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METHOD OF VALIDATION AND EQUIPMENT OF MS AND APPLICATION IN PHARMA INDUSTRY

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Abstract : *Verification is the process of approving documentation showing that the following process / method or activity consistently produces a product that leads to the expected results (predetermined requirements). The pharmaceutical industry validation program includes various components related to processing, refining, equipment, equipment, or equipment. This review briefly describes one of the most preferred verification methods, device verification. Device validation details its type, the type of document required, and the application / importance of validation in the pharmaceutical industry. Today, device validation is becoming a regulatory requirement for pharmaceutical companies to precede the validation of new devices / devices. The verification process, on the other hand, requires detailed knowledge of the equipment to be verified. Therefore, verification is usually performed by the company that provides this equipment. Introduction Over the last few decades, mass spectrometry (MS) has evolved into a state-of-the-art drug analysis technology that covers both qualitative and quantitative aspects. In fact, the range of MS is expanding at an unprecedented rate, with new applications being developed almost every day. Related to this is the evolution of instrumentation to meet the ever-increasing demands on sensitivity and throughput, which can lead to increasing regulatory requirements.*

Keywords: **Mass spectrometry, Validation , Accuracy , refining** .

I. INTRODUCTION

The verification process is documented evidence that provides a high level of assurance of the desired results with pre-determined compliance. The term verification is widely used in the pharmaceutical industry. The term is derived from the word "valid" or "valid" and means "established by law". The concept of validation was first proposed by the Food and Drug Administration (FAD) in the mid-1970s to improve the quality of medicines. This is because various procedures, methods, or measures have been validated to check and improve quality. [1-2]

1) Verification method

Verification is divided into the following subsections.

1. Verification of analysis method

2. Process verification

3. Cleaning verification

4. Device Verification

An overview of the various types of verification processes and a detailed description of the phase of device verification and its importance in the pharmaceutical industry.

1. Validate Analytical Methods:

The purpose of analytical validation is to verify that the analytical method you choose provides reliable results that suit your purpose. There are various parameters that apply to validation of analytical methods. These are:

• specification

• Linearity

• Area

• Detection limit

• Quantitative limit

• Accuracy

•accuracy

•Reproducibility

•Reproducibility

2. Process validation: This type of validation provides documented evidence that provides a higher level of assurance that the process consistently produces products that meet all specified quality attributes and specifications. Process validation also guarantees process reproducibility and reduces the risk of manufacturing problems leading to increased production at certain qualities. There are four types, based on the production level of process validation:

1. Positive verification

2. Simultaneous verification

3. Retro-specific verification

4. Expansion.

3. Cleaning Verification: Cleaning verification provides a documented facility with a high level of assurance that certain systems / equipment or parts of equipment are consistently cleaned to a given quality and tolerance. increase. Pharmaceuticals are contaminated with various substances such as lubricants, suspended particles, prepared product residues, and microorganisms. Therefore, proper cleaning procedures play an important role in avoiding contamination and mutual contamination. [3]

4. Device Verification: Device Verification is a well-established, documented feature that demonstrates that each device functions correctly and produces acceptable and accurate results (predetermined results). The device verification process is based on the principle that devices must be designed, designed, maintained, and adapted to perform the operations they perform. Equipment is a fundamental part of the pharmaceutical industry. Therefore, it is of utmost importance to publish a device validation (documented device proof) before running the process in the pharmaceutical industry types of device verification. The device validation process is not a one-step activity, but it consists of various Phases with additional subsections or steps. These are:

I. Design qualification

II. Installation eligibility

III. Operational qualification

IV Performance qualification

V. Process certification

Device verification type:

