorbs and ionizes the analytes into the mass spectrometer. Two main parameters of DESI are important, that is, sample distance (capillary tip-to-sample and sample-to-collector) and spray angle (incident and ion-collection angle) [108]. In a comparative study between DART-MS and DESI-MSⁿ for the rapid screening of strobilurin fungicides in wheat, both methods proved to be successful in the detection of the analytes, although in the quantitative tests, reliable results were generated only with DART-MS [68].

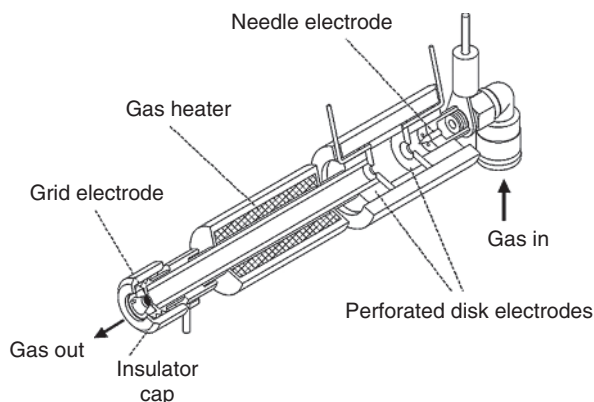
Whether to use singular or dual ambient ionization methods depends on the structural features of analytes and types of samples. Because ambient ionization techniques have been in use for just 10 years, a period shorter than when traditional ionization methods have been used, the blooming of diverse ambient ionizations with impressive analytical merits is still at an early stage, and much attention is paid to more commercialized ambient ionization technology as exemplified by DART currently.

1.4.2 Direct Analysis in Real Time

1.4.2.1 Mechanisms

DART is based on the reactions of long-lived electronic excited-state atoms or vibronic excited-state molecules with the analytes and atmospheric gases [112]. As illustrated in Figure 1.21, gas (typically helium, nitrogen, or argon) flows through a chamber where perforated disk electrodes produce ions, electrons, excited-state atoms, and molecules. Most of the charged particles are removed as the gas passes through grid electrodes and only the neutral gas molecules (i.e., metastable species) remain [113]. The insulator cap can protect the sample as well as the operator from exposure to high voltage [114].

Figure 1.21 Cutaway view of the DART Ref. [112]. ©The American Chemical Society, 2005.

