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An Historical Background of Mass Spectrometry and Its Application- A Review

S. Karthikeyan, M. Bakyalakshmi *, P. D Gokulan, K. L. Senthil Kumar

Department of Pharmaceutical Analysis, Sri Vijay Vidyalaya College of Pharmacy,
The T.N Dr. M.G.R Medical University, Tamil Nadu, India.
Email: bakyachemist@gmail.com & skarthikeyan51298@gmail.com
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ABSTRACT

Mass spectrometry's characteristics have raised it to an outstanding position among analytical methods unequalled sensitivity, detection limits, speed and diversity of its applications. In analytical chemistry, the most recent applications are mostly oriented towards biochemical problems, such as proteome, metabolome, high throughput in drug discovery and metabolism, and so on. Other analytical applications are routinely applied in pollution control, food control, forensic science, natural products or process monitoring. Other applications include atomic physics, reaction physics, reaction kinetics, geochronology, inorganic chemical analysis, ion–molecule reactions, determination of thermodynamic parameters and many others. Mass spectrometry has progressed extremely rapidly during the last decade, between 1995 and 2005. This progress has led to the advent of entirely new instruments. In this article we see about historical development of mass spectrometry and its modern application.

Keywords: Mass spectrometry, history , instrumentation , application

1. Introduction

Mass spectrometry is a powerful technique for identifying unknown molecular structure of a compound and probing the fundamental of principles of chemistry application of mass spectrometry involves the analysing and quantifying the various organic and inorganic compound A mass spectrometer generates multiple ions from the sample under investigation, it then separates them according to their specific mass-to-charge ratio (m/z), and then records the relative abundance of each ion type.

The first step in the mass spectrometric analysis is the production of gaseous form of ions of the compound, by electron ionization. Then molecular ion undergoes fragmentation. The ions are separated in the mass spectrometer according to their mass-to-charge ratio, and are detected in proportion to their abundance. A mass spectrum of the molecule is thus produced. It displays the result in the form of a plot of ion abundance vs mass-to-charge ratio. Ions provide information concerning the nature and the structure of their precursor molecule.[1]

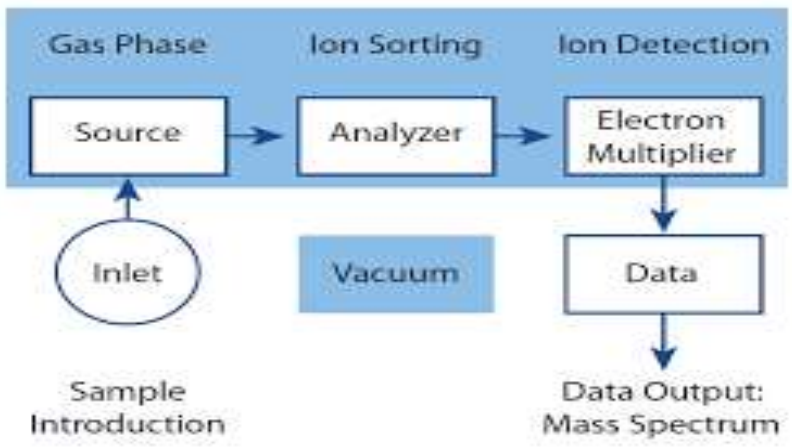

Figure 1 : Over view of mass spectrometry

2. History

A large number of mass spectrometers have been developed according to this fundamental scheme since Thomson's experiments in 1897. Listed here are some highlights of this development [3]

