Vol. 13(1), pp. 1-6, July-December 2021
DOI: 10.5897/BMBR2021.0288
Article Number: 99FBEF067986
ISSN 1538-2273

http://www.academicjournals.org/BMBR

ACADEMIC JOURNALS
expand your knowledge

Biotechnology and Molecular Biology Reviews

Review

A review on benefits of mass spectrometry for the small molecule drug discovery

Iqra Bano[1,2*], Usman Dawood Butt[3], Ali Hafiz Akbar[4], Syed Agha Hasnain Mohsan[3] and Safia Arbab[5]

[1]School of Pharmaceutical Sciences, Zhengzhou University, Zhengzhou, China.
[2]SBBUVAS, Faculty of Bio-sciences Sakrand, Sindh, Pakistan.
[3]Ocean College, Zhejiang University, Zhoushan 316021, China.
[4]School of Pharmaceutical sciences, Zhengzhou University, Zhengzhou, China.
[5]Key Laboratory of Veterinary Pharmaceutical Development, Ministry of Agriculture, Lanzhou Institute of Husbandry and Pharmaceutical Sciences, Chinese Academy of Agricultural Sciences, Lanzhou 730050, China.

Received 27 August, 2021; Accepted 12 October, 2021

The drug discovery is a very much time consuming as well as costly procedure. The Mass Spectrometry (MS) technology offers the aptitude for characterization, identification, as well as quantification of a target entity in a complex matrix and has settled into a leading analytical tool in the field of medicinal chemistry and drug discovery. However, by using specific MS-based techniques including personalized sample design, coupling to the gas and liquid chromatography and various ionization techniques, both qualitative as well as quantitative analysis of small molecular drug particles can be obtained. The current review describes MS strategies which are used to enhance and accelerate drug identification besides degradation linked impurities in active pharmaceutical ingredients (API) or articulated products. The level of protein expression is often termed as proteomics research. With use of MS technology, we can learn more reliable as well as dynamic ways of protein analysis.

Key words: MS, drug discovery, active pharmaceutical ingredients (API), spectroscopy.

INTRODUCTION

The development of a new drug to meet the patient's needs has become increasingly complex and costly procedure (Johnson et al., 2021). Besides, the entire process requires taking a new molecular entity, to determine a legalized target and generate a practicable lead applicant and marketing and universal launch of the formulation of a dosage. This whole procedure may take several years and can also be too much costly (DiMasi et al., 2003). The drug discovery comprised various stages including drug discovery basics, preclinical advancement, clinical development, and production of drug and the longest stage is a clinical development. The safety and pharmaceutical profile of the compound are defined during Phase I (Atanasov et al., 2021). The development of Phase II focuses on compound potency, the establishment of the pharmaceutical dosage spectrum, and the collection of acceptability and safety, and efficacy. The last task is to complete human safety and

*Corresponding author. E-mail: iqrashafi05@yahoo.com.