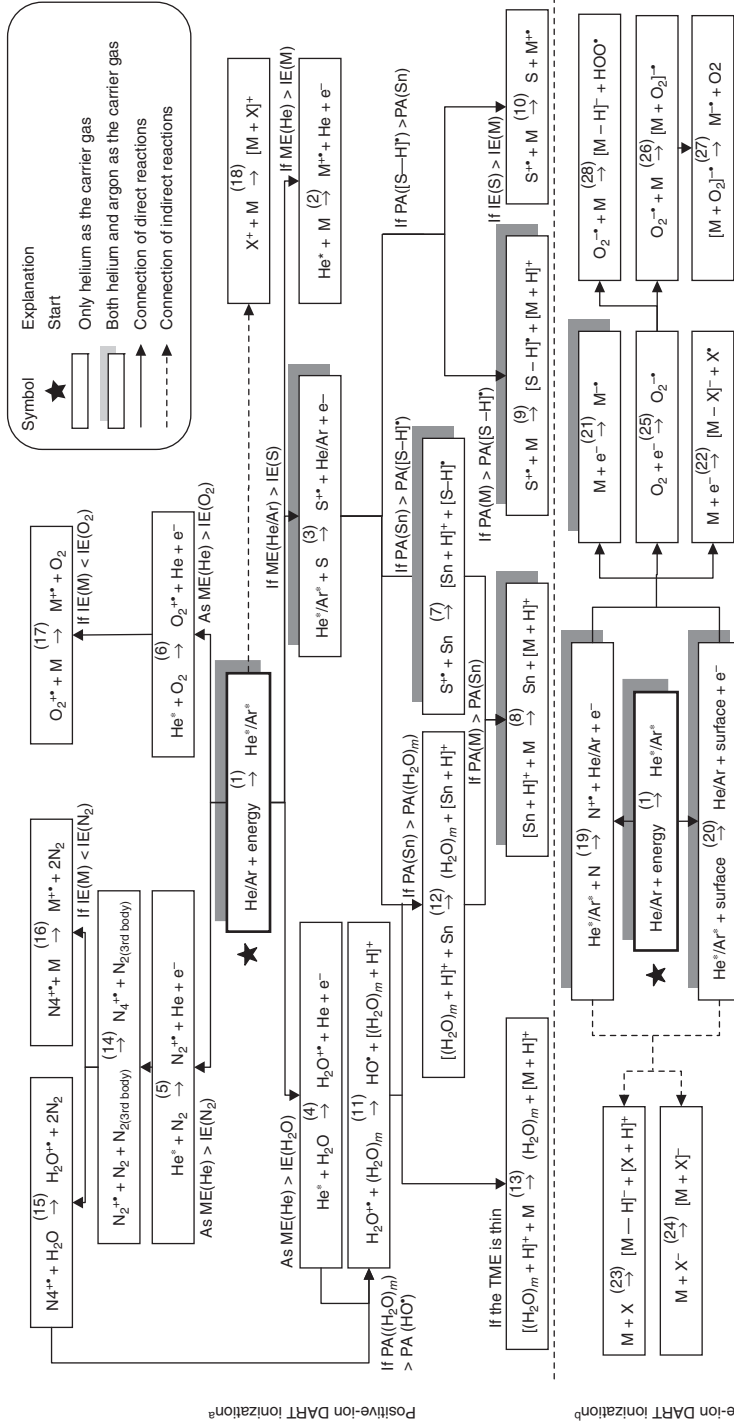


The ionization mechanisms are influenced by many factors, such as the charge, the type, and the metastable energy (ME) of carrier gas, the proton affinity (PA), ionization energy (IE) and concentration of analyte, and the presence of additives/dopants. There are multiple acceptable processes of ionization mechanisms, mainly Penning ionization (PI), proton transfer (PT), electron capture (EC), dissociative electron capture (DEC), and cation/anion attachment (IA). PI [115] is the process in which the noble carrier gas atom (i.e., helium, argon) can be effectively energized by glow discharge to an electronic or vibronic excited state (metastable state), and then the metastable carrier gas transfers energy to substances that possess lower IE [112, 116]. The ME value of noble carrier gases and the IE value of main reaction intermediates (i.e., reagent gases and solvents) are summarized in Table 1.3, from which it can be seen that He^* (metastable helium) possesses higher ME that can induce PI of most molecules (i.e., oxygen, nitrogen, water, and most solvents, such as acetonitrile and dichloromethane), while Ar^* (metastable argon) can only ionize certain solvents (e.g., dichloromethane) whose IE is below the ME of Ar [117, 118].

The main reactions of a DART ionization mechanism in both positive and negative ion mode are summarized in Figure 1.22. In positive ion DART, there are several branches of the reaction, and almost all the branches are initiated by the formation of metastable carrier gas atoms, mainly He^* or Ar^* (reaction 1). If the reactant (R) has lower IE value than the ME of excited-state He/Ar atom, it will be ionized and will generate radical cation $\text{R}^{+\bullet}$ as well as electron (e^-). R includes both analyte molecule (M, reaction 2) [119] and the reaction intermediates, for example, the solvent molecule (S, reaction 3) [120], H_2O molecule (reaction 4)

Table 1.3 IE and ME of carrier gases and IE of main reaction intermediates.

	Carrier gases		Reaction intermediates				
	He	Ar	Reagent gases		Solvents		
			O_2	N_2	H_2O	Acetonitrile	Dichloromethane
IE (eV)	24.59	15.76	12.07	14.55	12.62	12.2	11.33
ME (eV)	19.8	11.55					



^aS/Sn: neutral solvent molecule ($n = 1$ or 2); $m = 1, 2$, or 3 ; FI-fragment ion; TME: transient microenvironment; IE: ionization energy; ME: metastable energy; PA: proton affinity; ^bN: neutral molecule; ^aN: anlyte molecule.

