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LIQUID CHROMATOGRAPHY – MASS SPECTROMETRY

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Abstract:

Liquid Chromatography/Mass Spectrometry (LC/MS) is fast developing and it's the preferred tool of liquid chromatographers. Liquid chromatography-mass spectrometry (LC-MS/MS) is a technique that uses liquid chromatography (or HPLC) with the mass spectrometry. It is an analytical chemistry technique that combines the physical separation capabilities of liquid chromatography (or HPLC) with the mass analysis capabilities of mass spectrometry. (LC-MS/MS) is commonly used in laboratories for the qualitative and quantitative analysis of drug substances, drug products and biological samples. It has been persistently used in drug development at many different stages including Metabolic Stability Screening, Metabolite Identification as well as In Vivo Drug Screening, Impurity Identification, Peptide Mapping, Glycoprotein Mapping, Natural Products Dereplication, Bio-affinityScreening. LC-MS is now successfully applied to routine analysis in many areas, including therapeutic drug monitoring (TDM), clinical and forensic toxicology as well as doping control. This advancement in LCMS was originally and still is fueled by the need for more powerful analytical and bio-analytical techniques that can accurately and precisely discriminate target analytes from high complexity mixtures in a sensitive andselective way. With recent advancement in instrumentation, the use of liquid chromatography (LC) and mass spectrometry (MS) has become a powerful two-dimensional (2D) hyphenated technology.

Keywords: LCMS, HPLC, Peptide Mapping, Glycoprotein Mapping , Therapeutic Drug Monitoring (TDM),Forensic Toxicology.

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INTRODUCTION:

Liquid chromatography-mass spectrometry (LC-MS, or alternatively HPLC- MS)is an analytical chemistry technique that combines the physical separation capabilities of Liquid chromatography (or HPLC) with the mass analysis capabilities of mass spectrometry.

T

he Liquid Chromatography (LC) is a high performance liquid chromatography in which separation of components of mixture can be carried out by using liquid mobile and solid stationary phase. There are different types of chromatography like normal phase liquid chromatography, Reversed phase chromatography, Ion-exchange liquid chromatography ,Chiral separation and affinity liquid chromatography .

LC-MS also plays a role in pharmacognosy especially in the field of molecular pharmacognosy when it comes to the ingredients difference in the aspects of phenotypic cloning. The most important factor that has to be considered is howto make the biggest difference of active ingredients in plant cells between the test group of plants and controlled ones.

BASIC PRINCIPLES OF LCMS:

1. Liquid chromatography – High performance liquid chromatography

Liquid chromatography- High Performance Liquid Chromatography Present day liquid chromatography generally utilizes very small particles packed and operating at relatively high pressure, and is referred to as high performance liquid chromatography (HPLC); modern LC-MS methods use HPLC instrumentation, essentially exclusively, for sample.The basic principle in HPLC is adsorption. In HPLC, the sample is forced by a liquid at high pressure (the mobile phase) through a column that is packed with a stationary phase generally composed of irregularly or spherically shaped particles chosen or derivatized to accomplish particular types of separations. HPLC methods are historically divided into two different sub-classes based on stationary phases and the corresponding required polarity of the mobile phase .use of octadecysiyl (C18) and related organic-modified particles as stationary phase with pure or pH-adjusted water organic mixtures such as water –acetonitrile and water-methanol are used in techniques termed as reversed phase liquid chromatography (RP-LC). Use of materials such as silica gel as stationary phase with neat or mixed organic mixtures are used in techniquestermed normal phase liquid chromatography (NP-LC). RP-LC is most often used as themeans to introduce samples into the MS, in LC-MS instrumentation.