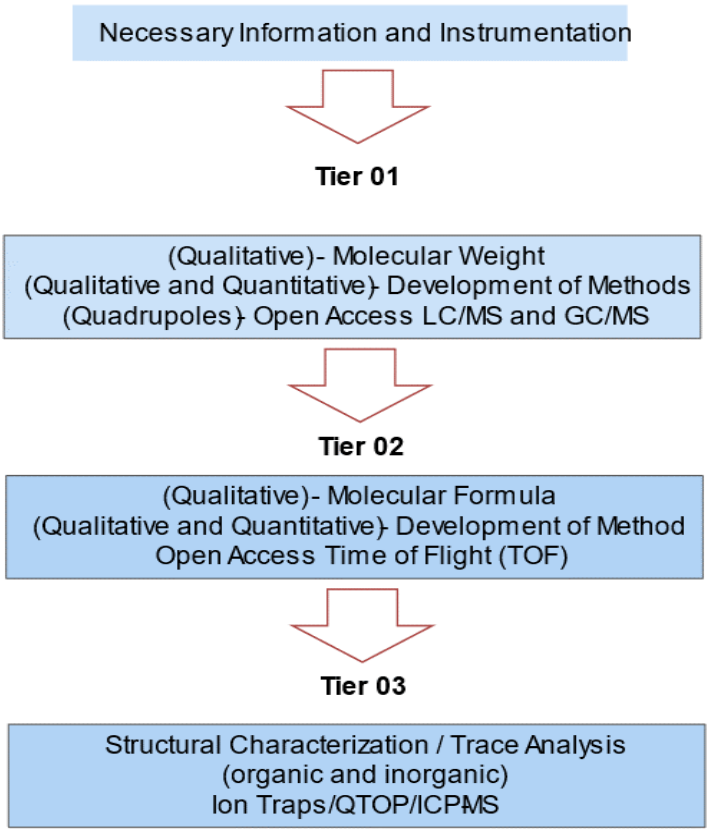

Figure 1. Flow scheme showing the tiered approach for utilization of mass spectrometry information and instrumentation during the various stages of drug development.

effectiveness programs, as well as to secure board approval for marketing activities in Phase III of clinical development (Weitzel et al., 2011). Spectroscopy focuses primarily on light dispersion and other radiation caused by an object that makes it possible for various object characteristics to be studied. The spectroscopy measurements are based on the wavelength of the observed radiation (Motoyaji, 2020). Spectroscopy of various molecular particles was extensively used because it permits the determination of the composition, physical and electronic structure (Zhang et al., 2020). Mass spectrometry (MS) is a type of spectroscopic technology to determine the quantity and type of chemicals in the sample by analyzing the mass-to-charge ion ratio. The principle of MS is that the compounds ionize into ions when samples are bombarded with electrons. The ion separation depends on its load-to-load ratio. A valuable tool for quantities of known material is MS. It also allows unknown compounds to be identified and the structure and chemical composition of various substances to be determined (Leurs et al., 2016). The linkage of MS to a chromatographic system has been done since long time in pharmaceutical research. In such cases the analyte is collected and then analyzed. The MS can be coupled with chromatographic systems online via three fundamental techniques which are gas chromatography (GC), liquid chromatography (LC) and capillary electrophoresis (CE). This study focuses on the application to support clinician development of orthogonal-mass spectrometric methodologies. Some excellent reviews of the use of LC/MS have been prepared throughout the entire drug process. Using MS for the early stage development of pharmaceutical products is not well documented in the literature, as regards the drug discovery and metabolism areas (Rufer, 2021). The proprietary nature of the work performed can be attributed to that. As plentiful of the technique progress evidence is likely to be used during this stage of process development, there have been hesitations to deploy the MS as a strong, routine method to control the synthesis of some vigorous medicinal ingredients (API) in the production process or as part of the dosage release control strategies (Mazurek et al., 2021). Figure 1 shows a flow scheme that shows the level approach. For example, fast analytical approaches that offer nominal molecular weight statistics are indispensable in the preliminary stages of a synthetic practice. Using LC/MS and GC/MS, which habitually offer the required