The process of verifying pharmaceutical devices in the pharmaceutical industry is very simple. The various stages of the process are thoroughly investigated and documented according to the approval of the pharmaceutical industry / company. The procurement process usually begins with the creation of the required documentation and user requirements specifications (URS). To run a validation project / plan (VP), you need to get a form change request (CR) from an existing facility. A validation project (VP) request is issued because management has previously agreed to continue. You can then use the approved VP to initiate the validation protocol required to ensure that all requirements documented in the URS and all cGMP requirements are met. The device verification process is basically divided into three phases. [4-5]

1. Phase 1 : Pre-verification phase.

2. Phase 2: Process verification phase.

3. Phase 3: Validdation maintenance phase.

1. Pre-verification Phase Design Certification (DQ):

This is a documented verification of the design of equipment and production equipment. The main purpose of design certification is to ensure that all system requirements are first clearly defined. The design certification process shows that all quality aspects are fully considered during the design phase. It defines the functional and operational specifications of equipment with all requirements, as detailed in the User Requirements Specification (URS) and applicable cGMP rules and regulations. The implementation of documented qualifications must demonstrate that a given design complies with :Functional Specifications (URS) Functional Specifications (FS) Bid Texts and Drawings Purchasing Specifications Supplier Qualifications Functional Specifications (URS): Contains a list of customer requirements / expectations for equipment. Typical customer requirements are as follows: [6]

- Unit size and footprint.
- Effectiveness and durability of equipment.
- Device operating speed.
- Equipment should be quiet and air polluted.
- Spare parts availability and also provide service at minimal cost.
- Overall good structure.
- Installation Qualification (IQ): The Installation Qualification is an accurate design in a undamaged format that receives the specified equipment, is installed on the target, and has parts, spares, service gauges, and other necessary connections. Or make sure the format is agreed. Document to verify that the device is properly installed and calibrated. The purpose of IQ isThe device is properly installed and adheres to the original (URS) design. Workplace conditions have been documented and confirmed to be suitable for operating equipment, according to the manufacturer's installation recommendations. [7]

  The installation documentation includes:

  - Supplier and manufacturer information.
  - Device name, color, model, serial number.
  - Installation and calibration date.

2. Process Verification Phase:

Certification of Operation: Certification of operation ensures that the installed device / equipment functions properly according to the operation specifications under the specified environmental conditions. Also, make sure your device is fully functional to meet pre-established performance standards and see how test results are recorded. The purpose of operational certification is to ensure that all dynamic conditions are in good agreement with the original (URS) design. For verification,

it includes traceable electrical stimulators and standards to verify that the device is being processed correctly as needed. Operational entitlements ensure a high level of functional verification of the device's compliance with the manufacturer's specifications and user-required specifications (URS). Operational entitlements, also known as process validation, include processing validation: Completed and approved operation of the equipment from the user and manufacturer's point of view with appropriate document review It depends not only on the functionality of the equipment, but also on the stability of each unit throughout the system that contributes to the analysis results. [8]

Performance validation documentation includes:

- Performance Certification Report .
- Process Stability Test Report (Long-Term Productivity) Product Record Acceptance (Customer Review) .
- Actual Product and Process Parameter Documentation.
- Documentation of routine test results.
- Revalidation: Revalidation is performed if the operational equipment and system change for any reason. Revalidating the equipment is very helpful in maintaining the verification status that the equipment and the entire system are functioning as one unit. The revalidation procedure also helps to regularly check verifications according to government guidelines.

  The revalidation is further subdivided as follows:

  - Periodic / Planned Revalidation .
  - Change Revalidation / Changes

  The periodic revalidation process is a revalidation process that is performed regularly in the pharmaceutical industry. This is especially required if the company makes changes to the formulation, process, manufacturing system, packaging, and support systems such as power / power, water, and steam. In the case of equipment revalidation, the analyst comes from the manufacturer and another well-qualified team for the revalidation process. Making small changes to a product can have a significant impact on the quality of the product and should be validated even after making small changes .During the initial validation, operational and performance tests could be rerun.

  Below are changes that require revalidation these are:

  - Raw material changes.
  - Manufacturing process changes.
  - Device / system changes.
  - Support system changes.
  - Change of packing material.