2. MASS SPECROMETRY:

Mass spectrometry (MS) is an analytical technique that measures the mass-to-charge ratio (m/z) of charged particles (ions). Although there are many different kinds of mass spectrometers, all of them make use of electric or magnetic fields to manipulate the motion of ions produced from an analyte of interest and determine their m/z. The basic components of a mass spectrometer are the ion source, the mass analyzer, the detector, and the data and vacuum systems. The ion source is where the components of a sample introduced in a MS system are ionized by means ofelectron beams, photon beams (UV lights), laser beams or corona discharge. In the caseof electrospray ionization, the ion source moves ions that exist in liquid solution into the gas phase. The ion source converts and fragments the neutral sample molecules intogas phase ions that are sent to the mass analyzer. Mass spectroscopy, organic molecules are bombarded with highly energetic beam of electrons and converted into positively charged ions. The collision between energetic electron and analyte moleculeoccurs at right angle so, high energy that imparts enough energy to the molecule with removal of the electron by electrostatic repulsion to leave the molecular ion in an excited state. When relaxation occurs, its result is the molecular ions undergo fragmentation to produce number of small ions of lower mass. These ions have a different charge and mass, which means that their speed and direction will be changed in an electric or magnetic field (in analyzer) . In analyzer, the magnetic field applies a force to each ion which is perpendicular to the plane, making them curve instead of travelling in a straight line to differing degrees depending on their m/z ratio. Thus, the magnetic field deflects the lighter ions more than the heavier ions. This deflection of each resulting ion beam is measured by detector. From this measurement, the mass-tooratios of all the ions which are produced in the source can be determined.

MASS ANALYZER:

They deflects ions down a curved tubes in a magnetic fields based on their kinetic energy determined by the mass, charge and velocity.The magnetic field is scanned to measure different ions.

Its task is to separate ions in terms of their mass-to-charge ratio and to direct the beamof focused ions to the detector.

The key performance parameters of an analyzer includes:

A.separation efficiency B.m/z measurement precision

C.range of the m/z values measured
There are many different mass analyzers that can be used in LC/MS. Some of them areSingle quadrupole, triple quadrupole, and ion trap, time of flight (TOF) and quadrupole-time of flight (QTOF).

2.2 ION INTERFERFACE SOURCES:
The various interfaces differ among themselves in the means of separating the analytes from the mobile phase and the method are used for ionization of the analyte.
The commonly used interfaces are :

1. Thermo spray ionization interfaces(TSI).
2. Particle beam ionization interface (PBI).
3. Atmospheric pressure chemical ionizations interface (APCI).
4. Electrospray ionization interface (ESI).
5. Atomspheric photo ionization.
6. Matrix-assisted laser desorption/ionization (MALDI).

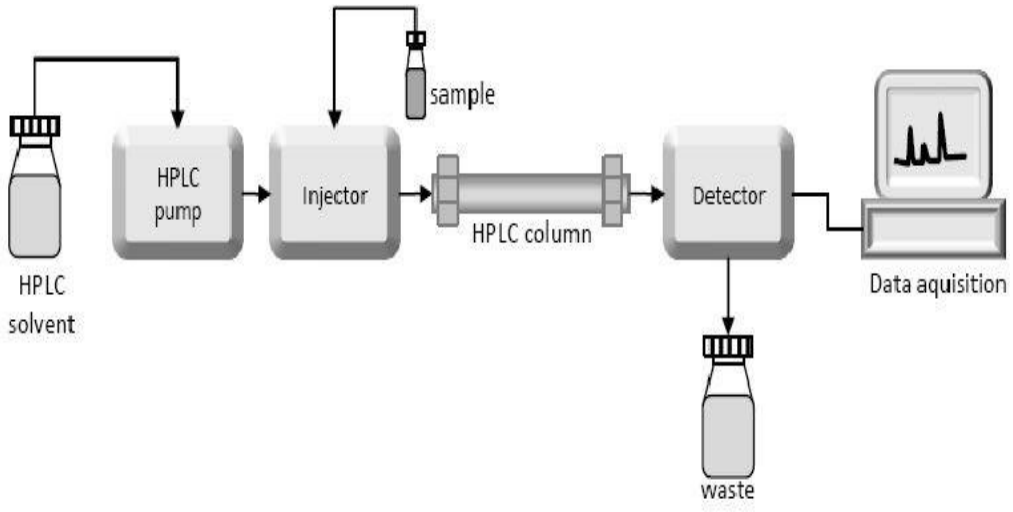
Problems in combining HPLC and MS :