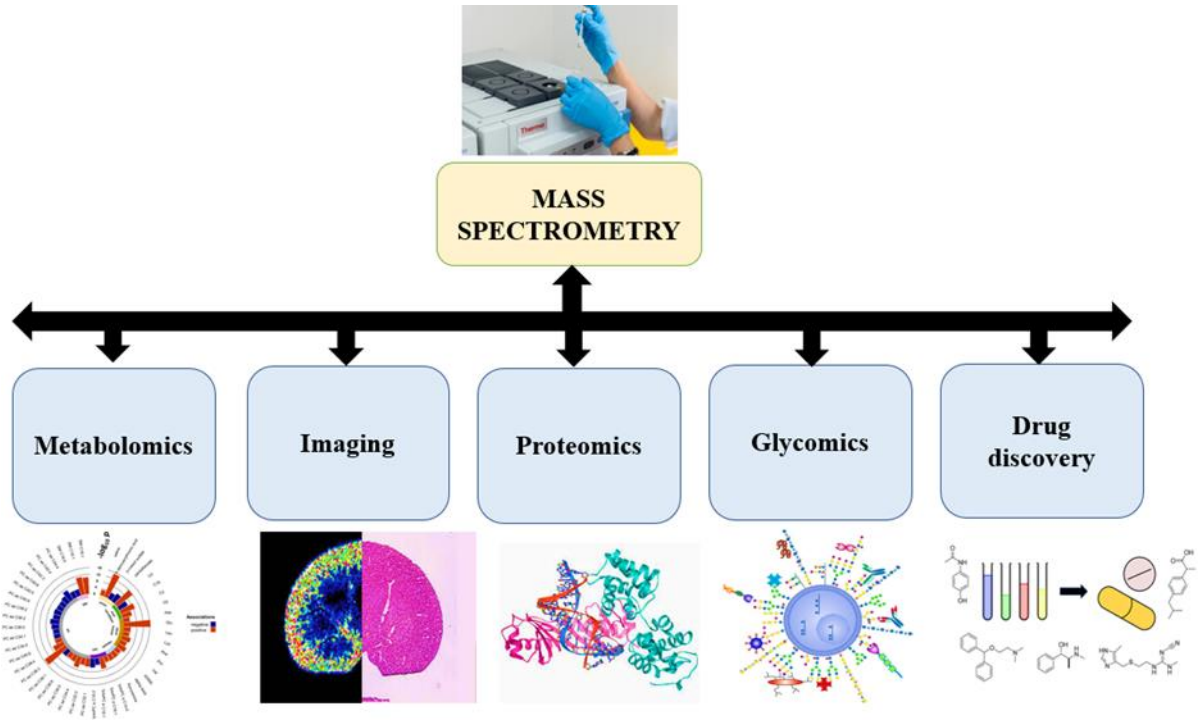

Figure 2. The uses of MS technology in various biological applications.

information and which all scientists involved in product detection can access easily, are often adequate to identify process-related impurities, together with process chemist knowledge and associated chemistry (DiMasi et al., 2003). This review reflects the multi-stage approach to lab analysis and characterization within the development of pharmaceutical products. It offers an understanding of several MS practices used to investigate contaminants and degradation particles found both in medicines and in the advancement of dosage forms. A brief review of employed quantitative tests during product design and some directions and applications for the future that control many advantages for MS will also be discussed.

TARGETED MS ASSAYS

MS can be applied for verification and quantitative validation of an identified biomarker and drugs in the last four decades; the speed, sensitivity and quantitative precision in biomolecular analysis have been increased by targeted MS approaches (Papac and Shahrokh, 2001). MS has become a powerful tool in proteomics research to accurately identify protein molecular mass and sequences (Mitra, 2021). Two main MS-based protein documentation approaches are available, counting sequencing and searching for a database of peptide mass fingerprints (PMF). Proteins are finally identified by computing methods from the peaks of the captured mass spectra, each peak representing an ion of a peptide fragment. The fragmentation of peptides and proteins provides sequence information to identify protein and to identify and locate post-translational or other covalent changes in tandem mass spectrometry (TMS) (Pepi et al., 2021). The uses of MS technology in various different biological applications are as shown in Figure 2. The triple quadrupole instruments present in MS has several advantages such as selectivity, sensitivity, and ability to monitor various reactions at a time during all the duration of chromatographic elution gradient; it, therefore, builds a targeted biomarker assay platform (Parker and Borchers, 2014). Millisecond rapid duty cycles can be easily attained because of the evolution of the computational processing speeds. It monitors a comprehensive list of single reaction transitions, the product and/or fragment ions; permitting rapid serial iterations of analysis of sequences of the multiple peptides. It should be noted that relying on a single reporting data is not strong enough when compared with monitoring several reporting data. By combining mass accuracy, predictable, innovative, and certifiable fragmentation outlines, and also the sequence-specific retention times generate trust in the interpretation of single transition data. By using Multiple Reaction Monitoring (MRM) for single sequences can be helpful to achieve trust when the number of transitions has been enhanced that act as an internal control to verify precursors' molecular weight and the retention time. By advancement in the computational power, it causes reduction in MS scan rates; capability of

