IJPSR (2022), Volume 13, Issue 1 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 25 December 2020; received in revised form, 16 May 2021; accepted, 29 May 2021; published 01 January 2022

MODERN ANALYTICAL TOOLS FOR THE DETERMINATION OF THE ACTIVE PHARMACEUTICAL INGREDIENTS: A REVIEW

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Keywords:

Active pharmaceutical ingredient, Drug development, High-performance Liquid chromatography, Pharmaceutical analysis

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ABSTRACT: Discovery of the drug molecule which has therapeutic values is the backbone of drug development. Pharmaceuticals have an important role in the prevention and treatment of diseases in humans and animals. However, gradual change in the process of drug synthesis from drug development to bulk production is a common complication in the drug development process. This change may result in the formation of impurities. Moreover, impurities can also be formed during transport and storage. The presence of more than the prescribed limit of impurities in the drugs may influence the purpose of the pharmaceuticals. Therefore, the evaluation of pharmaceutical drugs for the identification and quantification of impurities at various stages is essential. Several chemical and instrumental methods are used to assess the impurities. For this purpose, analytical instrumentations and methods play a crucial role. The current review highlights the development of impurities at various stages of drug development and pharmaceutical manufacturing. Moreover, this review put light on the recent advancement in the analysis of pharmaceuticals.

INTRODUCTION: In the development of pharmaceuticals, chemistry, pharmacology, and clinical sciences have played an important role. Drug discovery guided by chemistry, pharmacology, microbiology, and biochemistry has established a standard in research. The discovery of the drugs is not only dependent on the imagination of the chemist but the exchange of ideas between biologists and chemists [1]. Innovation of the drug molecules which has therapeutic values is the mother of drug development [2].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.13(1).61-69

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.13(1).61-69

Prior to new drug innovation, the investigation on the pre-drug discovery is based on understanding the initial cause of the disease to be treated, alteration of the genes in the disease condition, interacting proteins, and affected cells. Depend upon these facts; the molecule is developed to interact with the affected sites and become drug molecule [1]. These molecules are also known as active pharmaceutical ingredients (APIs) [2].

Development of a new drug from an original idea to the launch of the finished product is a complex process that can take 12-15 years and cost around 1 billion USD. In the drug development process, various steps are involved, which are shown in **Fig. 1.** The time required for the early synthesis of API molecule to the successful submission for registration of new drug is more. During this

procedure, various obstacles must be taken into considerations, and numerous entanglements may emerge. The gradual change in the process of drug synthesis is a well-known complication during development. Hence this may lead to a change in the impurity profile of the APIs. Such changes may produce major consequences, including difficult interpretation of toxicological and clinical studies [3]. The presence of impurities in APIs can have a significant impact on the quality safety of the products. Therefore, synthesis, characterization, and analysis of such molecules provide unique data regarding safety and therapeutic efficacy, which is required for the identification of drug candidates for further detailed investigations [2]. Moreover, in the pharmaceutical research field, the analytical assessment of bulk drug materials, intermediates, drug products, drug formulations, impurities, degradation products, and biological samples containing the drugs and their metabolites is very important. Therefore, monographs were established to characterize the quality of the bulk drug materials by setting a limit to their active ingredient content. Furthermore, from the drug development process to marketing, analytical techniques have an essential role in assessing the physicochemical stability of the drug, selection and design of the dosage form, quantitation of the impurities, and identification of the excess impurity to assess the toxicity profile [2]. This review highlights the various sources of impurities in the APIs and the role of various modern analytical techniques in determining the APIs.