HPLC	MS
Liquid phase operation.	Vaccum operation.
25-50 deg .c	200-300 deg .c
No mass range limitations	Up to 4000 Da for quadrupole MS
Inorganic buffers.	Requires volatile
1ml/min eluent flow is equivalent to 500 ml/min ofgas.	Accepts 10ml/min gas flow

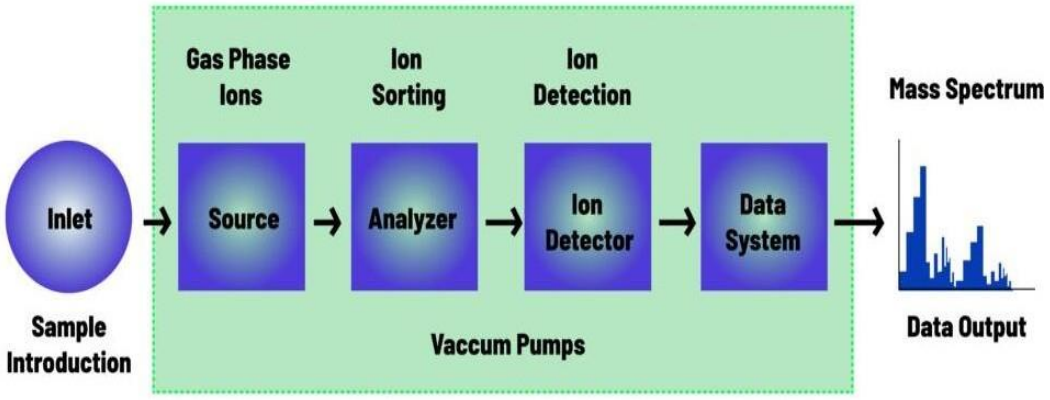
Combination of HPLC and MS:
HPLC not only separates things but also provides little extra informationabout how a chemical might be. In fact, it is hard in HPLC to be certain about purity of a particular peak, and if it contains only a single chemical. Adding a Mass Spectrometry to this will tell you the masses of all the chemicals present in the peak, which can be used for identifying them, and an excellent method to check for the purity.Even a simple mass spec can be used as a mass-specific detector, specific for the chemical under study.

More sophisticated mass detectors such as triple quadrupole and ion-trap instruments can also be used to carry out more detailed structure-dependent analysis onwhat is eluting off from the HPLC system.

