iJRASET
International Journal For Research in Applied Science and Engineering Technology

INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY

Volume: 11 **Issue:** VI **Month of publication:** June 2023

DOI: https://doi.org/10.22214/ijraset.2023.53931

www.ijraset.com

Call: 08813907089 | E-mail ID: ijraset@gmail.com

International Journal for Research in Applied Science & Engineering Technology (IJRASET)
ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor: 7.538
Volume 11 Issue VI Jun 2023- Available at www.ijraset.com

Exploring the Versatility of LC-ESI-MS/MS: Fundamentals, Applications, and Advancements at the Forefront of Analytical Science

Himanshu Sharma[1], C.P.S. Verma[2], Shanu Priya[3], Amardeep Ankalgi[4], Aditi Kaushik[5], M.S. Ashawat[6]
[1, 2, 3, 4, 5, 6]*Laureate Institute of Pharmacy, Kathog, Himachal Pradesh*

Abstract: ***This comprehensive review paper focuses on LC-ESI-MS/MS, a powerful analytical technique widely used in various scientific disciplines. It begins by explaining the working mechanisms and components of LC-ESI-MS/MS highlighting advancements in sensitivity, resolution, speed and data analysis. This paper explores the diverse applications of LC-ESI-MS/MS in pharmaceutical analysis, environmental analysis, metabolomics, and proteomics, discussing its advantages and limitations in each area. The review also emphasizes the integration of LC-ESI-MS/MS with other techniques like GC-MS, CE-MS, and MALDI-MS, showcasing their combined effects and enhanced capabilities. It presents recent developments and innovations in LC-ESI-MS/MS technology including improvements in sensitivity, resolution and data analysis. This paper discusses emerging trends in sample preparation, ionization methods, chromatographic columns, and mass spectrometry detectors. Addressing the challenges and limitations, the review identifies potential areas for improvement and future research directions. It emphasizes the untapped potential of LC-ESI-MS/MS in advancing scientific knowledge and solving complex analytical problems, calling for further collaboration and research in the field. In conclusion, this review paper provides a comprehensive overview of LC-ESI-MS/MS, emphasizing its fundamental principles, applications, recent innovations, and future perspectives. The findings underscore the significance of LC-ESI-MS/MS in modern science and its potential for further advancements.***

Keywords: LC-ESI-MS/MS, Liquid Chromatography-Electrospray Ionization Tandem Mass Spectrometry, Recent Developments, Innovations, Hyphenated Techniques, Synergistic Approaches, Mass Spectrometry Detectors, Data Acquisition, Data Analysis, Challenges, Future Perspectives,

I. INTRODUCTION

LC-ESI-MS/MS (Liquid Chromatography-Electrospray Ionization-Tandem Mass Spectrometry) has emerged as a powerful hyphenated analytical technique in modern science offering exceptional sensitivity, selectivity and versatility for the analysis of complex samples. The combination of liquid chromatography (LC), electrospray ionization (ESI), and tandem mass spectrometry (MS/MS) has revolutionized the field of analytical chemistry, enabling researchers to investigate various compounds in various scientific disciplines.

The fundamental principle of LC-ESI-MS/MS involves the separation of analytes using liquid chromatography followed by ionization of the separated analytes using electrospray ionization and their subsequent analysis by tandem mass spectrometry. This hybrid technique provides multiple stages of mass analysis including precursor ion selection, fragmentation, and product ion detection allowing for accurate identification, quantification, and structural elucidation of target analytes. [1]

The significance of LC-ESI-MS/MS in modern science stems from its broad applications and ability to address complex analytical challenges. From pharmaceutical analysis and environmental monitoring to metabolomics and proteomics, LC-ESI-MS/MS has found extensive utility across diverse scientific disciplines.

In pharmaceutical industry, LC-ESI-MS/MS plays a crucial role in drug discovery, development and quality control. It enables the analysis of drug compounds and their metabolites in biological fluids, facilitating pharmacokinetic studies, bioequivalence assessments, and therapeutic drug monitoring. Moreover, LC-ESI-MS/MS is invaluable in detecting impurities and degradants in pharmaceutical formulations, ensuring the safety and efficacy of drug products.

Environmental analysis also greatly benefits from the capabilities of LC-ESI-MS/MS. The technique enables the detection and quantification of environmental contaminants such as pesticides, pharmaceuticals and persistent organic pollutants in complex matrices like water, soil and air samples. LC-ESI-MS/MS can provide valuable insights into the fate and transport of these contaminants, aiding in environmental risk assessment and pollution control strategies.

Metabolomics, a rapidly growing field, relies on LC-ESI-MS/MS for comprehensive profiling of endogenous metabolites in biological samples.

By analyzing the metabolome, LC-ESI-MS/MS helps in understanding metabolic pathways, identifying biomarkers of diseases, and investigating drug metabolism.

The high sensitivity and selectivity of LC-ESI-MS/MS allow for the detection of low abundance metabolites, facilitating the exploration of metabolic alterations associated with various physiological and pathological conditions.

Proteomics, the study of proteins and their functions, also benefits from LC-ESI-MS/MS analysis. LC-ESI-MS/MS enables the identification and quantification of proteins in complex biological samples, paving the way for deciphering protein expression patterns, protein-protein interactions, and post-translational modifications. It plays a crucial role in biomarker discovery, elucidating disease mechanisms, and advancing our understanding of cellular processes. [2]

In recent years, LC-ESI-MS/MS has witnessed remarkable advancements and refinements. Instrumentation has become more sophisticated, offering higher resolution, faster scan speeds, and enhanced sensitivity. Advanced mass analyzers such as quadrupole-time-of-flight (Q-TOF) and Orbitrap analyzers provide accurate mass measurements and enable targeted and untargeted analyses with high confidence.

Moreover, sample preparation techniques have evolved, optimizing extraction, purification, and enrichment procedures for various sample types. Novel ionization techniques including ambient ionization methods have expanded the applicability of LC-ESI-MS/MS, allowing direct analysis of samples without extensive sample preparation steps.

In addition to these developments, the integration of LC-ESI-MS/MS with other hyphenated techniques such as gas chromatography-mass spectrometry (GC-MS), capillary electrophoresis-mass spectrometry (CE-MS), and matrix-assisted laser desorption/ionization-mass spectrometry (MALDI-MS) has created powerful analytical platforms with synergistic effects. These combined approaches enhance separation, selectivity and detection capabilities, opening new avenues for complex sample analysis and multidimensional profiling.

However, despite its numerous advantages, LC-ESI-MS/MS faces certain challenges. Matrix effects such as ion suppression and enhancement can significantly affect the accuracy and precision of quantitative analysis. Compound identification, particularly for unknown or novel compounds, remains a challenge due to the complex nature of the mass spectrometry data interpretation. Furthermore, the high complexity and dynamic range of biological samples pose analytical difficulties, requiring advanced data processing and analysis strategies.

Looking to the future, addressing these challenges and exploring new perspectives in LC-ESI-MS/MS is crucial for its continued advancement and widespread adoption. Efforts are being made to develop robust methodologies for overcoming matrix effects, including the use of isotopically labeled internal standards, calibration curves, and matrix-matched calibration.

Furthermore, advancements in data analysis including the application of machine learning algorithms and spectral libraries are aiding in the identification of unknown compounds and improving the reliability of LC-ESI-MS/MS analyses. The construction of comprehensive spectral libraries encompassing various compound classes and structures is vital for accurate compound identification and confident data interpretation.

The future of LC-ESI-MS/MS also relies on continuous advancements in instrumentation and technology. Instrument manufacturers are continually striving to improve sensitivity, resolution, and scan speeds. Novel ionization techniques coupled with advanced mass spectrometry detectors offer new opportunities for expanding analytical capabilities of LC-ESI-MS/MS.

