

Ion Mobility Spectrometry: Ion Source Development and Applications in Physical and Biological Sciences

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(Invited Paper)

Abstract—The utility of ion mobility spectrometry (IMS) has been steadily growing, and it cuts across diverse areas in physical and biological sciences. The development of ion sources, particularly in the context of IMS, is described. IMS ion sources operate efficiently in ambient environment and yield ions for a wide range of complex molecules including biological materials. While significant progress has been made in this area through the development of a variety of ion sources, further research to address several key issues, namely, ionization processes, reaction chemistry, and overall system miniaturization for field deployment of IMS, is the primary focus of current activities. Aside from reviewing the present state of the art of ion sources for IMS, this paper has discussed the wide range of applications and current trends of research in the field.

Index Terms—Applications, ion mobility spectrometry (IMS), ion sources.

I. INTRODUCTION

A WIDE variety of ion sources exists, and ion beams extracted from these sources show widely different characteristics. The highly diverse range of applications of ion sources has maintained strong activities in this field from the standpoint of both basic and applied research. The major application areas include advanced high-energy accelerators, fusion research, space thrusters, ion beam microscopy, microelectronics, materials processing, and many analytical measurements, such as secondary ion mass spectrometry (SIMS), field ion imaging, and ion mobility spectrometry (IMS). Specific needs of the beam parameters in these applications, by and large, determine the choice of a source and its operating conditions. For example, high-energy accelerators require high beam intensity and high beam brightness [1]. The key parameter of interest in fusion research, specifically in the context of neutral beam heating, is large beam current. Ion beam microscopy and imaging studies require focused beams with a submicrometer spot size and a current density of $> 1 \text{ A/cm}^2$. Ion beam lithography, such as

projection ion beam lithography, and focused ion beams (FIBs) are other application areas for fine FIBs [2]–[17]. Low energy spread and high beam brightness are the key requirements in these cases where beams from a source are coupled to a focusing lens system. A recent review described various source characteristics, corresponding beam parameters, and relevance of these sources in several current applications where FIBs are needed [18]. The beam characteristics are primarily related to the operational principles of sources. There is a significant body of literature dealing with this subject. A good digest of the development of various ion sources and their applications is included elsewhere [19]–[23]. Additionally, the proceedings of several topical conferences and workshops are good resources to follow the development in this field, particularly from the standpoint of ion source development for different applications [24]–[28].

This paper draws special attention to sources that have relevance to IMS. While work in the area of IMS has a long history, research in this field has rejuvenated due to the realization of its wide range of applications, including security screening, space research, basic and applied problems in biological science, as well as medical applications. In the context of IMS, the crux of the problem refers to understanding the ionization processes and developing sources with high ion yield in environmental conditions. This problem has engaged the scientific community with new enthusiasm. An excellent book by Eiceman and Karpas [29] discusses the underlying critical areas in this context. Several other articles have discussed the IMS development and critical issues in the area [30]–[32]. Noteworthy are efforts in a related area, i.e., in mass spectrometry. The pioneering work by Shahin [33], [34] on chemical ionization at atmospheric pressure coupled to mass spectrometry opened up important activities covering basic studies of the ionization processes and applications, particularly by mass spectrometrists in widely diversified fields. Another related work on atmospheric ionization was made by Eisele [35] who performed the first tandem mass spectrometric measurements of tropospheric ions. A review article [36] and an edited book [37] highlighted the development in the area of atmospheric-pressure ionization mass spectrometry.

In this paper, we have revisited the current state of the art of IMS, keeping an attention to the unique ion source issues and

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ion beam characteristics. The key application areas encompassing physical and biological sciences are discussed, and needs in those fields have been identified. Section II discusses the background of IMS development and current trends of basic research. Different types of ion sources and their key attributes are discussed in Section III. Current applications of IMS are highlighted in Section IV. Finally, the key problems and trends of research and applications are summarized in Section V.

II. IMS BACKGROUND

A. Historical Development of IMS

Fundamental research during the 1950s and 1960s led to the development of IMS as an analytical method for rapid separations [38]–[43]. This era provided the experimental and theoretical background to modern-day IMS. Early mobility studies were primarily performed in late 1800s to early 1900s [44]–[51]. The basic concept of relating ion mobility to ion identity was developed at reduced pressures with mobility cells coupled to mass spectrometers to study ion–molecule reactions, to determine the identity of ions, and to evaluate the correlation between mass and mobility of ions [38], [52], [53].

During the Cold War era, driven by the demand for instruments with rapid response times that can monitor air compositions for defense purposes, a high level of research activity during the mid to late 1960s at Georgia Institute of Technology and Franklin GNO Corporation led the development of IMS from a reduced pressure ion mobility research tool to an atmospheric-pressure rapid analytical technique for vapor-phase analyte analysis. Early low-pressure ion mobility studies, along with the observation of dependence of ionization detector responses to humidity in air during the development of several ionization detectors for gas chromatography [54]–[58], provided the basis of present-day radioactive ionization sources for the IMS. Due to the mass–mobility correlation observed in the early studies, IMS was thought to be “poor man’s mass spectrometer.” Practical applications of IMS later demonstrated that IMS cannot replace MS [59]; however, mass–mobility curves can be fitted to provide estimate of masses of analytes [60], [61].

