



Recent Advances and Developments in Hyphenated Techniques and their Applications

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Authors' contributions

This work was carried out in collaboration among all authors. Author MRJ designed the concept of the study. Author JVW wrote the first draft of the manuscript. Author LVK managed the data acquisition and author SKP managed the literature searches. Author BCN performed critical revision of manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Background: A hyphenated technique is blend or coupling of two distinctive analytical methods like chromatographic and spectral methods with appropriate interface.

Objective: This article describes about the various hyphenated techniques, a brief note on their instrumentation and working principles that are used in the current setup of industries. Like-wise their remarkable improvement and efficiency over the past decade. The techniques like single quadrupole inductively coupled mass spectrometry (ICP-Q-MS), ICP- Triple quadrupole mass spectrometry (ICP-QQQ), Liquid chromatography-Two -dimensional Gas chromatography mass spectrometry (LC-GCXGC-MS/MS), Two dimensional liquid chromatography (2D-LC), Fourier transform near infrared spectroscopy (FT-NIR), etc. are considered as recent improvements in this trend.

Conclusion: This development in the hyphenated techniques supports in different scientific fields, biomedical research, food and drug analysis. In addition to this improvement produced remarkable dimensional changes in the natural product analysis and elemental specifications.

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1. INTRODUCTION

Hirschfield in 1980 presented the expression "hyphenation" to indicate the consolidation of chromatographic and spectral techniques and hence use the benefits of both [1]. Chromatography produces almost unadulterated divisions of sample segments from the blend. Spectroscopy produces particular data for identification using standards or reference library spectra. Lately, hyphenated procedures attained considerably more important, ever-expanding and evergreen technique in the tackle of complex expositive issues. It created intensive changes in the qualitative and quantitative analysis of chemical and biological substances. It also created an impact on microanalysis. When the two different principles joined together creates more benefits to the users in the investigation of obscure mixes in complex regular item concentrates or divisions. The previous literature revealed the development in the hyphenated techniques up to the previous decade. Hence the present paper aims to update the scientific community on the further development. In the previous literature there are five equipments and its related hyphenated principle with its applications were discussed in detail.

2. IMPROVEMENTS ON HYPHENATED INSTRUMENTS

2.1 Single Quadrupole ICP-MS (ICP-Q-MS)

ICP MS instrument was launched in the year 2009 by Agilent Technologies [2]. This instrument considered as a quickest equipment for developing method in the multi-component trace examination. This instrument worldwide used in larger quantity in the industries in many applications. The working principle of ICP-Q-MS is producing a high temperature plasma supply of about 10,000°C from where the sample is transferred. The atoms within the sample are then ionized and passed on to the MS system. This MS system uses a quadrupole based mass filter system [3]. For fast and trace analysis (<1000 ppm) in liquid and solid samples. ICP-Q-MS basically uses inductively coupled plasma as an excitation source for ionizing the sample. The gases like argon or helium are commonly

used as a plasma matrix to retain the samples. Followed by the ionized atoms separated in the quadrupole and mass filter helps to separate and transmit only selective sample that is analyte ions of a characteristic (m/z) mass to charge ratio which is then sent to the detector. This whole process of the ions to detector is carried out in an electrostatic field. The schematic representation is shown in Fig. 1.

Sample is allowed to enter as a liquid by using a nebulizer or a pump. The nebulizer converts the liquid mixture to aerosol or fine droplets using Argon gas. The highly ionized vapor produced by the reaction between the argon gas and sample will be flow through a quartz glass and a strong magnetic field. The ionized analytes were passed to an interface which is located amidst two conical disk-made of nickel or platinum. This is done to only allow analyte particles to be sent into the collision cell. The ions pass on to the collision cell. In the collision reaction cell, the positive ions are separated from the neutral ions and photons thus reducing beam broadening and also removes the polyatomic interferences. In the next stage ions will be sent to the mass analyzer-quadrupole. The quadrupole mass analyzer consists of four parallel rods in which two have a negative charge and the other two have a positive charge. The strength of electromagnetic field is obtained by application of AC and DC voltage which can be increased or lowered. This field is responsible for the trajectories of the ions, and thus allowing only the analyte that has a specific mass to charge (m/z) ratio to pass on to the detector. The analyte ions are passed to the electron multiplier detector. ICP-Q-MS has many advantages like high sensitivity, good chromatographic detection, excellent precision and accuracy High control of interferences fast and rapid analysis. Limitations are it's a destructive technique and speed of analysis can be reduced by quadrupole scanning rates and time is taken for rinsing the samples and introduction of samples. [4] The ICP-Q-MS predominantly used for the characterization of atomic and polyatomic species in plasma and other applications in medical field, for trace analysis in bones, tissue, blood, mineral detection in rocks, soils, fossils, toxin determination in environment, metal detection in proteins or enzymes.

