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The Principle, Types, and Applications of Mass Spectrometry: A Comprehensive Review

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Abstract Mass spectrometry (MS) is a technique wherein chemical substances are identified in biological and non-biological material. It uses electric and magnetic fields to sort out gaseous ions based on their mass-to-charge ratios. The MS is a technique that uses a mass spectrometer and mass spectrograph as instruments that work by using electric/magnetic fields, and photographic techniques/non-electric means, respectively. The applications of MS include the identification of gases present in the atmosphere. However, applications of MS in medicine assume increased significance owing to the benefit it does in the management of patients, and public health as a whole. Several MS-based clinical diagnostic devices are already available, and many others are in the pipeline. This review presents a comprehensive analysis of the basics of MS, types of MS-based instruments, and their applications.

Keywords: *mass spectrometry, chemical substances, biological, techniques, medicine, mass spectrograph, patients, public health, diagnostic devices*

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1. Introduction

Mass spectrometry (MS) is a sensitive, quantitative, and analytical technique used in environmental, pharmaceutical, medical, forensic, food, and other sciences. This technique involves the separation of gaseous ions from the liquid or solid-state of the samples. After conversion into a gaseous state, these are separated based on their mobility in an electric and magnetic field [1]. The detected ions or separated ions are analyzed in a mass spectrum. A mass spectrum is a pattern showing the distribution of ions by mass in a sample. When a pure substance is present in the sample, MS shows a high m/z (mass/charge) value and the highest abundance in the mass spectrum [2]. When this technique is interfaced with high-performance liquid chromatography (HPLC) or gas-liquid chromatography (GLC), mass spectrometer functions as a powerful detector, which helps in detecting even trace amounts of a particular substance in a sample [3,4]. MS is also used to know the structural elucidations of organic, bio-organic, and organometallic compounds. It is also applied to know the molecular weight of an atom and is an emerging tool in the field of proteomics (the branch of the biochemistry involved in the structural analysis of proteins) [5].

2. Principle of Working of Mass Spectrometers

The sample for analysis in a mass spectrometer is subjected to high vapor pressure (heating), which causes the ions to fragment and ionize. The ionized ions in the sample are accelerated by applying voltage so that they move according to their mass in a mass analyzer. The ions carrying a similar charge will move with equal velocity to their counter ions in the mass analyzer. These ions are then made to pass through a magnetic force in the detector, which causes the relative ions with the same velocity to move in a perpendicular path or take a circular path. The charged ions when exposed to a magnetic field take a perpendicular path since the magnetic force provides a centripetal field (field towards the center). Then the ions with the same magnetic and electric charges are made to pass through undeflected, reaching the data system for their recording. The mass spectrum obtained in this process helps in further analysis of substances in the sample [6].

3. Components of a Mass Spectrometer

Mass spectrometer consists of three parts including the Inlet, a mass analyzer, and a detector [7] (Figure 1).

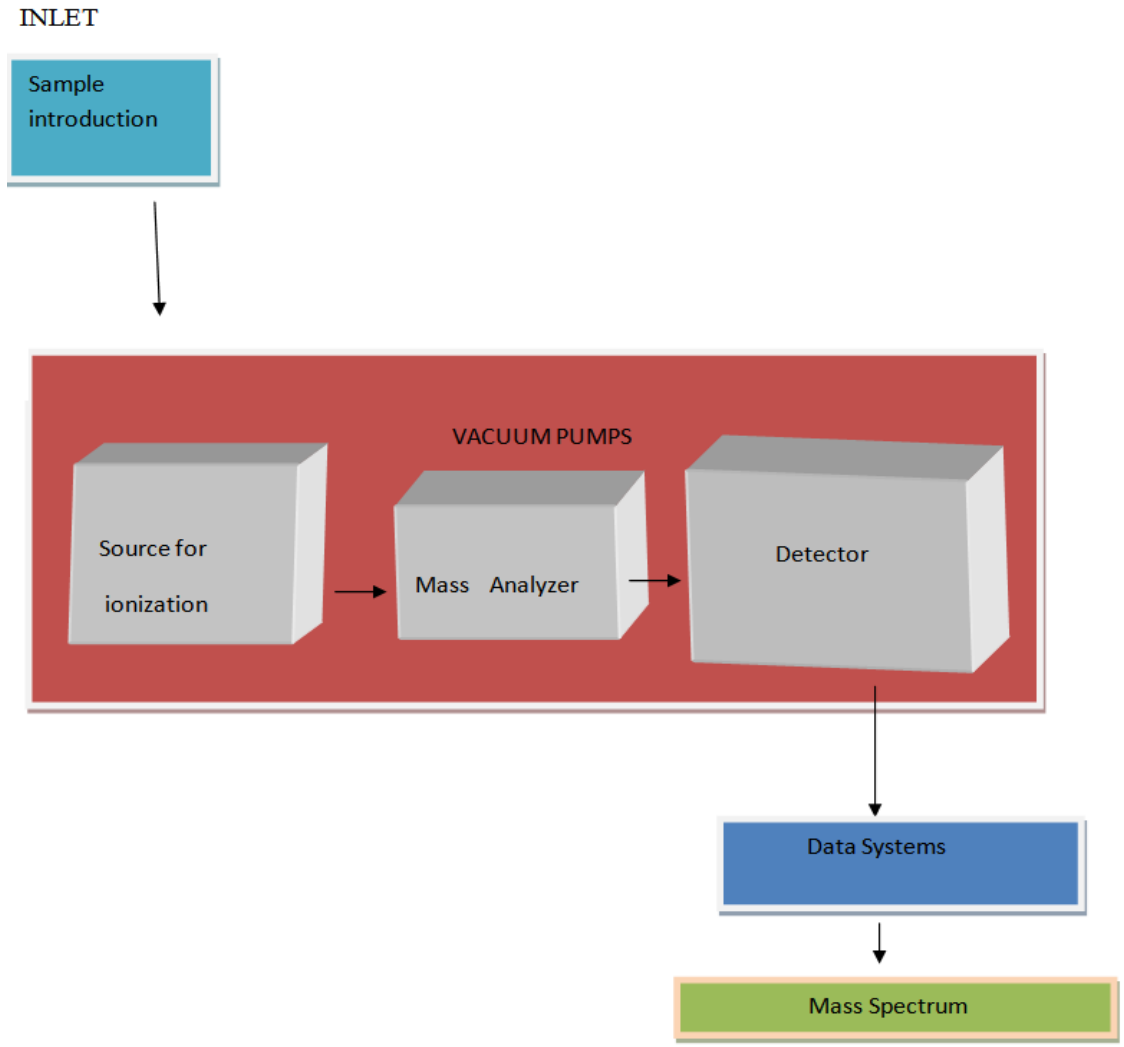

Figure 1. Schematic representations of parts of a mass spectrometer

3.1. Inlet

The inlet system is where the sample is placed before processing in the mass spectrometer. The selection of the inlet depends on the type of sample that is used for analysis. The sample molecules undergo ionization, and the ionization process prefers sample ions in the gaseous state. Hence the inlet system is designed in such a way that it can convert various types of samples into gas, by heating and later the samples are exposed to high vacuum pressures. The inlet responds fast and can sense even a minute change in the constitution of gas sample molecules.

The samples in the gas phase, and thermally stable are introduced into the source region with the help of a needle valve. The mass spectrometers are interfaced with chromatographic instruments so that purification of the sample takes place before it reaches the source of the mass spectrometer. This interfacing also makes the ionization process of the sample easier. There are various types of inlets for the introduction of samples [8] (Figure 2).

3.1.1. Direct Vapor Inlet

Here the sample is in the gas state and is directly introduced into the source with the help of a needle valve and the air that is present in the sample is ejected out. This is the simplest sample introduction method.

3.1.2. Direct Insertion Probe

Here the liquid or solid type of samples with low vapor pressure are introduced. The sample is loaded into a capillary tube which reaches the region with a high temperature that causes an increase in its vapor pressure. Later, the capillary tube allows the sample to reach the source for its analysis. This method is useful in detecting temperature-sensitive compounds.

3.1.3. Gas Chromatography

It is the common technique used for the separation of complex mixtures that are introduced into the mass spectrometer. Gas columns are used to regulate the flow of gas which helps in the separation of the sample that is later introduced into a source for analysis.

3.1.4. Liquid Chromatography

Thermally labile compounds and the compounds that are not separated by gas chromatography are introduced by liquid chromatography.

3.1.5. Direct Ionization of Sample

The sample which decomposes quickly, and samples that does not have a significant vapor pressure are directly ionized from the condensed phase. This sample inlet method works interfaced with liquid chromatography.

