INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

**Review Article**

# Role of LC-MS in Proteomics

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ARTICLE INFO

Published: 03 Sept 2025
Keywords:
Liquid Chromatography, Mass Spectrometry, Proteomics, Bioequivalence, Metabolite research.
DOI:
10.5281/zenodo.17048064

## ABSTRACT

Liquid Chromatography/Mass Spectrometry (LC/MS) is fast developing tool and is incredibly precise and sensitive. It's a really powerful tool for detection, identification, and mass determination of components in the presence of additional components are carried out by mass spectrometry using sample eluents from liquid chromatography and mass spectrometry. Liquid chromatography is used to identify pharmaceutical medication components, intermediates, and related compounds for both quantitative and qualitative applications. Liquid chromatography is mostly used in-vitro dissolution, bioequivalence, bioavailability, and metabolite research. Liquid chromatography mass spectrometry is also used in forensic labs, agrochemical firms, fundamental research, and the food industry.

## INTRODUCTION

Genome sequencing and deoxyribonucleic acid (DNA) microarray technologies, giving rise to the "–omics" era of research. Proteomics is the logical continuation of the widely-used transcriptional profiling methodology. Proteomics involves the study of multiprotein systems in an organism, the complete protein complement of its genome, with the aim of understanding distinct proteins and their roles as a part of a larger networked system. This is a vital component of modern systems biology approaches, where the goal is to characterize the system behavior rather than the behavior of a single component LC-MS-based proteomics, complex mixtures of proteins are first subjected to enzymatic cleavage, then the resulting peptide products are analyzed using a mass spectrometer; this is in contrast to "top-down" proteomics, (1), which deals with intact proteins and is limited to simple protein mixtures. A standard bottom-up experiment has the following key steps. (a) extraction of proteins from a sample, (b) fractionation to remove contaminants and proteins that are not of interest, especially high abundance house-keeping proteins that are not usually indicative of the disease being studied, (c) digestion of proteins into peptides, (d) post-

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**Relevant conflicts of interest/financial disclosures**: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

digestion separations to obtain a more homogeneous mixture of peptides, and (e) analysis by MS(2), . The two fundamental challenges in the analysis of MS-based proteomics data are then the identification of the proteins present in a sample, and the quantification of the abundance levels of those proteins. There are a host of informatics tasks associated with each of these challenges. Proteomics plays a central role in the discovery process due to its diverse applications – mechanism of disease process, drug targets, nutritional and environmental science (3), functional genomics etc.

**INSTRUMENTATION:** Liquid chromatography – Mass spectrometry (LC-MS) High-resolution chromatographic separation is combined with focused and sensitive mass spectrum detection in the analytical technique known as LC-MS. Combining LC with MS is a significant achievement in the history of chromatography(4), . Mass spectroscopy helps provide structural clarity and helps identify the constituent elements of a sample in LC-MS

**I. LIQUID CHROMATOGRAPHY:** HPLC (High Performance Liquid Chromatography): This type of chromatography is characterized by its ability to separate mixture components through the use of a solid stationary phase and a liquid mobile phase. There are diverse categories of chemical analysis, such as affinity liquid chromatography, reverse phase chromatography, ion-exchange liquid chromatography, chiral separation, and normal phase liquid chromatography

**a. Pump:** It is made up of materials that are inert to solvents or any combination of organic solvents and an aqueous buffer. Up to 10 mL/min of high mobile phase volume is delivered by it. Syringe pumps, constant-pressure pumps, and reciprocating pumps are the three main types of pumps that are employed.

**b. Sample Injector:** A sample volume is introduced into the chromatographic system using it. Typically, one can inject a sample volume ranging from 1µL to 100µL.Up to a 2 mL volume, the injector loop can be used to enhance the injection volume. Automatic and manual injectors are the two main types of injectors that are employed. Compared to manual injectors, automatic injectors are more precise, accurate, and comfortable to use.

**c. Columns:** It is a stationary phase made up of carbon chains combined with silica material. Typically, columns with lengths ranging from 50 to 300 mm are employed. Octadecyl (C18), Octyl (C8), Cyano, Amino, and Phenyl packings are the columns used in HPLC. Depending on the type of compound that needs to be separated, different columns are used (5).