- ✓ 1886: E. GOLDSTEIN discovers anode rays (positive gas-phase ions) in gas discharge.
- ✓ 1897: J.J. THOMSON discovers the electron and determines its mass-to-charge ratio. Nobel Prize in 1906.
- ✓ 1898: W. WIEN analyses anode rays by magnetic deflection and then establishes that these rays carried a positive charge . Nobel Prize in 1911.
- ✓ 1901: W. KAUFMANN analyses cathodic rays using parallel electric and magnetic fields.
- ✓ 1909: R.A. MILLIKAN and H. FLETCHER determine the elementary unit of charge.
- ✓ 1912: J.J. THOMSON constructs the first mass spectrometer (then called a parabola spectrograph). He obtains mass spectra of O2, N2, CO, CO2 and COCl2. He observes negative and multiply charged ions. He discovers metastable ions. In 1913, he discovers isotopes 20 and 22 of neon.
- ✓ 1918: A.J. DEMPSTER develops the electron ionization source and the first spectrometer with a sector-shaped magnet (180◦) with direction focusing .
- ✓ 1919: F.W. ASTON develops the first mass spectrometer with velocity focusing. Nobel Prize in 1922. He measures mass defects in 1923.
- ✓ 1932: K.T. BAINBRIDGE proves the mass–energy equivalence postulated by Einstein .
- ✓ 1934: R. CONRAD applies mass spectrometry to organic chemistry.
- ✓ 1934: W.R. SMYTHE, L.H. RUMBAUGH and S.S. WEST succeed in the first preparative isotope separation.
- ✓ 1940: A.O. NIER isolates uranium-235 .
- ✓ 1942: The Consolidated Engineering Corporation builds the first commercial instrument dedicated to organic analysis for the Atlantic Refinery Company.
- ✓ 1945: First recognition of the metastable peaks by J.A. HIPPLE and E.U. CONDON .
- ✓ 1948: A.E. CAMERON and D.F. EGGERS publish design and mass spectra for a linear time-of-flight (LTOF) mass spectrometer . W. STEPHENS proposed the concept of this analyser in 1946 .
- ✓ 1949: H. SOMMER, H.A. THOMAS and J.A. HIPPLE describe the first application in mass spectrometry of ion cyclotron resonance (ICR).
- ✓ 1952: Theories of quasi-equilibrium (QET) and RRKM explain the monomolecular fragmentation of ions. R.A. MARCUS receives the Nobel Prize in 1992.
- ✓ 1952: E.G. JOHNSON and A.O. NIER develop double-focusing instruments.
- ✓ 1953: W. PAUL and H.S. STEINWEDEL describe the quadrupole analyser and the ion trap or quistor in a patent . W. PAUL, H.P. REINHARD and U. Von ZAHN, of Bonn University, describe the quadrupole spectrometer in Zeitschrift fur Physik ¨ in 1958. PAUL and DEHMELT receive the Nobel Prize in 1989.
- ✓ 1955: W.L. WILEY and I.H. McLAREN of Bendix Corporation make key advances in LTOF design.
- ✓ 1956: J. BEYNON shows the analytical usefulness of high-resolution and exact mass determinations of the elementary composition of ions .
- ✓ 1956: First spectrometers coupled with a gas chromatograph by F.W. McLafferty and R.S. GOHLKE .
- ✓ 1957: Kratos introduces the first commercial mass spectrometer with double focusing.
- ✓ 1958: Bendix introduces the first commercial LTOF instrument.
- ✓ 1966: M.S.B. MUNSON and F.H. FIELD discover chemical ionization (CI)
- ✓ 1967: F.W. McLafferty and K.R. JENNINGS introduce the collision induced dissociation (CID) procedure.
- ✓ 1968: Finnigan introduces the first commercial quadrupole mass spectrometer.
- ✓ 1968: First mass spectrometers coupled with data processing units. 1969: H.D. BECKEY demonstrates field desorption (FD) mass spectrometry of organic molecules.