The first atmospheric-pressure IMS was introduced by the name of plasma chromatograph by Cohen and Karasek [62] and was followed by commercial production in 1971 by Franklin GNO Corporation [63]. Revercomb and Mason [64] further developed the fundamental equations of ion mobility as applied to present-day IMS. Since its inception, IMS has been extensively applied to on- and off-bench analytical purposes with or without being coupled to other separation techniques. As a stand-alone rapid separation technique [64], [65] or as detectors for GC and LC separation methods [66]–[68], IMS has been applied to numerous environmental, forensic, law enforcement, security, quality control, space exploration, and biomedical applications (see Section IV on applications). Tandem with mass spectrometry, IMS, with its rapid and unique separation mechanism, provides additional information to mass spectrometric data by separation of isomeric ions that are not separated by mass [69], [70]. When IMS is coupled to mass spectrometers,

the combination is called ion mobility–mass spectrometry (IMMS), and at present, it is extensively used in research laboratories to investigate ion–molecule reactions [71]–[74], ion structures [75]–[78], conformations of biomolecules such as peptides and proteins [79], [80], and separation of isomers [81], [82]. Separation by IMS prior to mass analysis allows one to rapidly analyze complex biological and environmental samples [83]. Two-dimensional data obtained from IMMS also facilitate easy interpretation of mass spectra by the following ways: 1) differentiating chemical noise, which usually complicates the mass spectra, from signal [83]–[85] and 2) classification of compounds and charge states and conformers of proteins and peptides based on trend lines [86]–[89]. One of the major contributions of IMS in conjugation with MS is the ability to rapidly separate gas-phase enantiomers either as diastereomeric complexes [90] or enantiomers themselves [91].

B. Highlights of the Current Trends of Research

Since the introduction of IMS, the technique has been under continuous development. Identification of suitable ionization sources, modifications in drift-cell designs, and amendments to IMS modes of operation and data acquisition are the focus of present-day IMS research as pertained to instrumental development. Developments in experimental methods include manipulation of ionization processes by addition of dopants in the carrier gas or spray solvent and variation in drift-cell environment for increased sensitivity, selectivity, and enhanced resolution. Several different drift-tube configurations exist, and the mobility spectroscopy is named after the drift-tube characteristics, namely, drift-time IMS [92], [93], aspiration IMS [94] or sometimes called Gerdien condenser, differential mobility spectrometry [95], and traveling-wave IMS [96], [97]. This paper focuses on ion source issues, and discussions on various sources are delineated hereafter.

III. ION SOURCES FOR IMS

Ion mobility measurements can be achieved at low, ambient, or high pressures. Thus, ion formation in an ion mobility spectrometer does not necessarily require any vacuum system as in many other cases. For example, the ion sources for high-energy accelerators, thermonuclear fusion research, and semiconductor applications such as ion beam lithography, ion implantation, or ion beam milling operate at a pressure in the range of millitorrs. The vacuum components make the overall system quite cumbersome and bulky, and these factors also pose operational constraints and transportability limitations. The operation of the IMS ion source at atmospheric pressure facilitates field applications. With the overall objective to achieve high sensitivity of IMS, one of the requirements is high ion flux through the IMS drift cell. In this pursuit, renewed interests have generated toward developing new ion sources and/or improving the current systems. Current ion source research and development activities are primarily focused at enhancing the understanding of the ion formation and ion transport processes.

The principal components of IMS are shown schematically in Fig. 1. Ion source is located in front of the reaction region.

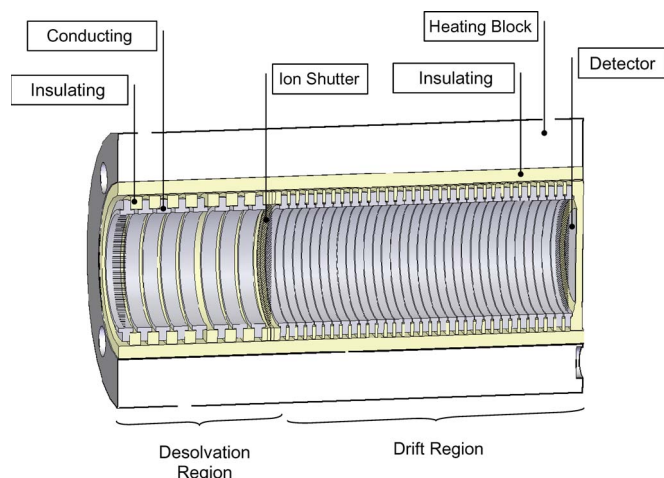


Fig. 1. Schematic diagram of an ion mobility spectrometer.

Electric field guides the ions from the source into the reaction region or desolvation region. Pulses of ions are then injected into the drift region where separation of ions occurs under the action of an external electric field and collisions with a counter-moving gas. At the end of the drift tube is located the ion collector, usually a plate where the ion current is registered. Based on the characteristic mobility values (which depend on the shape, size, polarizability, and collision properties of the ion species), different ion species arrive at the collector at different times. The details of the basic principles of IMS are described elsewhere [29]–[32].

The ion sources for IMS can be classified by the following several distinct ionization processes: 1) radioactivity-based ionization; 2) electrospray ionization (ESI) including secondary ESI (SESI) and desorption ESI (DESI); 3) surface ionization; 4) matrix-assisted laser desorption/ionization (MALDI); 5) atmospheric-pressure glow discharge/arc including afterglow discharge and direct analysis in real time (DART); 6) photoionization; 7) flame ionization; and 8) recent activities using nanoscale soft-ionization membrane in the context of source miniaturization to support restricted payload for space applications. Several other variants of ion sources have been used in mass spectroscopy [98], [99]. While radioactive sources are used in many IMS instruments, interests in nonradioactive sources have been steadily growing, particularly in the area of atmospheric-pressure desorption ionization including DESI, DART, MALDI, and new soft-ionization techniques. The key scientific principles and underlying technical issues for some distinct systems are discussed hereafter; emphasis is laid on current activities.