**d. Detectors and recorder:** The most crucial component of the HPLC is the detector. There are several types of detectors that are employed, including conductivity, UV-visible, PDA, electrochemical, refractive index (RI), and fluorescent detectors. The detector's signal can be recorded as a peak, and the corresponding data can be saved in software.

**II. Mass spectrometry:** An analytical method called mass spectrometry measures the mass-to-charge ratio of ionic species that are connected to the analyte that is being studied. Analytes can be thoroughly structurally elucidated as well as have their molecular mass and elemental content determined (6), using mass spectrometry (MS).

i. Ionization Sources and Interfaces
ii. Mass Analysers

**i. Ionization/Ion Source and Interfaces:** The liquid chromatography method separates liquid mixtures, most commonly consisting of methanol, acetonitrile, and water. This mixture-containing liquid is poured into the mass spectrometer's ion source. Given that the ion source is highly vacuumed, it is challenging to mass evaporate the liquid droplets without losing the component mixture because of the pressure difference. Interfaces are thus utilized to address this issue. The following is a description of the many interface types that are frequently seen in mass spectrometers.

**a. Direct liquid Introduction (DLI):** Direct Liquid Introduction (DLI), ionization is often achieved by vaporizing the solvent to produce a chemical reagent gas and ionization. Solvent systems in both the normal and reverse phases have been employed. Methanol/water and acetonitrile/water mixtures up to 60% water are the reverse-phase solvents that are used. Salt-containing buffers are generally prohibited because they increase the risk of capillary plugging during heating. Thermal energy and liquid flow rate are combined to operate Direct Liquid Introduction (DLI). Only a restricted flow rate of the liquid enters the contact. Analyte ions generated with the aid of thermal energy were subsequently introduced into the ion source via a pinhole diaphragm or capillary inlet (7,8).

**b. Atmospheric-Pressure Ionization (API):** Three main phases make up atmospheric pressure ionization (API): nebulization, evaporation, and ionization. The two primary methods of atmospheric pressure ionization (APCI) and electrospray ionization (ESI) are known as API. In atmospheric

**ii. Mass Analysers:** Ionization/Ion Source and Interfaces: The liquid chromatography method separates liquid mixtures, most commonly consisting of methanol, acetonitrile, and water. This mixture-containing liquid is poured into the mass spectrometer's ion source. Given that the ion source is highly vacuumed, it is challenging to mass evaporate the liquid droplets without losing the component mixture because of the pressure difference.

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**b. Atmospheric-Pressure Ionization (API):** Three main phases make up atmospheric pressure ionization (API): nebulization, evaporation, and ionization. The two primary methods of atmospheric pressure ionization (APCI) and electrospray ionization (ESI) are known as API. In atmospheric. Liquid chromatography coupled with mass spectrometry (pressure ionization (API), a mist of tiny droplets is created when a stream of liquid (solvent) carrying a sample is pushed through a thin capillary tube and nebulized in a huge chamber. The solvent evaporation causes the droplets to shrink and increase in surface charge. The highly charged droplets collide until

they transform into gas-phase ions. These gas-phase ions enter the low-pressure area of the ion source via the capillary (10), sampling opening. The main benefit of ESI is that it increases the amount of charge in ions by one to three when the molecule is 1000 DA or higher. As a result, the m/z ratio is consistently less than 2000.The molecular weight of peptides, proteins, biological samples, polymers, nucleotides, sugars, and organometallics can be determined using LC-MS with electrospray ionization (ESI).