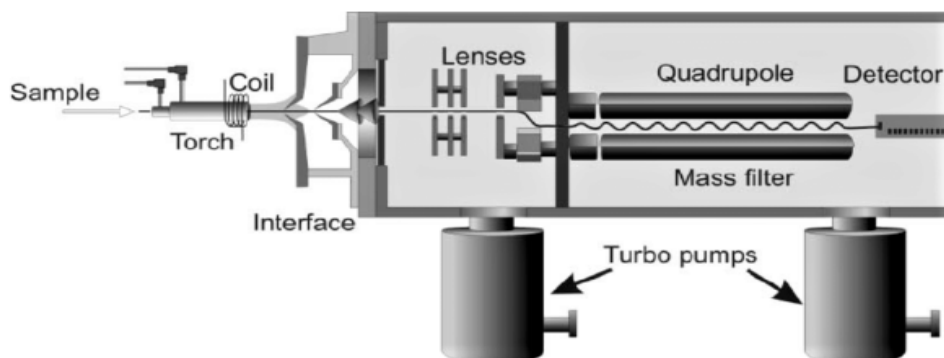


Fig. 1. Schematic diagram of ICP-Q-MS

2.2 Triple Quadrupole ICP-MS (ICP-QQQ)

Triple quadrupole ICP-MS was launched in 2012 by Agilent Technologies [5]. This instrument is highly efficient than the commonly used single quadrupole ICP-MS because of its higher advantage that is additionally added quadrupole which is placed before the collision cell. The main principle is the use of tandem mass spectrometer (MS/MS) which efficiently selects ions according to their mass to charge ratio by the use of two quadrupole mass analyzers namely (Q1 and Q2) which are separated by a collision reaction cell which is also called as Octupole Reaction system (ORS).

The triple quadrupole when compared with the single quadrupole ICP-MS, has an additional quadrupole system. The instrument schematic diagram represented the is shown in Fig. 2. The

Q1 mass filter controls the target analyte and rejects the other unwanted ions which is then passed into the collision cell. Any ions which do not have the specific mass to the charge ratio (m/z) will not be allowed to pass through the Q1. These ions are then passed to the collision cell where it is fragmented into daughter ions by the presence of inert gases like nitrogen or argon. After which the ions which are now fragmented pass through to the second Quadrupole and are again selected by their mass to charge ratio (m/z) and is passed to the detector. Advantages are higher efficiency in trace analysis, easy to fit and disconnection of interference, high improved detection limits, fast, reduces time consumption and disadvantages are difficult to set up the instrument by lab technicians from other backgrounds [6]. This technique applied basically in the fields like, Ultra trace analysis. Quantitative proteomics and phosphoproteomics and environmental analysis.