3. Verification maintenance phase

• Maintenance Qualifications (MQ): Maintenance entitlements confirm and validate acceptance of maintenance management to verify device / system integrity. Maintenance requires regular, documented reviews of processes and systems / equipment. This is a regular process that ensures that the equipment does not compromise its safety, quality, strength, and identity of the manufactured product due to either its contamination or its structure. The maintenance certification process includes regular maintenance and necessary repairs.

Maintenance credential documents include:

• External service record

• Maintenance contract details

List of Certified Service Technicians

Applying Device Verification: The following is the importance of device verification in the pharmaceutical industry.

1. Device validation reduces costs by reducing scrap, redo, and downtime.

2. Reduce the risk of non-compliance.
3. High customer satisfaction.
4. Analytical test method and calibration will be performed.
5. It also reduces testing during processing and final products.
6. It also raises employee awareness.
7. Simplify equipment maintenance.
8. Faster and more reliable test runs of new devices.
9. Support the creation of a facility verification master plan.
10. The verification document can be used as a template for inspection. (As legal evidence).

Equipment Of Mass Spectrometry:

Over the last few decades, mass spectrometry (MS) has emerged as a front-runner technique inpharmaceutical analysis, covering both qualitative and quantitative aspects. In fact, the area of use ofMS is increasing at such an unprecedented rate that new applications are getting developed almost ondaily basis. Coupled to it is advancement in the instrumentation, which is trying to keep pace with theever increasing demands on sensitivity and throughput, guided at times by the increasing stringency of regulatory requirements.Of the many analytical techniques used in drug discovery and development, MS is employed extensively for characterization and analysis of a wide range of biological and chemical entities. Because of the enhanced sensitivity, selectivity, and ease of automation that is available with liquid chromatography (LC) coupled with MS (LC-MS and LC-MS/MS), a large number of absorption, distribution, metabolism and elimination (ADME) assays with high throughput have been incorporated into drug discovery programs. In particular, tandem MS/MS has opened an avenue for broader and newer applications.Utilization of higher mass resolution and sensitivity in quantitative assays, a wide range of ionization methods, possibility of single ion monitoring (SRM) or multiple reaction monitoring (MRM) and availability of a variety of sample processing/clean-up methods has expanded the implications of MS even in the pharmaceutical industry. Accelerated advancements in this field are also adding worthwhile milestones in biotechnology, as well as various "-omics" (proteomics, lipidomics, metabolomics, etc).It is thus of importance for a pharmaceutical scientist to understand the variety of MS systems available in the market, including their areas of applications . Over the last few decades, mass spectrometry (MS) has emerged as a front-runner technique in pharmaceutical analysis, covering both qualitative and quantitative aspects. In fact, the area of use of MS is increasing at such an unprecedented rate that new applications are getting developed almost on daily basis. Coupled to it is advancement in the instrumentation, which is trying to keep pace with the ever increasing demands on sensitivity and throughput, guided at times by the increasing stringency of regulatory requirements. Of the many analytical techniques used in drug discovery and development, MS is employed extensively for characterization and analysis of a wide range of biological and chemical entities. Because of the enhanced sensitivity, selectivity, and ease of automation that is available with liquid chromatography (LC) coupled with MS (LC-MS and LC-MS/MS), a large number of absorption, distribution, metabolism and elimination (ADME) assays with high throughput have been incorporated into drug discoveryprograms. In particular, tandem MS/MS has opened an avenue for broader and newer applications.

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The field of application. [10]

Types of mass spectrometers:

In general, each mass spectrometer consists of three instruments associated with the three basic steps of MS analysis.

- An ion source for generating the analysis target and its kind of gas phase ions.
- A mass analyzer that separates mass-to-charge ratio (m / z) of an ionized object based on the mass-to-charge ratio (m / z).
- A detector that measures the amount of each mass-to-charge ratio (m / z). A wide variety of all three devices are available.