MS to change scanning focus in real-time (Kitteringham et al., 2009). The ultra-high pressure liquid chromatography is being used to separate the peptides; and before that, high-performance liquid chromatography had been used for the separation of fractioned peptide mixture (Li et al., 2021). The single chromatographic run can easily analyze various peptide biomarkers and drugs with several transitions for each peptide within the instruction of µs/scan (Xiao and Oefner, 2001). Further expansion in the list of peptides can be achieved by scheduling ranges of detection within chromatographic run; it therefore will allow enhancement in targeted analysis for a single injection. It is recommended that artificially prepared peptides that have been standardized must confirm accuracy in explaining the transition state conditions. Till now many software and programs have been designated like skyline programs, which provide help in numerous ways how to decline time that is used to develop the method. These programs calculate estimated collision energy of any peptide sequence entered by using the [CE = slope × (precursor m/z) + intercept]. Thereafter, it is verified extrinsically. The program can upload entire protein sequence or list of proteins, and also comprehensive proteome. Subsequently, digesting enzyme is nominated, algorithm will then estimate cleavage spots (Miller and Spellman, 2014). Many of the very positive characteristics were small molecules identified in the implementation of the targeted MS for peptide and protein analysis (Gillette and Carr, 2013).

MS AND CHARACTERIZATION OF DRUG INTERACTION SITES

A recent clinical and translational explosion of interest in targeted MS for peptide and protein measurement is rooted in a technological turn of the century (Bano and Sciences, 2018). For the characterization of the protein-lining area, MS practices can be effectively applied. This requires the digestion by endopeptidases of the protein-ligand complexes to generate the peptides and proteins (like ligand-modified-peptides) which are more conducive to MS analysis. Then these peptides are usually chromatographically separated by online MS analysis (Kumar et al., 2021). In addition, as tandem MS can induce the fragmentation of selected ions, the precise residues responsible for the binding can be determined with a detailed analysis of the corresponding spectrum of fragmentation (Bano et al., 2016). Besides the small-molecule-treated sample, the investigational design should predict a parallel analysis of an unprocessed preparation (control). Until the ions enter the weight analyzer, it is essential to maintain the protein ligand binding. Because of this, the probability of the interaction characterization rises with the binding stability, so these studies are addressed more sufficiently in covalent interaction situations (McCabe et al., 2021). The ligand-modified sequence(s) in a large unmodified cluster of peptides are often difficult to detect. The combination of different scan modes in hybrid systems makes use of recent MS-based applications to ionize the signal of interest effectively (Schulz et al., 2019). The diagnostic ion particle is selected as a fragment resulting from a fragmentation of the small molecule or medication. Only peptides released from this fragment can therefore be isolated and analyzed and positively nominated from the complex blend of peptides (Maia et al., 2020). The scanning process is then combined with other high resolution analysis scans (precision in mass labeling and charging determination) and improved ion scanning of product to cause fragmentation this is called a precursor ion scanning method (PIS) (Jian et al., 2021). The PIS measurements are very useful for simplifying analyses and for selecting the peptides of interest through ion filters. It has the advantage over other MS approaches; it does not require previous knowledge of analyses (both regarding mass/z and sequence); the amount of modified peptide and the limited capacities of the diagnostic ion selected for efficient filtering of the ions are limited by these methodologies (Aslebagh et al., 2019). These MS technologies were used to characterize a variety of PTMs such as nitration, phosphorylation, methylation or acetylation (Ito, 2007). In order to achieve a successful selection the changed peptides in the complex blend of large quantities of non-modified ions, hybrid MS technologies have not only led to major progress in the characterization of post translational modifications (PTMs) but correspondingly in the study of proteins in the biologically based specimens, even with small amounts of protein (Rinehart and Barber, 2017).