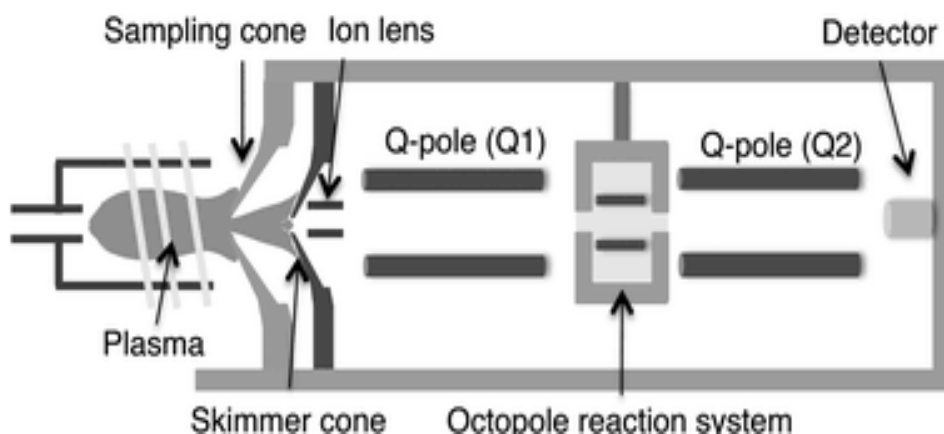


Fig. 2. Schematic representation of ICP-QQQ

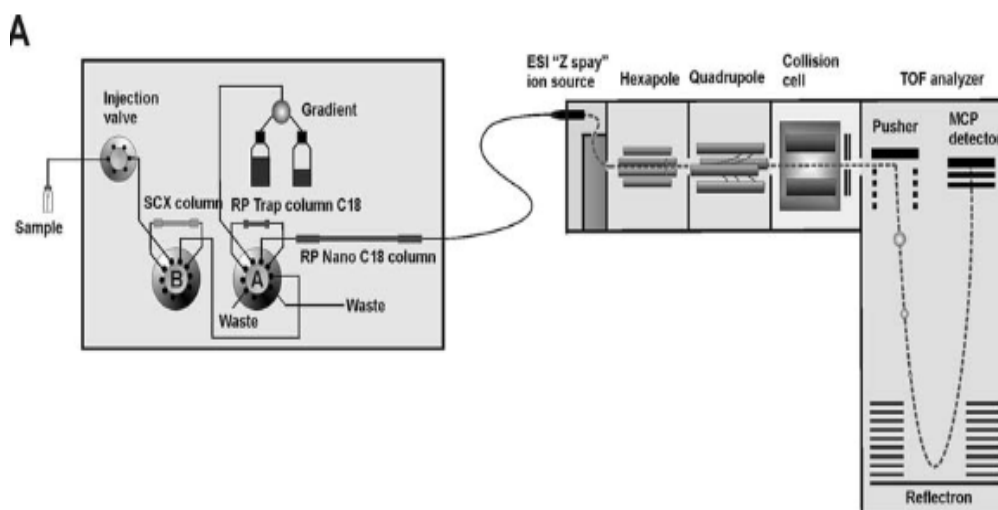


Fig. 3. Quadrupole time of flight LCMS (QTOF-LC-MS)

2.3 Quadrupole Time of Flight LCMS (QTOF-LC-MS)

Quadrupole Time of flight LCMS was launched by Agilent Technologies [7]. It is a superior ionization technology that gives high sensitivity. The working principle behind in this instrument is that two mass analyzers are used i.e., Quadrupole and Time of flight (TOF). The quadrupole filters the sample ions based on their mass to charge ratio and TOF analyzer measures the ions flight time [8].

The sample obtained from the LC system is passed through the nebulizer to produce fine droplets and enters in to the MS system later it passed on to a second nebulizer for mass accuracy. High volume drying gas counterflow reduces the noise and then the ions are passed through a sampling capillary. Further to a skimmer aperture in order to reduce beam broadening. Then they are passed through an octupole ion guide, the lenses present increase the ion transmission and increase sensitivity to a wider mass range. It is then passed to the first mass analyzer that is the Quadrupole. Fig. 3 shows the different parts of the system. [9] Quadrupole mass filter allows only target ions of specific mass to pass through. Then to the collision cell where the precursor ions generate product ions and neutral fragments led to a slicer which flattens the beam of ions for better sensitivity and improves mass accuracy. It is then passed into the flight tube and the reflectron compensates the line of velocity differences.

After passing through the reflectron the ions are sent to a plate detector where the signals of ion are converted from electrons to photons and back to electrons and finally to the detector. Advantages are high sensitivity, higher mass accuracy, ultrahigh resolving power, fast data acquisition rates, rapid polarity switching. Toxicological analysis and other applications include food safety, environmental analysis, [10] pesticide identification, identification, characterization and quantification of biomolecules, confirmation and identification of proteins are some applications of QTOF-LC-MS.