These are described in detail below.

1 Ionization source :

Electronic impact (EI)

The electron beam passes through the gas phase sample and collides with the neutral molecule of analysis (M) to produce positively charged or fragmented ions 4. This ionization is a more difficult type. In general, the energy provided by electrons, , which is roughly equivalent to to 70 eV, is sufficient to exceed the bond dissociation energy of most covalent bonds present in organic molecules. This method is applicable to all volatile compounds (> 103 Da), provides a reproducible mass spectrum, and provides fragmentation to the Can be used in both positive and negative modes, depending on the chemical structure of the analyte.

Chemical impact (CI):

Chemical Ionization (CI): Ionization begins when the reagent gas (R) is ionized by electron impact and then reacts with the analyte molecule (M) to produce the analyte ion5. It's a softer technique than El. Therefore, it provides molecular weight information in addition to fragmentation. Commonly used reagent gases are hydrogen, isopropane, ammonia, and nitrous oxide. An important change in Cl that applies for orthogonal use with HPLC is the generation of ions at atmospheric pressure. This technique is called atmospheric chemical ionization (APCI). A flow of liquid is guided and a spray is formed with a pneumatic (usually nitrogen) nebulizer. The plume of the emerging droplets is directed at the corona discharge electrode and is usually maintained at 1 ± 3.5 kV6.

Fast Atomic Impact (FAB):

Analysts in liquid matrices such as glycerol are impacted by a powerful particle stream. B. Ar, Xe or Cs with an energy of 4-10 KeV. The particles are accelerated by an electric potential, producing a fast jet of ions of interest 7. This is a soft ionization technique and is usually suitable for the analysis of low volatile species that produce large peaks in quasi-molecules. Ions [(M + H) + and (M-H)], and structurally important fragment ions, dimers, and cluster ions.

Field Ionization (FI):

Equipotential wires generated by high potential application result in a congested field around the needle tip8. The strength of the electric field is maximized at the peak point where ionization occurs. In FI, the sample is heated in vacuum and volatilized on the ionized surface. FI is suitable for use with volatile and thermally stable compounds. Fl sources are subject to change for use in detachable mode. It is suitable for non-volatile and / or heat-unstable materials, where the sample is placed directly on the surface prior to ionization (embedding the emitter in the analyte solution). This is called field desorption (FD) ionization.

Electrospray Ionization (ESI):

In this technique, ionization takes place at atmospheric pressure and is considered a soft ionization method. The solution is sprayed under normal pressure and exposed to a high electric field to generate an electric charge on the surface of the droplet (Fig.

1a). As the solvent evaporates, the droplet size decreases rapidly, producing polyvalent bare ions. It also applies to thermally unstable polymer substances.

Atmospheric Pressure Photoionization (APPI):

APPI is an improved APCI source that replaces the corona electrode with a UV lamp and uses photons to ionize gas phase molecules11. In APPI , vaporized samples pass through ultraviolet light (a krypton light source that emits at 10.0eV and 10.6eV). This has become an important source of ionization, as the high ionization potential (IP) of of standard solvents such as methanol and water directly produces ions from a relatively low solution with background .Does not ionize krypton lamps. Therefore, it is much more sensitive and has a higher signal-to-noise ratio than APCI or ESI. You can analyze relatively non-polar compounds**.**