A. Radioactive-Source-Based Ionization

Americium (^{241}Am) and nickel (^{63}Ni) are used as radioactive sources because these materials emit alpha and beta particles, respectively. The beta particles or electrons from ^{63}Ni have an average energy of ~ 17 keV, and these electrons ionize the ambient gas molecules. The alpha particles from ^{241}Am have energy > 5.4 MeV, and these particles can be very effective for

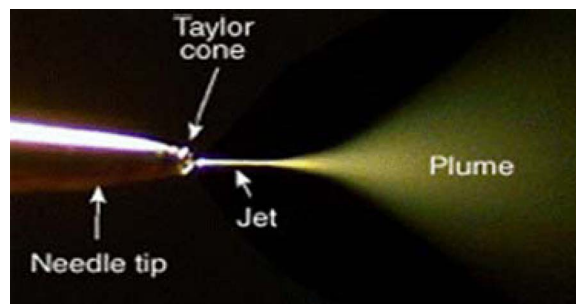


Fig. 2. Schematic of the operational scenario of an ESI source. This figure is reprinted from *J. Am. Soc. Mass Spectrom.*, vol. 15, G. A. Valasekovic, J. P. Murphy, and M. S. Lee, "Automated orthogonal control system for electrospray ionization," pp. 1201–1215, Copyright (2004). This figure also appears in [http://www.newobjective.com/resources/app_notes.html].

ionization in a small volume of gas. A 10-mCi source of ^{63}Ni generates about 10^9 ions/cm³/s [100].

B. ESI/SESI

While the principles of ESI were introduced by Chapman [101]–[103] and later demonstrated in 1968 [104], their utility was demonstrated in 1988 in experiments on identification of polypeptides and proteins of molecular weight of 40 000 Da [105]. A significant amount of activities in the field has been continuing to date.

Fig. 2 shows a schematic of the operational scenario of an ESI source. Typically, a bias voltage of about 2.5–4 kV is applied to the tip of a capillary through which flows the sample dissolved in a polar volatile solvent. The resulting electric field disperses the sample emerging from the tip into an aerosol of highly charged droplets. Solvent evaporation and charge repulsion result in the formation of less charged ions. Desolvation of charged droplets is enhanced by a coaxially introduced nebulizing gas flowing around the outside of the capillary. Either positively or negatively charged droplets are produced, depending on the polarity of the voltage applied to the capillary. Ion–molecule collisions need to be taken into account to determine the ion yield at atmospheric pressures. ESI was developed as a source for IMS measurements by Shumate and Hill [106]. In this development, a heated drift gas flowing against the direction of ion motion was introduced at the end of the drift region to desolvate ions generated by ESI and thus allowed the analysis of semivolatile and nonvolatile analytes by IMS. An additional desolvation gas, which was introduced in the desolvation region of the IMS by Khayamian *et al.* [107], provided enhanced solvent evaporation.

A major merit of ESI is that nonvolatiles and macromolecules can be ionized without fragmentation for analysis. This process of ionization is particularly helpful for mass spectroscopy of large biomolecules. Because ESI is a soft-ionization technique, it allows the studies of molecular complexes that have weak noncovalent interactions, such as protein–protein, enzyme–substrate, or protein–ligand complexes. This technique is well suited to polar molecules from less than 100 Da to more than 1 000 000 Da in molecular mass. Small molecules primarily form singly charged ions through ESI; however, formation of multiply charged ions is common with higher

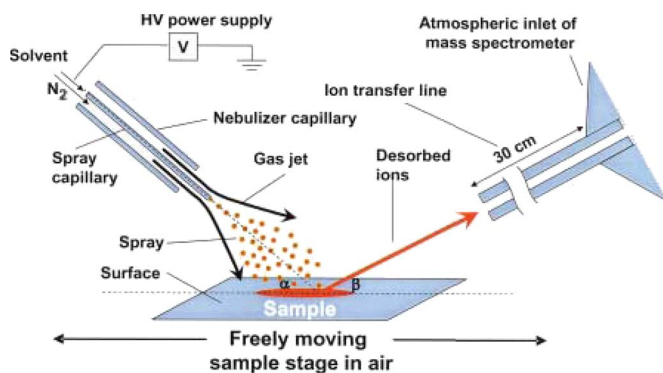


Fig. 3. Principles of DESI sources [112]. From Z. Takats, J. M. Wiseman, B. Gologan, and R. G. Cooks, "Mass spectrometry sampling under ambient conditions with desorption electrospray ionization," *Science*, vol. 306, pp. 471–473, 2004. Reprinted with permission from AAAS.

mass analytes or analytes with multiple ionization sites such as oligosaccharides, peptides, and proteins.

Along the line of ESI techniques, the secondary ESI (SESI) method was introduced by Chen *et al.* [108] as a nonradioactive ionization source for IMS. This method uses similar principles as atmospheric-pressure chemical ionization where the gas-phase reactant ions are produced by ESI. Ion–neutral interactions between ESI-generated charged particles and neutral gaseous sample molecules result in ionization of the sample molecules. The performance of ESI–IMS and SESI–IMS for illicit drug detection was investigated by determining the analytical figures of merit. It was noted that, in general, SESI had higher ionization efficiency for small volatile molecules compared with the electrospray method [109], [110]. SESI sources can be used for both vapor- and aqueous-phase analytes, such as explosives and chemical warfare agents.