- ✓ 1972: V.I. KARATEV, B.A. MAMYRIM and D.V. SMIKK introduce the reflection that corrects the kinetic energy distribution of the ions in a TOF mass spectrometer .
- ✓ 1973: R.G. COOKS, J.H. BEYNON, R.M. CAPRIOLI and G.R. LESTER publish the book Metastable Ions, a landmark in tandem mass spectrometry .
- ✓ 1974: E.C. HORNING, D.I. CARROLL, I. DZIDIC, K.D. HAEGELE, M.D. HORNING and R.N. STILLWELL discover atmospheric pressure chemical ionization (APCI).
- ✓ 1974: First spectrometers coupled with a high-performance liquid chromatograph by P.J. ARPINO, M.A. BALDWIN and F.W. McLafferty
- ✓ 1974: M.D. COMISAROV and A.G. MARSHALL develop Fourier transformed ICR (FTICR) mass spectrometry .
- ✓ 1975: First commercial gas chromatography/mass spectrometry (GC/MS) instruments with capillary columns.
- ✓ 1976: R.D. MACFARLANE and D.F. TORGESSON introduce the plasma desorption (PD) source.
- ✓ 1977: R.G. COOKS and T.L. KRUGER propose the kinetic method for thermochemical determination based on measurement of the rates of competitive fragmentations of cluster ions .
- ✓ 1978: R.A. YOST and C.G. ENKE build the first triple quadrupole mass spectrometer, one of the most popular types of tandem instrument .
- ✓ 1978: Introduction of lamellar and high-field magnets.
- ✓ 1980: R.S. HOUK, V.A. FASSEL, G.D. FLESCH, A.L. GRAY and E. TAYLOR demonstrate the potential of inductively coupled plasma (ICP) mass spectrometry .
- ✓ 1981: M. BARBER, R.S. BORDOLI, R.D. SEDGWICK and A.H. TYLER describe the fast atom bombardment (FAB) source .
- ✓ 1982: First complete spectrum of insulin (5750 Da) by FAB and PD .
- ✓ 1982: Finnigan and Scitex introduce the first commercial triple quadrupole mass spectrometers.
- ✓ 1983: C.R. BLAKNEY and M.L. VESTAL describe the thermos pray (TSP) .
- ✓ 1983: G.C. STAFFORD, P.E. KELLY, J.E. SYKA, W.E. REYNOLDS and J.F.J. TODD describe the development of a gas chromatography detector based on an ion trap and commercialized by Finnigan under the name Ion Trap
- ✓ 1987: M. GUILHAUS and A.F. DODONOV describe the orthogonal acceleration time-of-flight (oak-TOF) mass spectrometer. The concept of this technique was initially proposed in 1964 by G.J. O'Halloran of Bendix Corporation
- ✓ 1987: T. TANAKA and M. KARAS, D. BACHMANN, U. BAHR and F. HILLENKAMP discover matrix-assisted laser desorption/ionization (MALDI). TANAKA receives the Nobel Prize in 2002.
- ✓ 1987: R.D. SMITH describes the coupling of capillary electrophoresis (CE) with mass spectrometry .
- ✓ 1988: J. FENN develops the electrospray (ESI) . First spectra of proteins above 20000 Da. He demonstrated the electrospray's potential as a mass spectrometric technique for small molecules in 1984 . The concept of this source was proposed in 1968 by M. DOLE . FENN receives the Nobel Prize in 2002.
- ✓ 1991: V. KATTA and B.T. CHAIT and B. GAMEN, Y.T. LI and J.D. HENION demonstrate that specific non-covalent complexes could be detected by mass spectrometry.
- ✓ 1991: B. SPENGLER, D. KIRSCH and R. KAUFMANN obtain structural information with reflection TOF mass spectrometry (MALDI post-source decay).
- ✓ 1993: R.K. JULIAN and R.G. COOKS develop broadband excitation of ions using the stored-waveform inverse Fourier transform (SWIFT).
- ✓ 1994: M. WILM and M. MANN describe the nano electrospray source (then called micro electrospray source) .
- ✓ 1999: A.A. MAKAROV describes a new type of mass analyser: the orbitrap. The orbitrap is a high-performance ion trap using an electrostatic Quadro-logarithmic field

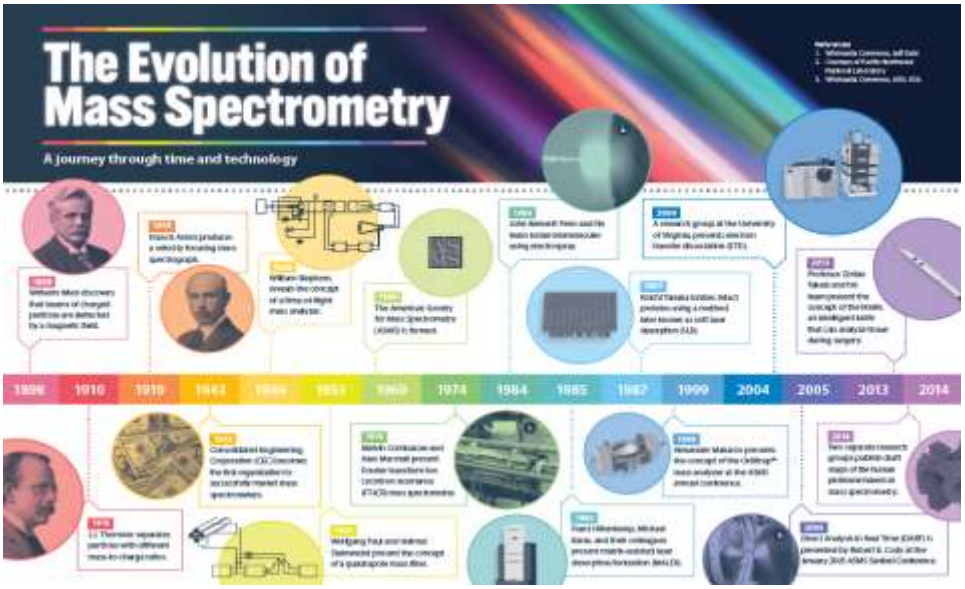

Figure 2 : Historical Development of mass spectrometry

3. Instrumentation [2]

A. Sample Inlet

- A sample stored in the large reservoir from which molecules reach the ionization chamber at low pressure in a steady stream by a pinhole called “Molecular leak”.