Moreover, multidisciplinary collaborations and data sharing play a pivotal role in the future of LC-ESI-MS/MS. Collaborations between researchers from diverse fields including chemistry, biology, bioinformatics and data science foster innovation and drive the development of novel applications and analytical strategies. Open-access databases and data repositories facilitate the sharing of LC-ESI-MS/MS data, leading to the standardization of workflows, the validation of scientific findings, and the advancement of analytical methodologies.

In conclusion, LC-ESI-MS/MS has become an indispensable tool in modern science offering exceptional capabilities for analysis of complex samples across various scientific disciplines.

The continuous research and development in LC-ESI-MS/MS technology coupled with collaborations, data sharing and innovative analytical strategies will unlock new opportunities, address challenges and shape the future of this powerful technique. By advancing LC-ESI-MS/MS, we can unlock new insights, facilitate breakthrough discoveries, and contribute to scientific advancements in fields ranging from pharmaceuticals and environmental monitoring to metabolomics and proteomics.

ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor: 7.538
Volume 11 Issue VI Jun 2023- Available at www.ijraset.com

II. FUNDAMENTALS OF LC-ESI-MS/MS

Liquid Chromatography-Electrospray Ionization-Tandem Mass Spectrometry (LC-ESI-MS/MS) is a hyphenated analytical technique that combines the separation power of liquid chromatography (LC) with the sensitive detection and structural elucidation capabilities of tandem mass spectrometry (MS/MS). This powerful technique has revolutionized the field of analytical chemistry enabling a comprehensive analysis of complex samples across various scientific disciplines.

The basic principle of LC-ESI-MS/MS involves three main steps: sample introduction and separation using liquid chromatography, ionization of separated analytes using electrospray ionization, and their subsequent analysis by tandem mass spectrometry. Let's delve deeper into each of these fundamental aspects:

A. Liquid Chromatography (LC)

Liquid chromatography is a separation technique that uses a liquid mobile phase to separate analytes based on their physicochemical properties. In LC-ESI-MS/MS, the sample typically dissolved in a suitable solvent is introduced into the LC system. The sample is then injected onto a chromatographic column where separation occurs based on the differential interactions between the analytes and the stationary phase of the column.

Different LC modes such as reversed-phase, normal-phase, ion-exchange, and size-exclusion chromatography can be employed based on the nature of the analytes and the separation requirements. Reversed-phase chromatography, which involves a hydrophobic stationary phase and a polar mobile phase, is the most commonly used mode in LC-ESI-MS/MS due to its versatility and compatibility with many analytes. [3]

The choice of LC column, column dimensions and mobile phase composition greatly influence the separation efficiency, resolution and sensitivity of the analysis. Researchers optimize these parameters to achieve optimal separation of target analytes considering factors such as analyte polarity, molecular weight, and sample matrix complexity.

B. Electrospray Ionization (ESI)

Electrospray ionization is a soft ionization technique used to convert analyte molecules into gas-phase ions suitable for subsequent mass spectrometric analysis. In LC-ESI-MS/MS, the eluting analytes from the LC column enter the ionization source where they are subjected to a high voltage, typically in the range of 3-5 kilovolts.

As the eluent is nebulized, solvent evaporation occurs generating highly charged droplets. These droplets undergo further desolvation resulting in the formation of analyte ions. The ions produced in gas phase are then transferred into the mass spectrometer for analysis. [4]

Electrospray ionization is particularly advantageous for LC-ESI-MS/MS due to its ability to ionize a wide range of analytes including polar and nonpolar compounds with high sensitivity. It offers excellent reproducibility and ionization efficiency, making it suitable for both quantitative and qualitative analyses.

C. Tandem Mass Spectrometry (MS/MS)

Tandem mass spectrometry involves the use of multiple stages of mass analysis to obtain more detailed information about analyte ions. In LC-ESI-MS/MS, the ions generated in the ionization source are subjected to a series of mass spectrometric scans including precursor ion selection, fragmentation, and product ion detection.

In the first stage of MS/MS, precursor ions of interest are selectively isolated based on their mass-to-charge ratio (m/z) using mass analyzers such as quadrupoles or ion traps.

These precursor ions are then subjected to collision-induced dissociation (CID) where they collide with inert gas molecules leading to their fragmentation.

The resulting fragments are then analyzed in the second stage of mass spectrometry, allowing for the determination of structural information and identification of the analytes. Multiple reaction monitoring (MRM) is a commonly used technique in LC-ESI-MS/MS where specific precursor-product ion pairs are monitored to achieve high selectivity and sensitivity in quantitative analysis. [5]

By combining LC, ESI and MS/MS, LC-ESI-MS/MS provides a comprehensive analytical platform that enables separation, detection and structural elucidation of various analytes. The next snippets will further explore the key components and instrumentation involved in LC-ESI-MS/MS and recent advancements and refinements in the technique.

ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor: 7.538
Volume 11 Issue VI Jun 2023- Available at www.ijraset.com

D. LC-ESI-MS/MS Instrumentation

The successful implementation of LC-ESI-MS/MS relies on the integration of various components and instrumentation. These include the LC system, ESI source, mass analyzer, and data acquisition system. [6] Let us delve into each of these components:

1) *LC System:* The LC system consists of pumps, injectors, and a chromatographic column. The pumps deliver the mobile phase at a constant flow rate, while injectors introduce the sample onto the column. The column with its stationary phase facilitates the separation of analytes based on their interactions with stationary and mobile phases.
2) *ESI Source*: The ESI source plays a critical role in ionizing the analytes. It typically consists of a capillary through which the LC eluent passes and an emitter at the tip where the electrospray is formed. The ESI source also includes nebulizing gas such as nitrogen to aid in the generation of charged droplets.
3) *Mass Analyzer:* Various types of mass analyzers can be employed in LC-ESI-MS/MS, including quadrupoles, time-of-flight (TOF) analyzers, ion traps, and hybrid instruments combining multiple analyzers. Quadrupoles are commonly used for the precursor ion selection, while TOF analyzers provide accurate mass measurements and high-resolution capabilities. Ion traps enable MS/MS fragmentation and subsequent product ion analysis.
4) *Data Acquisition System:* The data acquisition system controls the operation of LC-ESI-MS/MS instrument and collects the acquired data. It includes software for instrument control, data acquisition, and data processing. The software enables the selection of precursor ions, the acquisition of MS/MS spectra, and subsequent data analysis and interpretation.

E. Recent Advancements and Refinements:

LC-ESI-MS/MS has undergone significant advancements and refinements in recent years, enhancing its capabilities and expanding its applications. Here are some notable developments:

1) *High-Resolution Mass Spectrometry:* The integration of high-resolution mass analyzers such as Orbitrap and FT-ICR has significantly improved the mass accuracy and resolving power of LC-ESI-MS/MS. High-resolution mass spectrometry enables precise mass measurements and enhanced selectivity, particularly in complex sample matrices.
2) *Advanced Ionization Techniques:* Novel ionization techniques such as atmospheric pressure chemical ionization (APCI), atmospheric pressure photoionization (APPI), and desorption electrospray ionization (DESI), have expanded the ionization capabilities of LC-ESI-MS/MS. These techniques offer complementary ionization mechanisms and improve the analysis of challenging analytes.
3) *Miniaturization and Microfluidics:* Miniaturization of LC-ESI-MS/MS systems coupled with microfluidic devices has enabled high-throughput and point-of-care analyses. Microscale LC columns and integrated sample handling systems reduce sample and solvent consumption while maintaining analytical performance.
4) *Advances in Data Analysis:* The increasing complexity of LC-ESI-MS/MS data necessitates advanced data processing and analysis techniques. This includes the development of algorithms for peak detection, compound identification, and quantification. Furthermore, the integration of informatics tools and databases enhances metabolite annotation and facilitates data sharing and collaboration.
5) *Hybrid Techniques:* The combination of LC-ESI-MS/MS with other analytical techniques such as gas chromatography (GC), supercritical fluid chromatography (SFC), and capillary electrophoresis (CE) has enabled multidimensional profiling and expanded the coverage of analytes. [7] These hyphenated techniques offer complementary separation mechanisms and enhance the overall analytical capabilities.