2.4 Triple Quadrupole GC-MS

Triple quadrupole GC-MS was launched in 2011 by Agilent Technologies[11]. The basic principle is that it consists of two quadrupole mass analyzers with a collision cell between them for collision induced dissociation (CID) in order to convert the parent ions into daughter ions. Ion source generates the ion from the GC outlet [12]. The first step is the precursor ion isolation. Only the analyte ions pass through the quadrupole. Non analyte ions are vacuum pumped away from the quadrupole (neutral ions). This kind of a mass filtering eliminates most of the matrix ions. Gold plated Quartz inert source gives high temperature to avoid contamination. The collision cell contains the N₂ gas along with helium that reduces transmission of metastable helium gas. This process is also known as helium quenching. Then it is removed by the pump. Finally, only the analyte ions are passed to the Q2 and further

separated according to the m/z ratio and then detected. Advantages are easy to operate lower contamination rate reduces signal to noise ratio, highly efficient, greater detection sensitivity, efficient quantification, cost sufficient [13]. This technique is used for detection of chemical contaminants and residues in food products. Other applications include food safety, pesticide analysis, trace chemical analysis, soil analysis, forensic and criminal cases, security and chemical warfare agent detection, clinical toxicology.

2.5 MP-AES (Microwave Plasma Atomic Emission Spectrometry)

Microwave plasma atomic emission spectrometry) was launched in 2012 by Agilent Technologies. The MP-AES has high sensitivity and detection limits and is faster than the normal flame atomic absorption spectroscopy [14]. It runs completely on air instead of combustible gases that makes it low in cost. It is very useful in simultaneous multi-component analysis.

The fundamental principle implies that when any atom is activated by an external energy, radiation is absorbed in a distinctive sequence of wavelength creating an absorption spectrum when it comes back to normal state. Microwave plasma is utilized in this case. MP-AES utilizes microwave energy to create a plasma release utilizing nitrogen provided from a gas chamber or separated from encompassing air, which dispenses with the requirement for sourcing

gases in far off areas or far-off nations. The working of the MP-AES system is shown in Fig. 4. Samples are ordinarily nebulized before association with the plasma in MP-AES estimations. The atomized sample goes through the plasma and electrons are elevated to the energized state. The light discharged electrons come back to the ground state light is isolated into a spectrum and the power of every emanation line estimated at the detector. Advantages are [15] safe and easy to use, cost effective, higher sensitivity than flame atomic absorption, multi-element capability, eliminates usage of flammable gases There are various applications of this instrument like analysis of Hg, Pb, Cd, Cr in electronics and plastics Other applications include environmental monitoring for contamination, geo chemistry, food testing and agriculture, chemical and [16] petro-chemical field.

2.6 Orbitrap Fusion LC-MS (Tribid LC-MS)

Orbitrap fusion LC-MS (Tribid LC-MS) was Launched in 2013 by Thermo Fischer Scientific [17]. This is a fusion LC-MS system which combines three mass analyzers Quadrupole, orbitrap and Linear ion-trap mass analyzer and it gives the deepest analysis of complex analytical samples. The working principle consists of trapping, injection, excitation and detection. It is a particle trap mass analyzer that comprises of two external electrodes and a focal terminal, which empower it to go about as both an analyzer and detector.