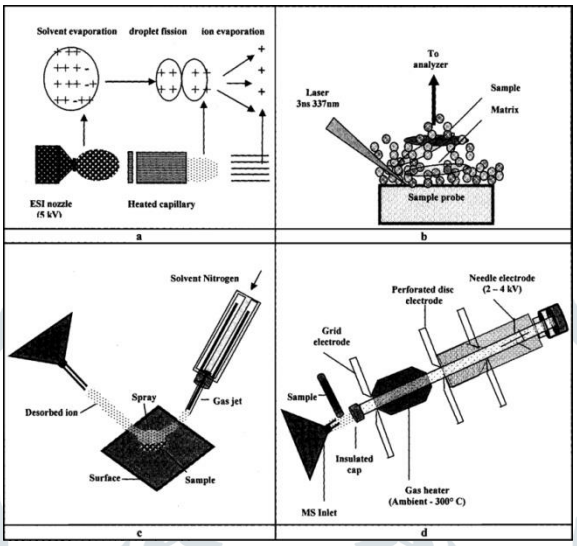

Fig.1. Schematic diagram of Ionization source a) Electrospray Ionization ,b)ionization (MALDI), c)ionization (DESI) and d) Real-time direct analysis (DART)

Real-time direct analysis (DART):

DART is a new source that overcomes many of the shortcomings of traditional ionization techniques and enables high resolution and accurate mass measurements of gases, liquids, and solids, further eliminating the need for sample preparation and modification. There are advantages 920. It is based on the long-lived electron-excited state of an atom or the vibration-excited state of a molecule and the atmospheric pressure interaction with the sample and atmospheric gas. The gas (He or N2) flows through the chamber where the discharge produces ions, electrons, and semi-stable atoms or molecules. Charged particles are removed from the molecule as the gas flows through the electrodes. Only neutral gas molecules and metastable states remain. The exit grid avoids ion-ion and ion-electron recombination and acts as an e-species, electron source via surface Penning ionization. By changing the polarity of the electrodes, DART can operate in both positive and negative ion modes. Detects drugs and metabolites in untreated US body fluids such as blood, urine (such as uric acid from a drop of urine on a glass rod), sweat and saliva directly without preparing a sample. It is also possible to identify alternative active ingredients added to the counterfeit product. For example, dihydroartemisinin (an antimalaria drug) and methyl stearate (used in counterfeit antimalaria drugs) were both detected in tablets with the same nominal mass and no sample pretreatment.

2. Mass spectrometer :

After the sample is ionized, its mass value needs to be analyzed. The ion beam is focused and sent to the mass spectrometer, which separates the ions based on the m / z value. Important parameters of a mass spectrometer are sensitivity, resolution, and mass accuracy. The different types of mass spectrometers are described as follows:

Quadrupole

As the name implies, four parallel rods form the electrodes, with positive and negative terminals for the DC (direct current) source and a variable phase shift radio frequency (AC) applied to each pair of electrodes. Accelerates between the bars while maintaining a stable trajectory in the two planes for the applied field. Ion separation at the quadrupole does not directly correlate with their kinetic energies, but with the relative motion of the ions in a dynamic electric field. Ions with different mass units can

be resolved by modulating the AC and DC potentials to adjust the center of the band. It is a widely used analyzer for combining mass measuring devices with separation techniques such as GC and HPLC. It is superior to other analyzers in terms of ease of quantification.

Ron trap

It consists of a pair of end electrodes and a pair of ring electrodes filled with approximately 1 mTorr of helium. The impulse of the electrostatic ion gate guides the entry of ions into the trap (Fig. 2b). The coupled DC voltage and RF are applied to the electrodes. First, the electric field causes the incoming ions to oscillate and be trapped in a potential well in the center of the analyzer. The trapped ions are focused at the center of the trap using a vibrational potential called the fundamental frequency applied to the ring electrode. Ions are stably trapped according to their m / z value. The ionization cycle is tuned to maximize the signal and reduce the effects of space charge due to too many ions in the trap. Collision with helium reduces the kinetic energy of the ions and causes the orbit to contract rapidly toward the center. This can trap the injected ions. The mass spectrum is obtained by scanning the RF and DC fields to charge destabilize the low mass ions. These destabilized ions are emitted from the holes in the end cap electrode and hit the detector. When you scan the field, ions are emitted from the cell as m / z increases and they are detected, resulting in a mass spectrum.