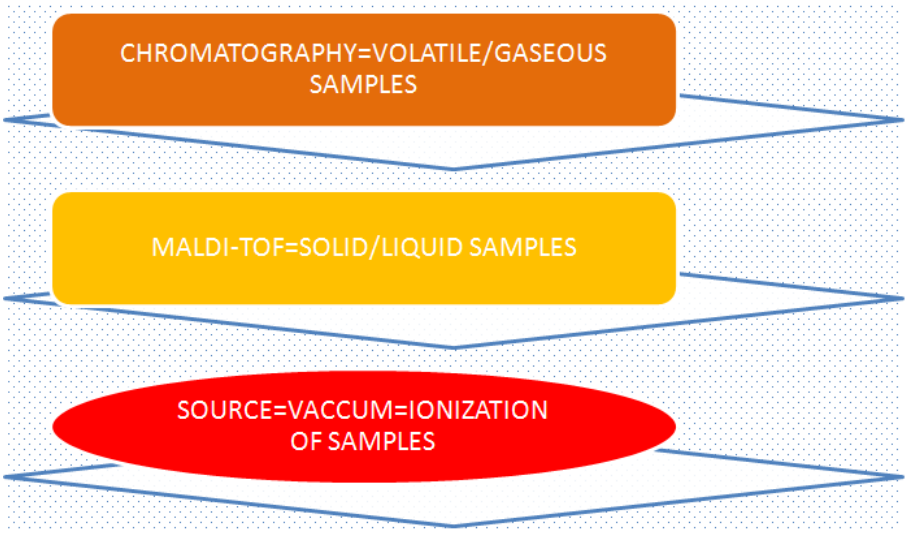

Figure 2. Diagrammatic representation of sample inlet for different types of samples

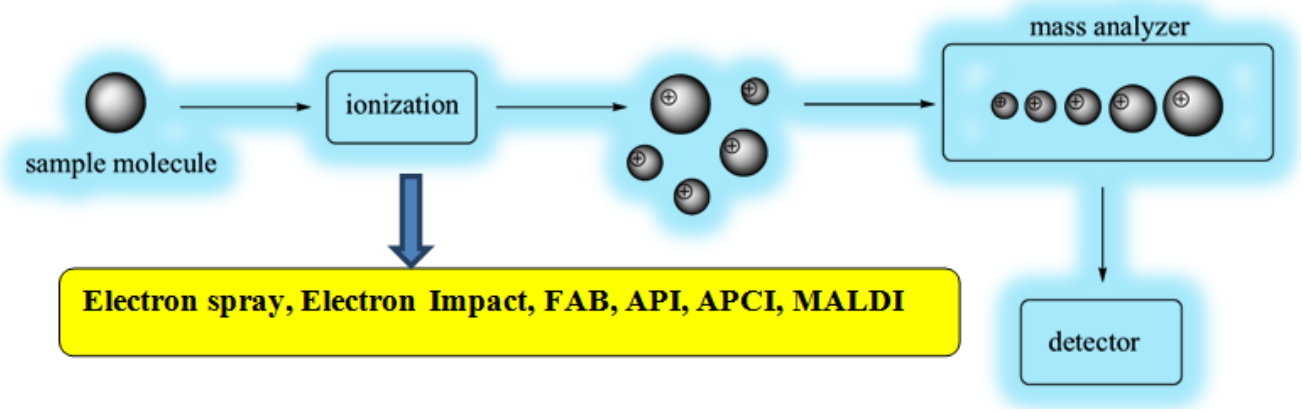

Figure 3. Diagrammatic representation of Ionization methods of mass spectrometers

3.2. Ionization Methods

After entering through the inlet, the samples are fragmented or ionized before they reach the mass analyzer, and this process is called ionization. The selection of an ionization method depends on the type of sample that is used for analysis. The process of ionization cleaves samples into either cation or anion or an adduct (addition product) (Figure 3). There are different ionization techniques used for a variety of samples. The ionization energy significantly controls the fragmentation of the ions which can be visualized in a mass spectrum obtained for analysis. The ionization may be soft or hard depending on the utilization of the energy for bombardment. A soft ionization requires less energy compared to hard ionization and is an incomplete process [9]. The various ionization techniques are discussed in the following sections.

3.2.1. Electron Spray Ionization Method

It is a commonly used hard ionization method used for the liquid type of samples. Here the liquid samples are exposed to high voltage, atmospheric pressure, and continuous flow of gas which degrades them into droplets. Later, these droplets are heated under vacuum pressure and the flow of gas which ejects ions from droplets reaches the mass analyzer with increased acceleration. This basic principle with improved sensitivity is used in nanospray, picospray, static nanospray, and desorption electrospray ionization techniques nowadays [10].

3.2.2. Electron Impact Ionization Method

It is used for gaseous samples and its interface with gas chromatography is easy. After the gas sample is introduced in the inlet, it is bombarded with an electron beam produced from a filament. The ions ejected are electrically neutral (radical ion) and reach the mass analyzer. This is a hard type of ionization where ions are completely fragmented [11].

3.2.3. Fast Atom Bombardment (FAB)

This method is used for low volatile, and large compounds like carbohydrates, proteins, and peptides which may be in solid or liquid forms. These samples are mixed with non-volatile matrix compounds like glycerol, ether, nitro benzyl alcohol and are bombarded with atoms like Argon or Xenon. This ejects charged sample ions as adducts, which are captured by the mass analyzer [12].

3.2.4. Atmospheric Pressure Ionization (API)

It helps in the ionization of a wide range of compounds that are in liquid form having a varied range of flow rates. Here, the ionization or fragmentation takes place partially

and outside the vacuum region. Hence, they require a mass spectrometer for further analysis. This ionization process generates intensely charged ions and therefore, it is coupled with liquid chromatography or mass spectrometry [13].

3.2.5. Atmospheric Pressure Chemical Ionization (APCI)

This ionization method is desired for non-volatile samples. Here, the samples in the heated form reach the corona discharge where the ionization occurs. The samples in the gaseous state are placed on corona discharge, where water clusters enter the vacuum system for electrospray ionization. The corona discharge helps in the fragmentation of sample by collision and transfer of protons between sample and eluent forming either positively or negatively charged molecules. The formation of the protonated molecule and its easy compatibility with liquid chromatography makes this method of ionization more preferred than the electron ionization method [14].

3.2.6. Matrix-Assisted Laser Desorption Ionization (MALDI)

In the MALDI method, the sample is mixed with a matrix that absorbs laser radiations at a low range and transfers a proton into the sample so that it produces a neutral ion. The generated neutral ions further enter the mass analyzer. MALDI is coupled with time-of-flight type of mass spectrometers and is used in imaging mass spectrometry [15]. These ionization methods are not frequently used in modern mass spectrometers except electron ionization, which is utilized for environmental work. The other ionization methods discussed above are employed in mass spectrometry research laboratories.

4. Mass Analyzer

The mass analyzer is also described as an ion collector and is an important component of the mass spectrometer. The mass analyzer collects the ions formed in the ion source and separates them based on their charge to mass ratio and sends them to a detector where these separated ions are converted into a digital output [16]. There are various types of mass analyzers as listed in Table 1.

Table 1. Types and characteristics of mass analyzers

Type of mass analyzer	Common Characteristic features
Quadrupole mass analyzer	High resolution High rate of transmission of ions
Time-Of-Flight (TOF) mass analyzer	
Magnetic sector mass analyzer	
Electrostatic sector mass analyzer	
Quadrupole ion trap mass analyzer	
Ion cyclotron resonance mass analyzer	

4.1. Quadrupole Mass Analyzer

It is a commonly used mass analyzer that is smaller, and cheaper. The quadrupole mass analyzer separates ions based on oscillations in an electric field (Figure 4). It is well suited for electrospray ionization which produces ions with charge distribution below m/z (mass/charge) 300. This mass analyzer can be easily linked with gas and liquid type chromatography [17,18].

4.1.1. Instrumentation

It contains four parallel metal rods with specific diameter-to-spacing and is connected electrically with a radio frequency voltage. The ions are made to pass through these rods and the ion which has a specific mass to charge ratio at a specified voltage reaches the detector. The ions with varied mass to charge ratios collide with the walls of the rods and are removed by the vacuum system. Thus, ions with a particular mass to charge ratio and at a specific voltage can be isolated easily by this type of mass analyzer. The advantages, applications, and limitations are depicted in Table 2.

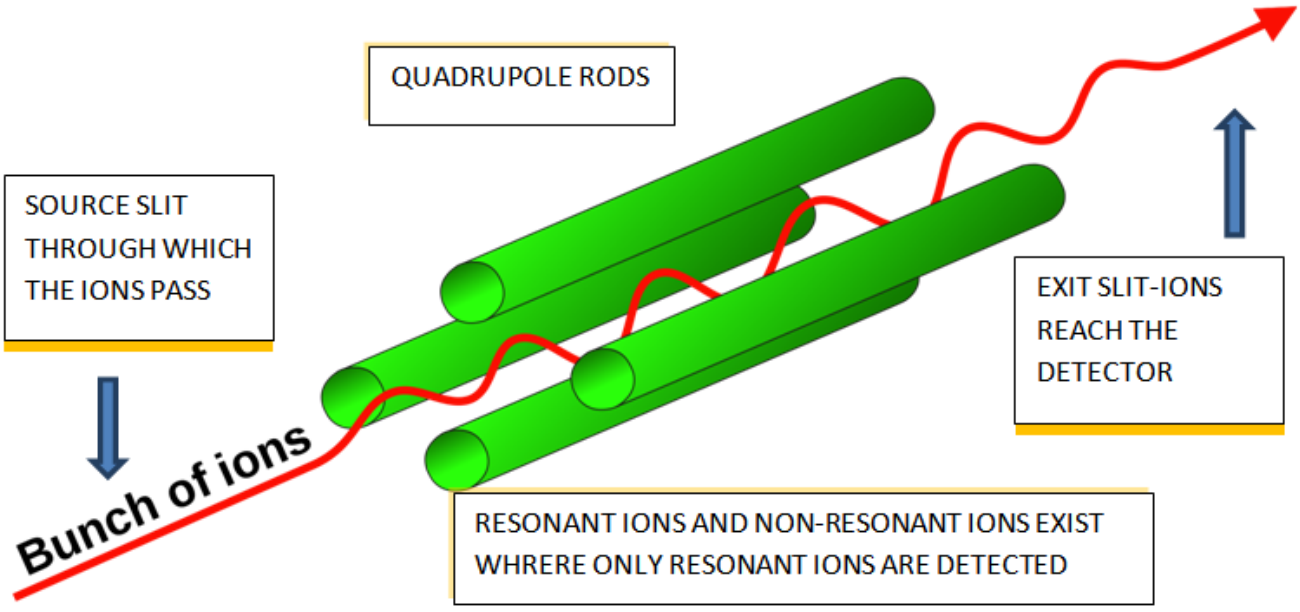

Figure 4. Working apparatus of a quadrupole mass analyzer

Table 2. Quadrupole mass analyzer applications, advantages and limitations

Mass analyzer type	Applications	Advantages	Limitations
Quadrupole mass analyzer	Bimolecular detection, to study ions with specific m/z ratio, liquid and gas chromatography, and mass spectrometry	Low cost, classical mass analyzer, good reproducibility, multipurpose instrument	Limited resolution, not suited for pulsed ionization techniques