Continued advancements and refinements in LC-ESI-MS/MS technology hold great potential for improving sensitivity, resolving power, speed, and data analysis capabilities. The next section will explore emerging trends and innovations in sample preparation, ionization methods, chromatographic columns, and mass spectrometry detectors.

F. Sample Preparation Techniques

The sample preparation plays a crucial role in the success of LC-ESI-MS/MS analysis. [8] The effective sample preparation ensures removal of interfering substances, enhances analyte recovery, and minimizes matrix effects. Here are some recent advancements in sample preparation techniques:

1) *Solid Phase Extraction (SPE):* SPE is widely used for analyte extraction and purification. Advances in sorbent materials such as mixed-mode and molecularly imprinted polymers have improved selectivity and sensitivity. Automated SPE systems streamline the process, reducing manual labor and improving reproducibility.

2) *Sample Derivatization:* Derivatization techniques are employed to improve the chromatographic behavior and ionization efficiency of analytes. Recent developments focus on derivatization strategies that are rapid, selective, and compatible with LC-ESI-MS/MS analysis. Examples include the use of reactive tagging reagents and in situ derivatization approaches.
3) *Microextraction Techniques:* Microextraction techniques such as solid-phase microextraction (SPME) and microextraction by packed sorbent (MEPS) offer a miniaturized and efficient sample preparation. These techniques minimize sample volume, reduce solvent consumption, and enhance analyte enrichment.
4) *Online Sample Preparation:* Online sample preparation techniques such as online solid-phase extraction (SPE) and online digestion have gained attention for their ability to streamline the workflow and improve automation. These approaches minimize sample handling steps, reducing the risk of contamination and improving throughput.

G. Ionization Methods

While electrospray ionization (ESI) is the most commonly used ionization method in LC-ESI-MS/MS, alternative ionization techniques have emerged offering unique advantages in certain applications. [9]

Here are some notable developments:

1) *Atmospheric pressure chemical ionization (APCI)***:** APCI is an alternative ionization technique that operates at higher gas flow rate and higher temperature compared to ESI. It is particularly useful for the analysis of nonpolar and thermally stable compounds. APCI offers complementary ionization mechanisms and improved ionization efficiency for certain analytes.
2) *Atmospheric pressure photoionization (APPI):* APPI uses photon irradiation to ionize analytes, making it suitable for compounds with low ionization potentials and high molecular absorption cross sections. It provides enhanced sensitivity for compounds that absorb in ultraviolet (UV) and vacuum ultraviolet (VUV) regions.
3) *Desorption Electrospray Ionization (DESI):* DESI is a versatile ambient ionization technique that enables the direct analysis of samples in their native state including surfaces and tissues. It offers spatially resolved analysis and has found applications in metabolomics, imaging mass spectrometry, and pharmaceutical analysis.
4) *Laser ablation electronization (LAESI):* LAESI combines laser ablation with ESI, enabling direct sampling and ionization of solid samples. This technique allows for analysis of complex samples such as tissues and biological materials without extensive sample preparation.

H. Chromatographic Columns

The choice of chromatographic columns in LC-ESI-MS/MS greatly influences separation efficiency, resolution and sensitivity. Recent developments in column technology have improved the performance and compatibility with LC-ESI-MS/MS. Some notable advancements include

1) *Sub-2 µm Particle Columns:* The use of sub-2 µm particle columns offers improved efficiency and faster separations. These columns allow for higher resolution and sensitivity, particularly for complex samples. [10] Additionally, advancements in column packing techniques and bonding chemistry have further improved column performance.
2) *Monolithic Columns:* Monolithic columns characterized by their interconnected porous structure, provide high permeability and low backpressure. They offer fast separations and are especially suitable for high-throughput analysis. Monolithic columns are gaining popularity in proteomics, metabolomics, and pharmaceutical analysis.
3) *Hybrid Columns:* Hybrid columns such as superficially porous and core-shell particles combine the advantages of fully porous particles with reduced pressure drops. These columns offer enhanced separation efficiency and increased sample loading capacity contributing to improved sensitivity and speed.
4) *Stationary Phase Innovations***:** Advances in stationary phase chemistry have expanded the selectivity and applicability of LC-ESI-MS/MS. New sorbents including various functionalized silica-based materials and alternative organic polymers provide tailored selectivity for different analyte classes. Surface modifications and stationary phase coatings have also been developed to minimize analyte-metal interactions and improve peak shapes.

Continued advancements in sample preparation techniques, ionization methods and chromatographic columns have further improved the performance and applicability of LC-ESI-MS/MS. The next snippets will explore the diverse range of applications where LC-ESI-MS/MS has been used and the advantages and limitations of the technique.

I. Mass Spectrometry Detectors

The choice of mass spectrometry (MS) detector in LC-ESI-MS/MS is critical for achieving accurate and sensitive analysis. Recent advancements in MS detector technology have focused on improving the sensitivity, dynamic range, and data acquisition speed. [11] Here are some notable developments:

1) *Triple Quadrupole (QqQ) Detectors:* Triple quadrupole mass spectrometers are widely used in LC-ESI-MS/MS for their exceptional sensitivity and selectivity. Recent improvements include higher transmission efficiency, faster scan speeds and enhanced collision cell designs enabling more efficient MS/MS fragmentation and detection of low-abundance analytes.
2) *Orbitrap Detectors:* Orbitrap-based mass spectrometers offer high-resolution and accurate mass measurements, enabling precise identification and quantification of analytes. Recent advancements have focused on improving scan rates, increasing the dynamic range, and enhancing signal-to-noise ratios for complex samples. Hybrid instruments combining Orbitrap with other analyzers further expand the capabilities of LC-ESI-MS/MS.
3) *Time-of-Flight (TOF) Detectors:* TOF detectors provide rapid data acquisition, wide mass range, and high sensitivity. Advances in TOF technology have led to improved mass accuracy, resolution, and sensitivity, particularly in the high-mass region. Coupling TOF detectors with other analyzers such as quadrupoles or ion mobility spectrometry enables enhanced selectivity and structural characterization.
4) *Ion Mobility Spectrometry (IMS) Detectors:* IMS detectors separate ions based on their size, shape, and charge, providing an additional dimension of separation in LC-ESI-MS/MS analysis. Recent developments in IMS technology have improved resolution, sensitivity, and data acquisition rates. The combination of IMS with other analyzers enhances structural characterization and improves identification capabilities.

J. Data Acquisition and Analysis

Efficient data acquisition and analysis are crucial for extracting meaningful information from LC-ESI-MS/MS experiments. Recent advancements in data processing and analysis have focused on improving accuracy, speed, and ease of use. [12] Here are some notable developments:

1) *Data-independent acquisition (DIA):* DIA methods acquire MS/MS spectra for all detectable ions within a defined mass range, allowing a comprehensive data collection for retrospective analysis. Recent developments in DIA techniques such as SWATH-MS have improved selectivity and reproducibility enabling large-scale profiling and targeted quantification.
2) *Data Processing Algorithms:* Advanced algorithms for peak detection, deconvolution, alignment and quantification has been developed to handle the increasing complexity of LC-ESI-MS/MS data. These algorithms provide robust and automated data processing, reducing manual intervention and improving data reliability.
3) *Metabolomics and Lipidomic Databases:* The availability of comprehensive metabolomics and lipidomic databases has facilitated compound identification and annotation. Integration with LC-ESI-MS/MS data allows for metabolite or lipid identification based on accurate mass, retention time, and MS/MS spectra, supporting metabolomic and lipidomic studies.
4) *Artificial Intelligence and Machine Learning:* Artificial intelligence and machine learning techniques are being applied to LC-ESI-MS/MS data analysis to improve compound identification, feature selection, and data interpretation. These approaches enable the extraction of hidden patterns and correlations contributing to more accurate compound identification and advanced data mining.