Time of flight (TOF)

It features simplicity, robustness, unlimited mass range, and fast data acquisition. The conventional TOF arrangement consists of tubes in which ions with different m / z are separated according to the difference. Velocity (Fig. 2c). It is called a linear TOF analyzer. The electric field accelerates the ions with the same kinetic energy obtained during ionization into a fixed-length, non-electric field drift tube. Ion separation is based on the relative velocity in the flight tube and is directly related to momentum, which is a function of mass. Normal flight time is 1 to 30 milliseconds. However, its main drawback is the spread of peaks due to fluctuations in ion velocity during the same m / z flight. Linear TOF equipment is also inherently limited by low resolution. The advent of electrostatic reflector-based TOF analyzers has proven to be an important milestone in mass analyzers. In a reflector-based TOF analyzer, ions are reflected by an electrostatic mirror for subsequent flight. This helps to harmonize the ions with the same m / z value and different kinetic energies to get equal velocities. This leads to improved performance of such equipment. Therefore, reflector-based TOF analyzers are gradually replacing traditional linear TOF analyzers. Despite the complex mechanism, the

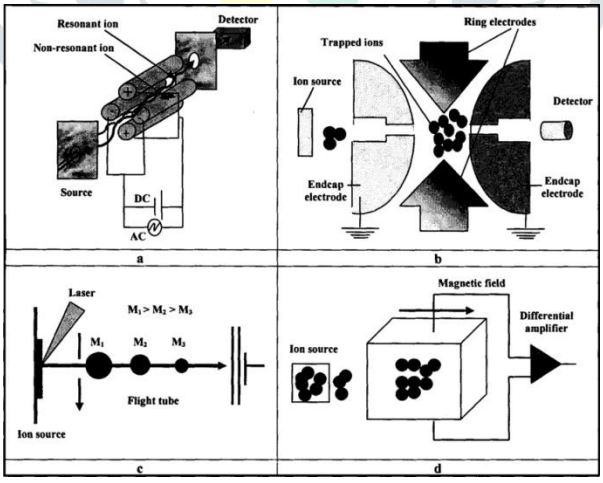

Fig.2 Different Mass Analyser a)quadrupole,b)ion trap , c)time-of-flight ,and d) Fourier transform ion cyclotron.

Fourier Transform Ion Cyclotron Resonance (FT-ICR)

FT-ICR is the most powerful mass spectrometer currently available. It provides ultra-high mass resolution and mass accuracy, non-destructive detection, high sensitivity, and multi-level MSn. The ions drift to a spatially uniform static magnetic field strength, circularizing their motion in a plane perpendicular to the direction of the magnetic field (Fig. 2d). The angular frequency in the trap cell is inversely proportional to the m / z value. The presence of ions between the pair of detector electrodes in the trap cell does not produce a measurable signal. It is important to apply radio frequency (RF) sweeps of a few milliseconds

across the cell to excite specific m / z ions into a larger orbital radius as a consistent packet. You can use the Fourier transform to measure all frequencies at the same time. Each frequency excites a specific m / z, so a mass spectrum is obtained. [11]

3. DETECTORS

In a mass spectrometer, the generated ions are separated, analyzed, digitized, and detected by an ion detector. The detector amplifies the subtle response to produce a useful mass spectrum. A common detector is a Faraday cup, in which fast ions collide with secondary electrons and are emitted. When an electron is generated, a current flows temporarily until the electron is recaptured. This is a simple and robust detector used when high sensitivity is not required. Another commonly used detector is a photomultiplier tube consisting of a series of dynodes.

Hyphen from MS

Because mass spectrometers are a highly selective technique, direct analysis of untreated and raw samples often results in error in characterization / identification or quantification. The composition of the matrix can affect the reaction of interest. In particular, the signal strength of the monitored species by other ions simultaneously generated by the ion source. The advanced components and high vacuum used in mass-produced equipment make them more susceptible to damage and contamination from unwanted components in the sample. These justifications prove that the MS needs to be hyphenated using hyphenation techniques.