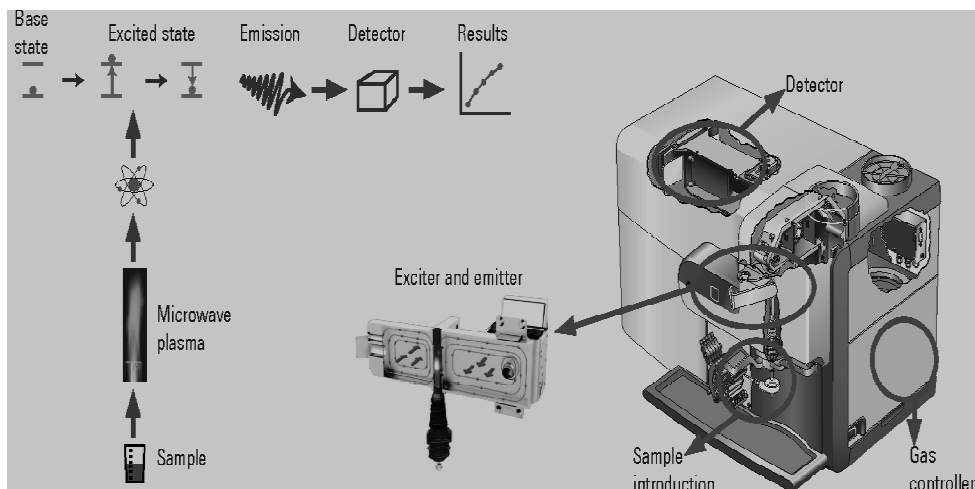


Fig. 4. Schematic representation of the working of MP-AES

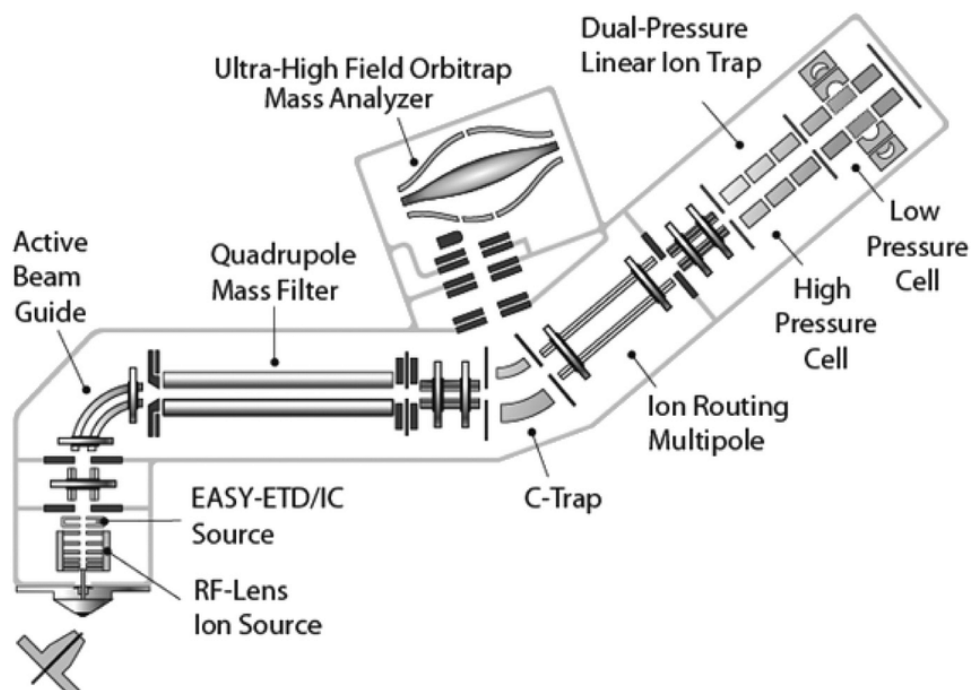


Fig. 5. Diagram of Tribrid LC-MS instrumentation

The instrumentation consists of ion source, lens, active beam guide, quadrupole mass analyzer, Orbitrap, Dual pressure linear ion trap filter, ion routing multipole and a detector as shown in Fig. 5. Particles entering the Orbitrap are caught through "electrodynamical crushing," after which they waver around the focal anode and in the middle of the two external electrodes [18]. Various particles waver at various frequencies, bringing about their detachment. By estimating the swaying frequencies induced by particles on the external electrodes, the mass spectra of the particles are procured utilizing picture current recognition. The quadrupole has four parallel metal rods. Each opposing rod pair is connected together electrically, and a radio frequency (RF) voltage with a DC offset voltage is applied between one pair of rods and the other. Ions travel down the quadrupole between the rods according to their specific m/z ratio. Linear ion trap analyzer stores the ions in a fixed linear trajectory [19]. Its major advantage is that it has increased capacity of trapping ions. This allows broader range and better quantification. Advantages are high and efficient performance, ultrahigh resolution up to 500,000 full width at half maximum (FWHM) removes interferences, excellent selectivity and sensitivity due to the use of three analyzers parallelly, determination of

detailed structure of small molecules, high accuracy and precision, improved sensitivity for extended coverage of low abundant proteins [20]. This method is applied in fields such as Glycoproteomics analysis, determination of peptide fragmentation patterns, ultra-trace analysis, multi elemental analysis, protein analysis, drug metabolite identification.