III. APPLICATIONS OF LC-ESI-MS/MS:

LC-ESI-MS/MS (Liquid Chromatography-Electrospray Ionization-Tandem Mass Spectrometry) has found extensive applications across diverse range of scientific disciplines due to its high sensitivity, selectivity and versatility. This hyphenated technique has revolutionized analytical chemistry enabling the analysis of complex samples and identification and quantification of a wide variety of compounds. [13] Here we explore some notable applications of LC-ESI-MS/MS in various scientific fields.

A. Pharmaceutical Analysis

In pharmaceutical industry, LC-ESI-MS/MS plays a crucial role in drug discovery, development and quality control. It allows for the identification and quantification of drug compounds and their metabolites in biological matrices such as plasma, urine, and tissues. LC-ESI-MS/MS facilitates pharmacokinetic studies, determining the absorption, distribution, metabolism, and excretion (ADME) profiles of drugs.

It also aids in drug metabolism studies, elucidating metabolic pathways and identifying potential drug-drug interactions. [14] Additionally, LC-ESI-MS/MS was used for impurity profiling, ensuring the purity and quality of pharmaceutical products.

B. Environmental Analysis

LC-ESI-MS/MS is widely employed in environmental monitoring to detect and quantify contaminants in air, water, soil and biological samples. [15] It enables the analysis of organic pollutants such as pesticides, herbicides, pharmaceuticals and industrial chemicals at trace levels. LC-ESI-MS/MS can detect and identify various target analytes with high sensitivity even in complex environmental matrices. This makes it invaluable for assessing environmental impact, identifying pollution sources, and monitoring the effectiveness of remediation efforts.

C. Metabolomics

Metabolomics, the comprehensive study of small molecules (metabolites) in biological systems, benefits greatly from LC-ESI-MS/MS analysis. [16] It allows researchers to profile and quantify metabolites in various biological samples including blood, urine and tissues. LC-ESI-MS/MS enables the identification of biomarkers associated with specific physiological conditions, diseases or drug responses. By analyzing metabolite profiles, researchers can gain insights into metabolic pathways, understand disease mechanisms, and develop personalized medicine approaches.

D. Proteomics

In the field of proteomics, LC-ESI-MS/MS is widely utilized for the identification and quantification of proteins and peptides. LC-ESI-MS/MS enables the analysis of complex protein mixtures such as biological fluids or cell lysates by digesting proteins into peptides and analyzing their mass spectra. [17]

This technique facilitates protein identification by matching the obtained peptide mass spectra against protein sequence databases. LC-ESI-MS/MS is also valuable for protein quantification allowing for the comparison of protein expression levels between different samples or under different experimental conditions.

E. Food and Beverage Analysis

LC-ESI-MS/MS plays a critical role in the analysis of food and beverages to ensure their safety, quality and authenticity. It is used for the detection and quantification of food contaminants such as pesticides, mycotoxins, veterinary drugs and food additives. [18] LC-ESI-MS/MS can identify and quantify allergens in food products, ensuring proper labeling and preventing allergic reactions. It is also employed in the analysis of food authenticity, detecting adulteration or substitution of high-value food products.

F. Forensic Analysis

LC-ESI-MS/MS has become an indispensable tool in forensic analysis, aiding in detection and quantification of drugs, metabolites and other compounds in forensic samples. It is used for toxicological analysis of biological samples such as blood, urine and hair to determine the presence and concentration of drugs and their metabolites. [19] LC-ESI-MS/MS is also employed in forensic chemistry for analysis of trace evidence such as gunshot residue, explosives and illicit substances.

G. Clinical Diagnostics

LC-ESI-MS/MS has significant implications in clinical diagnostics and healthcare. It is used for the analysis of biological samples such as blood, serum and urine to diagnose and monitor diseases. [20] LC-ESI-MS/MS enables the quantification of specific biomarkers associated with various diseases including cancer, cardiovascular disorders, neurological conditions and metabolic disorders. The high sensitivity and specificity of LC-ESI-MS/MS make it an invaluable tool for early disease detection, treatment monitoring, and personalized medicine.

H. Natural Products Analysis

LC-ESI-MS/MS is extensively employed in the analysis of natural products such as plant extracts, herbal medicines, and dietary supplements. It allows for the identification and characterization of bioactive compounds such as alkaloids, flavonoids, terpenoids, and phenolic compounds. LC-ESI-MS/MS aids in the quality control of natural products, ensuring their safety, purity, and efficacy. [21] It also facilitates discovery of new natural product molecules with potential therapeutic applications.

I. Metallomics

Metallomics is the study of metal-containing compounds in biological systems. LC-ESI-MS/MS is used for the analysis of metal ions, metalloproteins, and metal-containing biomolecules. It enables the determination of metal speciation, oxidation states, and metal-protein binding interactions. [22] LC-ESI-MS/MS plays a crucial role in understanding the role of metals in biological processes, such as enzyme function, metal homeostasis, and metal-related diseases.

J. Petroleum and Petrochemical Analysis

LC-ESI-MS/MS is employed in analysis of petroleum and petrochemical samples to characterize and quantify the various components present. It enables the identification and quantification of hydrocarbons, aromatic compounds, sulfur-containing compounds, and other contaminants. LC-ESI-MS/MS aids in the quality control of petroleum products, ensuring compliance with regulatory standards and assessing environmental impact.

K. Plant Metabolomics

LC-ESI-MS/MS is widely used in plant metabolomics research to profile and quantify metabolites in different plant tissues. It enables the analysis of primary and secondary metabolites such as sugars, organic acids, amino acids, flavonoids, and alkaloids. [23] LC-ESI-MS/MS aids in understanding plant metabolism, responses to environmental stimuli, and identification of bioactive compounds with potential agricultural and pharmaceutical applications.

These additional applications highlight the versatility of LC-ESI-MS/MS in various scientific fields. Its ability to analyze diverse sample types and provide sensitive and selective detection makes it a valuable tool for researchers and analysts across numerous disciplines. The continued advancements in LC-ESI-MS/MS technology and methodology will undoubtedly expand its applications and contribute to new discoveries in these fields.

IV. SYNERGISTIC APPROACHES AND HYPHENATED TECHNIQUES

In addition to its standalone capabilities, LC-ESI-MS/MS can be integrated with other hyphenated techniques to enhance analytical capabilities and expand the range of analytes that can be analyzed. [24] This synergistic combination of techniques provides complementary information and enables more comprehensive analysis, making it a valuable tool in scientific research.

One of the most widely used synergistic approaches involves coupling LC-ESI-MS/MS with Gas Chromatography-Mass Spectrometry (GC-MS). [25] GC separates volatile and semi-volatile compounds based on their vapor pressure and boiling points, while MS detects and identifies the separated compounds based on their mass spectra. The combination of GC-MS and LC-ESI-MS/MS allows simultaneous analysis of a wider range of compounds, enhancing the coverage and sensitivity of the analysis. This is particularly advantageous when analyzing complex samples with diverse analytes, such as environmental samples or biological fluids.

Another powerful combination involves coupling LC-ESI-MS/MS with Capillary Electrophoresis-Mass Spectrometry (CE-MS). Capillary electrophoresis (CE) is a technique that separates charged analytes based on their electrophoretic mobility. When coupled with MS, CE-MS provides excellent separation capabilities and sensitive detection. CE-MS is particularly useful for the analysis of polar and charged compounds that may not be easily amenable to LC.