B. Ionization

- Atoms are ionized by knocking one or more electrons off to give positive ions by bombardment with a stream of electrons. Most of the positive ions formed will carry a charge of +1.
- Ionization can be achieved by :
    - Electron Ionization (EI-MS)
    - Chemical Ionization (CI-MS)
    - Desorption Technique (FAB)

C. Acceleration

- Ions are accelerated so that they all have the same kinetic energy.
- Positive ions pass through 3 slits with voltage in decreasing order.
- Middle slit carries intermediate and finals at zero volts.

D. Deflection

- Ions are deflected by a magnetic field due to differences in their masses.
- The lighter the mass, the more they are deflected.
- It also depends upon the no. of +ve charge an ion is carrying; the more +ve charge, the more it will be deflected.

E. Detection

- The beam of ions passing through the mass analyzer is detected by a detector on the basis of the m/e ratio.
- When an ion hits the metal box, the charge is neutralized by an electron jumping from the metal onto the ion.
- Types of analysers:
    - Magnetic sector mass analysers
    - Double focussing analysers

- Quadrupole mass analysers
- Time of Flight analysers (TOF)
- Ion trap analyser
- Ion cyclotron analyser

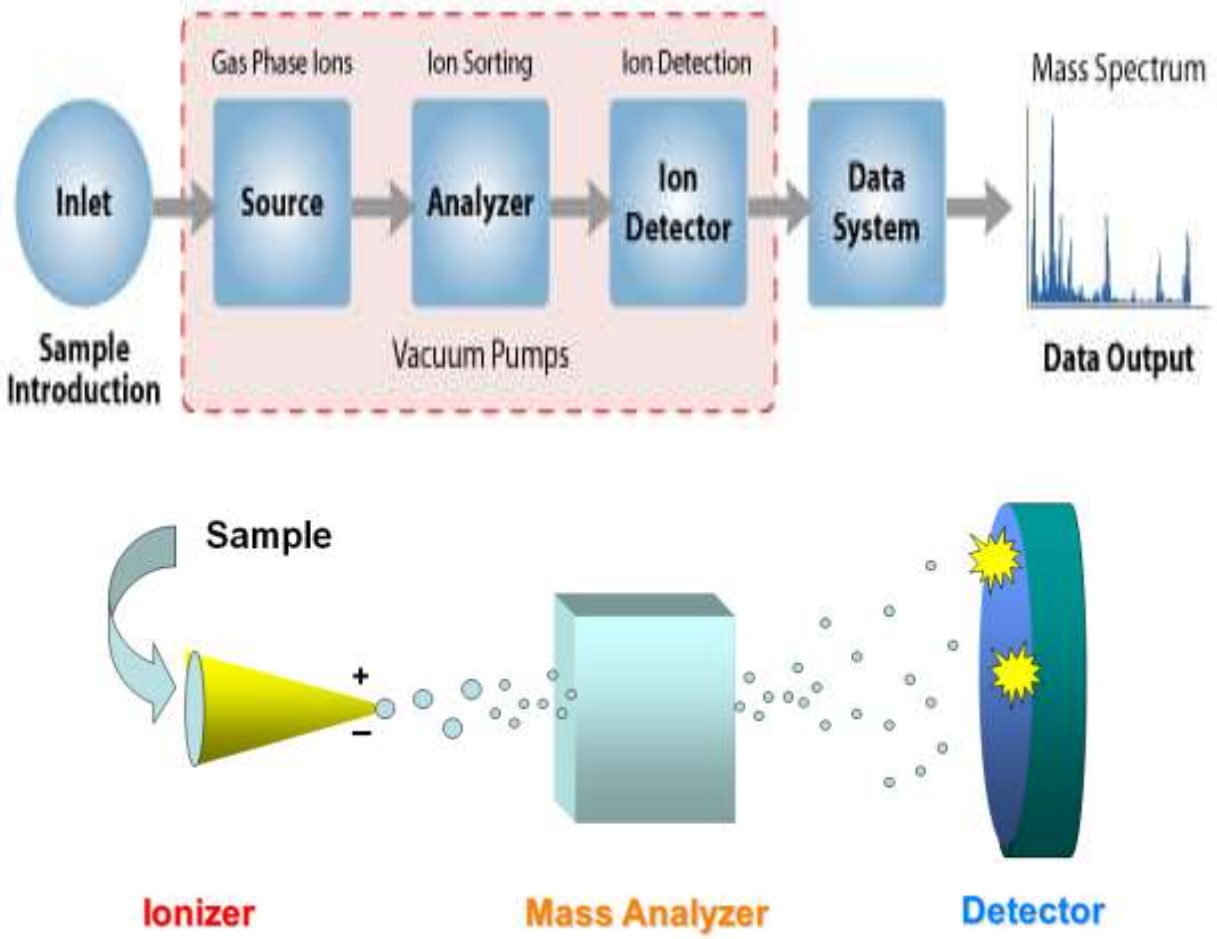

Figure 3 : Instrumentation of mass spectrometry

4.Application

4.1Metabolomic

Metabolomics is the analysis of all the small molecule metabolites in a biological system. This can be very challenging to analyse, given the complexity of the system and internal and external interferences. But MS coupled to liquid chromatography (LC-MS) based metabolomics applications remarkably changed its use in drug discovery. [4]

4.2 Biomarker discovery

Pushing the limits of detection and quantification in LC-MS specialized its use to biomarker research. Comparative analysis between a healthy person and patient biological specimens using MS can easily identify the significant differences between the two samples in terms of metabolites or proteins or lipids. Sometimes, quantification of biomarkers in mg range can be achieved by mass spectrometry, not possible with the conventional methods.

4.3 Biologics front-screening

A transition from conventional ligand-based assays to mass spectrometry-based assays has added practical value in biotech industries. The number of protein drugs and monoclonal antibodies has increased over the past few years, but there are no rapid quantification methods which can differentiate the isoforms of proteins or to determine if the protein is active or folded, etc. The power of mass spectrometry to overcome these disadvantages of ligand-based assays has taken centre stage and is currently being explored for biologics quantification. [5]

4.4 Genomics and epigenetic applications