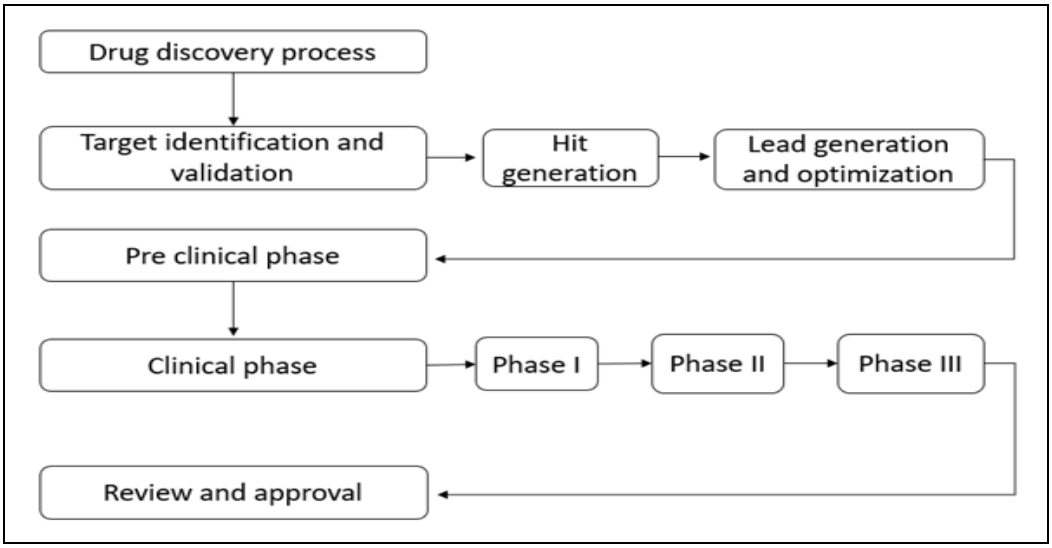

FIG. 1: SCHEMATIC REPRESENTATION OF DRUG DEVELOPMENT PROCESS

Sources of Impurities: The regulatory authority around the world, including the United States Food and Drug Administration (FDA) require that the drug substance and drug products should contain the impurities at the levels recommended by the International Conference on Harmonization (ICH) [4]. The sources of impurities depend on the quality of the starting materials, reagents, and solvents used during the synthesis, chemical reactions, reaction conditions, purification steps, and storage of the final product. Any change in the mentioned conditions may change the impurity profile of APIs [1].

Synthesis-related Impurities: Raw materials, solvents, intermediate and by-products are the main sources of the impurities in a drug substance during synthesis. Generally, the raw materials are manufactured at a lower purity requirement than the drug substance. Therefore, row materials can contain a number of components that can affect the purity of the drug substance. Similarly, the impurity present in the solvents may range from trace levels to a significant amount which can react with other chemicals used in the synthesis and can result in the formation of other impurities [1]. Intermediates are also not generally held to a purity level of the drug substance.

Therefore, guidelines are issued for the use of materials in the synthesis. The prediction of the by-products in the final drug product is not possible. The removal of the intermediate from the final product is costly and time-consuming, and its

presence may cause impurity generation due occurrence of simultaneous reactions. In pharmaceutical synthesis, the final intermediate is controlled by regulatory impurity testing [1].

Formulation-related Impurities: Interaction between drug and excipients used in the formulation can cause the generation of impurities in the final drug product. Moreover, during formulation process drug substance is subjected for a various condition which may produce degradation or other deleterious reactions such as heat degenerates thermolabile substances. Solution and suspension are commonly degraded by solvolysis or hydrolysis, respectively. Similarly, in solid dosage forms (tablet and capsule) water and other solvents are used for the granulation; therefore, solvolysis or hydrolysis can also occur.

Oxidation of the pharmaceutical ingredients or drug can act as a source of impurity in the final product. Similarly, light-sensitive materials can undergo photochemical reactions [1].