By combining CE-MS with LC-ESI-MS/MS, researchers can benefit from the complementary separation mechanisms of both techniques, allowing for the analysis of a wider range of compounds with different physicochemical properties. This combination has found applications in metabolomics and proteomics research where comprehensive profiling of small molecules and biomolecules is required.

Matrix Assisted Laser Desorption/Ionization-Mass Spectrometry (MALDI-MS) is another technique that can be combined with LC-ESI-MS/MS. MALDI is a soft ionization technique that allows the analysis of large biomolecules such as peptides, proteins, nucleic acids, and polymers. It involves the co-crystallization of the analyte with matrix compound and subsequent desorption and ionization of the analyte upon laser irradiation. When coupled with MS, MALDI-MS enables the analysis of biomolecules with high sensitivity.

By combining MALDI-MS with LC-ESI-MS/MS, researchers can leverage the advantages of both techniques. LC-ESI-MS/MS handles small molecules and metabolites, while MALDI-MS excels in analysis of large biomolecules. This combined approach provides a comprehensive analysis platform for various analytes, facilitating in-depth characterization and identification of complex mixtures and biological samples.

Liquid Chromatography-Nuclear Magnetic Resonance (LC-NMR) is a powerful combination that combines the separation capabilities of liquid chromatography with the structural information obtained from NMR spectroscopy. NMR spectroscopy is a technique used for structural elucidation and identification of compounds. By coupling LC-NMR with LC-ESI-MS/MS, researchers can achieve a comprehensive analysis where LC-ESI-MS/MS provides information on compound identification and quantification, while LC-NMR offers valuable structural insights. This combination is particularly useful for analysis of complex mixtures, natural products, and metabolites. These examples illustrate how the integration of LC-ESI-MS/MS with other hyphenated techniques allows researchers to overcome limitations and capitalize on the strengths of each technique. By combining the advantages of different analytical approaches, scientists can achieve enhanced separation, improved compound identification, and expanded analyte coverage. These synergistic approaches have revolutionized analytical chemistry, enabling researchers to tackle complex analytical challenges and explore new frontiers in scientific research.

V. RECENT DEVELOPMENTS AND INNOVATIONS

In recent years, LC-ESI-MS/MS has undergone significant advancements and witnessed several innovations that have enhanced its performance, sensitivity, and applicability. These developments have contributed to the expanding capabilities and widespread adoption of LC-ESI-MS/MS in various scientific disciplines. Let us delve into some of the notable recent developments and innovations in LC-ESI-MS/MS.

A. Advances in Mass Spectrometry Detectors

One area of considerable innovation lies in the development of novel mass spectrometry detectors. Manufacturers have introduced high-resolution mass spectrometers with improved sensitivity, resolution, and mass range capabilities. Hybrid mass spectrometers such as quadrupole-time-of-flight (Q-TOF) and orbitrap based instruments offer enhanced mass accuracy, dynamic range, and detection limits. [26] These advancements enable the identification and quantification of trace analytes in complex matrices pushing the boundaries of LC-ESI-MS/MS analysis. Furthermore, recent developments have focused on improving the capabilities of mass spectrometry detectors in terms of speed and data acquisition rates. Ultrafast scanning capabilities such as parallel reaction monitoring (PRM) and data independent acquisition (DIA) enable rapid and comprehensive data acquisition. These approaches coupled with advanced data processing algorithms allow for targeted and untargeted analysis, providing an in-depth coverage of complex samples with enhanced throughput.

B. Improvements in Ionization Techniques

Ionization is a critical step in the LC-ESI-MS/MS workflow and recent developments have focused on enhancing the ionization efficiency and expanding ionization techniques. One such innovation is the introduction of ambient ionization methods such as desorption electrospray ionization (DESI) and direct analysis in real-time (DART), which enable rapid in situ analysis of samples without extensive sample preparation. These ambient ionization techniques have found applications in various fields including clinical diagnostics, forensic analysis, and food safety monitoring. [27] Additionally, the use of novel ionization sources including atmospheric pressure photoionization (APPI) and atmospheric pressure chemical ionization (APCI) has expanded the ionization capabilities of LC-ESI-MS/MS, allowing for improved analysis of diverse analyte classes. APPI uses photoionization to ionize compounds, making it suitable for the analysis of non-polar and semi-polar compounds. APCI, on the other hand, facilitates the ionization of various analytes, including polar and non-polar compounds. These ionization techniques broaden the applicability of LC-ESI-MS/MS, enabling the analysis of complex samples with diverse analytes.

C. Advances in Chromatographic Columns and Stationary Phases

Efficient chromatographic separations are crucial to achieve high-resolution and sensitive LC-ESI-MS/MS analyses. Recent developments in chromatographic columns and stationary phases have focused on improving separation selectivity, efficiency, and robustness. Novel column chemistries such as superficially porous particles (SPPs) and core-shell particles offer improved peak capacity, reduced analysis time, and enhanced sensitivity. [28] These advancements have resulted in enhanced chromatographic performance allowing for improved separation of complex mixtures and increased detection sensitivity. Furthermore, advances in stationary phase technology have enabled the development of specialized columns for specific analyte classes and applications. Hydrophilic interaction liquid chromatography (HILIC) columns for instance are designed for the separation of polar compounds including hydrophilic metabolites and peptides. These columns provide enhanced retention and selectivity for polar analytes enabling their efficient analysis in LC-ESI-MS/MS workflows.

D. Miniaturization and Microfluidics

The miniaturization of LC-ESI-MS/MS systems and the integration of microfluidics has gained significant attention recently. Microfluidic platforms enable reduced sample and reagent consumption, faster analysis times, and increased portability of LC-ESI-MS/MS systems. Microscale LC systems coupled with miniaturized ESI sources have demonstrated high sensitivity and throughput for analysis of small volumes of samples. [29] These advancements are particularly valuable in applications where sample availability is limited, such as clinical diagnostics and environmental monitoring.

Moreover, the integration of microfluidics with LC-ESI-MS/MS has facilitated on-chip sample preparation including sample enrichment, purification, and fractionation. Microfluidic devices integrated with LC-ESI-MS/MS enable seamless sample processing and analysis, reducing the need for labor-intensive and time-consuming sample preparation steps. These advancements in miniaturization and microfluidics have contributed to the improved sensitivity, efficiency and ease of use of LC-ESI-MS/MS systems.

E. Data Processing and Analysis Tools

The increasing complexity and volume of LC-ESI-MS/MS data require robust data processing and analysis tools. Recent developments in data processing algorithms, statistical methods, and machine learning approaches have improved the reliability and efficiency of data analysis. Software tools with advanced features for peak picking, peak alignment, compound identification, and statistical analysis have been developed to streamline data processing workflows and enhance data interpretation. [30] These tools enable researchers to extract meaningful insights from complex LC-ESI-MS/MS datasets more effectively.

Moreover, advancements in data processing have led to the integration of LC-ESI-MS/MS data with other omics datasets such as genomics, transcriptomics, and proteomics. Integrative multi-omics data analysis approaches enable comprehensive system-level investigations, facilitating the understanding of biological processes and the identification of biomarkers. These integrated data analysis workflows allow for the identification of correlations between molecular changes and physiological conditions, leading to a deeper understanding of complex biological systems.

F. Integration with Omics Technologies

The integration of LC-ESI-MS/MS with other omics technologies has gained prominence recently. This integration allows for multi-omic analysis where LC-ESI-MS/MS provides metabolomic or lipidomic profiling alongside other omics data enabling a comprehensive understanding of biological systems. The integration of LC-ESI-MS/MS with omics technologies facilitates biomarker discovery, elucidation of metabolic pathways, and identification of key molecular interactions, opening new avenues for systems biology research. [31]

For example, the combination of LC-ESI-MS/MS with genomics data allows for the identification and characterization of metabolites associated with specific genetic variants or disease conditions. By integrating LC-ESI-MS/MS data with transcriptomics data, researchers can gain insights into the regulation of metabolic pathways and identify potential biomarkers for disease diagnosis and treatment.