C. DESI, DART, and MALDI

A recent article discusses some important developments in the area of DESI and DART, specifically from the point of view of current understanding of ionization methods and related new applications [111]. This is a family of atmospheric-pressure ionization techniques where desorption–ionization principles are utilized. Fig. 3 shows the principles of DESI operation [112]. Here, a stream of solvent droplet ions bombards the sample surface, typically at approximately a few kilo-electron volt energy. This impact causes desorption and ionization of molecules from the bombarded surface.

Similar to DESI, another process is known as extractive ESI (EESI), reported by Chen [113], which allows the ionization of liquid samples using ions produced by ESI as the primary ion source. In EESI, liquid samples are nebulized using a nebulizing gas and are allowed to interact with ions produced from an ESI source, resulting in the ionization of the sample molecules at atmospheric pressure, which can then be introduced into an IMS or mass spectrometer for analysis. SESI for volatiles, EESI for liquids, and DESI for solids, thus, are developments of ESI for various analytical purposes. Fig. 4 shows the schematics of an SESI and an EESI.

Sonic spray ionization (SSI), developed by Hirabayashi *et al.* [114] for mass spectrometric applications, uses pneumatic spray operated at extremely high nebulizing gas flow rates (5–25 atm) to facilitate the formation of ions. Polar compounds such as sugars, drugs, amino acids, peptides, and proteins are efficiently ionized using SSI [115]–[119]. Being an atmospheric-pressure ionization source, SSI can be developed as an alternative ionization source for IMS. SSI has been developed as desorption SSI (DeSSI) by Haddad *et al.* [120] and as electro-SSI (ESSI) introduced by Takats *et al.* [121]. DeSSI uses the primary ions produced by SSI to ionize stationary solid-phase analytes and thus allows the analysis of solid samples and provides cleaner spectra than DESI because high voltage is not needed to produce ions. The high-velocity supersonic DeSSI spray facilitates matrix penetration and thus provides more homogenous sampling and longer lasting ion signals. ESSI utilizes the sonic flow of nebulizing gas with electrospray to achieve efficient ionization and increased desolvation. In ESSI, solvent is electrosprayed from a fused-silica capillary with sonic gas flow coaxial to the capillary. Ions, as well as charged droplets, are produced under atmospheric pressure, and their intensities depend on the gas flow rate. Fig. 5 shows the schematics of the SSI, DeSSI, and ESSI setup. A microchip SSI developed by Pol *et al.* [122] as an atmospheric-pressure ionization source for mass spectrometry gives nanomolar detection limits, linear correlation between concentration and signal intensity, good reproducibility, and long-term signal stability.

DART utilizes a glow discharge plasma to generate excited species of an inert gas, such as helium, with high flow velocity (1–3 L/min). It is a soft-ionization method where ionization of sample molecules involves interaction of low-energy metastable species (~ 20 eV) generated by a discharge with the neutrals [123]. The exact mechanism for DART is still not well understood, and activities in this field are still continuing. Other desorption–ionization techniques use nonthermal plasmas generated by radio-frequency waves to ionize sample molecules [124]. Both DESI and DART are applicable to small organic molecules and also to large biomolecules in solids, liquids, and adsorbed gases.

MALDI is widely used to study biological samples, specifically in conjunction with time-of-flight mass spectroscopy. The source was initially developed for low-pressure ionization of large mass molecules such as proteins and peptides by Hillenkamp *et al.* [125] and Karas *et al.* [126]. This soft-ionization scheme is initiated by a laser, such as nitrogen, Nd:YAG, or CO₂ laser, and the analyte molecules are embedded in a matrix of crystallized molecules [127]. This matrix protects the analytes, particularly biomolecules, and facilitates strong optical absorption and ionization. Steiner *et al.* [128] demonstrated the feasibility of atmospheric-pressure MALDI as an ion source for IMS prior to mass analysis by a time-of-flight mass spectrometer. Although the source has not been sufficiently explored with AP-IMS systems, it provides a method for generation of singly charged ions of macromolecules at atmospheric-pressure conditions. Tanaka *et al.* [129] showed a major progress in the field of ionizing biomolecules as large as the 34 472-Da protein carboxypeptidase-A.