THE DETECTION OF DRUG IMPURITIES

During the development of HCPC methods, MS spectrometry is an important instrument for measuring chromatographical purity of APIs (Keykhosravi et al., 2019). The standard MS methods guide the comparison of content and various related substances from many validation procedures, toxicology paths based on component mass rather than UV spectrum, and retention time (Mazurek et al., 2021). The LC/MS often overcomes UV or diode array detection limitations because of analogous absorption properties of thoroughly connected impurities and a lack of adequate chromophore for short-sensitivity. Various examples of LC/MS used in an API purity evaluation can be found in the literature. The presence and number of unclean materials can possess a momentous influence on the worth and safety of the API during the drug synthesis process (Weitzel, 2011). Moreover, the LC/MS could be an integral element in the full characterization of impurity outlines. An example shown was a multidimensional evaluation of peptide

drugs. The advantages of LC/MS can be further enhanced by linking this approach with NMR analyses. Many API impurities involve more than simple information on molecular weight, in particular if impurities have the same molecular weights. This can be done by isolating and collecting impurities using prepared HPLCs. The MS can also be used for validation of distant peaks prior to additional classification with NMR (Nordon et al., 2001). Additional specialized methods have been assessed for profiling the impurities of drug substances. In combination with MS detection, this method was also grounded on uniform separation technique; however, the capillary electrophoresis (CE)/MS was used for profiling of impurities rather than conventional LC/MS (Phadke et al., 2019). A key factor in characterizing and specifying APIs was the identification of the potential metal contamination. Traditionally, this type of tests is used to ensure that the final API material comprises little or no inorganic material. For the identification of heavy metals, ICP-MS was shown (Chahrour et al., 2017). During phthalocyanine compound synthesis, the time-of-flight MS (TOF-MS) was used to screen cyclic, metallization and bromination reaction (Nordon et al., 2001). Low mass spectral data is providing molecular weight data which can simply identify molecular weights compared with theoretical ones (Atri et al., 2020). However, precise weight statistics were used to identify fractional ionizations that allow a detailed characterization of the structure of phthalocyanine dyes during the ionization process (Bano et al., 2021). When exposing to definite chemical and physical situations, it may be useful to determine potential process impurity pathways and degrading products observed in a drug subject during chemical synthesis (Schulz et al., 2019). The capability to find an empirical formulation for a pseudo-molecular ion and the distinguishing pieces of the molecular ion can also be accurately established (Masson et al., 2017).

CONCLUSIONS AND FUTURE PERSPECTIVE

In recent years, many developments in new devices and software have been made to help apply MS methods in product development. Recently, trace levels contaminations up to 0.1% or less present in the drug element have to be identified and quantitative. If quantity and confirmatory identification can be achieved in a single analysis, this might increase productivity and decrease costs. The characteristics of pharmaceutical products, especially regarding counterfeit medicines, are also possible applications of MS in the product development. The number of fabricated drugs that have raised up anxieties with supervisory authorities and therapeutic producers has recently increased. For the verification of APIs, as well as excipient and polymeric coatings found in therapeutic formulations, various kinds of MS techniques have been used for counterfeited medicinal products. In some cases, in the current regulatory environment, an even more specific resource of distinguishing pharmaceuticals is compulsory. In recent years, a stable isotopic isotope API characterization through the isotope ratio mass spectrometry (IRMS) provides highly specific method to determine the source of the pharmaceutical starting material. The review is not intended to be inclusive, but was written to emphasize the general practice of MS methods in the fields of drug progression and development over past years and the significant increase in those techniques. By means of information, rich knowledge (especially MS) will grow in products development in an earlier stage of the development of project knowledge. One can imagine that LC/MS will shortly turn out to be the "gold standard" for implementing a control approach, particularly for early phase development and the development of routine methods. The expected removal of boundaries between detection and verification is a successful consequence, replacing the continuum with a single integrated LC-MS/MS platform. This can determine how much these advanced technologies get older.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

REFERENCES

Aslebagh R, Wormwood KL, Channaveerappa D, Wetie AGN, Woods AG, Darie CC (2019). Identification of Posttranslational Modifications (PTMs) of Proteins by Mass Spectrometry. In: Woods A, Darie C (eds) Advancements of Mass Spectrometry in Biomedical Research. Advances in Experimental Medicine and Biology, vol 1140. Springer, Cham. https://doi.org/10.1007/978-3-030-15950-4_11