2.7 LC-GCXGC-MS/MS (5D Ultra-e)

(5D Ultra-e) was launched in 2013 by Shimadzu Company [21] and was developed by Prof. Dr. Luigi Mondello at the College of Messina and Chromaleont S. r. l. in Italy. This instrument is a unique technique that has a combination of comprehensive two-dimensional gas chromatography, HPLC system and a triple quadrupole mass spectrometer. The HPLC combined with the 2D-GC system increases its power and improves the productivity by enhancing the automation. The triple quadrupole mass spectrometer allows the target analysis of components in many complex analytes. The HPLC allows the separation of the analyte from any complex matrices. They can be specifically set up for targeted analytes. The eluent obtained from the LC is then injected into the GC system, this eluent contains only the required target

components. Any volume of sample can be injected since there are no loops or valves present. The solvent residues are eliminated by efficient temperature programs. Eluted components are inserted into the GC system. The two-dimensional GC system separated components more efficiently than the one-dimensional GC system. They are then sent into the highly efficient MS/MS which has a triple quadrupole system that analyzes the analytes by their mass to charge ratio and gives an accurate reading [22]. A 5D integrated software is then used to control all of these integrated systems as one. Advantages are LC along with the 2D-GC makes it much easier and gives more detailed characterization of complex samples, high speed and high sensitivity, triple quadrupole MS system gives specific analysis within trace concentrations, large volumes of samples can be injected, ease to use software manages all the integrated systems starting with just one click, powerful analysis of trace components, eliminates need for liquid nitrogen, high accuracy and precision [23]. The main application is detailed comprehensive analysis of coal tar and sulfur compounds.

2.8 2D-LC (Comprehensive Two-Dimensional Liquid Chromatography)

2D-LC was launched in 2014 by Shimadzu [24]. Two-dimensional chromatography is a kind of chromatographic method wherein the infused sample is isolated by going through two distinctive separation stages [25]. The principle

behind 2D LC is two distinctive chromatographic columns are associated in succession, and the gushing from the primary framework is moved onto the subsequent column. Regularly the subsequent column has an alternate separation component, so groups that are ineffectively settled from the primary column might be totally isolated in the subsequent column.

The two-dimensional liquid chromatography system consists of pumps, autosampler, columns and detector. The schematic representation of this system is given in Fig. 6. An auto sampler is basically a robotic device that brings the samples to the sampling station, or brings the sampling device to the trays along with the other samples. Then it is passed to the separating column and detected. Further again the process is repeated and the effluent from the first column is pumped into second column and it is detected [26]. The detectors used are UV detectors, mass spectrometer, fluorescence detector, refractive index detector. Two-dimensional chromatogram is produced. Advantages are high resolving power, high increase in peak capacity, overlapping of peaks in the first dimension can be resolved, closely related compounds can be separated, separate mixtures that one dimensional LC cannot separate effectively. Disadvantage is the extremely long timescale (normally a few hours to several hours) of extensive 2D-LC is plainly its main disadvantage. Chiral analysis, trace analysis, impurity profiling, herbal medicine, bioanalysis, food testing. etc., are some applications of 2D-LC.