**c. Atmospheric Pressure Chemical Ionization (APCI):** The two main processes in the Atmospheric Pressure Chemical Ionization process are the analyte evaporation/desolvation and the charged transfer reaction in the vapor phase, which produces the vapor phase ions.A liquid-containing sample is nebulized through a thin capillary tube and nebulized into a huge chamber in the atmospheric pressure chemical ionization process . Small droplets are created when the solvent evaporates at atmospheric pressure in a large heating chamber. There is ionization. Ionization typically occurs between 250 and 400 °C. The charges are subsequently transferred from the ions to the molecules via chemical processes. The mass analyzer's capillary aperture allows the resultant ions to pass through. For less polar and non-polar analytes with modest molecular weights, it is commonly employed. Chemical ionization at atmospheric pressure is used in MS analysis of samples pyrolyzed under controlled conditions. Analysis of moderately polar, non-labile materials can be done using online LC-MS using a heated pneumatic nebulizer interface in conjunction with APCI. Samples and biopolymers that are highly polar, thermolabile, and ionic require electrospray ionization at atmospheric pressure in addition to on-line separation by LC or CE. Atmospheric pressure ionization's formerly sluggish progress has been hastened by the ability to determine the molecular mass of proteins, nucleic acids, and other polymers via electrospray ionization.

**d. Electrospray Ionization (ESI):** The liquid sample used in electrospray ionization (ESI) was run through a stain-resistant steel capillary tube that was kept at a high positive or negative electric potential (approximately 3-5 kV). This leads to the formation of charged droplets at the capillary tip, which vaporize later. The solvent evaporation causes the droplets to shrink and increase in surface charge. The highly charged droplets collide until they transform into gas-phase ions (11), . These gas-phase ions enter the low-pressure area of the ion source via the capillary sampling opening.14 The main benefit of ESI is that it increases the amount of charge in ions by one to three when the molecule is 1000 DA or higher. As a result, the m/z ratio is consistently less than 2000.

**e. Thermo-spray and Plasma spray Ionization (TSPI):** Thermo-spray serves as both an ionization source and a liquid intake device. A variation on thermal spray is plasma spray. Thermo-spray involves passing a liquid sample solution through a heated capillary tube, causing the solvent to evaporate. The droplets that are charged form. The droplets get smaller and smaller as the solvent evaporates. On the surface of droplets, the density of electric charge rises. After that, the ions are sent into a mass spectrometer that uses an electrostatic voltage system.

Ions are not produced by the plasma spray per sec; instead, they are produced in the thermal spray. The quantity of ions can be enhanced by plasma or corona discharge(12) . The neutral molecules become increasingly ionized as a result of the electric discharge. This improvement causes the

molecule to ionize more. Because of its increased sensitivity, the plasma spray technique is frequently employed in clinical and medical analyses.

**f. Atmospheric pressure photo Ionization (APPI):** Using photons to excite and ionize the molecules is known as atmospheric pressure photoionization, or APPI. Analyte ionization from eluent and excitation are the two primary processes in atmospheric pressure photoionization (APPI). The eluent from LC vaporizes into gaseous phase, much as atmospheric pressure chemical ionization (APCI) in atmospheric pressure photo ionization. The APPI generates photons using a Kr lamp. High intensity photons produced by a Kr lamp are used to excite and ionize molecules. In order to reduce analyte ionization, the energy range is chosen. After that, the ionized analytes are put into the mass spectrometer (m/z) through a capillary aperture.

**g. Particle Beam Ionization:** In order to separate the solvent from the solute with the least amount of solute loss possible, Browner and his colleagues created the particle beam interface. Nebulization and evaporation share similarities with atmospheric pressure chemical ionization (APCI), thermospray (TSP), and electrospray ionization (ESI) processes (13), Eluent is delivered through a small tube into this liquid that has been separated from the HPLC or LC. Helium gas is injected into the liquid, causing a high-velocity spray of liquid droplets to form. The heating chamber is where the liquid droplets from the nebulizer get smaller and smaller as the solvent starts to evaporate. A beam of particles known as the spray of liquid droplets emerges from the heating chamber. After that, the beam goes through an ionization chamber in a manner akin to atmospheric pressure chemical ionization (APCI) and electrospray ionization (ESI).