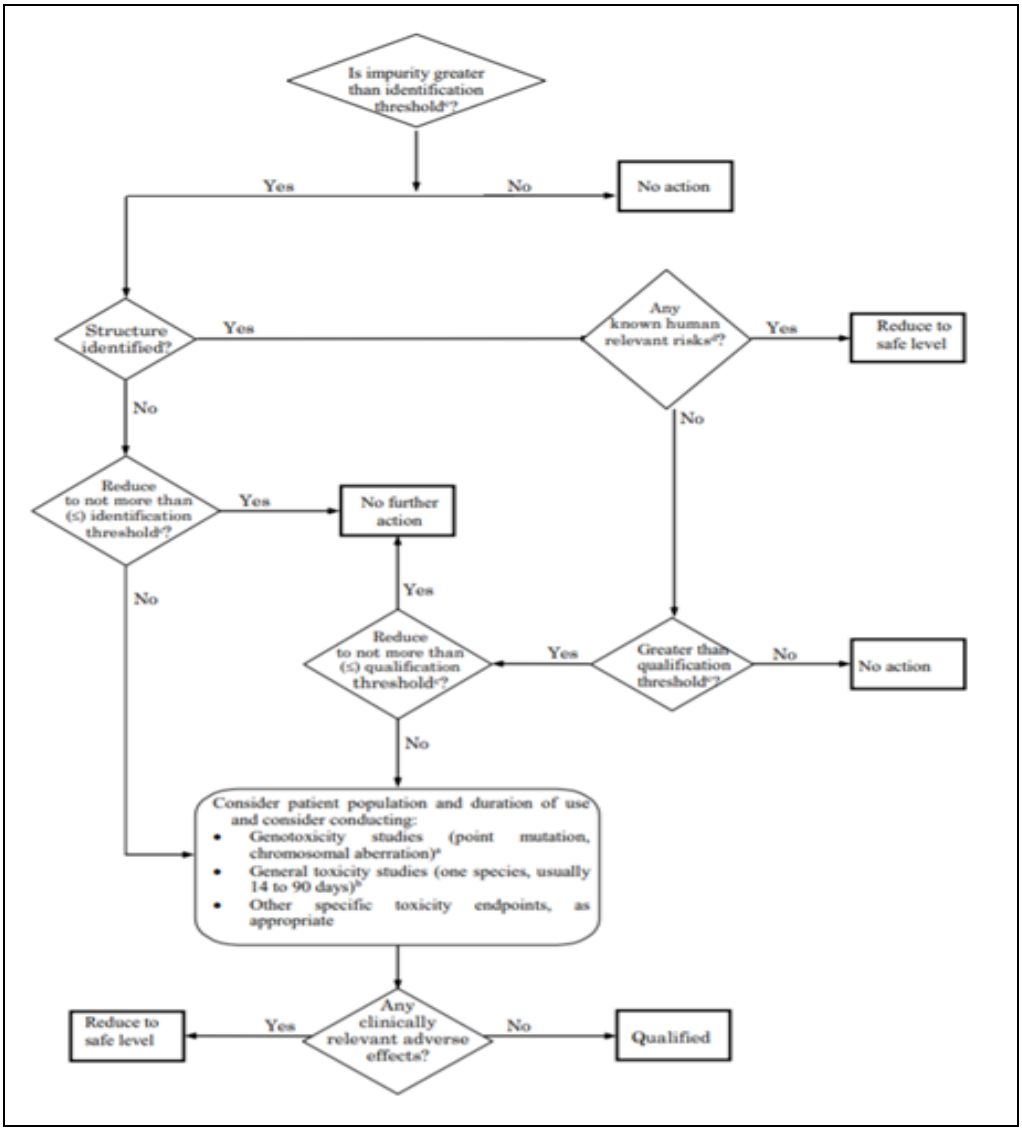

FIG. 2: DECISION TREE FOR IDENTIFICATION AND QUALIFICATION OF IMPURITIES

Degradation-related Impurities: The degradation of the API on storage can result in the formation of impurities. Hence, stability studies have an important role in prediction, evaluation and ensuring drug product safety [5]. These studies include assessment of API stability, compatibility of API with excipients, acceleration stability studies, stability of the final product, kinetic studies, and prediction of the expiry date, and routine stability studies of drug products on marketed sample or dispensed package under various conditions of temperature, light, and

humidity [1]. It is necessary to perform all the investigations on appropriate reference standards of drug and impurities to get meaningful specifications [1]. The assay methods in the monographs of the pharmacopoeia consist of mainly titrimetric, spectrometry, chromatography, and capillary electrophoresis [6-7]. These analytical methods based on proper analytical instrumentation must be employed to quantitate drug substance and their impurities **Fig. 2**.