Figure 1.22 Main reactions of DART ionization mechanism.

[112, 120], reagent gas molecule (i.e., N_2 , reaction 5, and O_2 , reaction 6) [116, 119, 121, 122], and so on. The M-branch is the simplest process based on the PI of analytes (reaction 2). In the S-branch, after the formation of $S^{+\bullet}$, the following three reactions after comparing the PA of neutral solvent molecule (Sn) and $[S-H]^\bullet$ are categorized: reactions 7 and 8, reaction 9, and reaction 10. In the H_2O -branch, subsequent to the generation of $H_2O^{+\bullet}$, reaction 11 will occur and $[(H_2O)_m + H]^+$ will be produced. If $PA(Sn) > PA((H_2O)_m)$, $[(H_2O)_m + H]^+$, together with the Sn, will subsequently transfer to reaction 12, prior to access to reaction 8. Conversely, if the transient microenvironment (TME) is thin, reaction 13 may occur. In the O_2 -branch and N_2 -branch, the $O_2^{+\bullet}$ and $N_2^{+\bullet}$ will be produced (reactions 5 and 6). Before reacting with M (reactions 16 and 17), $N_2^{+\bullet}$ will be converted into $N_4^{+\bullet}$ first (reaction 14). In addition, $N_4^{+\bullet}$ may react with H_2O (reaction 15), and the generated $H_2O^{+\bullet}$ will pass into reaction 11. Moreover, the process of cation attachment (reaction 18), typically ammonium adduct ($[M + NH_4]^+$) formation, may also occur where carbonyl-contained compounds and peroxides exist [116].

In negative ion DART, the metastable atoms He^*/Ar^* are also generated in reaction 1. Through reactions 2 and 3 [112], electrons will be generated by PI of the neutral (N) or surface together with He^*/Ar^* (reactions 19 and 20). Subsequently, four types of ionization mechanisms are shown [123, 124], including EC (reactions 21 and 25), DEC (reaction 22), PT (reaction 23), and anion attachment (reaction 24). The O_2 branch with some mechanistic details has been investigated (reactions 25–28) [125–127].

Once at relatively high concentrations, solvents or water can form clusters, mostly dimers, which have greater PA values than the corresponding monomers [120, 121]. Fragment ions will be produced only if the corresponding neutral has sufficiently low apparent potential or large enough enthalpies of formation to drive the reaction [112]. The degree of fragmentation relies on the choice of gas, the temperature, and the orifice potential. According to the mechanisms presented earlier, DART demonstrates its established advantages in not generating alkalimetal cation adducts, multiple charge ions, apparent suppression, and solvent effects.

1.4.2.2 Parameters

Like other detection methods, the parameters pertaining to both DART and MS need to be optimized so as to obtain the required amount of analyte ions and higher sensitivity, detectability, and reproducibility. These parameters mainly include gas temperature, chamber pressure, positional distance, gas flow rate, gas type, electrode potential.

The temperature of the gas flowing into the DART source is a rather important factor in the whole analysis. For most thermally stable analytes, a temperature of 350 °C is recommended [128]. However, for the release of temperature-dependent compounds the temperature is usually optimized from ambient temperature up to 500 °C [116]. Lower temperatures are appropriate for volatile organic compounds (VOCs) (i.e., common organic compounds and low boiling point compounds), while higher temperatures favor higher boiling point compounds and longer sugar chain saccharides [129, 130]. What is noteworthy

is that the temperature inside a DART source is different from the actual temperature in the ionization region (i.e., in the gap between DART source and mass spectrometer inlet) because of the cooling procedure of heated gas [130]. Temperature gradient and ramping of DART gas temperature can be used for the optimization of source conditions. A temperature gradient can facilitate separation of the pesticides through varying thermal desorption profiles of the compounds of interest [131]. Using temperature ramp technique, compounds having the same nominal mass can be thermally separated [132].

