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Review Article

A Comprehensive Review on Analytical Methods for The Estimation of Pharmaceuticals

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ABSTRACT

A proper approach that enables the scientist to analyse the drug molecule in the most exact, precise, and simple manner is necessary for the process of developing new medications. Finding the optimum approach for method development is crucial for the quantitative and qualitative estimate of pharmaceuticals in analytical chemistry. This research aids the author in comprehending the many analytical methods that may be used in the drug development process, including spectroscopy, chromatography, electrochemical methods, electrophoretic analysis, flow injection, and hyphenated method. All of these strategies use several independent methodologies and distinct analytical processes. We also talk about the current, unwavering trends that may be applied to all of these procedures to enhance their analytical behaviour. The validation of the document in terms of accuracy, precision, specificity, limit of detection, linearity, and range is necessary during the method development phase. Thus, this review article includes a concise assessment of the analytical approaches that are now accessible as well as the most recent developments in method development, method validation, and method development. Several chemical and instrumental techniques that are used in drug estimation have been developed over time in order to make medications function as intended. These medications must be recognised and quantitated since contaminants can form in them at different points during production, transit, and storage, making administration dangerous. Analytical tools and techniques are crucial in this regard. In determining the quality of the medications, this study emphasises the importance of analytical procedures and equipment. The study covers many analytical methods that have been used in the examination of medicines, including titrimetric, chromatographic, spectroscopic, electrophoretic, and electrochemical.

INTRODUCTION

The invention of a drug molecule that has demonstrated therapeutic value to fight, control, check, or cure illnesses is the first step in the drug development process. Identification of medication

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candidates for more in-depth research requires the synthesis, characterisation, and analysis of these molecules, which are also known as active pharmaceutical ingredients (APIs), as well as their examination to produce preliminary safety and therapeutic effectiveness data. Pre-drug discovery research is based on understanding the underlying causes of the diseases that need to be treated, the genetic changes that lead to the diseases, the interactions between proteins and the affected cells, and the changes that these affected cells bring about and how they affect other cells. Based on these data, a substance is created that interacts with the afflicted cells and may ultimately evolve into a drug molecule or active pharmaceutical ingredient (A.P.I). This is known as drug discovery and development, or R&D, which is the process of creating new products. The separation, estimation, and quantification of chemical substances acquired from both natural and artificial sources are all possible with the use of drug analysis in analytical chemistry. These substances generally consist of one or more chemical substances. [1] Qualitative and quantitative analysis are the first two main categories in the analytical chemistry process. Just the samples that can be obtained are estimated in qualitative analysis, and the total number of components in a compound should be recognised in quantitative analysis. For instance, because it considers life, the examination of a wide range of chemicals or products is beneficial for the analysis of medications. Several pharmaceuticals have been launched onto the market today, and the need for drugs is rising daily.[2] The recently developed pharmaceuticals are either a brand-new kind or a modified version of ones that are already on the market. These medications are described with reference to the commercially available medications and pharmacopoeial scenarios. To report on the best therapeutic agents for withdrawal on the market, pharmacopoeia had to be used in drug development. The analytical profile of a drug may occasionally not be available in pharmacopoeias during drug development. In that situation, it is required to prepare the crucial analytical techniques for the creation of new medications. [3] Many compounds are created by inventors during the medication development process, and they can simply assess their structure, behaviour, and assist detect impurities in a molecule. If every parameter has been set up to target the medication, bioassays will be run on the pharmaceuticals to determine how they will behave analytically. Scientists have recently concentrated on tiny chemical molecules as well as substances derived from natural or manmade sources. [4] High Performance Liquid Chromatography (HPLC), High Performance Thin Layer Chromatography (HPTLC), Liquid Chromatography-Mass Spectrometry (LC-MS), and other techniques are suitable for the analysis of these big or tiny compounds. These analytical methods are frequently employed for the detection of substances using mass spectrometry and the other methods previously discussed. [5] High performance liquid chromatography (HPLC), a highly helpful technique, was a key and improved method for drug analysis. The liquid chromatography-mass spectrometry approach was also crucial for the analysis of pharmaceutical medications and helpful for research into the metabolism of pharmaceuticals. These methods can also be used to analyse, estimate, and identify pharmaceutical goods that include impurities, products that have undergone degradation, or products that are utilised to separate out and describe a drug's potential from diverse natural and synthetic sources. [6,9,11]

The following requirements are important for the analyst to build the best, appropriate, simple, and accurate method:

- Data are necessary to address every analytical challenge.