4.2. Time-Of-Flight (TOF) Mass Analyzer

The ions in this mass analyzer are produced by bombarding the sample with brief pulses of electrons or laser-generated photons. These ions are separated based on the time needed by the ions to travel and reach the detector (Figure 5). There is no magnetic field in this type of analyzer. The ions with a high m/z ratio take a longer time to reach the detector. It is a simple and direct technique and is compatible with ions formed on the surface like laser desorption and plasma desorption mass spectrometry. The pulsed character of TOF provides precise ionization-time and ionization region. The use of reflectrons in TOF improves resolution. The reflectrons are optic devices that allow ions to pass through a mirror. The ions with high energy (kinetic) will hit the mirror and take a longer time to reach the detector compared to the ions with low energy. An electron multiplier detector is used for good resolution [19,20,21]. The advantages, applications, and limitations are depicted in Table 3.

4.3. Magnetic Sector Mass Analyzers

A magnetic sector mass analyzer uses both static electric field and magnetic field to affect the path of charged ions, the ion with greater velocity, more charge, and least mass is deflected to the detector (Figure 6) [22,23].

Table 3. Advantages, applications, and limitations of Time-Of-Flight (TOF) mass analyzer

Mass analyzer type	Applications	Advantages	Limitations
Time-Of-Flight (TOF) mass analyzer	MALDI ionization method is compatible with TOF mass analyzer, photoelectron photo ion coincidence spectroscopy uses TOF mass analyzer for mass analysis	Fastest mass analyzer with moderate cost, suited for pulsed ionization techniques like MALDI (Matrix Assisted Laser Desorption Ionization), high resolving power	Requires sophisticated pulsed ionization methods, detects limited dynamic range of ions in TOF

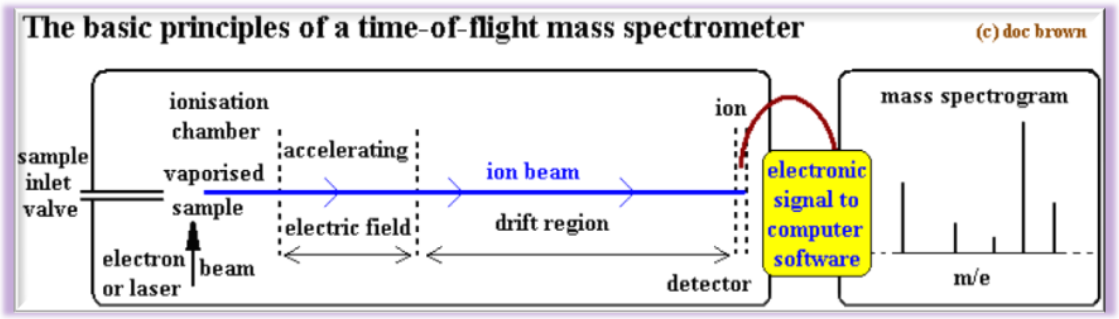

Figure 5. The working apparatus of a Time-Of-Flight (TOF) mass analyzer

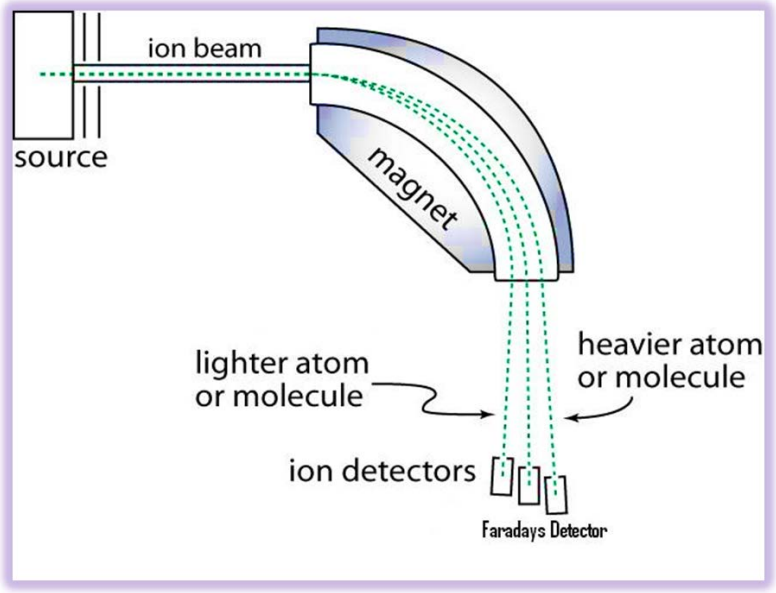

Figure 6. Working model of a magnetic sector mass analyzer

Table 4. Advantages, applications, and limitations of magnetic sector mass analyzers

Mass analyzer type	Applications	Advantages	Limitations
Magnetic Sector mass analyzers	Helps in isotope ratio measurements, mass focusing	High resolution and high sensitivity, good reproducibility, best quantitative performance	Not suited for pulsed ionization methods, high cost of analyzer and maintenance

4.3.1. Instrumentation

It consists of a horseshoe-shaped and curved tube or flight tube where the sample ions in the vapor state are passed through a magnetic field. The charged ions are deflected into a circular motion with a radius perpendicular to the applied magnetic field. Here the ions are knocked out from the source sample by the bombardment of an electric field that carries charge (positively charged) within the inlet system. The charged ions experience centrifugal and centripetal forces and the ions with high speed, low mass, and more charge reach the detector. Before they are collected by the Faraday collector, these ions take the straight path that is facilitated by accelerating plates and maintaining a constant velocity. These instruments may be single focusing or double-focusing mass sector analyzers. The resolution in a single focusing mass sector analyzer is low due to the lack of uniformity of ion energies. The high resolution of the double-focusing mass sector analyzer is due to an energy reduction of ions before they reach the magnetic field, thereby increasing resolving power with stable ion energies. The advantages, applications, and limitations are depicted in Table 4.

4.4. Electrostatic Sector Mass Analyzer

In this type of mass analyzer, the ions are separated using an electric field and work as energy focusers. It consists of two curved plates of equal and opposite potential. When the ions travel through an electric field, they are deflected by the force on the ions because the electric field is equal to the centripetal force on the ions (Figure 7). Therefore, the ions with the same kinetic energy are focused on the detector and the ions with varying energies are dispersed. The magnetic sector and electrostatic sector mass analyzers, when used separately, they work as single focus sector mass analyzers. However, when both these instruments are combined, they work as double-focusing sector mass analyzers that are routinely used [24]. The advantages, applications, and limitations are depicted in Table 5.

Table 5. Advantages, applications, and limitations of electrostatic sector mass analyzers

Mass analyzer type	Applications	Advantages	Limitations
Electrostatic sector mass analyzer	Accurate measurements, organic MS analysis uses double-focusing sector mass analyzers, used in Isotope ratio measurements	Highly reproducible, sensitive, high resolution when used as double-focusing sector mass analyzer, forms a classical mass spectrum	Not suited for pulsed ionization methods (MALDI)