**III. Mass Analyzer:** Following ionization, the ions are moved to a mass analyzer, where they are separated based on their mass-to-charge (m/z) ratio. The mass analyzer is typically used to measure the object's reaction, speed, time, and rate.

a. Quadrupole
b. Time of flight
c. Ion trap
d. FTICR (Fourier transfer ion cyclotron resonance)

**a. Quadrupole Mass Analyzer:** The most practical and widely used mass analyzer is this one. It is made up of two plains with parallel rods that are positioned between a detector and an ion source. The mass analyzer, or the ion separation process based on m/z in time or space. Four hyperbolic or cylindrical rods arranged in a radial array parallel to one another make up the linear quadrupole mass analyzer. An oscillating radio frequency alternating current (RF) voltage is superimposed on opposite rods that are charged in a +ve or -ve direct current (DC) potential (14) . When DC and RF are combined and applied to the rods, the ions of a specific m/z have stable paths and are sent in the direction of the detector. Conversely, ions with an unstable mass and energy are released onto the rods. The ions that were added to the quadrupole using a modest accelerating potential imply. As the ions pass through the quadruple filter, they oscillate in a plane that is perpendicular to the rod length. Consequently, by providing DC and RF power at a consistent ratio, ions carrying m/z will flow in the direction of the detector. The ratio of the DC to RF potential determines the resolution. The quadrupole can scan at up to 1000 m/z and is often operated at less than 4000 m/z. Because of the unit mass resolution, mass accuracy is rarely greater than 0.1 m/z.

**b. Time of flight analyzer (TFA):** The moment the most reliable application of flight is in a wide range of ion sources and inlet systems. There is no magnetic field here, so electrostatic maintenance and calibration are straightforward and uncomplicated. After being removed from the source, the ions are exposed to an accelerating voltage. The mass of the ion and its charge determine how long the drift or flight will take to complete (15), . For singularly charged ions (z = 1, m/z = w), the duration required to arrive at the mass of the ions determines the detector. Lighter ions will strike the detector first when they trend in that direction. All of the ions are simultaneously scanned and identified. It is possible to employ extremely fast mass range scanning for very large m/z values. Figure 6 below displays the Time Flight mass analyzer schematic diagram.

## IV. Detectors

One crucial component of a mass spectrometer is the detector, which generates current in direct proportion to the number of ions that strike it. After the ions are created and exit the analyzer, they must be found and converted into a signal. The types of detectors that are frequently used are described below.

### a. Point Ion Collectors Detectors

In this, the mass spectrometer's ion collectors are positioned at a fixed point. Every ion is concentrated on the detector, which is positioned in a single spot. The data can be recorded along with the arrival of ions through the electric current flow(16) . The number of ions that reach the point ion detector determines how much electric current flows there.

### b. Array Detector

A group of point collectors arranged in a plane is called an array detector. In an array detector, the ions arrive at a spot or across a plane. Using a point ion collector, the ions with mass-to-charge (m/z) values are separated and recorded along a plane. In an array detector, spatially distinct ions having a mass range are concurrently detected (17,18)

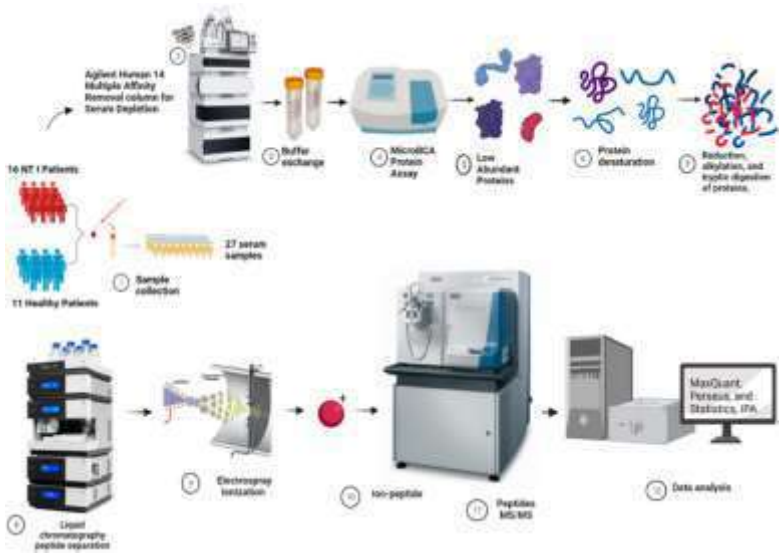

**Fig 1.0 Summarises the sample preparation and analysis of NT1 proteins, tryptic digestion of proteins into peptides, LC-MS analysis of peptides processing**