Analytical Techniques:

Titrimetric Methods: In the year 1835, Gay-Lussac invented the volumetric method for analysis which is subsequently known as titration. Recent modernization of titration methods such as the non-aqueous titration method, which can be expanded to weak acid and bases, is commonly used in drug analysis. In most methods, an endpoint is determined by potentiometrically; hence, the precision of the methods is high. In functional group analysis procedures, titrimetric methods are useful in the determination of kinetic measurement (rate of reaction). The advantages of this method including time and labor requirement less, high precision and reference standard are not required [1]. This method is recently used to determine potassium sparing diuretic drug candidates, valganciclovir hydrochloride, sildenafil citrate, and aceclofenac sodium [8-11].

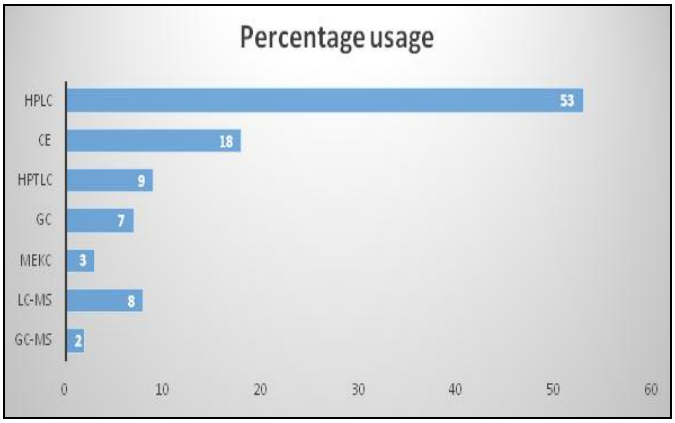

FIG. 3: PERCENTAGE OF VARIOUS CHROMATO-GRAPHIC TECHNIQUES FOR ANALYSIS OF IMPURITY IN THE DRUGS

Chromatographic Techniques: For many years, chromatography is the technique of choice for the assessment of the purity of the drugs and products. It is widely used in the pharmaceutical industry [12]. Percentage use of various chromatographic techniques for analysis of impurities in drugs is shown in **Fig. 3**.

High-Performance Liquid Chromatography: In the year 1980, HPLC was first time used for the assay of bulk drugs [3]. Further, this method became the main in USP XXVII and to a lesser extent, but widely used method in European Pharmacopoeia [6-7]. Among the various chromatography techniques, HPLC is most commonly used in the analysis of the impurities in the drugs as shown in **Fig. 1**. [3] The selection of appropriate detecting method in HPLC play an important role as it has to detect all the components. UV detector is the most commonly used detector in HPLC; UV detector provides multiple wavelength scanning program, which facilitates monitoring several wavelengths simultaneously. Thus, UV detector guarantee detection of all the components; however, the quantity of the components should be adequate **Fig. 4** [1].