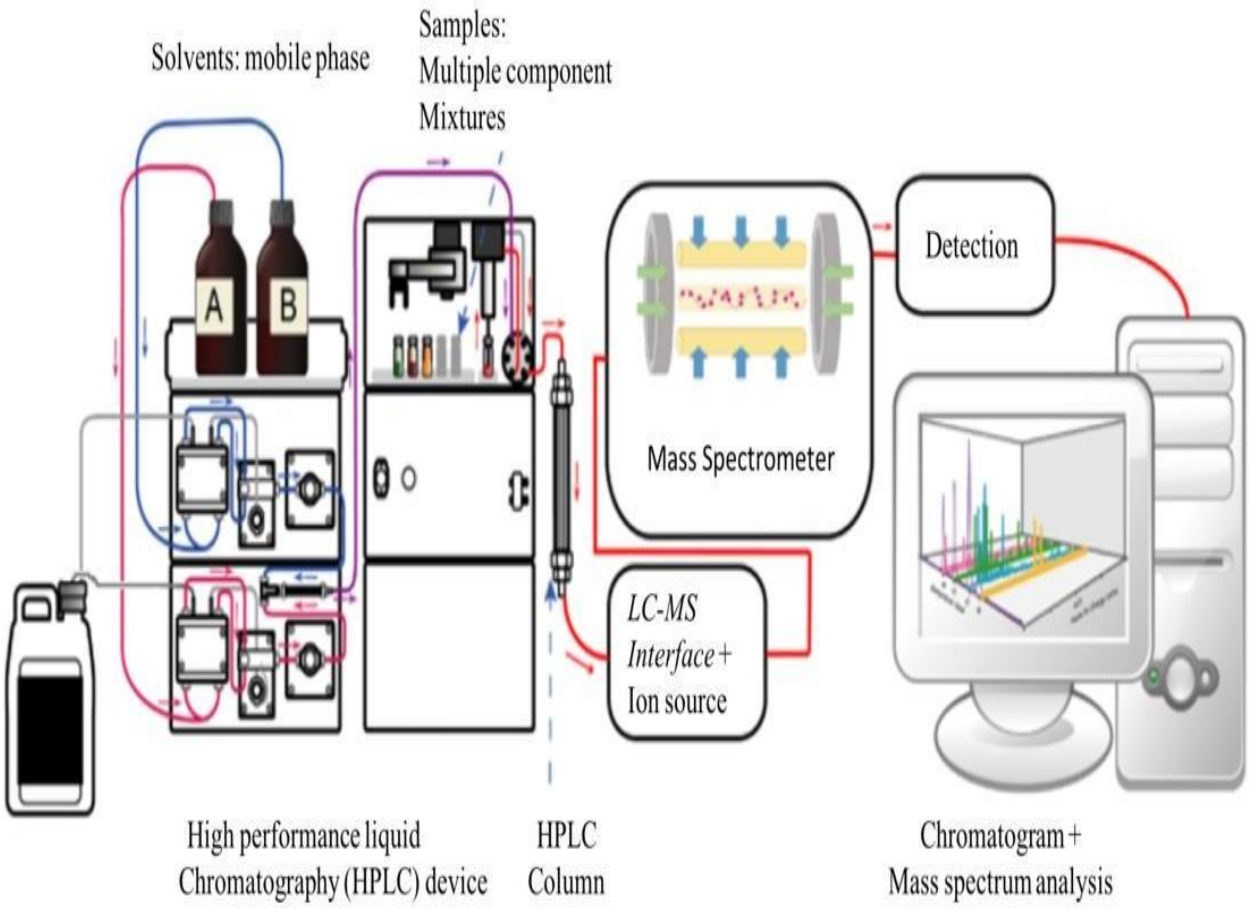
INSTRUMENTATION OF LCMSINSTRUMENTATION OF HPLC:



INSTRUMENTATION OF MS :



INSTRUMENTATION OF LCMS :



ADVANTAGES OF LCMS :

1. There are various advantages of LCMS over other chromatographic methods of which few are as follows;
2. Selectivity**:** Co-eluting peaks can be isolated by mass selectivity and are notconstrained by chromatographic resolution.
3. Peak assignment: A molecular fingerprint for the compound under study is generated, ensuring correct peak assignment in the presence of complex matrices.
4. Molecular weight information**:** Confirmation and identification of both knownand unknown compounds.
5. Structural information: Controlled fragmentation enables structural elucidationof a chemical.
6. Rapid method development: Provides easy identification of eluted analytes without retention time validation.
7. Sample matrix adaptability**:** Decreases sample preparation time and hence savestime.
8. Quantitation**:** Quantitative and qualitative data can be obtained easily withlimited instrument optimization.

Various Applications of LCMS:

1.Molecular Pharmacognosy:

LCMS determines the contents and categories of different groups of cultured plant cells and select the pair of groups with the biggest different content of ingredient for the study ingredient difference phenotypic cloning.