- Sensitivity is required.
- It's crucial to work accurately.
- Recommended range for drug analysis
- Accuracy is needed while developing a procedure.

The method validation process, in which the documents are checked as part of any method development process, is also included in the method development process. In order to analyse the method, the many needs for the validation of documents include:

- Quality control
- Approval by the specified international organisations for product development
- Registration of pharmaceutical or pesticide goods should be necessary.
- Only after acceptance is accomplished through testing does the validation procedure take place.
- The product should also be verified after the quality control division completes its required tasks. [7]

The "compound" that will become the drug molecule is put through a series of safety tests and experiments to show that it is absorbed in the blood stream, distributed to the right site of action in the body, adequately metabolised, and demonstrates its non-toxicity. As a result, it can be regarded as safe and effective. Preclinical research, including in vitro investigations, is carried out after the drug is finished. This includes animal testing to verify kinetics, toxicity, and carcinogenicity tests. The regulatory authorities approve the clinical studies following the pre-clinical testing. Clinical trials determine whether or not the treatment is acting according to the suggested mechanism and determine the best dosage and schedule, while the latter two stages produce statistically significant data about the drug's effectiveness, safety, and overall benefit-risk relationship. At this phase, the possibility for drug interactions with other medications is assessed, and the long-term efficacy of the drug is tracked. The medications are made available to patients when the clinical studies are successfully completed. [20,22]

Table 1: provides a review of the various phases of clinical trials.

Phase of clinical Trial	Number and type of subject	Investigations
Phase 1	50-200 healthy subjects (usually) or patients who are not expected to benefit from IMP	Is the IMP safe in humans? What does body do the IMP? What does IMP do to the body? Will the IMP work in patients?
Phase 2	100+400 patients with target disease	Is the IMP safe in patients? Does the IMP seem to work in patients?
Phase 3	1000+5000 patients with the Target disease	Is the IMP really safe in patients? Does the IMP really work in patients
Phase 4	Many thousands or millions of patients with the target disease	Just how safe is th new medicine? How does the new medicine compare with similar medicines?

ANALYTICAL TECHNIQUES FOR METHOD DEVELOPMENT

Spectroscopic techniques [23]

The most crucial technology for the method development procedure was spectroscopic technique. This method is based on the natural absorption of UV rays and other chemical processes as described in our pharmacopoeias. [24] The quantitative measurement, characteristics transmission, and wavelength function are the

foundation of spectroscopy. This strategy has the major benefit of saving time and labour costs. Also, this method is quite accurate and precise. This approach was specifically used in pharmaceutical analysis to examine the dose forms in the pharmaceutical industry, which has been steadily growing. [26.29] Aspects of the colorimetric approaches include the following as well:

- Complex reaction formation
- Oxidation and reduction processes
- Catalytic ions' impact

1. *UV-Visible Spectroscopy*

The energy, radiation, or excitation of electrons is the foundation of the UV visible spectroscopy technique. With the UV-Visible technique, the energy light used to excite electrons is what determines the sample's wavelength. The absorbance ranges from 200 to 800 nm. Only when conjugated pi electrons are present does the absorption take place. [30]

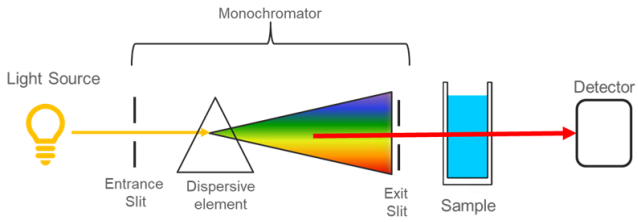

Figure 1: Schematic diagram of UV-Visible spectroscope

2. *FTIR Spectroscopy*

A few atoms and molecules vibrate or are excited when infrared spectroscopy causes the absorption to move into its lower energy state. This technique helped scientists create a novel way by identifying the functional group and the original peaks with relation to the molecule. [33,34]

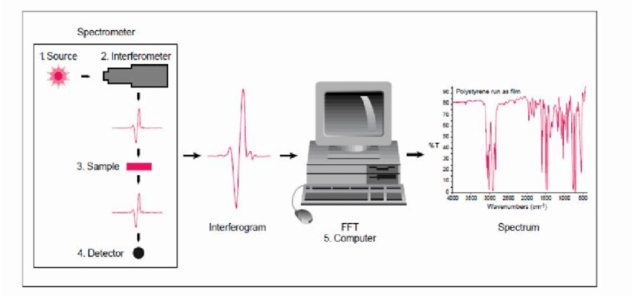

Figure 2: Schematic representation of FTIR spectrophotometer

3. *Mass Spectroscopy (MS)*

The samples of molecules used in mass spectroscopy were ionised by high energy electrons. The variations in the magnetic field and the acceleration of the electrostatic waves, which preserve the precise weight of molecules, were used to precisely measure and evaluate the mass of each charge. [36]

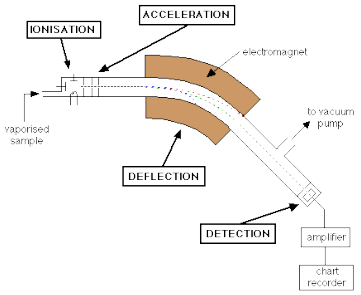

Figure 3: Diagram of Mass spectrometer

4. *Nuclear Magnetic Resonance Spectroscopy (NMR)*

In the recent years, scientists have developed a variety of ways to solve the analytical issues with novel pharmacological compounds. For the creation of pharmaceuticals, the nuclear magnetic resonance spectroscopy method was extensively employed. [15] This method helped with drug identification and quantitative drug analysis to identify compounds in the medications. Also, this method's technique helped analyse drug composition, chemical products, and identify the medications employed in biological fluids and pharmaceutical formulations.

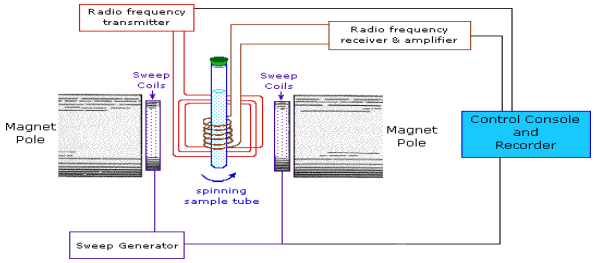

Figure 4: Representation of Nuclear Magnetic Resonance

5. Fluorimetry and Phosphorimetry

Fluorimetry and phosphorimetry methods were continuously improving in our pharmaceutical sectors for the study of tiny samples. Fluorimetry allows for the analysis of very sensitive systems without sacrificing method specificity or precision. In earlier investigations, a steady increase in the number of applications for fluorometry or phosphorimetry was seen. [20] These approaches for estimating various medications quantitatively that are available in the form of biological fluids have been used for some time.

Titrimetric techniques

The titrimetric method of analysis has its roots in the middle of the 18th century, maybe. Gay-Lussac created the volumetric technique in 1835, which eventually gave rise to the name "titration." Even though the assay method is very old, there are signs of modernization, such as the spread of non-aqueous titration, the extension of the range of applications of titrimetric methods to (very) weak acids and bases, and the improvement of method precision through potentiometric end point detection. Titrimetric approaches have been demonstrated to be helpful in kinetic measurements, which are then used to determine reaction rates, with the introduction of functional group analysis processes. These approaches have a number of benefits, including the fact that they save time and effort, are very precise, and do not require reference standards. For the determination of captopril, albendozole, and gabapentin in commercial dosage forms in the past, titrimetric techniques were employed. The nonaqueous titration technique was used to determine the presence of sparfloxacin. Titrimetry has previously been employed for the determination of medicines' breakdown products in addition to its usage in drug quantification. [31]

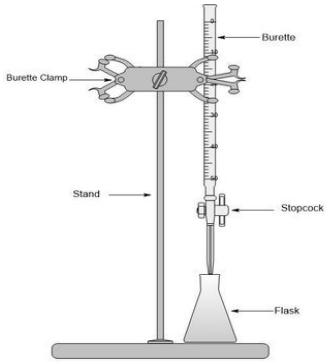

Figure 5: Titrimetric Techniques

CHROMATOGRAPHIC TECHNIQUE

1. High Performance Thin Layer Chromatography (HPTLC)

High Performance Thin Layer Chromatography, for starters (HPTLC)This method was employed all around the world to identify, estimate, and verify the analytical profile of pharmacological compounds. It is a very sophisticated method that will be acknowledged as a key instrumental method for drug analysis. [29] In the pharmaceutical industry, it is possible to test a variety of medicinal components because of its quick separation action and adaptable nature. The key benefit of this approach is the ability to quickly test drugs while also making crude drug sample handling and cleaning simple. This method enables us to describe the chromatogram for a wide number of parameters without time constraints.

2. High Performance Liquid Chromatography (HPLC)

In order to better understand how different molecules function within complicated mixtures of molecules found in chemical and biological systems, high performance liquid chromatography, or HPLC, is utilised. The first

HPLC techniques for the analysis of bulk medicinal compounds came in the year 1980. (United States Pharmacopoeia, 1980). This has evolved into the main approach in USP XXVII (United States Pharmacopoeia, 2004), as shown in Table 2, and to a lesser degree, but still one of the most used ways in Ph. Eur. [4] (The European Pharmacopoeia and Council of Europe, 2002). The HPLC technique has good specificity, and it is also possible to achieve a level of accuracy that is sufficient.

It must be noted, nevertheless, that the astounding specificity, precision, and accuracy can only be achieved if thorough system suitability testing are conducted prior to the HPLC analysis. Because of this, paying for high levels of specificity, precision, and accuracy is also expensive. The most often used system for chromatographic procedures, according to the literature review, has been HPLC. To ensure that all the components are identified in liquid chromatography, the choice of detection method is crucial. One of the most often used HPLC detectors is the UV detector, which has the ability to simultaneously monitor various wavelengths. This is only achievable by using a multiple wavelength scanning software. The UV detector ensures that all UV-absorbing components are identified if it is present in sufficient quantities. In an integrated circuit (IC) chip, a photodiode array (PDA) is a lined array of discrete photodiodes used for spectroscopy. It is positioned at the spectrometer's picture plane to enable simultaneous sensing of a variety of wavelengths. To ensure that all of the peaks are recognised when a variable wavelength detector (VWD) is employed, a sample must be injected repeatedly with varying wavelengths. While using PDA, all the substances that absorb within a certain wavelength range may be discovered in a single examination after the wavelength range has been programmed. By comparing the spectra within a peak, PDA detectors may also determine peak purity. PDA detector is used in the pharmaceutical industry to create iloperidone technique. When detecting analytes such alcohols, sugars, carbohydrates, fatty acids, and polymers that have limited or no UV absorption, one should use a refractive index detector. By minimal noise, decent trace detection performance is ensured. While it has the lowest sensitivity of any detector, this one is nonetheless effective at large analyte concentrations. The refractive index detector was used by Lakshmi and Rajesh to examine the volgibose content pharmaceutical formulations. [37]

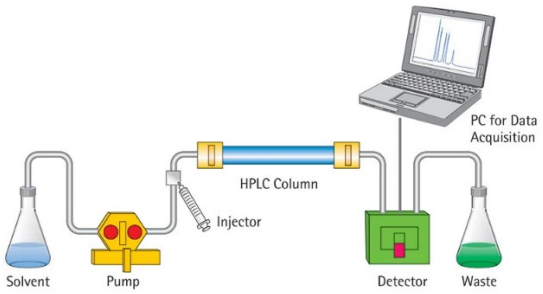

Figure 6: Schematic layout of HPLC system

3. Thin Layer Chromatography (TLC)

Although being a historical method, it is nevertheless very useful in the research of drugs. An adsorbent solid phase is thinly placed on a solid substrate in thin layer chromatography, which is frequently composed of glass, plastic, or aluminium. Many factors affect how successful this type of chromatographic separation is. The adsorbent must first demonstrate high selectivity towards the components being separated in order for there to be discernible variations in the rate of elution. For the separation of any specific combination, certain adsorbents may be either too strongly or too weakly adsorbing. Several adsorbents are listed in Table 3 in ascending order of adsorptive power. Thin layer chromatography is a favoured method for the analysis of a variety of organic and inorganic substances due to its distinctive advantages, which include less sample clean-up, a vast selection of mobile phases, flexibility in sample separation, high sample

loading capacity, and low cost. TLC is a useful technique for discovering unidentified ingredients in bulk pharmaceuticals. The certainty that all possible medication components are separated is rather high. The great specificity of TLC has been exploited for quantitative analytical applications via spot elution and spectrophotometric analysis. The presence of certain steroids, pioglitazone, celecoxib, and noscapine has been detected using TLC. Ashour et al. TLC is essential in the early phases of drug development since there is limited knowledge about the contaminants and degradation products in the drug material and drug product. Several pharmaceutical pollutants have been found and named using TLC. [41,42]

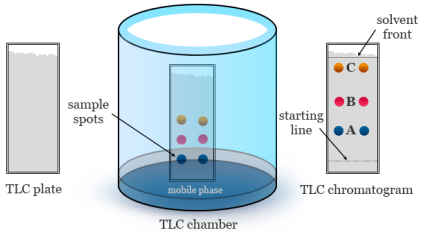

Figure 7: Diagrammatic representation of Thin layer Chromatography

4. Gas Chromatography

Moving on to a different chromatographic method, gas chromatography is an effective method for separating substances to find volatile organic molecules. Accurate quantitative measurement of complex mixtures, including traces of substances down to parts per trillion in some specific circumstances, is made possible by combining separation and online detection. A significant role is played by gas liquid chromatography in the examination of pharmaceutical products (Watson, 1999). The use of this technology is restricted to the production of high-molecular mass products like polypeptides or thermally unstable antibiotics. Derivatization is essentially required because of the relative non-volatility of the pharmacological ingredients, which is its fundamental restriction. Gas chromatography has recently been applied in the measurement of residual solvents in betamethasone valerate as well as the testing of pharmaceuticals such isotretinoin cocaine. Another crucial method for analysing pharmaceutical contaminants is gas chromatography. Residual solvents classified as impurities by the International Conference of Harmonization are evaluated by the GC employing a range of detectors in recent years to estimate the process-related impurities of the pharmaceutical industry.[43]

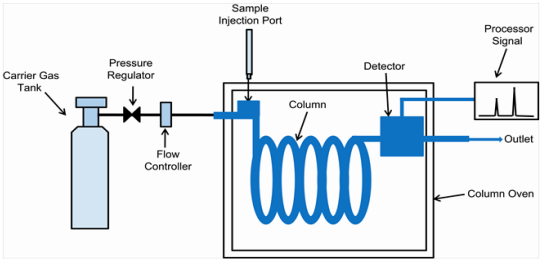

Figure 8: Schematic layout of Gas chromatography

Electrochemical Techniques

Currently, there is a greater need for electrochemical methodology in the pharmaceutical industry than there was in the past for the study of medicinal molecules. Also, a variety of samples are provided for both the quantitative examination of pharmaceutical ingredients as well as drug analysis. [26] Recent advancements in electrochemical methods have made it possible to analyse medications like trimipramine, desipramine, and imipramine, among others, using amberlite XAD-2, titanium dioxide nanoparticles, and carbon plates containing glassy carbon. The following methods, including chronocoulometry, cyclic voltammetry, electrochemical impedence spectroscopy, and adsorptive strip pulse voltammetry, were employed to ascertain the electrochemical behaviour of these compounds. [27]

Electrophoretic Technique

Capillary electrophoresis is the correct term for this method, which is crucial for drug analysis in the pharmaceutical industry (CE). The quantitative examination of materials was carried out by this practical approach electromagnetic field using

capillary electrophoresis, which is entirely based on the electric charge ions. For the separation and analysis of medication components, this method was helpful. The area of traversing the components of a specific peak is directly proportional to the compound concentration and owing during the electrophoresis process, the solute (sample) was passed via capillary to the detector. [32]

Flow Injection Analysis (FIA)

Ruzicka and Hansen introduced the flow injection analysis technique (FIA) in the US and Denmark. This method is based on the automated chemical experiments. The automation of chemical analysis is therefore strongly pursued by FIA, and it is the primary instrument used for chemical analysis measurement in the presence of chemical and physical equilibrium, according to the study's authors. [33]

Kinetic Technique of Analysis

The kinetic approach was created in 1950 and is utilised in automated devices for the examination of numerous pharmaceutical components. The notion of kinetic methodology, which aids scientists in chemical instrumentation processes or is highly relevant in pharmaceutical drug research, data analysis, and method creation, was the major application made. Because the current procedures for drug analysis might halt their flow system and adding reagent continuously was sluggish, this approach was entirely dependent on an automated system. [34]

Hyphenated Techniques

A hyphenated technique is created by combining a separation technique with an online separation approach. In the recent two decades, hyphenated methods and their use in pharmaceutical analysis have advanced significantly. The examination of pharmaceuticals has utilised a number of hyphenated methods, including LC-MS GC-MS LC-NMR (Lindon et al., 2000), CE-ICP-MS. The detection of pharmaceuticals in biological materials is a crucial stage in the creation of new medications. The detection of pharmaceuticals in biological materials is a crucial stage in the creation of new medications. The technique of choice for developing bioanalytical methods is HPLC in combination with several forms of detection, including ultraviolet, fluorescence, and mass spectrometry. For the examination of meloxicam in biological samples and pharmaceutical formulations, a review of HPLC with UV or MS/MS' detection has recently been published. Using the same analytical technique, L-ascorbic acid and acetyl salicylic acid in aspirin C effervescent tablet were simultaneously determined (Rui et al., 2012). A method for the qualitative and quantitative determination of metabolites after oral administration of Rhizome coptidis and Zuojinwan preparation in rat urine has been developed using liquid chromatography-electrospray ionization-mass. Using water (containing 0.1% formic acid) and acetonitrile (30:70 v/v) as the mobile phase, urine samples were separated on a C18 column. New compounds are routinely found in clinical and forensic samples, and recreational drug usage is an issue that is getting worse. The primary analytical phase for the creation of novel pharmaceuticals and drug products is the determination of the medication's base material from biological sources. The following hyphenated strategies were employed to boost the possibility of drug analysis: [44]

- Nuclear magnetic resonance and liquid chromatography (LCNMR)
- Mass spectrometry using liquid chromatography (LC-MS)
- Infrared spectrometry and liquid chromatography (LC-IR)
- Mass spectrometry and gas chromatography (GS-MS)
- Mass spectrometry-capillary electrophoresis (CE-MS)
- Mass spectrometry, photodiode array, and liquid chromatography (LC-PDA-MS)

- Mass spectrometry, liquid chromatography, and mass spectrometry (LC-MS-MS)
- Nuclear magnetic resonance, mass spectrometry, and liquid chromatography (LC-NMR-MS)
- Nuclear magnetic resonance, photodiode array, liquid chromatography, and mass spectrometry (LCPDA-NMRMS)

MODERN TRENDS IN ANALYTICAL TECHNIQUES FOR PHARMACEUTICAL DRUG DEVELOPMENT

Automated Development in High Performance Thin Layer Chromatography (HPTLC)

The advanced method of improving Thin Layer Chromatography is called High Performance Thin Layer Chromatography (HPTLC) (TLC). With the use of a thin layer chromatography plate, automation in the HPTLC technique helps to overcome the size of the droplets and the applied location of the sample. Due to its benefits over the dependability for the quantitative estimation of various analytes in microgram and nanogram amount, this approach has become the most efficient instrument in recent times. [36]

Automated injection technique

As strict Good Laboratory Practice (GLP) and Manufacturing Practice (GMP) regulations demand in-depth analysis of large quantities of samples during all stages of the process, and manufacturing of a pharmaceutical formulation, automation is a key requirement in modern pharmaceutical analysis and quality control. [39]

Development of Reverse Phase-High Performance Liquid Chromatography (RP-HPLC)

This method is easy to use and effective for identifying the enzymes ATP, AMP, ADP, NADP+, NAD+, NADPH, AND NADH in human erythrocytes. Reverse phase-high performance liquid chromatography was used to analyse these enzymes using supecosil LC18 coloums of 5 m, and the enzymes were identified using ultraviolet visible spectroscopy. Reverse phase-high performance liquid chromatography and reverse phase chromatography both use a polar mobile phase or a non-polar, aqueous stationary phase. [45]

CONCLUSION

The primary goal of pharmaceutical medications is to benefit people by keeping them healthy and preventing sickness. The medication must be devoid of impurities or other disturbances that might damage humans in order for it to fulfil its intended function. This study aims to give a detailed literature assessment of the instrumentation used in pharmaceutical analysis as well as an emphasis on the function of various analytical instruments in the assay of medicines. The study also emphasises how the approaches developed, starting with the more traditional titrimetric method and progressing to the more sophisticated hyphenated technique phases. In the current study, we look at the drug development process as it is based on analytical methods. The procedures used to manufacture drugs are exceedingly precise and were made public by scientists. The many approaches UV-Visible spectroscopy, Mass spectrometry, Infrared spectroscopy, Nuclear magnetic resonance, Fluorimetry, and phosphorimetry have been used as spectroscopic techniques for the quantitative and qualitative evaluation of pharmaceuticals. High performance thin layer chromatography (HPTLC), High performance liquid chromatography (HPLC), which is a potent separation technique, and thin layer chromatography were useful for bulk drug screening, and gas chromatography to determine the impurities in pharmaceuticals are chromatographic techniques that are used in the process of separating drugs. The electrochemical and electrophoretic methods were employed to identify the medicines. By using voltammetry, chronocoulometry, pulse voltammetry, and other

electrochemical techniques, the electrochemical approach aids scientists in determining the electrochemical nature of pharmaceuticals. Drugs were quantitatively estimated by applying electromagnetic field using the capillary technique in electrophoretic analysis. The flow injection analysis (FIA) and kinetic approach were applied to identify the flow system in an analytical process and to support the findings.The different approaches in conjunction with two or three methods, such as LC-NMR, LC-MS, LC-IR, GC-MS, CE-MS, LC-PDAMS, LC-MS-MS, LC-NMR-MS, LCPDA-NMR-MS, etc., are known as hyphenated techniques for the analysis of medicines. We came to the conclusion that the data is valuable in the process of analytical drug development, method development, or validation based on the methodologies for method development that are now available, recent trends, and the process of method validation or development.

CONFLICTS OF INTEREST

None.

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