**Applications:**

**1. Quantitative Bioanalysis of various Biological Samples:**

LC-MS/MS methodology includes sample preparation, separation of components and MS/MS detection and applications in several areas such as quantification of biogenic amines, pharmacokinetics of immunosuppressants and doping control (19). Advancement including automation in the LC-MS/MS instrumentations along with parallel sample processing, column switching, and usage of more efficient supports for SPE, which drives the trend towards less sample clean-up times and total run times–high-throughput methodology-in today's quantitative bio analysis area. Newly introduced techniques such as ultra-performance liquid chromatography with small particles (sub-2μm) and monolithic chromatography offer improvements in speed, resolution and sensitivity compared to conventional chromatographic techniques.

**2. Qualitative and Quantitative Analysis of Complex Lipid Mixtures:**

It is a LC-MS-based methodology for the investigation of lipid mixtures (20) where it has described, and its application to the analysis of human lipoprotein-associated lipids is demonstrated. After an optional initial fractionation on Silica 60, normal-phase HPLC-MS on a YMC PVA-Sil column is used first for class separation, followed by reversed-phase LC-MS or LC-tandem mass spectrometry using an Atlantis dC18 capillary column, and/or nanospray MS, to fully characterize the individual lipids. The methodology which was applied here is for the analysis of human apolipoprotein B-associated lipids. This approach allows for the determination of even low percentages of lipids of each molecular species and showed clear differences between lipids associated with apolipoprotein B-100-LDL isolated from a normal individual and those associated with a truncated version, apolipoprotein B-67-containing lipoproteins, isolated from a homozygote patient with familial hypobetalipoproteinemia. The methods described should be easily adaptable to most modern MS instrumentation.

**3. Peptide Mapping :**

Confirmation of the expression of recombinant proteins is important from the quality control viewpoint. Some of the methods applied for this include analysis of amino acid sequence by peptide sequencer and other simpler methods such as peptide mapping by HPLC or mass mapping by MALDI-TOF MS. For example, Protein analysis and peptide mass mapping of a model sample of horse heart myoglobin is done by LC/MS using a quadrupole mass spectrometer.

**4. In Determination of Molecular Weight:**

The molecular weights of known and unknown chemicals are determined using LC-MS. It offers details on the molecular weight, composition, identity, and amount of sample constituents. The molecular masses of proteins, nucleic acids, polymers, and peptides can be determined using LC-MS.

**5. In Determination of Assay of Drug and Intermediates:**

In the pharmaceutical sector, LC-MS is used to determine the assay of drug substances, drug products, intermediates, and chemicals associated with them.

**6. LC-MS in Doping Test:**

The 4-Methyl-2-hexaneamine doping agent can be detected in urine using the LC/ESI-MS in positive mode. When analyzing the urine samples, an internal standard of tuaminoheptane is added. The unknown substance is thought to be 4-methyl-2-hexaneamine, an analog found in

nutritional supplements and presumed main amine. The standard, 4-methyl-2-hexaneamine, has two unresolved peaks at RT 3.43 and 3.78 minutes that are the same as those of the unidentified molecule

**7. Clinical chemistry and toxicology:**

For certain clinical chemistry and toxicology analytes, liquid chromatography (LC) paired with tandem mass spectrometry (MS/MS) offers eloquent advantages over traditional testing by immunoassays. The tested analytes include oestradiol, testosterone, thyroid hormones, immunosuppressants, vitamin D, steroids for newborn screening programs, and clinical and forensic toxicology. While immunoassays are commonly used in the clinical laboratory, the analytical sensitivity and specificity are inferior for many of the analytes tested in routine clinical laboratories. Moreover, LC–MS/MS can be multiplexed for high testing throughput and multiple analyte detection.

**8. Proteomics:**

The spectacular development of instrumentation for LC-MS of peptides over the last decade has almost left protein sample preparation, including extraction and digestion, as the one major critical point in proteomic workflows in the overall performance of proteomic experiments. Cleanness of samples in relation to non-protein contaminants dramatically affects the protein identification rate.