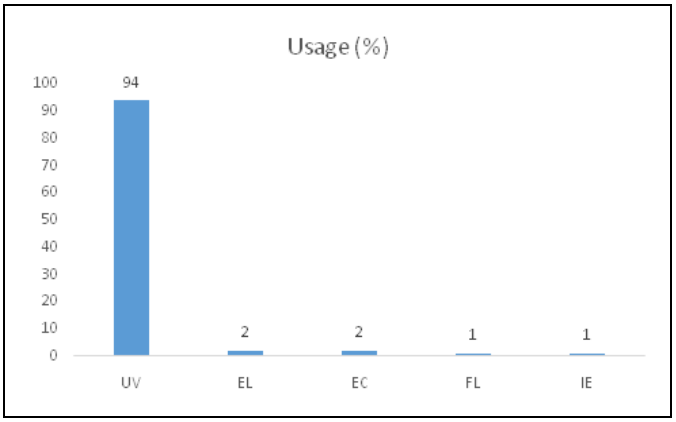

FIG. 4: USAGE OF VARIOUS DETECTORS IN HPLC ANALYSIS OF DRUGS

A photodiode array (PDA) is a lined array of discrete photodiode on an integrated circuit chip for spectroscopy. PDA is fixed on the image plane of the spectrometer, which provides simultaneous detection of various wavelengths. In this detection method, depending upon components to be identified, the wavelength can be predetermined; hence, a compound that absorbs in a given wavelength can be identified in a single assessment. In contrast with PDA, in a variable wavelength detector, multiple sample injection is required along with a change in wavelength to detect all the peaks. PDA can also be used in the assessment of purity by comparing matching spectra within a peak [1].

It is used in the method development of enalapril maleate [13]. Analytes such as alcohol, sugar, carbohydrates, fatty acids, *etc.*, has restricted or no UV absorption; in such case refractive index detector is used. The sensitivity of this is lower compare to other detectors; however, it is appropriate at high analyte concentration [1]. A study has reported the use of a refractive index detector in pharmaceutical formulations [14]. Among various liquid chromatographic detectors, fluorescence detector is the most sensitive detector (10-1000 times more sensitive than UV detector) for strong UV absorbing material used as an advantage in the measurement of specific fluorescence species samples. This detector has important role in the assessment of pharmaceuticals [15].

Revers phase chromatography with UV detector is the method of choice due to this combination provide better reliability, reproducibility, sensitivity and analysis time. The use of various detectors in HPLC analysis is shown in **Fig. 5** [3]. Despite the various advantages of HPLC, it has its own limitations such as the cost of column is high, more solvent required, and lack of long term reproducibility due to propriety column packing [3].

From the last decade of 20th century, a combination of liquid chromatography and mass spectroscopy has emerged as method of choice in drug analysis in both quality control and assurance [16-17].

Reversed-Phase High-Performance Liquid Chromatography: Reversed-phase high-performance liquid chromatography (RP-HPLC or RPLC) consists of polar mobile phase and non-polar stationary phase [18]. The isolation of the components depends on the hydrophobic binding of the solute molecule (present in the mobile phase) to the immobilized hydrophobic ligands (stationary phase) **Fig. 5**. [19].

This method of separation is considered a gold standard in pharmaceutical analysis. The silanol activity of the stationary phase of RPLC should be inhibited to facilitate proper analysis of basic drugs; such drugs may react with negatively charged silanols resulting in broadening of peak and tail [18]. Recently, Ergen H. *et al.* showed linearity, accuracy, precision, specificity, robustness, solution stability, and system stability for assay of polyvinyl alcohol in ophthalmic solution by RP-HPLC [20].