Atanasov AG, Zotchev SB, Dirsch VM, Orhan IE, Banach M, Rollinger JM, Barreca D, Weckwerth W, Bauer R, Bayer EA, Majeed M, Bishayee A, Bochkov V, Bonn GK, Braidy N, Bucar F, Cifuentes A, D'Onofrio G, Bodkin M, Diederich M, Dinkova-Kostova AT, Efferth T, El Bairi K, Arkells N, Fan T-P, Fiebich BL, Freissmuth M, Georgiev MI, Gibbons S, Godfrey KM, Gruber CW, Heer J, Huber LA, Ibanez E, Kijjoa A, Kiss AK, Lu A, Macias FA, Miller MJS, Mocan A, Müller R, Nicoletti F, Perry G, Pittalà V, Rastrelli L, Ristow M, Russo GL, Silva AS, Schuster D, Sheridan H, Skalicka-Woźniak K, Skaltsounis L, Sobarzo-Sánchez E, Bredt DS, Stuppner H, Sureda A, Tzvetkov NT, Vacca RA, Aggarwal BB, Battino M, Giampieri F, Wink M, Wolfender J-L, Xiao J, Yeung AWK, Lizard G, Popp MA, Heinrich M, Berindan-Neagoe I, Stadler M, Daglia M, Verpoorte R (2021). Natural products in drug discovery: advances and opportunities. Nature Reviews Drug Discovery 20(3):200-216.

Atri V, Causon T, Hernandez-alba O, Mutabazi A, Veuthey J, Cianférani S, Guillarme D, Atri V, Causon T, Hernandez-alba O, Mutabazi A, Veuthey J (2020). Adding a new separation dimension to MS and LC-MS : What is the utility of ion mobility spectrometry ? To cite this version: HAL Id : hal-01702282.

Bano I, Baloch AR, Arbab S, Sajjad H, Talpur MSH, Khalid A (2021). A Novel Concept for Nano-Selenium Supplementation to Fight against COVID-19. International Journal of Clinical and Experimental Medicine Research 5(3):264-268.

Bano I, Sajjad H, Sajjad M, Talpur H, Leghari A, Mirbahar KH (2016). Role of selenium on oxidative stress and male reproductive system. Pakistan Journal of Biochemistry and Molecular Biology 49(4):75-79.