Characterization and Identification of Compounds:

Carotenoids: Because carotenoids are not thermally stable, separation of mixtures and removal of impurities is usually carried out by reversed phase HPLC (particularly HPLC) instead of gas chromatography The small samples of carotenoids which were isolated from biological matrices such as human serum or tissue prevent structural analysis by Nuclear Magnetic Resonance. Hence, only the most sensitive analytical methods are adequate such as Liquid Chromatography / Mass Spectrometry and HPLC with photo diode-array UV / visible absorbance detection. At the minimum level, carotenoid identification may be confirmed by combining data such as HPLC retention times, photodiode-array absorbance spectroscopy, mass spectrometry and tandem mass spectrometry. Upto date, five LC/MS techniques have been used for carotenoid analysis including moving belt, particle beam, continuous flow fast atom bombardment, electrospray and Atmospheric Pressure Chemical Ionization (APCI). Among these LC/MS interfaces, electrospray and APCI are probably the easiest to use and are rapidly becoming the most widely available. These techniques provide comparable sensitivity (at the low pmol level) and produce enormous molecular ions.

Proteomics[10, 11]

Liquid Chromatography / Mass Spectrometry (LC/MS) has become a powerful technology in proteomics studies in drug discovery which includes target protein characterization and the discovery of biomarkers.

A. Glycopeptides Characterization

MS-based glyco-proteomic studies are used to characterize the glycopeptides under examination. This involves pinpointing the glycosylation site, the type of glycan involved and the peptide backbone core. In present, with MS-based strategies, tandem MS fragmentation and data analysis problems provide efficient characterization of intact glycopeptides and then analysis of the peptides is done via Liquid Chromatography–Tandem Mass Spectrometry (LC-MS/MS).

B. peptide mapping

In earlier days protein drugs were made from proteins refined from living organisms. However, they are recently produced using recombination technology. Insulin, interferon, and erythropoietin are some of the protein drugs made by recombination which are available in the market 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 modelsample of horse heart myoglobin is done by LC/MS using a quadrupole mass spectrometer.

Products of Degradation[12]:

LCMS was used to separate, identify and characterize the degradation products under certain conditions of hydrolytic, oxidative, photolytic and thermal stress. A complete mass fragmentation pathway of the drug was first established with the help of LC-MS / MS studies. The stressed samples were subjected to LC-MS studies. It is done to exchange mass studies to obtain their accurate mass, fragment pattern and number of unstable hydrogens. The MS results helped to assign provisional structures to degradation products. Few examples are Identification and characterization of degradation products of Irbesartan, stressed degradation products

of Prulifloxacin. Whereas, in hydrolytic degradation is done by decomposing the drug under hydrolytic conditions, resolving the products on a HPLC column, characterizing the major products by LC-MS/MS studies, and postule World Journal of Pharmacy and Pharmaceutical Sciences probable degradation pathways with the help of studies at different time points. For example, Identification and Characterization of Hydrolytic Products of Atorvastatin.

Quantitative and Qualitative analysis :

Quantitative Bioanalysis of various Biological Samples[13]

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 immunosuppresants and doping control. 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.

Qualitative And Quantitative Analysis Of Complex Lipid Mixtures[14]

It is a LC-MS-based methodology for the investigation of lipid mixtures 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.

Phytoconstituents / Plant Metabolomics[15-19]

LC–MS provides a tool for differentiating this immense plant biodiversity dueto this technique's capability of analyzing a broad range of metabolites including secondary metabolites (e.g., alkaloids, glycosides, phenyl propanoids, flavanoids, isoprenes, glucosinolates, terpenes, benzoids) and highly polar and/or higher molecular weight.

Molecules. LC– MS is one of the major untargeted analytical techniques to determine global metabolite profiles, which helps in the identification and relative quantification of all peaks in the chromatogram as ions that are initially defined by retention time and molecular mass.