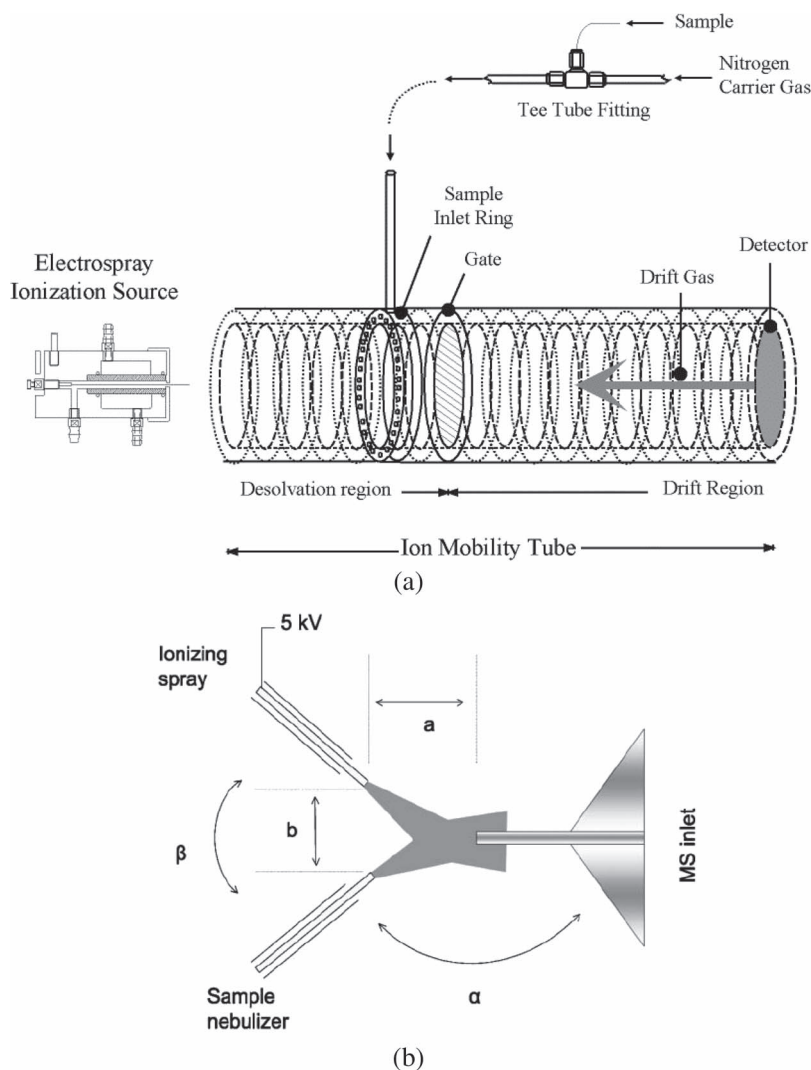


Fig. 4. Schematic diagram of (a) SESI and (b) EESI [113]. From H. Chen, A. Venter, and R. G. Cooks, (2006) "Extractive electrospray ionization for direct analysis of undiluted urine, milk and other complex mixtures without sample preparation," *Chem. Commun. (Camb)*, no. 19, pp. 2042–2044, 2006. Reprinted with permission from The Royal Society of Chemistry.

D. Nanoscale Soft-Ionization Membrane

A novel submicrometer-scale soft-ionization source shows very attractive results with high ionization yield, $\sim 100\%$, and almost no fragmentation. Note that the ionization yield is significantly lower, $\sim 0.01\%–10\%$, in the cases where the characteristic system length is much larger than the collision mean free path. This new soft-ionization source is developed using nanoscale electromechanical system fabrication technique. Small holes were micromachined through a $0.3\text{-}\mu\text{m}$ -thick silicon nitride membrane with $0.03\text{ }\mu\text{m}$ thick of gold coating on both sides [130]. A potential of about 10 V is applied across the membrane, and this yields an electric field of $> 10\text{ MV/cm}$ over a region ($\sim 0.3\text{ }\mu\text{m}$). This length scale is smaller than the mean free path of the neutral gas molecules flowing through the holes. As a result, ionization of the neutral gas molecules occurs, and the electrons and ions that are produced quickly pass through this high-field region without gaining much energy. This system produces only positively charged ions, and primarily singly charged state ions are generated.

Due to the large ionization yield and no ion fragmentation, the source runs efficiently at high pressures, $\sim 1\text{ torr}$, and it does not require any high-vacuum or differential pumping system. This operating pressure is very similar to Martian atmospheric pressure ($\sim 5\text{ torr}$). This miniaturized source is considered a strong candidate for its coupling with IMS for space exploration endeavors.

E. Corona/Glow Discharge

Ion sources based on corona and glow discharge ionization have attracted a lot of attention, particularly over the radioactivity-based ionization sources; the early work by Shahin [33], [34] is noteworthy. These sources do not pose any threat of radioactive materials. Additionally, intense ionization is attainable in a small volume with corona and glow discharge. Recent developments on corona discharge sources include a multithread corona discharge source, a hollow-cathode discharge source, a pulsed corona discharge source, and a plasma source.