Cancer is a well- known disease characterized by mutations in the functional genes. Recent studies have shown the importance of epigenetics in causing cancer and other related diseases. These epigenetic changes can be easily quantified using mass spectrometry. Chromatographic separations were a challenge before and now, with recent advances in HPLC and mass spec techniques, this approach has been made possible[6]

4.5 Forensic lab

Did you know that the detector sensors we find at the airports are nothing but compact mass spectrometry instruments? They are used as homeland security checks for identification of illegal drugs, explosive compounds, exotics or to confirm substance drug abuse. Steroid overuse especially by athletes and celebrities can be easily measured using MS. In Forensic studies, MS really comes in handy to identify the barely detectable traces left by the suspect. In toxicology studies, MS is used to detect potential toxins by analysing the blood samples. This will help determine the poison dose in the blood of victims and identify the time and death of the person .

A more recent scientific progress is analysing the nicotine levels (smoking) or chemical pollutants in human lungs just by a simple inhaler MS system.

4.6 Newborn screening

With advances in science over the past 25 years, we are able to screen newborns for the risk of diseases like cardiovascular disease or diabetes etc. by using MS/MS. This approach gives less false positives compared to the conventional newborn screening methods and includes testing of different biological specimens. For example, lysosomal storage disorders are asymptomatic during childhood, but progress with symptoms to advanced stages. MS has the capacity to identify these types of risks during childbirth using biomarkers or metabolomics-based studies. [7]

5. Conclusion

Recent development in mass spectrometry led to expensive technique when compared to other analytical technique thus it's used for rare or expensive product. Due to its speed and sensitivity, mass spectrometry has also played a pivotal role in many phases of drug discovery. Drug reaction optimization, structural analysis of library products, and the evaluation of library compound quality are just few examples of how this technique can be employed.

Mass spectrometry is also becoming increasingly used in geologic research for petroleum composition measurement and carbon dating. The technique can also be used to test water quality or potential food contamination. In short, mass spectrometry is becoming very prominent in all sorts of clinical and other research endeavours. Thus, a basic grasp of the technology is necessary to understand all the possible productive interactions

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