An improved LC-MS/MS method was developed for continuous determination, qualitative and quantitative analysis for several medicinal plants. Few examples of them are Eclipta prostrata L. which is one of the Chinese medicinal tonics, eleven bioactive constituents of Radix Angelicae Pubescentis and its related preparations. Active extracts of Terminalia ferdinandiana (Kakadu plum) fruit were analysed by non-targeted LCMS technique.

Automated Immunoassay in Therapeutic Drug Monitoring [20] Therapeutic drug monitoring (TDM) of certain drugs with a narrow therapeutic indexhelps in improving patient outcome. The need for accurate, precise, and standardized measurement of drugs poses a major challenge for clinical laboratories and the diagnostics industry. Different techniques had developed in the past to meet theserequirements. Nowadays liquid chromatography–tandem mass spectrometry (LC-MS/MS)-based methods and immunoassays seem to be the most widespread approaches in clinical laboratories. Mass spectrometry–based assays can be analytically sensitive, specific and capable of measuring several compounds in a single process. This is a cost-effective approach in monitoring patients receiving multidrug therapy (e.g., antibacterial therapy for Tuberculosis patients). The selectivity provided by successive mass filtrations is an added advantage of tandem mass spectrometry over immunoassays, as is shown for immunosuppressant drugs. 5. Two Dimensional (2-D) Hyphenated Technology[21] The use of LCMS has become a powerful two dimensional (2D) hyphenated technology for the use in a wide variety of analytical and bio analytical techniques for the analysis of proteins, amino acids, nucleic acids, amino acids, carbohydrates, lipids, peptides, etc and/or in the main classification in the field of genomics, lipidomics,

metabolomics, proteomics, etc. LCMS was preferred originally and it can be intensified by the need of more powerful analytical and bio analytical techniques that can exactly distinguish the target analytes with high complexity mixtures in a sensitive and particular way.

Future Prospects of LCMS Metabolomics[23, 24]

1. At present, mass spectrometry (MS) based metabolomics has been widely used to obtain new insights into human, plant, drug and biomarker discovery, nutrition research, food control and microbial biochemistry. The next 5–10 years will inevitably witness increased inter-laboratory cooperation in order to collate as much LC-MS-based metabolite data as possible. In-house MS/MS libraries will likely become more available to interested collaborators with similar model samples and instrumentation, increasing the knowledge base of all participating laboratories. The integration of NMR to LC-MS-based metabolic profiling and metabolomic studies will likely increase, either through the offline analysis of collected LC fractions or through hybrid LC-NMR-MS instrumentation. In contrast, GC-MS is unlikely to become an integrated component to an LC-MS strategy, due to the fundamental differences in the two techniques and the inherentdifficulty in utilizing such complementary information for unknown biomarker characterization. However, GC-MS will remain a tool for quantifying those metabolites not amenable to LC-MS analysis due to relatively poor ionization efficiencies.
2. New informatics tools for the combined automated generation of candidate empirical formula and stereoisomer generation for detected metabolite features may become available, as well as algorithms designed to predict the chemical structure of unknown metabolites based on CID MS/MS fragmentation spectra.
   It has been more positive for MS-based metabolomics that the number and quality of spectral databases has increased more significantly over the past 5 years. However, this growth creates other problems that need to be addressed soon to allow for palpable progress in metabolomics. Two major issues are conspicuous, which could be best addressed by coordinated and unified actionsin future.
3. Only 5–10% of the known metabolites had been reported in compound centric databases. A significant rise in MS, MS/MS, and MSn spectra from authentic chemical standards should be tackled through an international initiative bringing together both organic chemistry and metabolomics groups, and likely involving both the academic sector and commercial companies.
4. Despite the indisputable presence of naturally occurring unknown metabolites (i.e., not discovered previously) from untargeted metabolomic studies, it is ambiguous whether this phenomenon is distorted due to errors in adduct/ fragment elucidation and chemical/background noise. This problem can be partially consigned by a newer frontier of metabolomic databases characterized by well-construed mass spectra containing all adduct and fragment species for reference substances. Moreover, saving full scan (MS1) spectral data from authentic chemical standards showing the divergence of adduct formation would enable the development of estimated methods to deal with the illustration of mzRTfeatures in LC/MS-based untargeted metabolomic studies.
5. There are two opposite trends in spectral databases. The first is that in addition to human competence, more and more estimated MS methods are still being used to improve the quality of reference accurate mass spectra. This includes the signal processing and filtering to remove co-isolated peaks, automatic illustration of formulae to fragment peaks, and recalibration of spectra or even the annotation of fragment structures. In addition to the augmented information, all these steps serve as an additional quality control of the spectra, including detection, for example, fragment peaks that cannot be deciphered with a formula that is a subset of the parent ion.