**9. Pharmacovigilance:**

Pharmacovigilance which is referred to as Drug Safety. It is one of the pharmacological sciences which relates to the collection, detection, assessment, monitoring, and also prevention of adverse side effects with pharmaceutical products. The detection and monitoring can be done by LC-MS based disease modifying technique which provides detailed profiles.

**10. Proteins Nanoflowers:**

Analytical method of LCMS can be employed for the detection of General nanoflowers. It helps in the development of drug delivery systems, biosensors, biocatalysts, and bio - related devices is anticipated to take multiple directions. New synthesis principles, new types of hybrids nanoflowers, and detailed mechanisms are expected to emerge. The application of nanoflowers in bio-catalysis and enzyme mimetics, tissue engineering, and the design of highly sensitive bio-sensing kits, as well as industrial bio-related devices with advanced functions, various and controllable syntheses, biocompatibility, and modifications of hybrid nanoflower structures and properties, should receive increasing attention.

**11. Phytochemicals:**

To conduct a study on ingredient difference phenotypic cloning, LCMS analyses the composition and classification of several groups of cultivated plant cells and chooses the two groups with the greatest variation in ingredient content. Characterization and Identification of Compounds Carotenoids: Since carotenoids are not heat-stable, reversed-phase HPLC, in particular, is typically used to separate mixtures and remove contaminants rather than gas chromatography.

**12. Two Dimensional (2-D) Hyphenated Technology:**

With its application in a multitude of analytical and bioanalytical techniques for the analysis of proteins, amino acids, nucleic acids, carbohydrates, lipids, peptides, etc., as well as in

the primary classification in the fields of genomics, lipidomics, metabolomics, proteomics, etc., LCMS has developed into a potent two-dimensional (2D) hyphenated technology. The initial preference for LCMS may have stemmed from the need for more potent analytical and bioanalytical procedures that could definitively and specifically separate the target analytes from high-complexity mixtures.

**13. LC-MS in Proteomics:**

Biomarker discovery, disease mechanism studies (e.g., cancer, Alzheimer's).Drug target validation. Functional analysis of proteins and pathways, post-translational modification analysis (e.g., phosphorylation, glycosylation).

**14. Other applications:**

In pharmacokinetics Drug metabolism, excretion, and absorption are all studied using LC-MS. For the quantitative and structural elucidation of pharmaceuticals and their metabolites in biological samples (plasma, urine, saliva, serum, etc.), bioanalytical procedures are employed. In Bioavailability and Bioequivalence study Comparative bioequivalence studies that analyze medications or metabolites quantitatively in the biological matrix, pharmacodynamics, clinical trials, and in vitro dissolution tests

**Advantages**

- High sensitivity and specificity
- Ability to detect thousands of proteins in one run
- Suitable for complex biological samples
- Requires complex instrumentation and expertise
- Data interpretation can be computationally intensive
- Dynamic range of protein expression in biological samples can be a limitation

**Future Scope**

- Single-cell proteomics using advanced LC-MS systems.
- Real-time clinical diagnostics.
- Improved accuracy

## CONCLUSION:

Liquid Chromatography–Mass Spectrometry (LC–MS) has become a cornerstone in modern proteomics due to its high sensitivity, specificity, and ability to analyze complex protein mixtures. It enables the identification, characterization, and quantification of thousands of proteins in a single experiment, making it invaluable for biomarker discovery, disease diagnostics, drug development, and systems biology. The combination of powerful separation techniques with advanced mass spectrometric detection allows detailed insights into protein expression, post-translational modifications, and protein–protein interactions. Although challenges such as data complexity, reproducibility, and dynamic range limitations still exist, continuous advancements in instrumentation, bioinformatics, and sample preparation are overcoming these barriers. Overall, LC–MS has revolutionized proteomics and will continue to play a central role in advancing biological and clinical research.

## ACKNOWLEDGMENT

The authors are thankful to the management of Gokaraju Rangaraju College of harmacy for providing facilities.

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HOW TO CITE: M. Prathibha Bharathi, K. Malleshwari, D. Vijaya Durga, T. Bhavana, B. Madhavi, Role of LC-MS in Proteomics, Int. J. of Pharm. Sci., 2025, Vol 3, Issue 9, 384-394. https://doi.org/10.5281/zenodo.17048064