The Vapur atmospheric pressure interface (IonSense, Saugus, MA) has an influence on the chamber pressure by increasing the collection of ions desorbed from the surface to maintain the MS vacuum in a normal operating pressure [133]. The pressure in the interface chamber, which has an effect on both the pressure in the atmospheric pressure interface (i.e., pirani gage pressure) and the pressure of the MS analyzer, needs to be optimized. An investigation shows that maximum response and low signal-to-noise ratio (S/N) of analytes are obtained at pirani gage pressure of 250 Pa and MS analyzer pressure of 1.2×10^{-5} Pa [134]. The chamber pressure can be adjusted by the restrictor valve of the membrane pump linked to the interface chamber with more carrier gas suction. This results in a satisfactory transport of ions through the ceramic ion transfer tube of the interface to the MS inlet, and a minimized background signal as well. If the pressure in the chamber is too low, ions will be sucked out, while at high pressure ions will not reach the MS inlet [134]. Instead of Vapur interface, a confined interface connecting the DART outlet and MS sampling orifice is introduced, combined with an extra vacuum pump for better ionization efficiency of DART by reducing random diffusion and increasing collision reaction probability of gaseous analytes [135].

Various positional distances are also of great importance, for example, the DART exit to the ceramic tube inlet, the ceramic tube outlet to the heated capillary inlet, the DART exit to the MS orifice, and the DART exit to the sample. The gap between the DART exit and the ceramic tube inlet is approximately 8–10 mm, and the distance between the ceramic tube outlet and the heated capillary inlet is generally 2 mm so that suction from a low-capacity vacuum pump can evacuate the region [136]. The distance between the DART exit and the MS orifice is allowed adjustment varying from 5 to 90 mm to suit different DART sources or mass analyzers [137, 138]. Closer or wider spacing can be realized either by partially unscrewing the ceramic insulator cap to achieve a closer spacing or by unscrewing the DART source and moving it away from the MS [116]. The samples are always held at a gap distance of about 2–5 mm from the exit of the DART gun [137].

As for carrier gas flow rates, variations from a few milliliters per minute to several liters per minute are recommended [116]. Although flow rates are not significantly correlated with signal intensities, high flow rates (≥ 4 – 4.5 L min^{-1}) will lead to the formation of a liquid jet [139]. Referring to the type of carrier gas, helium is most commonly utilized owing to its higher ME value than IE of most analytes, while nitrogen is often used as a reaction intermediate or in standby mode for the reduction of helium consumption. For better distinction of the molecular ions from fragment ions, the substitution of argon as carrier gas

can help achieve high sensitivity and accuracy by minimizing the fragmentation when analyzing labile compounds [117, 118]. DART electrode potentials were by default set to needle (glow discharge) electrode -3500 V, electrode 1 -150 V, and electrode 2 (grid) -250 V [116].

1.4.2.3 Devices

Table 1.4 shows multiple assorted samplers or devices of DART. By dipping into the solution prior to positioning in the helium gas stream of the DART, some capillary tubes or glass rods are suitable for analyzing liquid samples. The DIP-it sampler (IonSense) [140–142], consisting of a glass sampling tube and a hollow plastic handle, is a commercial liquid sampler introduced mainly for rapid qualitative analysis. In conjunction with a customized DIP-it carrier on the linear rail (LR) [143], medium sample throughput (12 sample loads) and accurate positioning can be achieved. Comparatively, a high throughput (96 sample loads) autosampler device AutoDART-96 (Leap Technologies, Carrboro, NC) has been widely applied [134, 144, 145]. In this device, a robotic arm can automatically grip the DIP-it sampler, and place it in a 96-well plate to pick up liquids for analysis. Compared to manual sampling, the use of a robot deck can improve repeatability.