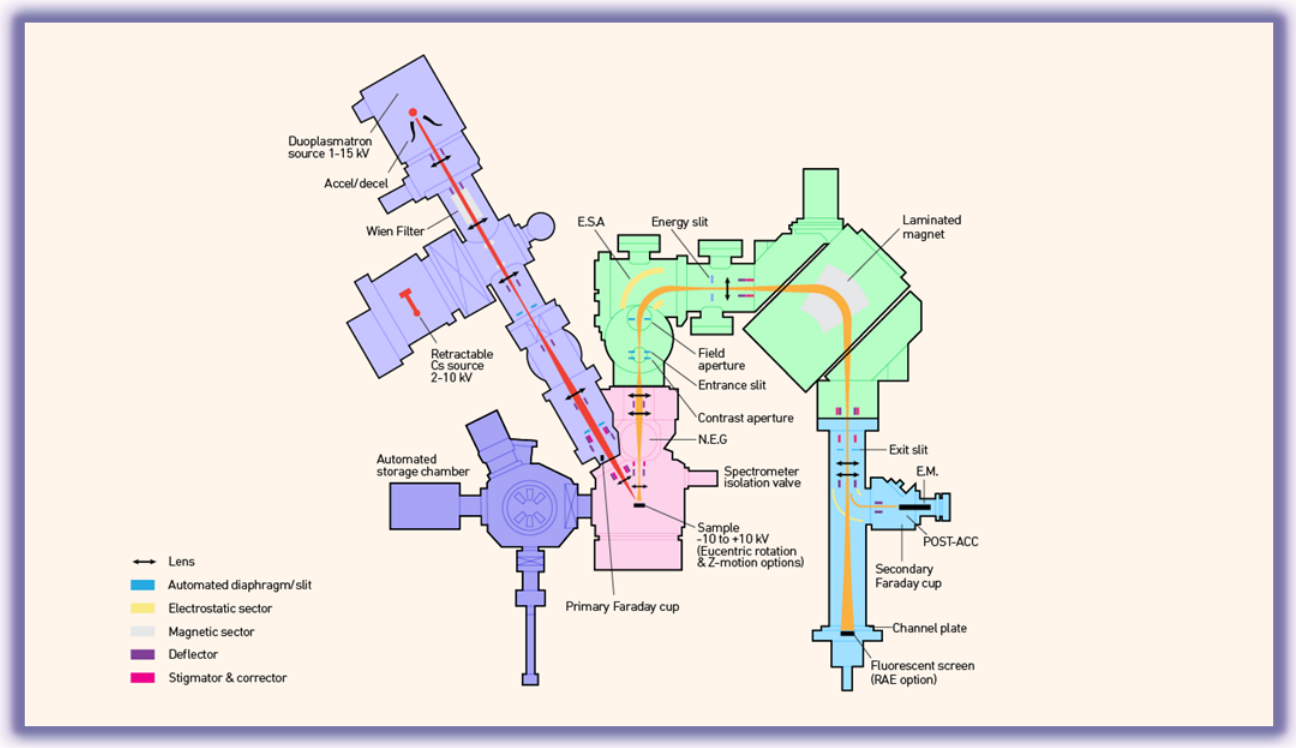

Figure 7. Working apparatus of a double focusing magnetic mass analyzer

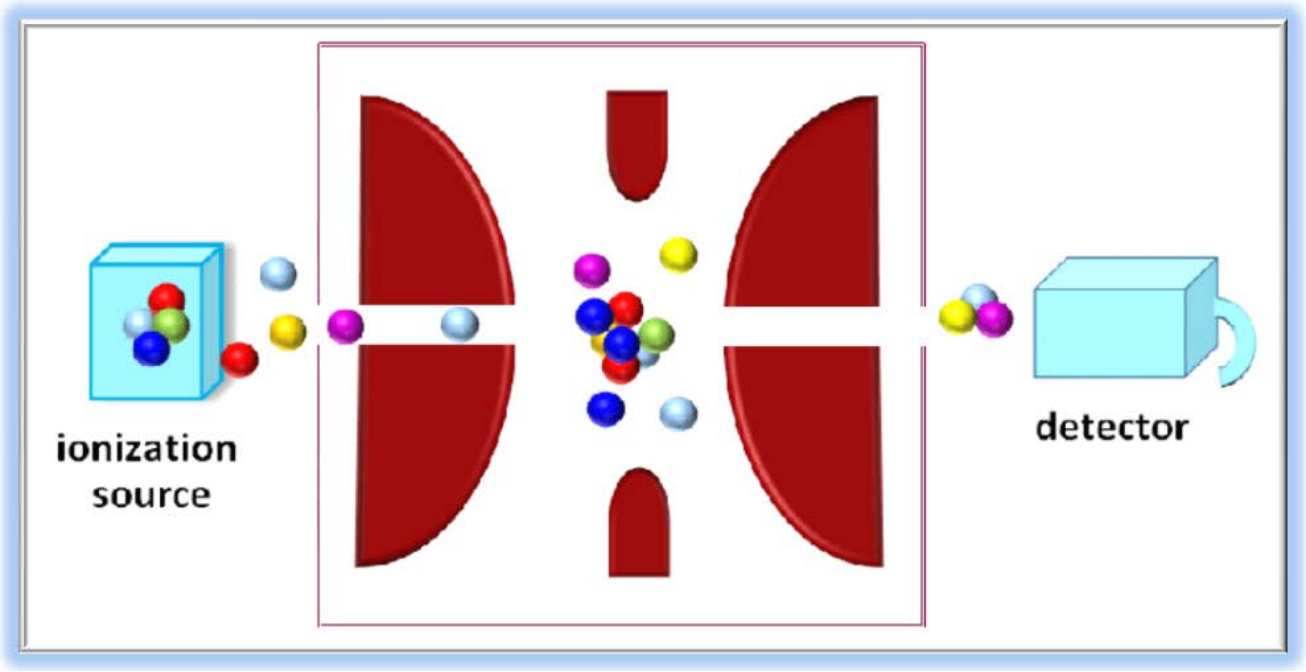

Figure 8. The working apparatus of an ion trap mass analyzer

4.5. Ion Trap Mass Analyzers

In an ion trap mass analyzer, the ions are trapped using dynamic electric fields. It is also called radiofrequency (RF) trap or Paul trap, named in the honor of the scientist who invented the device. Ion trap analyzers use both electric and magnetic fields to capture or trap ions inside the mass analyzers. These mass analyzers work by using a constant direct current. The oscillating radio frequency electric fields and the arrangement of rods (in quadrupole) in the ion trap process vary from other mass analyzers (Figure 8) [25,26].

In 3D ion trap analyzers, the rods with electrodes are placed parallel to each other and a ring electrode is placed halfway between the end cap electrodes. Here, the ions are trapped in a circular path based on the applied electric field in contrast to a linear ion trap analyzer where there are no circular or ring electrodes.

The ions are trapped by a radio frequency field of constant frequency having variable power and stored in a quadrupole ion storage device. The trapping of ions in this device provides time for the ions to interact with other ions and neutral molecules. This causes alterations in ion motions due to imperfect electric fields and results in unexpected changes in the mass spectrum. From the ion storage device, ions of higher mass reach the detector, and the ions with less m/z ratio collide with the walls of the analyzer and do not reach the detector. The mass spectrum is obtained by scanning the field so that the ions with a high m/z value are ejected from the cell and are detected. The use of radiofrequency voltage causes rapid reversals of the field direction of the ion so that ions are accelerated and deaccelerated in the axial direction. In this process, the ions that become unstable leave the ion storage device and reach the detector. The advantages, applications, and limitations are depicted in Table 6.

4.6. Ion Cyclotron Resonance Mass Analyzer

In this mass analyzer, the ions are captured in a trap containing a super/strong magnetic field with electric trapping plates. These trapped ions under the strong magnetic field move in a circular path based on their rotational frequency or cyclotron frequency. This frequency depends on the respective mass carried by ions. These ions move in a circular path close to each other by giving an excitation pulse or electric field in which the resonant ions move in a large circular orbit. These excited or resonated ions come close to the electrodes and generate current, which is amplified and sent to the detector. Here the ions are measured based on a time-varying current induced by circulating ions (Figure 9) [27]. The advantages, applications, and limitations are depicted in Table 7.

Table 6. Advantages, applications, and limitations of quadrupole ion trap mass analyzers

Mass analyzer type	Applications	Advantages	Limitations
Quadrupole ion trap mass analyzer	Used along with gas and liquid chromatography, to study ion chemistry and screening target compound	Highly sensitive, compact mass analyzer	Quality of mass spectrum is least, ions are subjected to different voltages, very poor dynamic range

Table 7. Advantages, applications, and limitations of ion cyclotron resonance mass analyzers

Mass analyzer type	Applications	Advantages	Limitations
Ion cyclotron resonance mass analyzer	Used in the surface characterization of materials by laser desorption method, to study ion chemistry, high-resolution electron spray experiments for high mass analytes	Highest mass resolution in protein and peptide measurements, suited for Pulsed ionization methods like MALDI, ion remeasurement possible, stable mass calibration	Very expensive, low quality of detection, limited range of detection

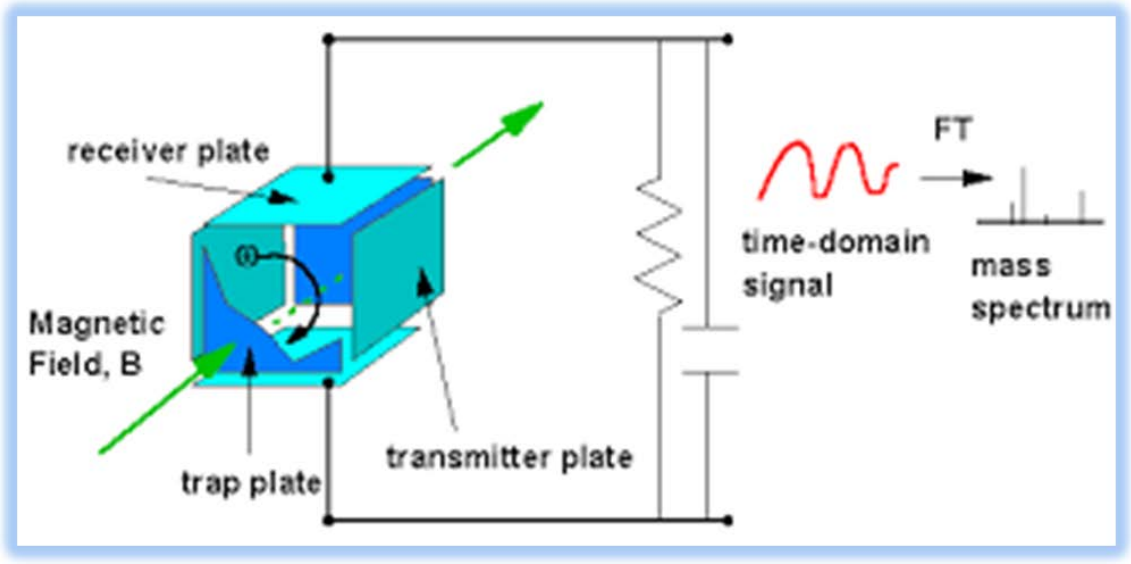

Figure 9. Ion cyclotron resonance mass analyzer

5. Detector

A detector in a mass analyzer collects a signal from incident ions either by generating secondary electrons which are further amplified or by inducing current from moving charged ions. (ionization product). Photographic plates are the oldest type of detector located at the end of a mass analyzer. The generated ions strike the photographic plates according to their mass to charge ratio and produce a spot on the surface of the plate. The darkness of spots indicates the intensity of that particular ion [28]. There are different types of detectors having varied properties as shown in Table 8.