Proteomics[25]

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 performanceof proteomic experiments. Cleanness of samples in relation to non-protein contaminants dramatically affects the protein identification rate. The current trend in simplifying sample preparation steps and handling minimal quantities of biological material has led to the integration of protein extraction, digestion, and fractionation in a single pipette tip that holds a small disk of membrane-embedded separation material, the so-called StageTip. Extrapolating these protocols to plant material is challenging given protein scarcity and the abundance of interfering compounds in plant cells, but it is an exciting challenge because the benefits for research of SM

will outweigh development efforts.

Pharmacovigilance[24]

Pharmacovigilance (PV or PhV), which is referred to as Drug Safety. It is one ofthe pharmacological science 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.

Organic/Inorganic Hybrid Nanoflowers[25]

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 hybrid nanoflowers, and detailed mechanisms are expected to emerge.

The application of nanoflower 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.

CONCLUSION:

In this chapter, we reviewed basic principles and most recent advances of LC-MS/MS methodology including sample preparation, separation and MS/MS detection andapplications in the several areas such as quantification of biogenic amines, pharmacokinetic and TDM for immunosuppresants and doping control. Until now, together with advancement including automation in the LC-MS/MS instrumentations along with parallel sample processing, column switching, and usage of more efficient supports for SPE, they drive the trend towards .less sample clean-up times and total run times–high-throughput.

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REFERENCES:

1. Beckett AH and Stenlake GH. Practical Pharmaceutical Chemistry, fourth ed., CBS Publishers and distributors, New Delhi, 2005.
2. Sharma BK. Instrumental methods of chemical analysis, twenty third ed., Goel Publishing House, Meerut, 2004
3. Arpino, Patrick. “Combined liquid chromatography mass spectrometry. Part III. Applications of thermospray”. Mass Spectrometry Reviews, 1992; 11:
4. doi:10.1002/mas.1280110103. 4. Arpino, Patrick. “Combined liquid chromatography mass spectrometry. Part I. Coupling by means of a moving belt interface”. Mass Spectrometry Reviews 1989; 8: 35. doi:10.1002/mas.1280080103.
5. Murray, Kermit K. “Coupling matrixassisted laser desorption/ionization to liquid separations”. Mass Spectrometry Reviews 1997.
6. James J Pitt, Principles and Applications of Liquid Chromatography-Mass Spectrometry in Clinical Biochemistry, Clin Biochem Rev. 2009 Feb; 30(1): 19–34.
LC-MS: Why use it, and what is it, Metabolite Services at JIC,
8. 8. He CM1, Cheng ZH1, Chen DF Qualitative and quantitative analysis of flavonoids in Sophora tonkinensis by LC/MS and HPLC. Chin J Nat Med. 2013 Nov;11(6): 690-8.
9. 9. Richard B. van Breemen Liquid chromatography/mass spectrometry of carotenoids Pure 84 Appl. Chem., 69(10): 2061-2066,
10. 10. Wu, S.-W., et al. "A novel LC-MS2 product dependent parallel data acquisition function and data analysis workflow for sequencing and identification of intact glycopeptides," Analytical Chemistry, May, 2014; 86: 5478–86.
11. Peptide Mapping and Small Protein Separations with Charged Surface Hybrid (CSH) C18 and TFA-Free Mobile Phases M.A. Lauber, S.M. Koza, K.J. Fountain Waters Application Note 720004571EN 2013
12. Shah RP1, Sahu A, Singh S, Identification and characterization of degradation products of irbesartan using LC-MS/TOF, MS(n), on-line H/D exchange and LC- NMR.J Pharm Biomed Anal. 2010 Apr 6; 51(5): 1037-46.
13. 13. Nair Anroop et. al. / Quantitative Bioanalysis by LC-MS/MS: A Review JPBMS, 2010; 7(01): 1-9.
14. Sommer.U et.al., LC-MS-based method for the qualitative and quantitative analysis of complex lipid mixtures, J Lipid Res. 2006 Apr; 47(4): 804-14.
15. Ju-Seop Kang (2012). Principles and Applications of LC-MS/MS for the Quantitative Bioanalysis of Analytes in Various Biological Samples, Tandem Mass Spectrometry - Applications and Principles, Dr Jeevan Prasain (Ed.), ISBN: 978-953-51-0141-3.
16. Oksman-Caldentey K-M, Inz´e D. Plant cell factories in the post-genomic era: new ways to produce designer secondary metabolites. Trends Plant Sci. 2004; 9(9): 433–440.
17. Lifeng Han, Erwei Liu, Agyemang Kojo, et al., “Qualitative and Quantitative Analysis of Eclipta prostrata L. by LC/MS,” The Scientific World