These integrative approaches provide a holistic view of biological systems, bridging the gap between genotype and phenotype and paving the way for personalized medicine and precision healthcare.

These recent developments and innovations highlight the dynamic nature of LC-ESI-MS/MS and its continuous evolution as a powerful analytical technique.

With the ongoing advancements, LC-ESI-MS/MS will continue to play a pivotal role in scientific research, enabling breakthrough discoveries and addressing complex analytical challenges. The integration of cutting-edge technologies, advanced data analysis approaches and multidisciplinary collaborations will drive the future development and application of LC-ESI-MS/MS, opening new frontiers in scientific exploration and knowledge discovery

VI. CHALLENGES AND FUTURE PERSPECTIVES:

Despite its significant advancements, LC-ESI-MS/MS still faces certain challenges and limitations that researchers strive to overcome. Addressing these challenges and exploring future perspectives is essential for advancing the capabilities and applications of LC-ESI-MS/MS in modern science. Let us delve into some of the key challenges and potential directions for future research in LC-ESI-MS/MS.

A. Matrix Effects and Sample Complexity

One of the primary challenges in LC-ESI-MS/MS analysis is the presence of matrix effects and complexity of samples. Complex matrices such as biological fluids, environmental samples, and food extracts often contain several endogenous and exogenous compounds that can interfere with analyte detection and quantification. These matrix effects can lead to ion suppression or enhancement affecting the accuracy and reliability of analytical results.

To address this challenge, researchers are exploring various strategies including sample preparation techniques, advanced chromatographic methods, and selective sample extraction approaches. Novel sample preparation methods such as solid-phase microextraction (SPME) and solid-phase extraction (SPE) aim to remove interfering matrix components, enhance analyte recovery, and improve the overall sensitivity and selectivity of LC-ESI-MS/MS analyses. Additionally, the development of selective stationary phases and innovative chromatographic column assists in mitigating matrix effects and enhancing separation performance.

Furthermore, the integration of LC-ESI-MS/MS with high-resolution mass spectrometry (HRMS) enables accurate mass measurements and application of advanced data processing algorithms such as mass defect filtering and isotopic pattern analysis. These approaches enhance the selectivity and specificity of LC-ESI-MS/MS analysis, allowing more accurate identification and quantification of target analytes within complex matrices.

B. Quantitative Analysis and Method Validation

Accurate and precise quantification of analytes is crucial in various applications such as pharmaceutical analysis and clinical diagnostics. [32] However, achieving reliable quantitative results in LC-ESI-MS/MS analyses can be challenging due to factors such as matrix effects, ion suppression, and instrument variability. Robust and comprehensive method validation protocols are necessary to ensure the accuracy and reproducibility of quantitative LC-ESI-MS/MS measurements.

Method validation in LC-ESI-MS/MS involves assessing various parameters including linearity, sensitivity, precision, accuracy, and selectivity. Validation guidelines such as those provided by regulatory bodies like FDA and EMA provide a framework for method validation ensuring the reliability of analytical results. Additionally, the use of appropriate internal standards, calibration curves, and quality control samples is essential for accurate quantification and reliable data interpretation.

Future research in quantitative LC-ESI-MS/MS analysis aims to develop standardized protocols and guidelines for method validation considering the diverse range of analytes and matrices encountered in different applications. Furthermore, advancements in data processing and statistical analysis tools will contribute to the development of more robust and automated approaches for quantitative LC-ESI-MS/MS analysis, reducing user-dependent variability and enhancing the reliability of quantitative measurements.

C. The Identification of Unknown Compounds

In many LC-ESI-MS/MS applications, there is a need to identify and characterize unknown compounds in samples. However, identification of unknowns poses significant challenges due to the vast chemical space and structural diversity of potential analytes. Traditional approaches for compound identification such as spectral matching and database searching may be limited in their scope and may not provide reliable results for unknown compounds.

To overcome this challenge, researchers are exploring innovative strategies such as data-independent acquisition (DIA), data mining, and spectral libraries. [33] Data-independent acquisition methods such as SWATH-MS acquire comprehensive MS/MS spectra of all detectable analytes in a sample enabling retrospective analysis and identification of unknown compounds. Data mining approaches involve the mining of large spectral databases and the application of machine learning algorithms to predict compound identities based on spectral patterns and structural features.

Moreover, the construction of comprehensive and curated spectral libraries encompassing various compound classes and structures is critical for accurate and reliable compound identification. Efforts are being made to improve the coverage and quality of spectral libraries facilitating more confident identification of unknown compounds in LC-ESI-MS/MS analyses.

D. Advancements in Instrumentation and Technology

The future of LC-ESI-MS/MS heavily relies on continuous advancements in instrumentation and technology. Instrument manufacturers are continually improving the performance and capabilities of LC-ESI-MS/MS systems aiming for higher sensitivity, resolution, and scan speeds. The development of novel ionization techniques such as ambient ionization methods can expand the application range of LC-ESI-MS/MS, enabling direct analysis of samples without extensive sample preparation.

Furthermore, the integration of LC-ESI-MS/MS with other hyphenated techniques such as ion mobility spectrometry (IMS) and gas chromatography (GC) can enhance the selectivity and separation capabilities of LC-ESI-MS/MS analyses. [34] Combined approaches provide complementary information enabling comprehensive characterization of complex samples.

Additionally, advancements in mass spectrometry detectors, such as high-capacity ion traps, quadrupole-time-of-flight (Q-TOF) analyzers, and Orbitrap mass analyzers, offer improved sensitivity, mass accuracy, and dynamic range. These developments enable the analysis of low-abundance analytes, enhance the detection of trace-level contaminants, and improve the overall performance of LC-ESI-MS/MS systems.

E. Multidisciplinary Collaborations and Data Sharing

The future of LC-ESI-MS/MS lies in multidisciplinary collaborations and data sharing. Collaboration between researchers from various fields including chemistry, biology, bioinformatics, and data science fosters the development of innovative LC-ESI-MS/MS applications and analytical strategies. [35] Sharing data, methodologies and expertise accelerates scientific progress and facilitates standardization of LC-ESI-MS/MS workflows.

Moreover, the establishment of comprehensive data repositories and open-access databases allows researchers to access and analyze publicly available LC-ESI-MS/MS data. This collective knowledge contributes to the development of standardized analytical methods, benchmark datasets, and best practices in LC-ESI-MS/MS analysis. Data sharing also enables reproducibility and validation of scientific findings, promoting transparency and scientific rigor.

In conclusion, addressing the challenges and exploring future perspectives in LC-ESI-MS/MS is essential for advancing its capabilities and applications in modern science. Overcoming challenges related to matrix effects, quantitative analysis, compound identification, and instrument performance requires collaborative efforts, methodological advancements, and technological innovations. With continued research and development, LC-ESI-MS/MS will remain a powerful analytical technique enabling breakthrough discoveries and contributing to scientific advancements in various fields.

VII. CONCLUSION

In conclusion, LC-ESI-MS/MS has emerged as a versatile and indispensable analytical technique in modern science. Its ability to combine liquid chromatography with tandem mass spectrometry provides researchers with a powerful tool for analysis of various compounds in various sample matrices. Through this review paper, we have explored the fundamentals, applications, synergistic approaches, recent developments, challenges, and future perspectives of LC-ESI-MS/MS.

We began by introducing LC-ESI-MS/MS, highlighting its significance in modern science and outlining the structure of the paper. Moving on, we discussed the fundamental principles and working mechanisms of LC-ESI-MS/MS along with the key components and instrumentation involved in the technique. We also highlighted the recent advancements and refinements that have further improved the performance of LC-ESI-MS/MS.