Table 8. Types and properties of detectors used in mass analyzers

Types of detectors	Properties of detectors
Electron multipliers or Channel electron multipliers Faraday cups Photographic plates Scintillation counter Resistance Anode encoder Image detector High mass detection detector Conversion dynodes Helium leak detectors Cryogenic detectors Multi – Pixel photon counter Other detectors	High amplification Fast response High collection efficiency Low cost Long term stability

The choice of a detector is based on the required sensitivity, speed, and other application-specific requirements like heat stability, and available space, among others. Each type of detector mentioned above is briefly discussed in the following sections.

5.1. Electron Multiplier Detectors

The electron multiplier detectors are used for ions with less than 10-15 amperes. These detectors analyze or detect secondary electrons produced after the primary ion particles strike the detector surface. The signal generated is solely dependent on the intensity of the strike. The electron multiplier detectors may use a discrete dynode electron multiplier or a continuous dynode electron multiplier [29].

5.2. Discrete Dynode Electron Multiplier (DDEM)

Dynode helps in the multiplication of electrons and the discrete dynode electron multiplier (DDEM) consists of about 15 to 18 dynodes arranged in a box and grid fashion. All the dynodes are coated with metal oxide and are surrounded by circular magnets. The metal oxide coating enhances the emission of secondary electrons and magnets make the emitted secondary electron move in a circular path (Figure 10) [30].

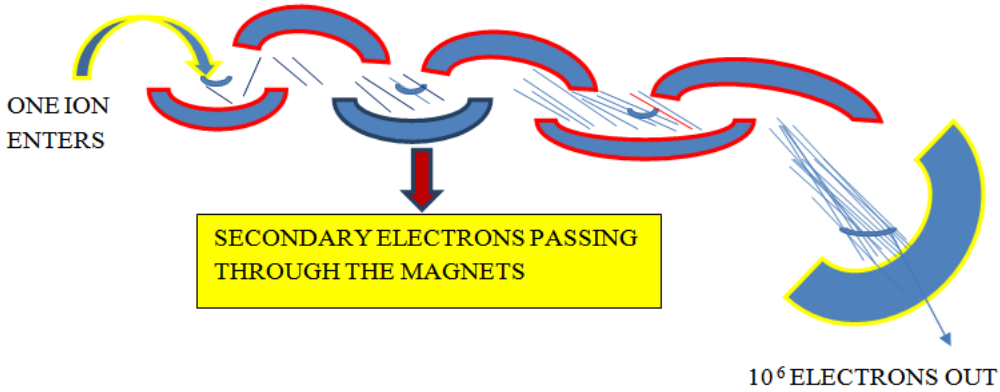

Figure 10. Diagrammatic representation of DDEM

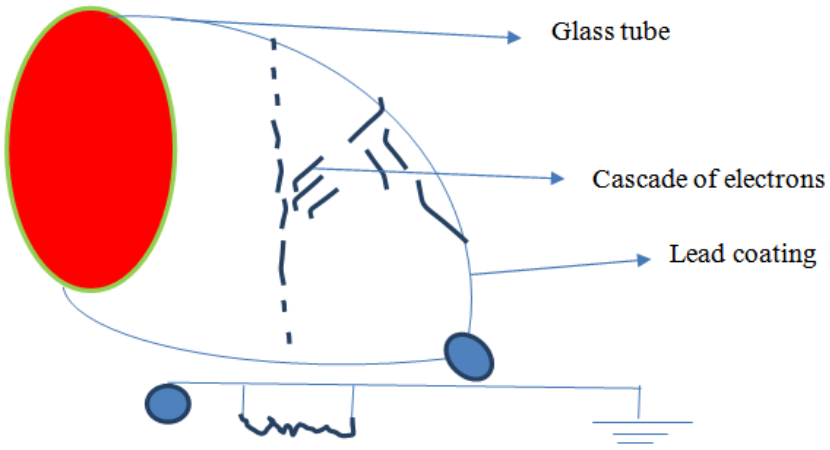

Figure 11. Diagrammatic representation of CDEM detector

5.3. Continuous Dynode Electron Multiplier (CDEM)

The continuous dynode electron multiplier (CDEM) consists of a curved tube with dynodes made up of lead-coated glass. This allows the production of desired resistance between the anode and cathode. Inside this tube, there is a continuous fluctuation of voltage that accelerates the electrons. The curved shape of the tube, in turn, helps in the production of secondary electrons (Figure 11) [31].

The advantages, applications, and limitations of the CDEM are depicted in Table 9.

5.4. Channel Electron Multiplier (CEM)

The channel electron multiplier (CEM) is made up of a small glass tube that is coated on the inner side with a high resistant semiconducting material that serves as a dynode. When high voltage is applied, an electrostatic field is created across the tube. The charged particles or photons enter this tube, where they are continuously accelerated by the electrostatic force until they touch the dynode surface. This in turn, causes the emission of secondary electrons from the semiconducting material. Thus, an increased electron flow can be seen along the channel of this detector (Figure 12) [32]. This enables the collection of about 10^8 electrons within a duration of 8 nanoseconds. Thus, standard CEMs have a capacity of detecting 5 million particles per second. It is used in nuclear physics labs to measure charged particles in pulse mode operation, residual gas analysis, plasma analysis, etc.

5.5. Faraday Cup Collectors

The Faraday cup collectors have a hollow conductive tube that is made up of metal to catch charged particles. This cup is connected to the ground through a high resistor. When ions strike the collector, there is a noise in the resistor which is sensed by the amplifier, which in turn amplifies the ions. A plate is held at -80V in front of the collector to prevent the ejected secondary electrons from escaping (Figure 13). It is used for isotope analysis [33].

Table 9. Advantages, applications, and limitations of continuous dynode electron multiplier (CDEM) detector

Type of detector	Applications	Advantages	Limitations
Continuous dynode electron multiplier (CDEM)	Atomic and molecular collision studies, imaging spectroscopy, electron spectroscopy	Multiple dynodes result in a longer lifetime and better sensitivity	More voltage is required for operation

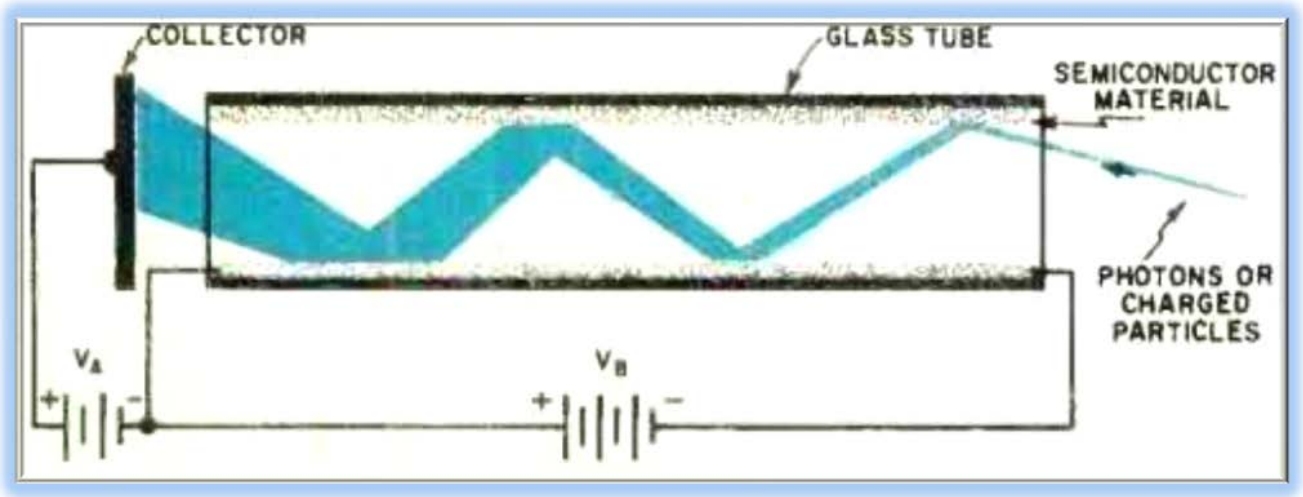

Figure 12. Diagrammatic representation of channel electron multiplier

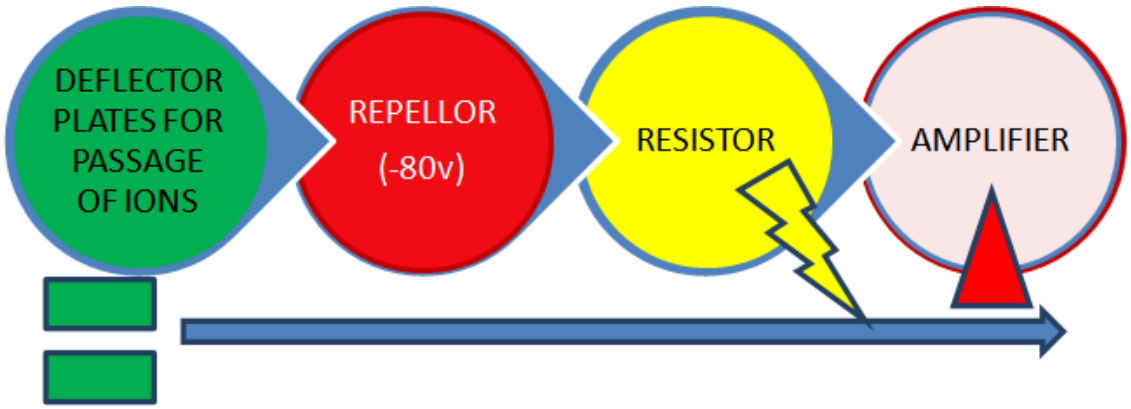

Figure 13. Schematic representation of Faraday cup collector

The advantages, applications, and limitations of the Faraday cup collectors are depicted in Table 10.