Table 1. Commercially available tandem mass spectrometers

Types	Commercially available instruments	Features Available with various ionization sources such as ESI,	Manufactures
Hybrid quadrupole	6410 Triple- Quadrupole LC/MS; 6500 Quadrupole-TOF LC/MS	capillary - ESI, nano-ESI, APCI, multimode ESI/APCI, APPI, and MALDI	Agilent Technologies
	Quadrupole-TOF (QSTAR Elite); Triple quadrupole LC/MS (API 5000, 4000, 3000, 2000)	Increased resolving power, mass accuracy at least 2 orders of magnitude	Applied Biosystems / MDS Sciex
	Quadrupoleiontrap-TOF (ultra-TOF-Q); BioTOF-Q	Available with combination of ESI and MALDI ion sources	Bruker Daltonics
	LCMS-QIT-TOF	High precursor ion selection, higher mass resolution and accuracy	Shimadzu
Hybrid trap	Q TRAP; 4000 Q TRAP	Selectively full scan, MS3 possible	Applied Biosystems
	LTQ™ Orbitrap; LTQ (2D); LXQ; MAT95XL-TRAP	Trapping instruments are capable of MSn experiments hence of great importance in routine analysis	Thermo Electron
TOF-TOF and hybrid	4800 MALDI TOF/TOF	High sensitivity, ultra-high performance, opti-beam on-axis laser system	Applied Biosystems/ MDS Sciex
	AXIMA-TOF2 high energy CID MALDI-TOF/TOF	Gridless ion path, CID with high collision energy	Shimadzu
	MALDI-TOF/TOF	Higher mass resolution, faster data acquisition, with new laser technique	Bruker Daltonics
	DART AccuTOF; APCI/ESI AccuTOF; GC AccuTOF	High resolution, exact mass measurement, with DART, nondestructive analysis in real time possible	JEOL

All isolation techniques that are orthogonal to the MS act as independent components of the system, whereas the MS is a dependent component whose output is the former function. Since both gas chromatography (GC) and MS work in gas phase species, their binding is fairly simple and efficient in terms of sample pretreatment and physical laboratory space. However, it does not have the ability to analyze heat-unstable and non-volatile components. In contrast, liquid chromatography (LC) in combination with MS can process a wide variety of samples. Another advantageous feature of LC is its super-selectivity with various chromatographic supports. The most common is Reverse Phase Liquid Chromatography (RPLC) using hydrocarbon bonded phases, especially the most commonly used C18 phase today.

Tandem Mass Spectrometry (Tandem MS)

Tandem mass spectrometry (MS / MS) was developed to elucidate unknown structures and advance mass spectrometry applications for analyzing complex mixtures with minimal sample purification. This technique introduces additional specificity for recognizing specific components in the mixture. The tandem MS is equipped with a total of two mass spectrometers in succession. Similar to LC / MS, the samples are sorted by MS1, then decomposed into fragments in collision cells, and then these fragments are sorted by MS2. In other words, the first mass spectrometer (MS1) selects an ion with a specific m / z value, the so-called precursor or parent ion. It is generated by primary fragmentation. The latter then goes into the fragmentation area or collision cell. The daughter ions are then analyzed on a second spectrometer (MS2. [12]

Pharmaceutical applications :

Drug candidate synthesis and screening

Synthesis and screening of drug candidates Modern drug discovery practices rely heavily on the synthesis of combinatorial libraries. Due to the routine preparation of large libraries for read detection, the focus is primarily on analytical techniques focused on throughput and quality. Analytical and preparative RPLC combined with MS offers such a possibility. On the other hand, the attractiveness of the FT-ICR is increasing in the pharmaceutical industry because it can provide more information for each measurement. This device has evolved rapidly and is currently used in many fields. The FT-ICR contributes to the dereplication and chemical fingerprinting of natural products, including: B. Determining the elemental composition of bioactive large marine organisms and of such natural products. B. Antibiotics. Different approaches based on different combinations The development of ionization and mass spectrometry techniques is also essential for proteomics.