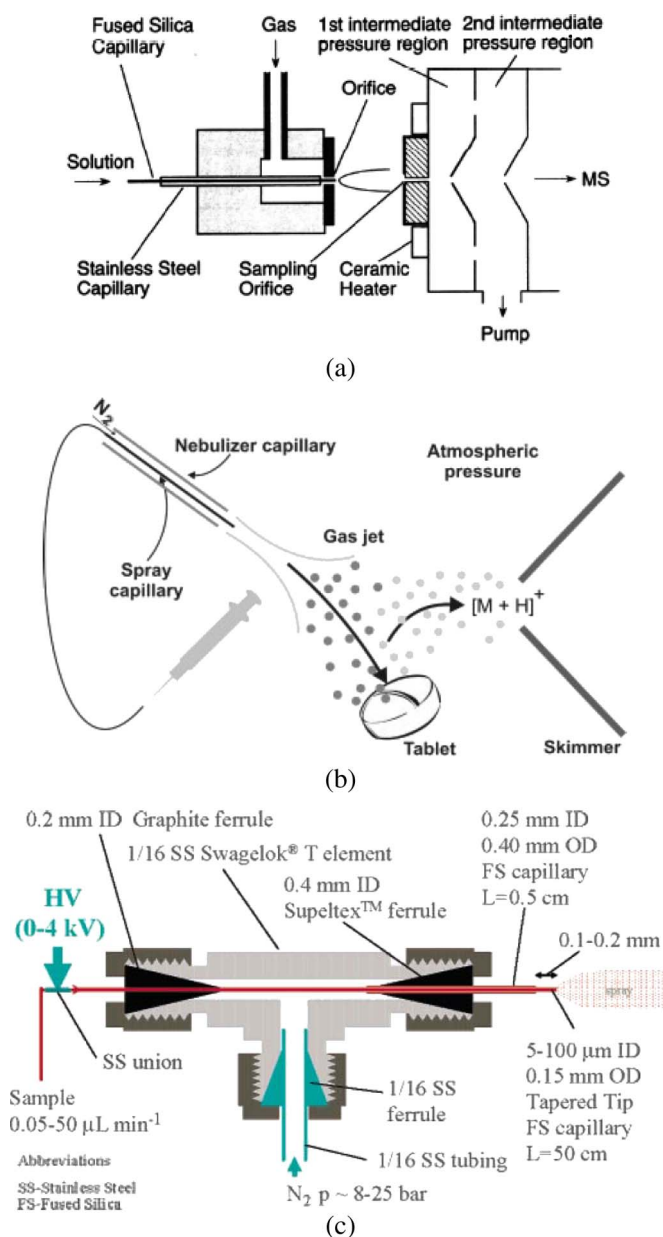


Fig. 5. Schematics of (a) SSI [114]. Reprinted with permission from “Sonic spray mass spectrometry,” A. Hirabayashi, M. Sakairi, and H. Koizumi, *Anal. Chem.*, vol. 67, pp. 2878–2882, 1995. Copyright 1995 American Chemical Society. (b) DeSSI [120]. “Desorption sonic spray ionization for (high) voltage-free ambient mass spectrometry,” R. Haddad, R. Sparrapan, and M. N. Eberlin, 2006. Copyright John Wiley & Sons Limited. Reprinted with permission. (c) ESSI setup [121]. Reprinted with permission from “Electrosonic spray ionization. A gentle technique for generating folded proteins and protein complexes in the gas phase and for studying ion–Molecule reactions at atmospheric pressure,” Z. Takats, J. M. Wiseman, B. Gologan, and R. G. Cooks, *Anal. Chem.*, vol. 76, pp. 4050–4058, 2004. Copyright 2004 American Chemical Society.

In the corona/glow discharge sources, electrons that are responsible for ionization growth are not as energetic as in the case of radioactive sources, and thus, the scale size for ion source can be made much smaller. In contrast to the continuous discharge produced by traditional sources, pulsed corona sources produce ion packets at predetermined frequencies that can also be synchronized with IMS scanning frequency and allow the elimination of the requirement of ion gate for

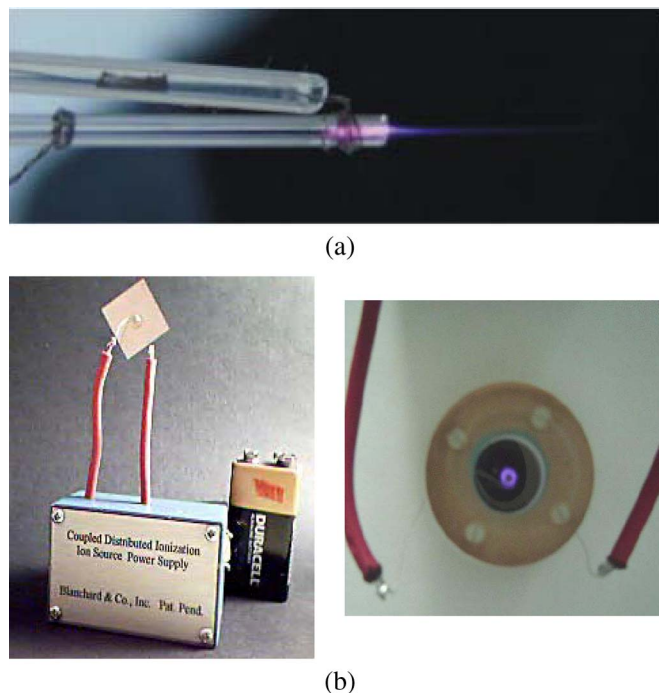


Fig. 6. (a) Pencil-type microplasma source [135]. Reprinted from *Spectrochimica Acta Part B: Atomic Spectroscopy*, vol. 62, A. Michels, S. Tombrink, W. Vautz, M. Miclea, and J. Franzke, “Spectroscopic characterization of a microplasma used as ionization source for ion mobility spectrometry,” pp. 1208–1215, Copyright (2007). (b) Disc-type microplasma source [134].

ion injection. Increase in sensitivity and ability to adjust the ionization rate of the pulsed corona discharge are its advantages over traditional corona discharge sources. In the work by Xu *et al.* [131], corona discharge ionization has been shown in single pulses in a miniaturized IMS system, and the mechanisms and kinetics of corona discharge ionization used in the miniature IMS are explained. A pulsed potential was used along with a steady dc bias. For ion generation, a threshold dc potential was noted for a given pulse height, and this dc threshold was shown to decrease linearly with increasing the pulse height. Because the ions are concentrated in a very small volume, this pulsed discharge ionization source has the advantage that it can yield high sensitivity for a miniaturized IMS. However, pulsed corona discharge has been reported to add complexity that is dependent upon the source conditions [132].