The applications of LC-ESI-MS/MS were explored across various scientific disciplines including pharmaceutical analysis, environmental analysis, metabolomics, and proteomics. Notable examples were discussed, illustrating the versatility and utility of LC-ESI-MS/MS in these fields. We also examined the advantages and limitations of the technique in these applications.

Synergistic approaches and hyphenated techniques were then explored, focusing on the integration of LC-ESI-MS/MS with other analytical techniques such as GC-MS, CE-MS, and MALDI-MS. The benefits and enhanced capabilities of these combined approaches are discussed, accompanied by successful application examples.

Next, we delved into recent developments and innovations in LC-ESI-MS/MS technology. Improved sensitivity, resolution, speed and data analysis capabilities have been achieved through advancements in instrumentation, sample preparation, ionization methods, chromatographic columns and mass spectrometry detectors. These advancements have expanded the application scope and facilitated a more comprehensive and accurate analysis of complex samples.

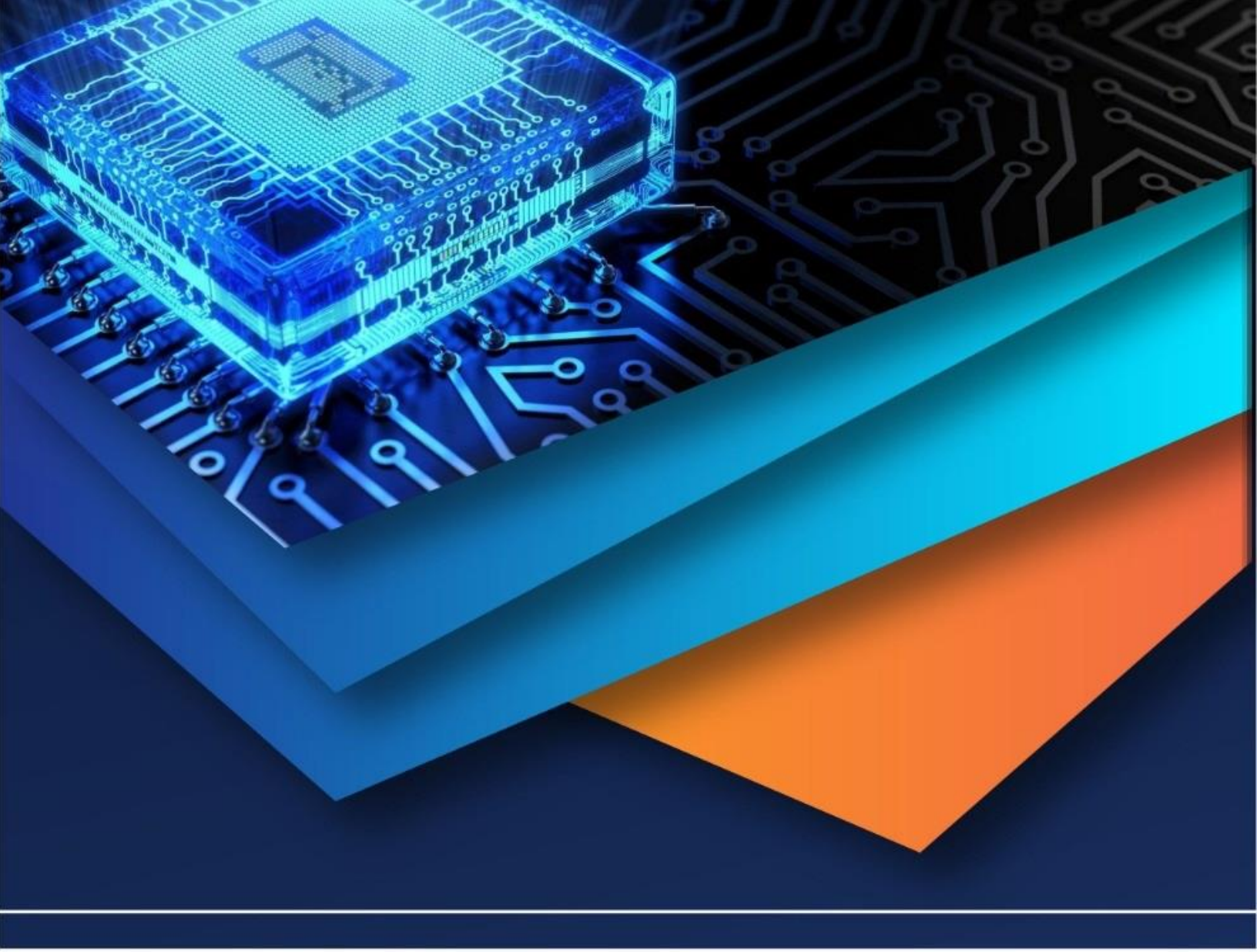
However, LC-ESI-MS/MS also faces challenges including matrix effects, chromatographic optimization, quantitative analysis and data analysis complexities. These challenges demand ongoing research and innovation to overcome them successfully. Furthermore, future perspectives for LC-ESI-MS/MS were discussed, including the development of miniaturized systems, advancements in ionization methods, and integration of advanced data analysis techniques.

In conclusion, LC-ESI-MS/MS has proven to be a valuable analytical technique with immense potential for advancing scientific knowledge and solving complex analytical problems. Its continued development coupled with addressing the existing challenges will pave the way for further advancements and applications in various scientific fields.