For a number of direct surface-desorption/ionization methods referring to a DART ion source, samplers made of porous materials are developed successively. Multiple sample holders are positioned in-line between the DART source exit and the mass spectrometer inlet, and passed through by the helium gas stream in perpendicular direction to the axis. Fabrics, swabs/disks, and filter paper have been successfully employed for certain applications: for application of antimalarial insecticide on mosquito netting [146] and fragrant galaxolide on fabric [137] and detection of multiple pesticide residues on fruit and vegetable surfaces by swabs/disks [131, 147, 148] and strobilurin fungicides in wheat by filter paper [68]. The auxiliary devices of TM or tweezers can hold the swabs/disks and fabrics for introducing analytes into the MS inlet. Metal mesh is another thermal desorption holder used for identification and quantitative analysis of liquid samples (i.e., liquid food product or extract), which demonstrates the advantage of larger sample loads, and longer lasting signal yield than DIP-it. The commercial metal

Table 1.4 Multiple assorted devices of DART.

Sampler	Examples	Specimens	Auxiliary devices
Tube/rod	DIP-it, capillary tube, glass rod	Liquids	AutoDART-96 + 96-well plate, LR
Porous surface	Swabs, disks, fabrics, metal mesh	Fruit and vegetable surfaces netting, fragrant fabric liquids	Tweezers, LR, TM TM TM, XZ-TM, ID-CUBE
Plate	TLC/HPTLC plate and paper 96-well plate	Turmeric, propolis, extracts of fruit juices	3DS, auto slider 3DS
Clamp	Tweezer, fingers	Entire sample surface	LR
Standardized-holder	Tablet holder	Tablet, corn kernel	3DS
Customized-holder	Tee-shape	Crushed Allium	Tee-shape

screen is usually divided into three units. The first unit is the common medium throughput (10 sample loads) transmission-mode DART (TMDART) [146, 149]. This metal screen is most commonly made of nonconducting materials. An alternative medium-throughput metal screen made by heat-conducting material and termed as thermally assisted DART (TA-DART) was also proposed [150]. Owing to the direct heating grid, rapid vaporization of liquid can be achieved in less than 20 s, and, by modulating the electrical current flow, either rapid desorption for single component samples, or slower desorption for mixtures can be realized. The second unit is the high-throughput XZ-TM-DART (IonSense) (96 sample loads) [151], which allows for analyzing 96 samples within 20 min. The third unit is a metal grid of Open Spot cards (IonSense) coupled with the ID-CUBE ion source (IonSense) (1 sample load) [152]. Similar to TA-DART, an electric current to the metal grid can thermally desorb and introduce the analytes into the helium gas flow within 20 s.

To solve the problem of poor desorption when the gas stream does not vertically pass through the surface of the sample, the adjustment of angle (i.e., 20°, 30°, 45°, between the DART gas stream and the desorption surface) was proposed [153]. With the aid of mechanization, an auxiliary device named 3+D Scanner (3DS) with three-dimensional adjustment in horizontal, vertical, and angled directions was developed accordingly [128]. After drying, the analyte can be *in situ* analyzed at the surface of a glass plate, a thin layer chromatography (TLC) plate or a high performance thin layer chromatography (HPTLC) plate (2D), or a 96-well plate (3D). As compared with the conventional DART-MS, more than two orders of magnitude of linear dynamic range were achieved by TLC/DART-MS [128]. In order to further simplify analytical procedures, a novel plasma assisted multiwavelength laser desorption ionization technique (PAMLDI) integrated with TLC/DART-MS was developed and utilized for analyzing low molecular weight (MW) compounds [100].

The clamp-like tweezer [154–156] or fingers [147, 157] can grasp the entire sample for direct surface analysis. With the LR [147, 149, 157] at a constant speed, the sample-introducing process can be more stable and uniform. The analysis of a solid tablet can be fulfilled with the tweezer holder (1 sample load) or the tablet carrier (10 sample loads) [158] coupled with 3DS as well.

Additionally, a novel confined DART (cDART) device can analyze gaseous analytes by introducing a Tee-shaped interface between the DART source outlet and the mass spectrometer orifice [135]. Following the high-purity nitrogen gas being carried into the container, the gaseous samples were ionized in a flow tube instead of in open air.

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