Bano I, Sciences A (2018). Research progress on the role of melatonin

and its receptors in animal reproduction : A comprehensive review. October 2017. https://doi.org/10.1111/rda.13188
Chahrour AO, Malone J, Collins M, Salmon V, Greenan C, Bombardier A, Ma Z, Dunwoody N (2017). Development and validation of an ICP-MS method for the determination of elemental impurities in TP-6076 active pharmaceutical ingredient (API) according to USP ⟨232⟩/⟨233⟩. Journal of Pharmaceutical and Biomedical Analysis. https://doi.org/10.1016/j.jpba.2017.06.045
DiMasi JA, Hansen RW, Grabowski HG (2003). The price of innovation: New estimates of drug development costs. Journal of Health Economics 22(2):151-185.
Gillette MA, Carr SA (2013). Quantitative analysis of peptides and proteins in biomedicine by targeted mass spectrometry. Nature Methods 10(1):28-34.
Ito K (2007). Impact of post-translational modifications of proteins on the inflammatory process. Biochemical Society Transactions 35(2):281-283.
Jian L, Yuan X, Han J, Zheng R, Peng X, Wang K (2021). Screening for illegal addition of glucocorticoids in adulterated cosmetic products using ultra-performance liquid chromatography/tandem mass spectrometry with precursor ion scanning. Rapid Communications in Mass Spectrometry 35(3):1-2.
Johnson AR, Forster SP, White D, Terife G, Lowinger M, Teller RS, Barrett SE (2021). Drug eluting implants in pharmaceutical development and clinical practice. Expert Opinion on Drug Delivery 0(0). https://doi.org/10.1080/17425247.2021.1856072
Keykhosravi S, Rietveld IB, Couto D, Tamarit JL, Barrio M, Moussa F (2019). Criterion towards Regulatory Considerations. Materials 2p.
Kitteringham NR, Jenkins RE, Lane CS, Elliott VL, Park BK (2009). Multiple reaction monitoring for quantitative biomarker analysis in proteomics and metabolomics. Journal of Chromatography B: Analytical Technologies in the Biomedical and Life Sciences 877(13):1229-1239.
Kumar SP, Sherpa DD, Sahu AK, Jadav T, Tekade RK, Sengupta P (2021). Innovation in bioanalytical strategies and in vitro drug-drug interaction study approaches in drug discovery. Bioanalysis 13(6):513-532.
Leurs U, Mistarz UH, Rand KD (2016). Applications of Mass Spectrometry in Drug Development Science pp. 253-289. https://doi.org/10.1007/978-1-4939-4029-5_7
Li Z, Zhang X, Liao J, Fan X, Cheng Y (2021). An ultra-robust fingerprinting method for quality assessment of traditional Chinese medicine using multiple reaction monitoring mass spectrometry. Journal of Pharmaceutical Analysis 11(1):88-95.
Maia TM, Staes A, Plasman K, Pauwels J, Boucher K, Argentini A, Martens L, Montoye T, Gevaert K, Impens F (2020). Simple Peptide Quanti fi cation Approach for MS-Based Proteomics Quality Control. https://doi.org/10.1021/acsomega.0c00080
Masson GR, Jenkins ML, Burke JE, Masson GR, Jenkins ML, Burke JE, Masson GR (2017). Expert Opinion on Drug Discovery An overview of hydrogen deuterium exchange mass spectrometry (HDX-MS) in drug discovery discovery. Expert Opinion on Drug Discovery 12(10):981-994.
Mazurek S, Pichlak K, Szostak R (2021). Quantitative determination of vitamins a and e in ointments using raman spectroscopy. Processes 9(1):1-9.
McCabe JW, Hebert MJ, Shirzadeh M, Mallis CS, Denton JK, Walker T E, Russell DH (2021). the Ims Paradox: a Perspective on Structural Ion Mobility-Mass Spectrometry. Mass Spectrometry Reviews 40(3):280-305.
Miller RA, Spellman DS (2014). Mass spectrometry-based biomarkers in drug development. Advances in Experimental Medicine and Biology 806:341-359.
Mitra G (2021). Emerging Role of Mass Spectrometry-Based Structural Proteomics in Elucidating Intrinsic Disorder in Proteins. Proteomics 21(3-4):1-14.
Motoyaji T (2020). Drug Discovery : Recent Progress and the Future Revolution of Small Molecule Drug Discovery by Affinity Selection. Mass Spectrometry Technology 68(3):191-193.
Nordon A, McGill CA, Littlejohn D (2001). Process NMR spectrometry. Analyst 126(2):260-272.
Papac DI, Shahrokh Z (2001). Mass Spectrometry Innovations in Drug Discovery and Development 18(2).
Parker CE, Borchers CH (2014). Mass spectrometry based biomarker discovery, verification, and validation - Quality assurance and control of protein biomarker assays. Molecular Oncology 8(4):840-858.
Pepi LE, Sanderson P, Stickney M, Amster IJ (2021). Developments in mass spectrometry for glycosaminoglycan analysis: A review. Molecular and Cellular Proteomics 20:100025.
Phadke R, Mundhe A, Gosar A (2019). Drug Impurity profiling an emerging task to Pharmaceutical Industries now days - A Review. 9(March).
Rinehart J, Barber KW (2017). The ABCs of PTMs Karl. Physiology & Behavior 176(3):139-148.
Rufer AC (2021). Drug discovery for enzymes. Drug Discovery Today pp. 1-12.
Schulz S, Becker M, Groseclose MR, Schadt S, Hopf C (2019). ScienceDirect Advanced MALDI mass spectrometry imaging in pharmaceutical research and drug development. Current Opinion in Biotechnology 55:51-59.
Weitzel KM (2011). Bond-dissociation energies of cations—Pushing the limits to quantum state resolution. Mass spectrometry reviews 30(2):221-235.
Xiao W, Oefner PJ (2001). Denaturing high-performance liquid chromatography: A review. Human Mutation 17(6):439.
Zhang X, Li Q, Xu Z, Dou J (2020). Mass spectrometry-based metabolomics in health and medical science : a systematic review. RSC Advances pp. 3092-3104.