REFERENCES

[1] Star-Weinstock, M., Williamson, B.L., Dey, S., Pillai, S. and Purkayastha, S., 2012. LC-ESI-MS/MS analysis of testosterone at sub-picogram levels using a novel derivatization reagent. Analytical chemistry, 84(21), pp.9310-9317.
[2] Gnann, H., Weinmann, W., Engelmann, C., Wurst, F.M., Skopp, G., Winkler, M., Thierauf, A., Auwärter, V., Dresen, S. and Bouzas, N.F., 2009. Selective detection of phosphatidylethanol homologues in blood as biomarkers for alcohol consumption by LC-ESI-MS/MS. Journal of mass spectrometry, 44(9), pp.1293-1299.
[3] Zwiener, C. and Frimmel, F.H., 2004. LC-MS analysis in the aquatic environment and in water treatment–A critical review: Part I: Instrumentation and general aspects of analysis and detection. Analytical and bioanalytical chemistry, 378, pp.851-861.
[4] Rosen, A.L. and Hieftje, G.M., 2004. Inductively coupled plasma mass spectrometry and electrospray mass spectrometry for speciation analysis: applications and instrumentation. Spectrochimica Acta Part B: Atomic Spectroscopy, 59(2), pp.135-146.
[5] Seger, C. and Salzmann, L., 2020. After another decade: LC–MS/MS became routine in clinical diagnostics. Clinical biochemistry, 82, pp.2-11.
[6] Liu, S., Hughes, C. and A Lajoie, G., 2012. Recent advances and special considerations for the analysis of phosphorylated peptides by LC-ESI-MS/MS. Current Analytical Chemistry, 8(1), pp.35-42.
[7] Islam, A.K.M.M., Hong, S.M., Lee, H.S., Moon, B.C., Kim, D. and Kwon, H., 2018. Identification and characterization of matrix components in spinach during QuEChERS sample preparation for pesticide residue analysis by LC–ESI–MS/MS, GC–MS and UPLC-DAD. Journal of food science and technology, 55, pp.3930-3938.
[8] Mohamed, R., Richoz-Payot, J., Gremaud, E., Mottier, P., Yilmaz, E., Tabet, J.C. and Guy, P.A., 2007. Advantages of molecularly imprinted polymers LC-ESI-MS/MS for the selective extraction and quantification of chloramphenicol in milk-based matrixes. Comparison with a classical sample preparation. Analytical Chemistry, 79(24), pp.9557-9565.
[9] Ghosh, C., Shinde, C.P. and Chakraborty, B.S., 2012. Influence of ionization source design on matrix effects during LC–ESI-MS/MS analysis. Journal of Chromatography B, 893, pp.193-200.
[10] Lurie, I. and Li, L., 2009. Use of High-Temperature Liquid Chromatography with Sub-2 µm Particle C18 Columns for the Analysis of Seized Drugs. Journal of Liquid Chromatography & Related Technologies®, 32(18), pp.2615-2626.
[11] Beyer, J., Peters, F.T., Kraemer, T. and Maurer, H.H., 2007. Detection and validated quantification of toxic alkaloids in human blood plasma—comparison of LC-APCI-MS with LC-ESI-MS/MS. Journal of Mass Spectrometry, 42(5), pp.621-633.
[12] Siqueira, W.L., Zhang, W., Helmerhorst, E.J., Gygi, S.P. and Oppenheim, F.G., 2007. Identification of protein components in in vivo human acquired enamel pellicle using LC− ESI− MS/MS. Journal of proteome research, 6(6), pp.2152-2160.
[13] Chhonker, Y.S., Sleightholm, R.L., Li, J., Oupický, D. and Murry, D.J., 2018. Simultaneous quantitation of hydroxychloroquine and its metabolites in mouse blood and tissues using LC–ESI–MS/MS: An application for pharmacokinetic studies. Journal of Chromatography B, 1072, pp.320-327.
[14] Star-Weinstock, M., Williamson, B.L., Dey, S., Pillai, S. and Purkayastha, S., 2012. LC-ESI-MS/MS analysis of testosterone at sub-picogram levels using a novel derivatization reagent. Analytical chemistry, 84(21), pp.9310-9317.
[15] Zocolo, G.J., Pilon dos Santos, G., Vendemiatti, J., Vacchi, F.I., Umbuzeiro, G.D.A. and Zanoni, M.V.B., 2015. Using SPE-LC-ESI-MS/MS analysis to assess disperse dyes in environmental water samples. Journal of chromatographic science, 53(8), pp.1257-1264.
[16] Aslam, A., Zhao, S., Lu, X., He, N., Zhu, H., Malik, A.U., Azam, M. and Liu, W., 2021. High-Throughput LC-ESI-MS/MS Metabolomics Approach Reveals Regulation of Metabolites Related to Diverse Functions in Mature Fruit of Grafted Watermelon. Biomolecules, 11(5), p.628.
[17] André, M., Le Caer, J.P., Greco, C., Planchon, S., El Nemer, W., Boucheix, C., Rubinstein, E., Chamot-Rooke, J. and Le Naour, F., 2006. Proteomic analysis of the tetraspanin web using LC-ESI-MS/MS and MALDI-FTICR-MS. Proteomics, 6(5), pp.1437-1449.
[18] Valese, A.C., Molognoni, L., de Sá Ploêncio, L.A., de Lima, F.G., Gonzaga, L.V., Górniak, S.L., Daguer, H., Barreto, F. and Costa, A.C.O., 2016. A fast and simple LC-ESI-MS/MS method for detecting pyrrolizidine alkaloids in honey with full validation and measurement uncertainty. Food Control, 67, pp.183-191.
[19] Östin, A., Bergström, T., Fredriksson, S.Å. and Nilsson, C., 2007. Solvent-assisted trypsin digestion of ricin for forensic identification by LC-ESI MS/MS. Analytical chemistry, 79(16), pp.6271-6278.
[20] Ramani, A.V., Sengupta, P. and Mullangi, R., 2009. Development and validation of a highly sensitive and robust LC-ESI-MS/MS method for simultaneous quantitation of simvastatin acid, amlodipine and valsartan in human plasma: application to a clinical pharmacokinetic study. Biomedical Chromatography, 23(6), pp.615-622.
[21] Boccalandro, H.E., González, C.V., Wunderlin, D.A. and Silva, M.F., 2011. Melatonin levels, determined by LC-ESI-MS/MS, fluctuate during the day/night cycle in Vitis vinifera cv Malbec: evidence of its antioxidant role in fruits. Journal of Pineal Research, 51(2), pp.226-232.
[22] Kutscher, D.J., Sanz-Medel, A. and Bettmer, J., 2012. Metallomics investigations on potential binding partners of methylmercury in tuna fish muscle tissue using complementary mass spectrometric techniques. Metallomics, 4(8), pp.807-813.
[23] Aslam, A., Zhao, S., Lu, X., He, N., Zhu, H., Malik, A.U., Azam, M. and Liu, W., 2021. High-Throughput LC-ESI-MS/MS Metabolomics Approach Reveals Regulation of Metabolites Related to Diverse Functions in Mature Fruit of Grafted Watermelon. Biomolecules, 11(5), p.628.
[24] Kalariya, P.D., Talluri, M.K., Patel, P.N. and Srinivas, R., 2015. Identification of hydrolytic and isomeric N-oxide degradants of vilazodone by on line LC–ESI–MS/MS and APCI–MS. Journal of Pharmaceutical and Biomedical Analysis, 102, pp.353-365.
[25] Zhang, H., Bayen, S. and Kelly, B.C., 2015. Co-extraction and simultaneous determination of multi-class hydrophobic organic contaminants in marine sediments and biota using GC-EI-MS/MS and LC-ESI-MS/MS. Talanta, 143, pp.7-18.
[26] van Bergen, W., Heck, A.J. and Baggelaar, M.P., 2022. Recent advancements in mass spectrometry–based tools to investigate newly synthesized proteins. Current Opinion in Chemical Biology, 66, p.102074.
[27] Ayala-Cabrera, J.F., Montero, L., Meckelmann, S.W., Uteschil, F. and Schmitz, O.J., 2023. Review on atmospheric pressure ionization sources for gas chromatography-mass spectrometry. Part I: Current ion source developments and improvements in ionization strategies. Analytica chimica acta, 1238, p.340353.
[28] Wu, Y., Zhang, N., Luo, K., Liu, Y., Bai, Z. and Tang, S., 2022. Recent advances of innovative and high-efficiency stationary phases for chromatographic separations. TrAC Trends in Analytical Chemistry, p.116647.

[29] Mohan, J.M., Amreen, K., Javed, A., Dubey, S.K. and Goel, S., 2022. Emerging trends in miniaturized and microfluidic electrochemical sensing platforms. Current Opinion in Electrochemistry, 33, p.100930.
[30] Liu, S., Hughes, C. and A Lajoie, G., 2012. Recent advances and special considerations for the analysis of phosphorylated peptides by LC-ESI-MS/MS. Current Analytical Chemistry, 8(1), pp.35-42.
[31] Zhou, J., Wang, M., Carrillo, C., Hassoun, A., Collado, M.C. and Barba, F.J., 2022. Application of omics in food color. Current Opinion in Food Science, 46, p.100848.
[32] Jáuregui, O., Sierra, A.Y., Carrasco, P., Gratacós, E., Hegardt, F.G. and Casals, N., 2007. A new LC–ESI-MS/MS method to measure long-chain acylcarnitine levels in cultured cells. Analytica chimica acta, 599(1), pp.1-6.
[33] Alder, L., Greulich, K., Kempe, G. and Vieth, B., 2006. Residue analysis of 500 high priority pesticides: better by GC–MS or LC–MS/MS. Mass spectrometry reviews, 25(6), pp.838-865.
[34] Darie-Ion, L., Whitham, D., Jayathirtha, M., Rai, Y., Neagu, A.N., Darie, C.C. and Petre, B.A., 2022. Applications of MALDI-MS/MS-Based Proteomics in Biomedical Research. Molecules, 27(19), p.6196.
[35] Brambilla, F., Lavatelli, F., Merlini, G. and Mauri, P., 2013. Clinical proteomics for diagnosis and typing of systemic amyloidoses. PROTEOMICS–Clinical Applications, 7(1-2), pp.136-143.



10.22214/IJRASET

45.98

IMPACT FACTOR: 7.129

IMPACT FACTOR: 7.429

INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY