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APPLICATIONS OF GAS CHROMATOGRAPHY IN PHARMACEUTICAL INDUSTRIES

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ABSTRACT

The pharmaceutical industry continually evolves to meet stringent regulatory requirements and consumer expectations for safe and effective therapeutic products. These pharmaceutical products may develop impurities at various stages of their development, storage, and transportation, which puts them at risk of being administered; thus, they must be detected and quantified. Central to this evolution are active analytical instruments, which play a crucial role in pharmaceutical research, development, manufacturing, and quality control. The instruments employ advanced technologies to analyze and assess the properties of pharmaceutical compounds by regulatory standards, fostering innovation. All equipment used in the production of pharmaceuticals shall be properly validated and calibrated to demonstrate that it is suitable for its intended purpose. Instruments that are used in the pharmaceutical industry are LC/MS-acquired to provide reliable and accurate data. These pharmaceutical products would do their best if they were free from impurities and administered in.

KEYWORDS: pharmaceutical, impurities, residues, quantification.

BACKGROUND

In the development of pharmaceuticals, innovation and the progress of pharmaceutical research in pharmacology and clinical science play a crucial role (Barry, 1991). The invention of new medications for various diseases has improved life expectancy and quality of life. Every single drug is a combination of excipients and APIs (active pharmaceutical ingredients). APIs are the compounds that possess the chemical ingredients used to treat a

particular disease. These APIs are mainly produced in some countries: the USA, India, China, and Europe. APIs are the major compounds that are biologically and chemically active and do the work in our body. The companies that produce APIs always look for faster and more economical methods; however, the production of APIs generates waste (Kupiec, 2004). For the reduction of waste in the production of APIs, the companies should follow a greener path. The production of drugs involves the addition of excipients to satisfy the needs of patients. Excipients are compounds that are biologically and chemically inactive substances and do not possess any therapeutic properties. Common excipients include lubricants, adhesives, glidants, flavours, colours, and sweeteners. The purpose of adding excipients is to deliver APIs into the body. The drug that is being manufactured should ensure the quality and safety of the drug before marketing. The purity of the drug determines the quality of the drug.

The pharmaceutical products depend on the accuracy of the analytical instruments. Analytical methods play an important role in the adequate realization of product quality credits. However, genuine quality can only be reached if the analytical method undergoes a correct validation process (Jocelyn Paré & Yaylayan, 1997). Analytical validation is a formal and documented tool that measures the ability of an analytical method to provide a reproducible result. By detecting, correlating, and comparing the information about the functional roles of an identical gene using LC/MS, we gain an understanding of cellular biology. High-performance liquid chromatography, or high-pressure liquid chromatography, is a particular form of column chromatography normally used in biochemistry and analysis to identify and quantify active compounds. The choice between checking the peak purity of new chemical entities, monitoring reaction changes in scale-up, assessing new formulations, and carrying out both quality control and assurance on the drug products (Rohde et al., 2022). NMR, which plays a vital role in pharmaceutical studies linked to the purity determination of library compounds, has major studies targeting the evaluation of impurity levels along with structural information, degradation pathways, residual solvent, isomeric composition, and molar ratios of the drug molecule. Gas chromatography (GC) plays a crucial role in the identification and quantification of existing pollutants in the environment. It is also fundamental for analysing nonpolar and semi-polar, volatile and semi-volatile chemicals.

1. GAS CHROMATOGRAPHY (GC)

Gas chromatography is an analytical instrument that is used for the separation of complex compounds based on their polarity. Based on the polarity of the carrier gas flowing through

the column, the sample gets adsorbed in the stationary phase of the column. The inert gases like either helium or nitrogen are used as carrier gas used in gas chromatography. Samples of liquid are vaporized before being injected into the carrier stream. A substance with greater interaction with the stationary phase remains in the column for a longer time and therefore separates from one with a lesser interaction. (Jwaili, 2019). Gas chromatography is applied in various fields including pharmaceutical fields such as impurity profiling, residual solvent analysis, functional group identification, metabolomics, analysis of drugs of abuse and clinical toxicology.

Principle

In gas-liquid chromatography, the stationary phase is a thin layer of non-volatile liquid bound to solid support, and separation occurs via the process of partition. In gas-solid chromatography, a solid adsorbent is used as a stationary phase, and separation occurs through the adsorption process (Becker, 2007). Gas-liquid chromatography is the method that is most frequently utilized. The intended separation sample is first turned into vapors and then combined with the gaseous mobile phase. A sample's more soluble components move more slowly in the stationary phase while its less soluble components move more quickly. As a result, the components are divided based on their partition coefficient.

1.1 Impurity Profiling

During the synthetic process, raw materials, intermediates, and/or byproducts can lead to impurities in pharmaceutical compounds (Custers et al., 2014). Profiling of impurities reveals the need for and scope of the process in pharmaceutical science by obtaining and evaluating data that establishes their biological safety. Impurities include residual solvents, by-products, transformation products, degradation products, interaction products, and related products. Impurity profiling involves the identification, elucidation of structures, and quantification of impurities and degradation products in bulk drugs and pharmaceutical formulations. Increasing the safety of drug therapy requires the identification and determination of impurities by selective methods. Impurities have become increasingly important in modern pharmaceutical analysis because unidentified, potentially toxic impurities pose a risk to health. Impurities can be identified by various chromatographic techniques. The isolation and the characterization of impurities can be achieved simultaneously during the chromatographic separation process. Due to the ease of access to bench-top instrumentation and their distinctive advantages of versatility, sensitivity, profiling substructure analysis, and rapid

selective quantitative determination of targeted compounds even in mixtures, hyphenated techniques are increasingly used for impurity determination. Unlike GC, HPLC, MS, or NMR, hyphenated techniques are not widely used due to their heavy instrumentation costs. Currently, these sophisticated techniques are mostly used to monitor, characterize, and identify impurities.

1.2 Residual solvent analysis

Pharmaceuticals use the term "residual solvent analysis" to describe the examination of organic volatile contaminants that arise as a byproduct of drug product production or during packaging and storage. Drug producers are required by GLP standards to make sure that these residues are either eliminated or are only present in trace amounts in the finished goods. Remaining solvent analysis is a common use of gas chromatography. The two primary detectors utilized to find these volatiles are mass spectrometry (MS) and flame ionization detectors (FID). The most common methods for introducing samples into a gas chromatograph are the solid-phase microextraction method, the static headspace sampler/dynamic head space analyzer, and direct injection of a solution containing bulk drug material or drug product (Hu, 2017).

1.3 Functional group identification

GC in conjunction with IR and UV detectors, are used for identifying functional groups in medicinal molecules. Functional group identification was done using GC-IR before the development of rapid FTIR instruments. The functional groups present in the sample were absorbed in infrared light (IR) by the GC and it was separated later using a column and placed on a salt window in the IR instrument. This method, is similar to GC-MS, involves separation and then infrared spectroscopy identification. GC-UV is another method for identifying particular functional groups and chemicals in complex mixtures. Compound separations are accomplished via an external capillary gas chromatograph connected to the same gas flow cell as well as a micro gas chromatograph integrated into the gas flow cell. 168–330 nm is typically the wavelength range in which analysis is carried out (Lagesson et al., 2000). GC-UV is a versatile tool that can be used to measure flavors, dust, petroleum, and cigarette smoke. The identification of functional groups by comparison with a reference spectrum library is another significant use of GC-UV.

1.4 Gas chromatography in metabolomics

Gas chromatography in conjunction with mass spectrometry has been widely applied in the field of metabolomics research. Drug evaluation, clinical toxicology, nutrigenomics, and functional genomics can all benefit from metabolomics research. GC is renowned for its strong resolving capacity and great reproducibility as a separation technique. GC is connected to time-of-flight (TOF) equipment, which provides precise mass determination to four decimal places, and mass analysers such as the triple quadruple (QqQ), which can be utilized for both qualitative and quantitative analysis. Chemical or electron ionization can ionize compounds that are eluting from a GC column. Applications span a variety of industries, including the food and agricultural sectors, as well as the pharmaceutical and disease biomarker research domains (Capitan et al., 1999). Typically, electron ionization occurs around -70 eV. This procedure is done to ionize the samples, which a mass spectrometer will subsequently detect. The substances are identified by comparing the measured mass spectrum with the mass spectrum stored in the database. Mass spectra and retention times can be recorded in databases to create extremely accurate 2D databases for chemicals that can be shared throughout analytical platforms(Gould et al., 2023).

Compounds that can be volatile or that can be derivatized into a volatile form utilizing a variety of derivatizing agents can be used for GC-based metabolomics studies. Derivatization is the process of changing a compound's chemical structure to facilitate GC identification. Derivatizing agents come in two varieties: selective and non-selective reagents. These derivatizing chemicals aid in changing the volatile character of the drug, enhance stability, and enhance peak tailing and resolution in chromatography. Derivatives are frequently made via salivating, acylating, or alkylating certain functional groups. Analysing biological fluids, a dry stage is carried out before derivatization since moisture can stifle the reaction. By choosing the appropriate reagents, the derivatization process can also be carried out in aqueous solutions. There are many easy-to-use derivatization kits accessible. A common derivatization agent that produces TMS derivatives is trimethylsilyl. The metabolomics database contained several TMS derivatives. The advantage of this technique is expanded to include a wider range of metabolites by the development of new derivatization protocols for non-volatile compounds, which also allow for overlap with other platforms such as liquid chromatography. It is also possible to employ many instruments in tandem to comprehensively map an organism's or sample's profile through the measurement of metabolites with a variety of physiochemical characteristics. Another advantage of this

technique, it is possible to quantify the discovered metabolites using an external standard method or an internal one by employing QqQ detectors. Ions will be specifically eliminated both before and after fragmentation using this approach and guarantees that only ions from the precursor ion will reach the detector. Selected/multiple reaction monitoring is the term used to describe this kind of tandem MS investigation and enhances the crucial parameters of selectivity and sensitivity for the identification of metabolites. Accurate quantization in complicated biological samples can be carried out at extremely low levels if isotopically labelled internal standards are accessible and reasonably priced.

1.4 Clinical Toxicology

Clinical toxicology can benefit from molecular ion formation, a wider spectrum of substances that can be analysed with GC, its high sensitivity, and its quicker analysis times. Clinical toxicology is the typical use for supersonic GCMS (Butera & Butera, 2024). In some circumstances, this is also used to confirm or reject LCMS analysis findings. This technique is typically used to identify and measure toxins and venoms.

CONCLUSION

The fact that GC is limited to volatile substances or molecules that can be chemically modified to become volatile at a temperature where they disintegrate is one of its main drawbacks. Strongly held components occasionally pass slowly along the column by raising the temperature in the temperature programming when an unknown mixture of chemicals is injected. However, depending on the type of column, there is a maximum limit to what it can bear. This is an additional drawback of gas chromatography. GC is widely used in the pharmaceutical and clinical fields for both research and quality control purposes, such as quality assurances, production, pilot plant developments for active pharmaceutical ingredients, bulk drugs, and formulations, despite the few limitations mentioned above. Due to its high detector sensitivity and high resolving power, it is also employed for the identification of impurity components in pharmaceutical biotechnology, pharmacognosy, and pharmaceutical process control.

ABBREVIATIONS

GC: Gas Chromatography

NMR: Nuclear Magnetic Resonance

API: Active Pharmaceutical Ingredients

MS: Mass Chromatography

HPLC: High Performance Liquid Chromatography

FID: Flame Ionization Detectors

IR: Infrared Spectroscopy

GLP: Good Laboratory Practices

FTIR: Fourier Transform Infrared Spectroscopy

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