Table 10. Advantages, applications, and limitations of Faraday cup collectors

Type of detector	Applications	Advantages	Limitations
Faraday cup collectors	It is used to measure beam intensities at a low beam energy Spectroscopy	High precision, simple construction, signals are stable and reproducible	Low sensitivity

5.6. Photomultiplier Tube (PMT)

The photomultiplier tubes (PMT) are sensitive detectors of light in the range of visible, ultraviolet, and near-infrared regions of the electromagnetic spectrum (it covers the frequency of electromagnetic radiation). PMT detectors multiply the current from the incident light a million times via multiple dynode systems. The dynode is an electrode in a vacuum that multiplies electrons through secondary emission. The secondary emission amplifies a tiny current a million times till it reaches the next dynode. The incident light strikes the photocathode of PMT. The photocathode is a thin vapor conducting material (an alloy of antimony and Cesium) present on the inside and at the entry point of PMT. On striking the photocathode, the primary electrons which eject from the surface by the photoelectric effect are released. The ejection of electrons from a material that absorbs light or electromagnetic radiation is called the photoelectric effect. The focusing electrode of PMT directs the primary electrons onto the first dynode which causes secondary emission into the next subsequent series of dynodes. A large number of electrons from dynodes reach the last stage of PMT i.e., the anode. This large flow of electrons creates a pulse in the anode of PMT which is recorded by an oscilloscope (Figure 14) [34].

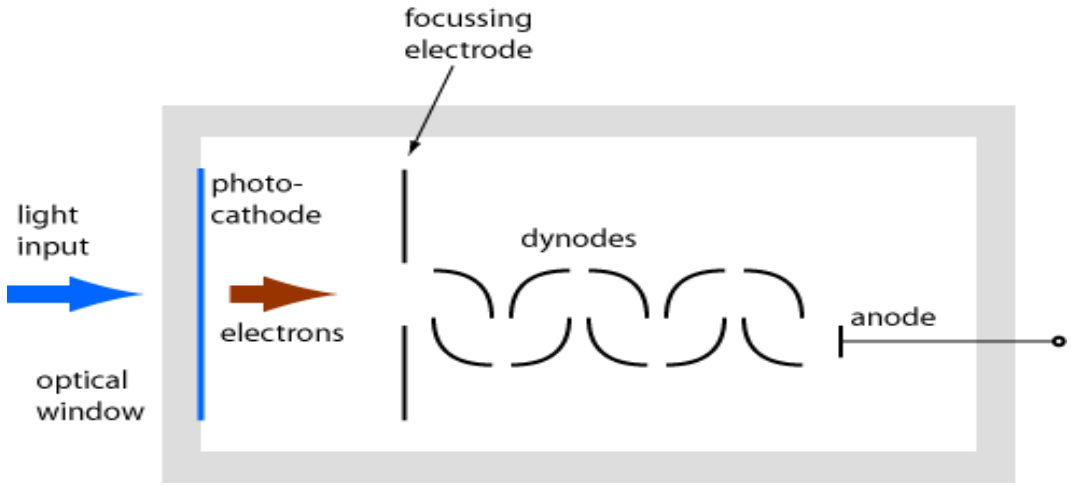

Figure 14. Working apparatus of a photographic plate detector

The advantages, applications, and limitations of the photomultiplier tube detectors are depicted in Table 11.

Table 11. Advantages, applications, and limitations of photo multiplier tube detectors

Type of detector	Applications	Advantages	Limitations
Photomultiplier tube detectors	Used in a physics lab to study ionizing radiations and particle radiation in experiments, used as a detector in many spectrophotometers (measuring light intensity in a spectrum), used in blood analysis equipment like flow cytometer to measure various components of blood	Longer lifetime, simple and oldest method, great resolution, high speed, can detect the ions of all masses	Poor sensitivity, poor precision, poor quantification, easy fragility, short range of ion detection

5.7. Scintillation Counter Detectors

The scintillation counter detectors are radiation detectors that work on the principle of the scintillation effect. Scintillation is the process where light is generated from ionizing radiation. It consists of a scintillator, a photomultiplier tube, and a signal processor. The scintillator generates light when the ionizing radiation strikes it. The scintillator is a transparent crystal made of phosphor, plastic, or organic liquid which causes fluorescence from radiation [35].

5.7.1. Photomultiplier Tube (PMT)

Fluorescence on the striking of radiation excites photocathode of PMT and emits electrons due to the photoelectric effect (emission of electron on hitting of light on the surface of a material). The electron emitted by the excited ion via photon is absorbed by the photomultiplier tube and accelerates the incident electron to multiply so that there is the emission of secondary electrons. This generates a voltage pulse in a signal processor which is amplified and recorded (Figure 15).

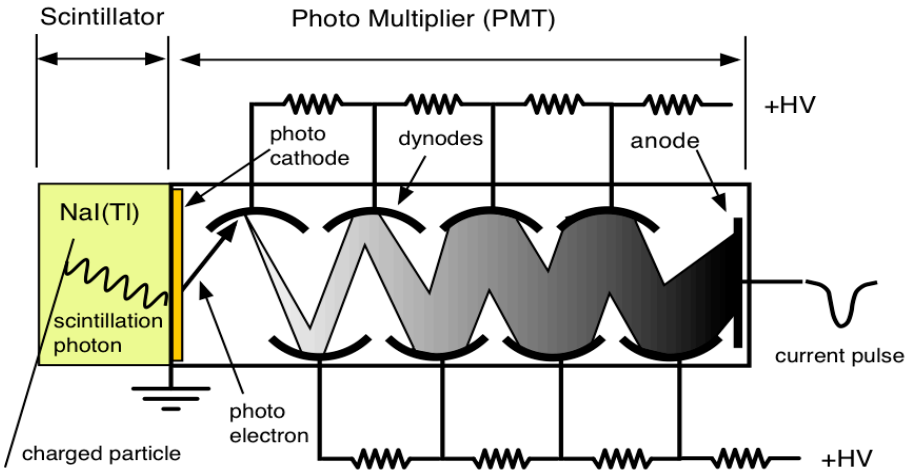

Figure 15. Schematic representation of a scintillation counter detector

The advantages, applications, and limitations of the scintillation counter detectors are depicted in Table 12.

Table 12. Advantages, applications, and limitations of scintillation counter detectors

Type of detector	Applications	Advantages	Limitations
Scintillation counter detectors	Measures radiations, handheld survey meters, monitoring radioactive contamination, medical imaging, security purposes, safety of nuclear plants, assess radon levels in water	Stable and highly sensitive method of detection	Quenching/interference in the energy transfer process, high cost

5.8. Resistance Anode Encoder Image Detector (RAE)

The resistance anode encoder image detector (RAE) is a position-sensitive detector that records digital images of ions. It has two cascaded microchannel electron multiplier plates which detect and amplify soft X-rays, UV electromagnetic radiations, and charged particles that strike the first plate. RAE image detector further creates a signal and generates an electron image on the resistance anode (Figure 16) [36].

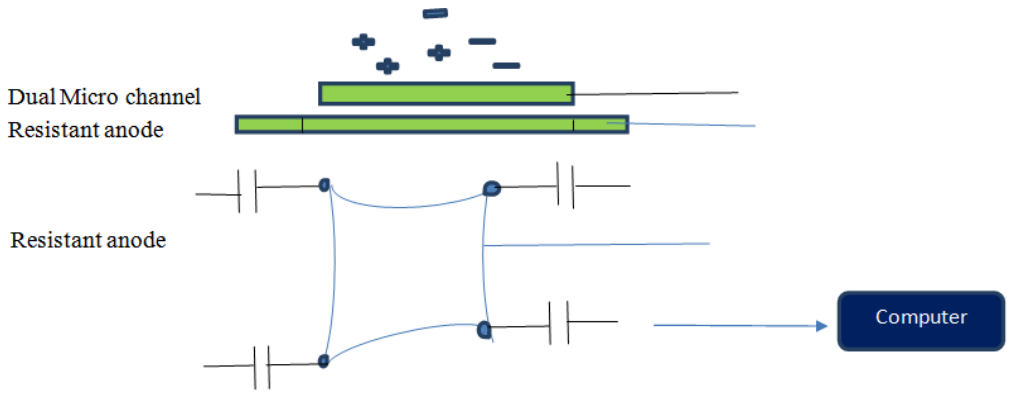

Figure 16. Schematic representation of a resistant anode encoder detector

The advantages, applications, and limitations of the resistance anode encoder image detectors are depicted in Table 13.