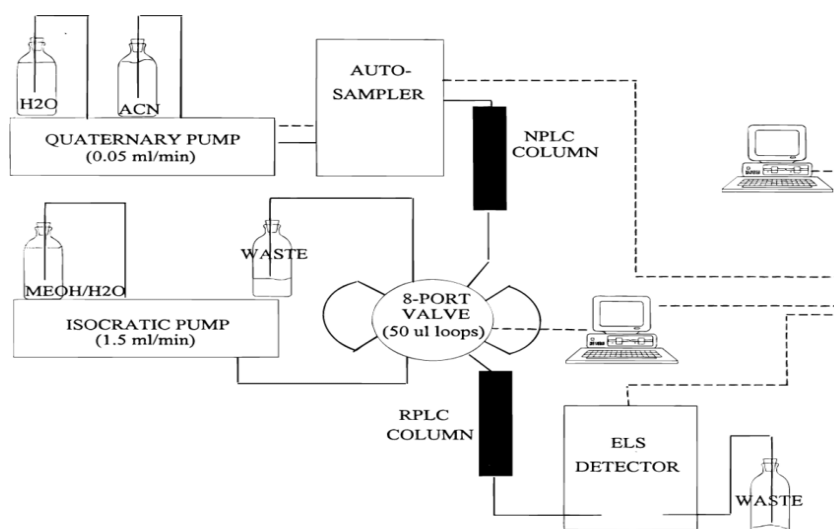


Fig. 6. Schematic representation of 2D-LC

2.9 FT-NIR (Fourier Transform Near-infrared Spectroscopy)

FT-NIR was launched in 2011 by Thermo Fisher Scientific [27]. The near infrared spectrum ranges from 12000-4000cm⁻¹. It consists of overtone and combination bands that are seen as absorption frequencies in the mid infra-red region. These bands give the vibrations of the atoms that make up the substance. This is basically because each substance is made up of a specific and unique combination of atoms and two distinct materials cannot give the same near infrared spectrum. Fourier Transform near infrared spectroscopy technique was mainly introduced in order to overcome the limitations that were produced by the dispersive NIR instrument. This method measures all the infrared frequencies at the same time and thus is less time consuming. This spectrometer uses an interferogram which already has the frequencies encoded in it. By using the fourier transform technique, it is then transformed into a spectrum of frequency vs intensity.

The main difference between the FTIR and FT-NIR is the former uses silicon carbide source and the latter uses QTH (quartz, tungsten, halogen)

source which is more suitable for near infrared range, the method is the same for both the instruments [28]. The working representation of the instrument is shown in Fig. 7. The source is a halogen light source, this beam is then transformed into interferometer that has the beam splitter which then splits the radiation emitted into two. There are two mirrors, fixed and moving mirror which then reflects the beam back into the beam splitter, where they combine into one and is passed to the detector. The two beams combine constructively or destructively varying the optical path. It is then detected as an interferogram. This information that is collected by the interferogram, which gives an infrared spectrum by a mathematical process is call as Fourier Transformation. An internal reference laser is utilized to regulate the interferometer [29]. Advantages are instrument is mechanically simple, non- destructive, requires no sample preparation, reliable, robust mechanism, extremely accurate and precise, no degradation of optical throughput, internal calibration reduces errors, quick method, reproducible results are obtained, multiple component analyzed, simultaneously cost effective [30]. It is an appealing technology in the food industry and other applications include rapid raw material identification and chemical analysis.