Metabolite Identification and Bioanalysis :

The drug discovery program is highly sought after for rapid and accurate methods in drug metabolism and pharmacokinetics (DMPK) research. The tandem LC-MS system enables rapid analysis of chemically diverse drug candidate panels. The LC-MS-based in vivo pharmacokinetic screening approach allows analysis of large samples and reduces the time available for results. The traditional setup uses a separate autosampler / HPLC column and MS system, and the samples are injected separately. Strategies used to improve throughput include high performance chromatography, automated data processing, and pooling strategies (cassette administration, individualized pooling, simple sample screening, etc.). Using two autosamplers and a column in parallel with one triple quadrupole mass spectrometer reduces the equilibration time of HPLC columns and the general delay associated with sample loading. LC-MS and LC-MS / MS technologies are also very useful in identifying metabolites because they have the ability to predict and detect metabolites in complex samples of urine, bile, and plasma. Metabolite predictions are based on the fact that metabolites are produced from selected in vivo reactions. The software then overlays the predicted metabolites on the resolved metabolites and performs detection based on the fragmentation overlap. In addition, metabolites generally retain most of the core structure of the parent drug, thus exhibiting a similar fragmentation pattern and producing a mass spectrum showing the major substructure. [16]

Impurity identification and profiling

Impurities in the drug substance are synthetic by-products, precursors, intermediates, etc., and drugs are degradation products produced during storage. Due to the stringent regulatory requirements set by various international organizations, including ICH, toxic impurities are of particular concern during safety assessment, process research, and dosage form development, regardless of source. Mass fingerprinting techniques such as LC-MS / TOF, LC-MSn, or the recently introduced LC-MSn-TOF have proven to be highly useful tools for online characterization and structural elucidation of trace concentrations of impurities. I am. Alternatively, use a mass-based sorting tool to make a specific separation. When new contaminants are encountered, retention times, molecular weight information, and substructure fragmentation patterns obtained using MSn and / or TOF can help with rapid identification. CE-MS is also implemented in pharmaceutical impurity profiling.

Stability studies of drugs and drug formulations :

During the development phase, pharmaceuticals and formulations are stress tested under a variety of stress conditions such as temperature, humidity, acidity, alkalinity, oxidation and light. This facilitates validated development of analytical methods and provides estimation information for future formulation and packaging studies. These studies provide a practical approach to structural elucidation of degradation products using the latest LC-MS or LC-MS / MS techniques, as well as information obtained from them such as retention times, molecular weights, fragmentation patterns, etc. Has become important to. Strategies for identifying degradation products in the early stages of development require fast, sensitive LC-MS analysis methods. As a result, you can create a structural database from the results. It is used to identify unstable structures within drug structures and to quickly identify degradation products produced during these studies. These techniques will later be extended during the analysis of long-term, accelerated study stability samples to obtain useful and relevant information. [14]

2.CONCLUSIONS

The unique analytical advantages of mass spectrometry, including speed and sensitivity, coupled with recent advances, promise to make this technology the flagship in connection with a variety of pharmaceutical applications. With recently developed

ionization techniques such as DART and DESI and analyzers such as Orbitrap, MS can study all types of components. In addition, MS / MS, MSN, and MS / TOF add the ability to analyze the structure of compounds present in small and / or complex mixtures. MS sensitivity and high-throughput capabilities should make it a powerful tool in the early stages of drug discovery, including combinatorial chemistry and DMPK research. The same applies to routine analysis such as impurity profiling, stability testing and quality control. The mild nature of the relatively new ionization technology and the structural analysis capabilities of the MS allow mass spectrometry to be expanded into newer fields.

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