Table 13. Advantages, applications, and limitations of resistance anode encoder image detectors

Type of detector	Applications	Advantages	Limitations
Resistance anode encoder image detectors (RAE)	Used in position measurements of low energy photons, neutrons, and charged particles in various nuclear physics experiments, nuclear medicine imaging, low-dose medium resolution radiography	Positive sensitive detector, discriminates various species	Background count rate is high

5.9. High Mass Detection Detector

The high mass detection detector detects ions of high mass (>200 Daltons in residual gas analysis, 10-1000 Daltons in LC/MS, and 700-2000 Daltons in GC/MS). This instrument requires high energy conversion dynodes to increase the detection efficiency. The conversion dynodes help in increasing the emission of secondary electrons from high mass ions since it has a metal surface that can withstand a high voltage (>20KV). This potential effectively releases the secondary electrons and also directs the electrons towards the channel electron multiplier (CEM). The CEM surface has low negative potential and hence will not recapture the secondary electrons. After amplification, the resultant signal is recorded (Figure 17) [37].

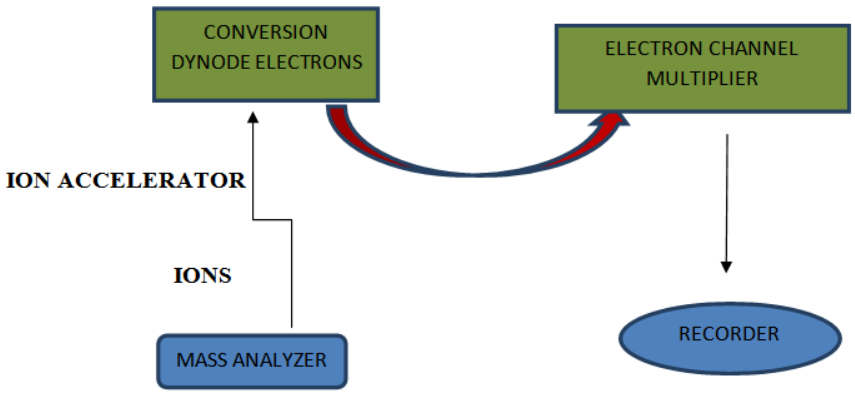

Figure 17. Schematic representation of a high mass detection detector

The advantages, applications, and limitations of the high mass detection detectors are depicted in Table 14.

Table 14. Advantages, applications, and limitations of high mass detection detectors

Type of detector	Applications	Advantages	Limitations
High mass detection detectors	Residual gas analysis	Detects ions of high mass, high detection efficiency	Conversion of dynode may tend to recapture electrons.

5.10. Vacuum Leak Detector

A vacuum leak detector is also called a mass spectrometer leak detector. It is used to locate and measure the size of leaks within and outside of the device. Considering the inertness of helium, it is the most preferred element to detect leaks in a device. Also, helium doesn't react with any of the materials in the device. The detection of leaks whether it is gas or a liquid enables the integrity of the products and also improves consumer safety. Helium is passed through the ionization chamber, which in turn generates ions. The ions are accelerated using voltage and later they are passed through the magnetic field. The accelerated ions move in a circular path according to their mass. The generated signals are recorded, and the current is measured. The measured current is proportional to the concentration of helium. The leak can be detected based on pressure or vacuum testing. In the pressure testing method of leak detection, the same pressure of helium gas is maintained and in the vacuum testing method, compressed air is used to create high pressure for the detection of leaks (Figure 18) [38].

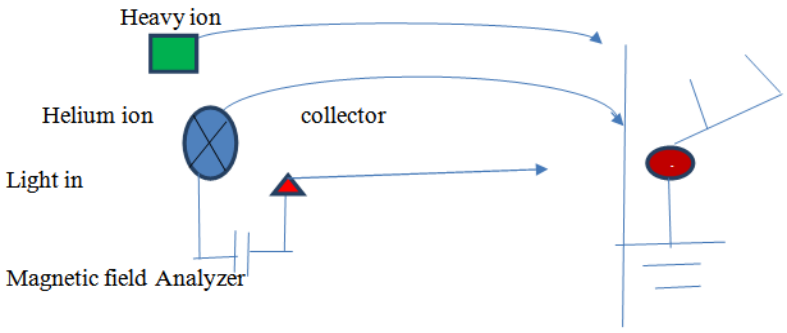

Figure 18. Schematic representation of a helium leak detector

The advantages, applications, and limitations of the vacuum leak detectors are depicted in Table 15.

Table 15. Advantages, applications, and limitations of vacuum leak detectors

Type of detector	Applications	Advantages	Limitations
Vacuum leak detectors	Production industries like refrigerators, air conditioners, air packed foods, automotive parts, carbonated beverage containers. aerosol package, gas bottle, tyre valves, fire extinguishers	Very fast, more reliable, easy to operate, improve product quality	Low sensitivity and less accurate

Table 16. Advantages, applications, and limitations of cryogenic detectors

Type of detector	Applications	Advantages	Limitations
Cryogenic detectors	Helps to know existence of massive neutrinos (neutral subatomic particles), identify DNA sequences of macro molecules, research for fabrication of new materials and medications	High efficiency, more sensitivity, produces photon when ions strike detector, high mass large ions can also be analyzed with minimum time	Maintaining low temperatures is essential for high efficacy

Table 17. Advantages & applications of multipixel photon counter (MPCC) detectors

Type of detector	Applications	Advantages
Multipixel photon counter (MPCC) detectors	Widely used in magnetic resonance or positron emission tomography (PET) detector research	Good cost performance and compact size, great photon detection ability, displaces photo tubes in near future, and used in nuclear medicine and high energy physics

5.11. Cryogenic Detectors

Cryogenic detectors work at low temperatures and help molecular biologists to analyze short DNA sequences with improved sequences efficiency and without vector contamination. It detects the energy of any striking particle independent of its velocity. It consists of individual electrospray ions which strike through a metal tube and detect their image charge. When ions of known energy are sampled then measurement of their velocity helps to detect their mass. Several thousand ions are measured in a few minutes [39,40].

The advantages, applications, and limitations of the cryogenic detectors are depicted in Table 16.

5.12. Multipixel Photon Counter (MPCC) Detector

The multipixel photon counter (MPCC) detector is a type of semi-conducting photon detector. It is made up of semiconductors that together form pixels. When the current is applied, the photons strikeout and blow the electrons which creates a signal. The signal in turn is detected by a detector. This type of detector is immune to high magnetic fields [41,42]. The advantages, applications, and limitations of the multi-pixel photon counter (MPCC) detectors are depicted in Table 17.

6. Other Detectors

6.1. Tandem Quadrupole Detector

The specialty of this detector is the availability of a wide range of ionization and accuracy of results. The advantages of this detector are the quantitative measurement of the isolated compound and the detection of all other associated components [43,44].

6.2. Bipolar MALDI TOF Detector

It can detect positive and negative ions during the isolation of a compound. In this detector, high mass ions can be easily isolated [45].

6.3. Flexar MS Detector

With the flexar MS detector, the advanced design in the ion source and MS technology provides soft ionization [46].

7. Data System

After ionization, the released ions are detected in a detector that is connected to a computer. The computer displays the results as a spectrum of ions which is known as the mass spectrum.

8. Mass Spectrum

The mass spectrum is the pattern of distribution of ions by mass in a sample. It is the most common form of data representation in a sample using the mass spectrometer. A histogram is attached to the mass spectrometer, and this represents the graphical approximate distribution of the data either numerically or categorically. The spectra formed by various samples differ in the pattern of the mass spectrum because of the use of various ionization methods for the fragmentation of different types of samples. For example, straight-chain alkanes and alkyl groups differ in the peaks formed in the mass spectrum [47].

Similar to a histogram, in the graphical representation of a spectrum, the x-axis represents the m/z (mass to charge) ratio, and the y-axis denotes the intensity of the signal generated. The graph is then compared with a standard curve for that particular sample. This standard curve has the sample with a known pattern, which forms the basis for the identification of the unknown sample which is detected by the spectrometer [48].

8.1. Mass Spectrum Analysis

The analysis of a mass spectrum helps in the identification of chemical formulas, characteristic fragment patterns, and possible fragment ions from a mass spectrum (Figure 19) [49].

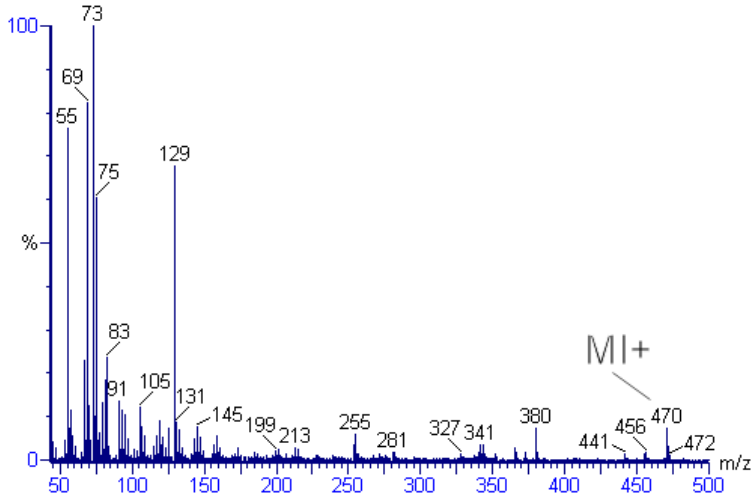

Figure 19. Mass spectrum of Brassica sterol by electron ionization

The peak in the mass spectrum with the greatest intensity is called the base peak. The analysis of a mass spectrum is done by identifying the molecular ion with a high m/z ratio which has the highest peak (base peak). For example, in the above mass spectra, the highest m/z ratio is 73, which is the most abundant peak within a cluster of small peaks along with its m/z ratio. The mass spectrum is analyzed to determine the mass difference (Δm) between each major peak which gives an idea of whether the fragmented ion is obtained by gain or loss of protons. The 'Δm' values from the above spectrum are 14, 4, 2, 8, 8, etc. The mass spectrum is also used to identify the presence of heteroatoms. These heteroatoms are not carbon or hydrogen and the 'Δm' values in the above graph showing a value greater than 16 indicate a heteroatom. The identification of heteroatoms helps us to understand that the heteroatoms change the physical and chemical properties of the substance of analysis. In the above spectrum, the Δm of 24 (129-105) indicates the presence of alkaline earth metal Magnesium. Other applications of the mass spectrum include the identification of the remainder of the molecule, naming the identified molecule, and verifying the identified molecule using software to rule out any error.