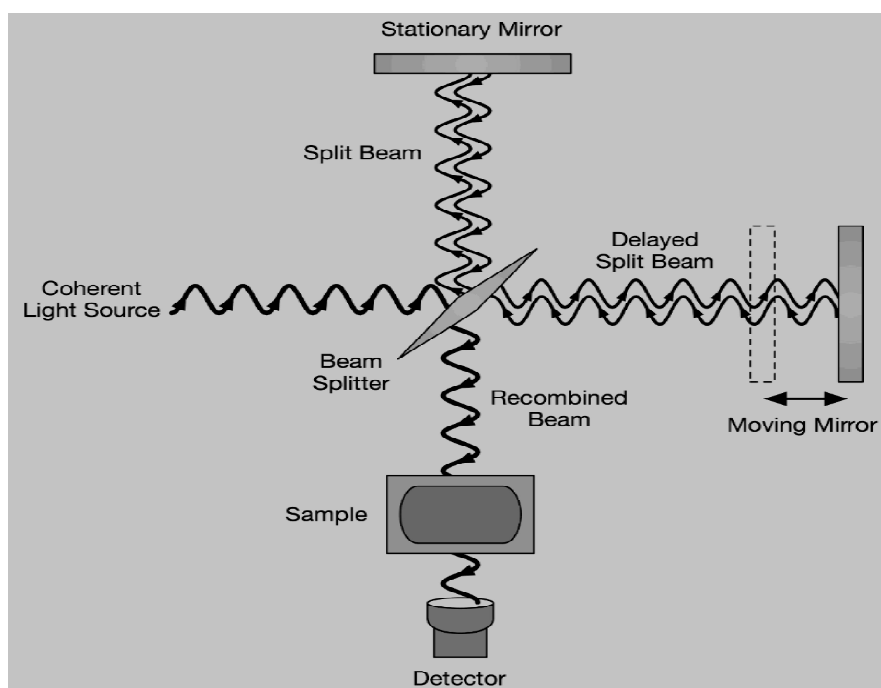


Fig. 7. Working of FT-NIR

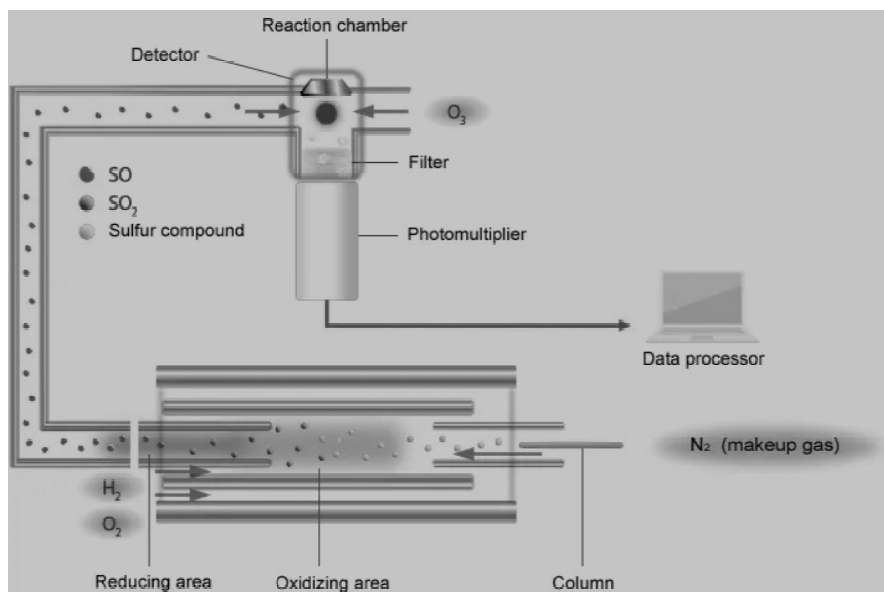


Fig. 8. Instrumentation and parts of SCD-GC

2.10 SCD-GC (Sulfur Chemiluminescence Detector for Gas Chromatography)

SCD-GC was launched in 2016 by Agilent Technologies [31]. Gas chromatography with sulfur chemiluminescent detection (SCD) gives a fast and exceptionally explicit intends to distinguish and evaluate different sulfur compounds that might be available in incidental oil feeds and products, for example, gas, gaseous petrol [32]. The detection method of sulfur chemiluminescence is a two staged process, the sample moiety is reduced in air and then hydrogen produces sulfur monoxide. The sulfur monoxide is transferred to a reaction chamber which is when it reacts with ozone and then produces sulfur dioxide and light. The light is detected by a photo multiplier tube and the intensity of the signal gives the amount of the sulfur present in the sample as it is directly proportional.

Furnace: $R-S + O_2 \rightarrow SO_2 + H_2 + \text{other products of combustion}$
 $SO_2 + H_2 \rightarrow SO + H_2O$

Reaction Cell: $SO + O_3 \rightarrow SO_2^* + O_2$
 $SO_2^* \rightarrow SO_2 + \text{UV light}$

In a GC the sample solution is injected and then a stream of gas transports the sample into a separation column, this gas is called as a carrier gas and helium or nitrogen is used. After

separation the detector determines the number of components that elute out of the column. The standard sample peak retention time and peak area are compared with the test sample and thus the concentration is calculated. The instrumentation and the parts of this equipment is depicted in Fig. 8. In this case the detector used is sulfur chemiluminescence detector. The detector utilizes a double plasma burner to accomplish high temperature ignition of sulfur-containing mixes to form sulfur monoxide (SO). A photomultiplier tube recognizes the light delivered by the chemiluminescent response of SO with ozone. This outcomes in a direct and equimolar reaction to the sulfur mixes, without obstruction from most sample lattices. Advantages are high selectivity and sensitivity, detection limit for the trace sulfurs detection are down to ppb levels, no quenching effects, sulfur specific detection for GC, linear response is obtained [33]. The main use of this technique is detection of sulfur components in petroleum products.

3. CONCLUSION

These hyphenated techniques offer shorter analysis times, expanded automation, higher sample throughput, better reproducibility, and diminished contamination. The momentous upgrades seen in these methods are required to improve joined selectivity and increment the measure of bonafide information received while

there may be a lot of advantages to these methods a major drawback is that it is very high-cost process. These techniques have huge applications in various industrial fields and in different and diverse areas of research and development. Advances in analytical techniques for the separation and detection of substances has empowered the identification of compounds in complex mixtures, in addition to making it conceivable to acquire the metabolic profile of plants, evading the re-isolation of known compounds by the procedure of dereplication. The hyphenated techniques are a boon in the modern world because its rapid and efficient and separation and quantification is achieved simultaneously.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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