Journal, vol. 2015, Article ID 980890, 15 pages 18. Jin Li et.al., "An Improved LC-MS/MS Method for Simultaneous Determination of the Eleven Bioactive Constituents for Quality Control of Radix Angelicae Pubescentis and Its Related Preparations," The Scientific World Journal, vol. 2015, Article ID, 2015; 365093: 10.
Dr. I.E. Cock et al., GC-MS and LC-MS analysis of Kakadu plum fruit extracts displaying inhibitory activity against microbial triggers of multiple sclerosis, Pharmacognosy Communications Volume 5 | Issue 2 | Apr-Jun 2015
18. Gunnar Brandhorst and Michael Oellerich Liquid Chromatography–Tandem Mass Spectrometry or Automated Immunoassays: What Are the Future Trends in Therapeutic Drug Monitoring?, Clinical Chemistry 2012; 58(5): 821–825.
19. Steiner WE, English WA (2012) Emerging Trends in Liquid Chromatography and Mass Spectrometry Instrumentation for Analytical & Bioanalytical Techniques. J Anal Bioanal Techniques 3:e106. doi:10.4172/2155-9872.1000e106
20. Wu AHB, French D, Implementation of liquid chromatography/mass spectrometry into the clinical laboratory, Clin Chim Acta (2012).
21. Thomas O metz et.al., The future of liquid chromatography-mass spectrometry (LC-MS) in metabolic profiling and metabolomic studies for biomarker discovery, Biomark Med. 2007 Jun; 1(1): 159–185.
22. Chi Chen, Frank J. Gonzalez & Jeffrey R. Idle, LC-MS-Based Metabolomics in Drug Metabolism, Drug Metabolism Reviews, 2007; 39(2-3): 581- 597.
23. Guodong Chen, Application of LC/MS to proteomics studies: current status and future prospects, Drug Discovery Today, May 2009; 14(9–10) 465–471.
24. Sami Ahmed Khalid, Pharmacovigilance of Herbal Remedies: Current State and Future Prospects, Conference: The 6th annual post-graduate conference, the medical & health Science studies,, At Soba Medical Campus, Khartoum, Sudan.
25. Lee et al., Organic–inorganic hybrid nanoflowers: types, characteristics, and future prospects, J Nanobiotechnology, 2015; 13(54): 1-10.