In plasma ionization sources, a layer of dielectric material other than air is sandwiched between two electrodes. This forces electrons to cross the dielectric layer and form well-defined plasma, the size of which depends on the electrode dimension. Such dielectric barrier discharge (DBD)/distributed–diffused plasma ionization sources produce stable discharges and extend the longevity of the discharge electrodes by suppressing point-to-point corona ionization. Various configurations of such microplasma sources are available. Pencil-type microplasma source developed by Laroussi and Lu [133] or disc-type microplasma developed by Blanchard [134] has been implemented in IMS [135]. Fig. 6 shows the pencil- and disc-type DBD microplasma ionization sources. Microplasma ionization source developed by Dutton introduces sample orthogonal to carrier gas into the plasma and avoids dilution of sample by the carrier gas [136].

Multithreaded corona sources developed to minimize the instability and improve the efficiency and reproducibility of corona discharge sources also have higher ionization efficiencies and detection sensitivities than that obtained using traditional single-point electrodes [137]. Another alternative to radioactive ion source is a variable ionization potential source or electron lamp, which ionizes neutrals by emitting either a very soft X-ray radiation or electrons [138].

Because corona discharge ionizes all neutrals present in the environment in which discharge takes place and effects the ionization of analytes of interest, researchers at the Jet Propulsion Laboratory developed the source to primarily produce $(\text{H}_2\text{O})_n\text{H}^+$ ions by introducing gas-phase H_2O molecules into the discharge region. This hollow-cathode ionizer thus selectively ionizes molecules of proton affinity greater than H_2O and minimizes interference from ionization of gases such as O_2 , CO , and CO_2 .

F. Photoionization

Photoionization sources have several desirable characteristics with respect to all others described earlier. For example, except for radioactivity-based sources, the other techniques require a high electric field in most circumstances, and this may not be operationally desirable. In a photoionization source, the photons from a photoionizer strike a photocathode that emits low-energy photoelectrons. These electrons can attach to molecules and yield negative ions. The photoionizer can also be used for direct photoionization of molecules to form positive ions.

However, photoionization sources are limited to chemicals that can be easily ionized by low-energy photons and are thus primarily used for detection of chemicals with low ionization potentials. Because of the low percentage of ionizable molecules present in an aqueous sample, the use of photoionization as ionization source is limited to gas-phase analytes. Recently, Robb and Blades [139] have developed an atmospheric-pressure photoionization source that results in increased sensitivity for analytes in the presence of LC solvents that have high ionization potential. In this development, photoionizable dopants are added into an LC eluent to form "photoions" by photoionization. These photoions, through various ion-molecule reactions, ionize the analytes present in the LC eluent and make possible the application of photoionization for various liquid-phase samples.

Ions produced by this process have minimal fragmentation because the photon energy is typically slightly above the ionization potential of the molecule. The ionization process may occur at subatmospheric pressure (about 1 torr) where the ions are less subject to ion-molecule collisions and fragmentations.

IV. IMS APPLICATIONS

The utility of the aforementioned ion sources is realized in IMS for a highly diverse range of applications including industrial applications, environmental studies, forensic applications, security screening, and, over and above, biological and medical systems. As discussed in details in the subsequent sections

covering these application areas, the only requirement in detection by IMS is the ability to ionize and introduce the analyte into the IMS as gas-phase ions. Solid-phase analytes can be desorbed and ionized using thermal desorption, desorption ESI, SSI, surface ionization, or laser ablation. Liquid-phase analytes can be ionized by ESI or MALDI. Radioactive ionization, corona discharge ionization, photoionization, chemical ionization, and SESI are the methods that can be used to ionize gas-phase neutrals. Gaseous neutrals (volatiles or desorbed) are introduced into the desolvation region between the ionization source and ion gate. After ionization, the ions are pulsed into the drift region of the IMS for separation and detection. Fast analysis time and high sensitivity of IMS allows the application of IMS in the fields of industrial, forensic, environmental, security, and biological applications.

A. Industrial Applications

IMS has been applied to diverse analytical applications. Identification of wood species by chemical ionization of thermally released vapors from the samples and analysis by IMS [140] and evaluation of waste sites for toxic chemicals [141] have been demonstrated. The technique can also be applied at semiconductor industries to perform ultratrace analysis for volatile organic compounds and purity of polymers [142]. Application and potential of IMS for space exploration purposes have been reported [32]. Potential of IMS application in food industry in the analysis of food products for safety and quality reasons is also possible [143]. Various methods to determine bacterial presence in food is achieved by monitoring volatile metabolites released upon enzymatic metabolism of biochemical substrates [144], [145] or by determination of biogenic amines released upon degradation of food products [146], [147].

B. Environmental Studies

Detection of environmental contaminants usually requires highly sensitive analytical instruments due to dilution of the contaminants in the environment they are in. The contaminants can be present in all types of matrices such as water, air, and soil. Due to the complexity of the environmental matrices, a detection system with high separation power is essential. Contaminants range from highly polar to highly nonpolar in their chemical behavior. Thus, the instrument should be able to detect trace concentrations and handle all types of samples. Monitoring of the contaminants requires portability of the instrument and fast response. Keeping all these requirements in consideration, IMS serves as the most suitable environmental detection and monitoring analytical technique. Partial discharge ion sources or radioactive ion sources are the common ionization sources applied to detection of volatile compounds of high electronegativity by IMS. Detection and monitoring of perfluorocarbons [148], chlorinated and fluorinated substances [149], and industrial pollutants such as hydrazine and methylhydrazine [150] are some potential applications of IMS. Detection and monitoring of highly polar vapors in air, such as vapors of chlorinated solvents and explosives, can also be performed using photoemissive electron sources for ionization