9. Applications of Mass Spectrometry

9.1. Proteomics

MS helps in the characterization and sequencing of various proteins. It uses soft ionization methods like electrospray/MALDI for protein studies [50,51]. Among several applications, MS is used to perform peptide sequencing, identify proteins with variable molecular weights, protein expression under different conditions, identify protein using different stimuli expressed after post-translational modifications, and study protein interactions like protein-ligand, protein-protein, and protein-DNA interactions.

9.2. Genomics

MS is used in the genomic analysis of nucleic acids, proteins, and peptides. These are separated by methods like MALDI which separates the molecules using ionization based on size followed by the detection which is accurate and consumes less time (milliseconds). MS helps to perform DNA sequencing and the short oligonucleotide sequences can be distinguished, which otherwise would require gel electrophoresis. Single Nucleotide Polymorphism (SNP) can be detected using MS, wherein a large number of SNPs can be precisely identified in a genome [52,53].

9.3. Monitoring Volatile Anesthetic in Patient's Breath during Surgery

The anesthetic drug propofol is used as an intravenous sedative during major surgeries. The metabolites of propofol can be detected even in low concentrations. The surgeons can evaluate the patient's condition regarding the loss of consciousness by estimating the drug present in the expired air using a portable proton transfer reaction (PTR) time-of-flight (TOF) mass spectrometer. Thus, a mass spectrometer helps in analyzing the anesthetic content in a patient's breath during the surgery [54].

9.4. Determination of Pesticide Residues in Food

Pesticides are used in food production and to control insects, rodents, weeds, bacteria, molds, and other parasites. The pesticides sprayed on crops in increased quantities become toxic to the soil in which it is grown. The presence of remnant pesticides in food can lead to health hazards among humans and other livestock. The pesticide content of a food product can be estimated using MS wherein the sample purification is done using High Performance/Ultra-High-Performance Liquid Chromatography. Later, using ionization methods of the mass spectrometer, the pesticide quantity can be detected in an appropriate detector of the mass spectrometer. Thus, Multi residue Liquid chromatography-mass spectrometry (LC-MS) appears to be an ideal, extremely sensitive, and highly specific technique for testing food products [55].

Identification of drugs of abuse and analyzing drug metabolites in blood, urine, and other body fluids using

MS have been explored previously [56,57,58]. The drug of abuse or substance of abuse is a chemical substance that is used for pleasure, especially among adults under the age of 30 years. Some psychoactive substances or drugs used for depression including barbiturates and heroin/stimulants like cocaine and amphetamine and hallucinogens like opioids can be estimated using MS. These can be administered orally, intravenously, by inhalation via smoke/snorting, and may become an addiction, and result in severe personality changes, inculcate criminal or anti-social behavior among people after a long time of usage.

Identifying drug of abuse in biological samples provide scientific evidence against criminals and victims in a court of law. Biological samples like blood, urine, hair, saliva, etc., can be assessed. Initially, the screening of samples for drug abuse was done by immunoassays like Enzyme-Linked Immunosorbent Assay (ELISA), Radio Immunoassay (RIA), Enzyme Multiplied Immunoassay (EMIT), and Cloned Enzyme Donar Immunoassay (CEDIA). These immunoassays are non-specific and hence confirmation is done by analytical methods like Gas Chromatography-Mass spectrometry (GC-MS) and Liquid Chromatography-Mass spectrometry (LC-MS). The GC-MS/LC-MS are highly sensitive and have good separation power to enhance the identification and confirmation of drugs of abuse. Advanced techniques like High-Performance Liquid Chromatography (HPLC), Ultra-High-Performance Liquid Chromatography (UHPLC)-TOF mass spectrometers are used for screening and identification of the substance of abuse.

9.5. Identification of Environmental Pollutants

Environmental pollutants like nitrogen oxide, sulfur dioxide, plastic, lead, particulate matter, etc., which harm both animals and humans can be identified by MS. The selective nature of LC and sensitivity of MS are coupled together to perform environmental analysis. LC-MS helps in detecting steroid estrogen, and nitrosamines in wastewater, analyses polar, ionic, and heat-sensitive substances, antibiotics in pesticides, and detects perfluorinated organic (PFO) compounds found in cleaning products, textiles, photographic materials, etc. Thus, LC-MS helps in assessing and controlling environmental pollution [59].

9.6. Geochemistry

The study of the chemical composition of the earth, its rocks, and minerals is called ‘Geochemistry’. Radiogenic isotopes are used to trace the origin of a compound by geochemists. The isotopic ratio is used as a unique technique to determine the origin of a compound. This isotopic ratio is useful both for geologic and environmental studies. The analysis of the radiogenic isotope ratio is performed by thermal ionization MS. The materials assessed may include and are not limited to ancient teeth, oceanic sea mass, rock, and fluids. Variation in the abundance of isotopes is used to predict the age of the sample [60].

9.7. Analysis of Aerosol Particles

Aerosols are particles that may be solid, or liquids suspended in gas that measure in the range of 3 nm to 100 micrometers. They are produced either naturally or by human influence and may contain wind-blown suspension or combustion of biomass (organic material) or fossil fuels (oil, natural gas, coal, etc.,). Analyzing aerosols helps in predicting global climate change, the extent of regional air pollution, and its potential consequences on human health. Analysis of aerosols is complex because it contains different chemicals in a single particle. Therefore, it can be done either by electron ionization mass spectrometer or by using TOF aerosol mass spectrometers [61,62,63].

9.8. Emerging Medical and Biomedical Applications

The analysis by limited proteolysis-mass spectrometry (LiP-MS) revealed several changes in cerebrospinal fluid proteins that may potentially be associated with aging [64]. MS may be used to assess the role of proteins, like Tau protein, amyloid-β (Aβ), among others, and proteins including OMD, CD44, VGF, PRL, and MAN2B1 in the development and management of neurodegenerative disorders like Alzheimer’s disease and Parkinson’s disease, respectively [65,66,67]. Because of the increasing emergence of microbes resistant to multiple antibiotics, MALDI-TOF MS may be applied to identify, screen, and predict such organisms [68,69,70]. Liquid chromatography-electrospray ionization tandem mass spectrometry (LC-ESI-MS/MS) was recently suggested as a method to perform proteomic analysis to detect antimicrobial resistance and virulence determinants [71]. MS and its applications appear invaluable to both medical and non-medical fields as evidenced by the results of a recent study. This study showed that MS has a wide spectrum of applications in the fields of pain management, transplant medicine, clinical toxicology, designer drug testing, genetic metabolic disorder testing, nutrition and dietary exposure to heavy metals, compositions of herbals and supplements, forensic pathology, pharmacogenomics, and performance-enhancing drugs and peptides, among others [72]. MS imaging, a novel tool can be applied to characterize and identify tumor tissues. This could prove beneficial in the identification of biomarkers in cancer disease diagnosis [73]. Moreover, MS-based applications have also been found effective in the diagnosis of other diseases like osteoarthritis, and non-alcoholic fatty liver disease, among others [74,75,76].

10. Conclusion and Future Perspectives

MS is an analytical technique used for measuring known chemical compounds and identifying unknown chemical substances in samples that may be biological or non-biological. As we generally assume, mass spectrometers are not large instruments as they were a decade ago. Currently, they are handy, portable, and are frequently used in the identification of proteins, estimating molecular size, and molecular weight, studying

protein-protein interactions, and the sequence of attached amino acids in a protein. At the genetic level, MS verifies nucleic acids, DNA sequences, and polymorphisms (gene variants) and helps in learning gross genetic changes occurring (if present) at the generation level or impacts of environment on genes. Mass spectrometers are also used for detecting pesticide content in food. This must be made mandatory in developing countries such as India to prevent excessive usage of pesticides to enhance crop production. MS also help in checking the particulate content of the air, which warns about the effects of pollutants on living conditions and thereby enabling local governments to initiate precautions and minimize pollution. MS can be used to estimate the amounts of toxic substances or substances of abuse present in the human body fluids, blood, organs, etc for medico-legal, and forensic purposes. They are also used to assess the gases in human breath, especially in critically ill conditions, or during major surgeries. MS helps geologists to predict the age of fossils, and rocks, among others. Mass spectrometers have a wide range of applications and can be used to assist in the diagnosis and management of patients. However, due to the high cost, there is a lag in its use, and therefore, the governments, especially in the developing nations should take initiatives to subsidize the cost and make them more feasible/affordable. The availability of mass spectrometers will enrich research-oriented approaches even in the rural parts of the countries that generally have limited resources.

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