[151]. Metal plate or metal-coated window when irradiated with a flash lamp or pulsed laser beam generates electrons which produce primary negative reactant ions (for example, O_2^-). These primary reactant ions then ionize the analytes to allow detection by IMS. Headspace analysis of environmental samples allows the measurement of volatile organic contaminants in water, such as gasoline components [152]. Industrial emissions [153] and effluents [154] can also be monitored for the determination and detection of toxic pollutants released into the environment. IMS can also be applied for the detection of aromatic and aliphatic hydrocarbons, halogenated hydrocarbons, and gasoline additives [155]–[159]. IMS with ESI can be applied for the detection of nonvolatile inorganic anions and cations in aqueous environmental samples [160], [161]. Trace-level detection of nonvolatile by-products of chemicals used for disinfection of drinking water, such as chlorinated and brominated haloacetic acids, was achieved using ESI-FAIMS [162]. Determination of herbicides and pesticides in environmental samples can also be achieved by IMS [163], [164]. Application of SPME [165] coupled to IMS equipped with photoionization has been demonstrated for the determination of VOCs (BTEX, naphthalene, chlorinated alkenes, and chlorinated benzenes) in underground and surface-water samples [166].

C. Forensic Applications

Drugs in solid-, liquid-, or gas-phase samples are almost exclusively detected by IMS in the positive-ion detection mode of the instrument. Detection of drug residues on surfaces by IMS [167], [168] is a widely used technique practiced by law enforcement personnel to monitor illegal drug use and trafficking. IMS can also be applied for rapid detection of illicit drugs in saliva [169], urine [113], [168], [170], [171], sweat [172], and hair [173], [174]. Analysis of fire debris to determine the cause of arson through detection and differentiation of flammable liquids is one of the potential forensic applications of IMS [167], [175]. Screening of tear-gas spray cans and clothing to determine the presence and identity of residues [176], [177] and analyzing pharmaceutical formulations for quality control purposes can also be performed by IMS [178].

D. Security Applications

Traditional explosives and chemical warfare agents are primarily detected in the negative- and positive-ion detection modes of IMS, respectively [31], [179], [180]. Liquid explosives, such as peroxide-based explosives, are more commonly detectable in the positive-ion detection mode [181]. Charge transfer, proton abstraction, or adduct formation reactions between the negative mode reactant ions and the neutral explosive molecule are the mechanisms that ionize the explosives for detection by IMS. Solid-phase microextraction (SPME) combined with IMS allows preconcentration of analytes prior to analysis for ultratrace detection in field samples [182], [183]. Trace-level determination of chemical warfare agents in water using SPME for extraction, followed by analysis by IMS, has been also reported [184]. Application of IMS for rapid detection of biological threats has also been demonstrated. As low as

five aerosol particles containing *Erwinia herbicola*, a Gram-negative bacteria, in 1 L of air was detected by pyrolysis gas chromatography–IMS (Py-GC/IMS) [185]. Differentiation of bacteria by Gram type has also been reported using Py-GC/IMS [186]. *In situ* derivatization of bacterial lipids, followed by IMS analysis, can be applied to differentiate bacterial strains [187].

E. Biological and Medical Systems

Traces of many VOCs that are volatile metabolites exhaled with human breath can be directly correlated to specific diseases [165]. These biomarkers can then be monitored by IMS for rapid screening and diagnosis for illness. Monitoring levels of VOCs in human breath for carbonyl sulfide, carbon disulfide, and isoprene of patients with chronic liver diseases [188], carbon monoxide in patient's breath with asthma [189], and isoprene and decane in patients with lung cancer [190] are some of the examples where IMS can be employed. Bacterial infections result in the release of biogenic amines that can be monitored to diagnose the type and extent of infections. SPME as an extraction method for analysis of target analytes by IMS was first demonstrated by Orzechowska *et al.* [191] in 1997. Since then, many applications of SPME for IMS analysis have been reported. Coupling of SPME for the extraction and concentration of target analytes prior to IMS analysis enables rapid detection of trace analytes without extensive sample preparation. Detection of drugs in urine by using SPME coupled with surface-enhanced laser desorption–ionization [192] and SPME–thermal desorption–IMS [171] has been demonstrated. Liu *et al.* [193] coupled SPME with radioactive ionization and thermal desorption to measure biological volatile organic compounds released from *Eucalyptus citriodora* leaves and drugs from aqueous solutions by IMS. The applications of IMS to study biological systems have been enunciated in a recent book [194].

V. SUMMARY

The developments of ion sources, particularly in the context of IMS, have been described. IMS ion sources operate efficiently in ambient environment and yield ions for a wide range of complex molecules including biological materials. While significant progress has been made in this area through the development of a variety of ion sources, as described in this paper, further research to address several key issues, namely, ionization processes, reaction chemistry, and overall system miniaturization for field deployment of IMS, is the primary focus of current research activities. An important activity in the area of standards from the standpoint of particle size, ionization, and efficiency of transport has been undertaken at the National Institute of Standards and Technology [195]. This work has relevance to comparison of performance of different IMS systems and also develops standardized operational principles. Aside from reviewing the present state of the art of ion sources for IMS, this paper has discussed the utility of these ion sources in the pursuit of a wide range of applications of IMS and current trends of research in the field. IMS plays a very

important role in both physical and biological sciences, and its merit as an important diagnostic tool for medical problems has been highlighted.

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