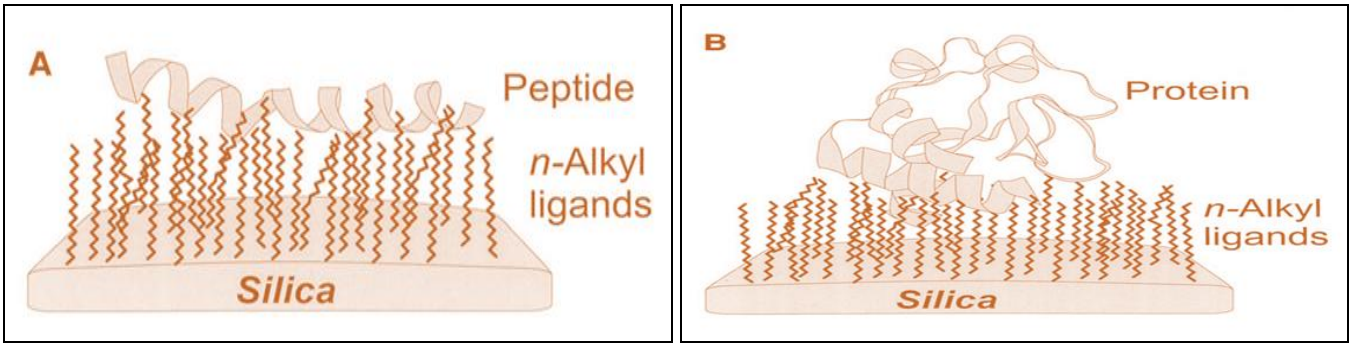

FIG. 5: DIAGRAMMATIC PRESENTATION OF THE ATTACHMENT OF PEPTIDE AND PROTEIN TO RP-HPLC

Ultra-high Performance / pressure Chromatography: In the early 2000s, there was a need for improved liquid chromatography performance in terms of throughput and resolution in pharmaceutical industries. Therefore, UHPLC was developed in the year 2004. It consisted packed column with particles of sub-2µm along with chromatographic assembly, which provides pressure stability up to 1000 to 1500 bar. In the drug discovery and development process, high productivity and less cost are required in quality control, pharmacokinetics, and drug metabolism analysis process. In such conditions, UHPLC can be performed typical pharmaceutical separation in 2-10 min intervals, and the complete method can be developed in 1-2 days. UHPLC decreases analysis time by 5-9 times than conventional HPLC [21]. Recently, this method was used in the assay of captopril; similarly, UHPLC with mass spectroscopy is also reported in the analysis of chemical constituents of crude drug [22-23].

Supercritical Fluid Chromatography: Supercritical fluid chromatography (SFC) is an analytical technique developed in the year 1960s. When a liquid is heated with increased pressure

beyond its critical point, it shows a particular behavior as chromatographic eluent [24]. Diffusivity and viscosity of such fluids is act as gas leading to a high kinetic performance at lower pressure, while the density and solvating power are equivalent to that of liquid, providing good solubility of the analytes. Despite this, the use of gas and liquid chromatography is predominant than SFC in the pharmaceutical industry [18].

However, for the last five years, SFC having an interest in the analytical process in the pharmaceutical community. This is due to significant modification of mobile phase components and composition, use of new stationary phase, and commercialization of state of the art system with a design that is based on the recent UHPLC instrumentation. It was providing improved instrument reliability and performance.25 Studies have reported the use of UHPLCSFC in the pharmaceutical drug analysis [26-28]

Hydrophilic Interaction Chromatography: Hydrophilic interaction chromatography (HILIC) is considered as an alternative method for RPLC for polar and ionizable drugs which cannot be retained by RPLC, such as metabolites and another biologically relevant compound. In this technique, the stationary phase hydrophilic in nature, and the mobile phase consisted of a polar aprotic solvent with water and salted [18]. The advantages of HILIC, including its action, are similar to the RPLC. The retention of hydrophilic substances is better. It requires less column backpressure, and its sensitivity increases with mass spectroscopy (MS) [29]. Currently, it is used in the assessment of polar substances, which cannot be analyzed by RPLC, such as anticancer drugs [30-31].

Combination of Liquid Chromatography with Mass Spectroscopy Devices (LC-MS): MS is the most needed technique in pharmaceutical industries, including research, analysis, development, and manufacturing. The high-resolution MS is used in structural elucidation, while low-resolution MS is useful in routine assessment applications. Miniaturized low-resolution MS is used as a benchtop size MS system [32-33]. This system is used for the assessment of reactions in the pharmaceutical process and drug discovery. Literature suggested the use of MS in forensic sciences, pharmaco-kinetics, determination of bioavailability and bioequivalence study, determination of molecular weight, and determination of assay of drug and intermediates [34].

The use of a compact MS analyzer in LC (LC-MS) also involves the identification and quantification of APIs and their degradation products or trace impurities as reported for the analysis of a mixture of loratadine [35]. A study was found in which MS detector was implemented in the HPLC/UHPLC equipment.

UHPLC-UV/MS was compared with HPLC-UV for the impurity profiling of APIs such as peptides, bleomycin sulphate, tyrothricin, vancomycin HCL, and bacitracin peptide.

Results showed UHPLC produces increased resolution and decreased limit of detection and in run time. Moreover, MS detectors facilitate direct identification of impurities and components without the need for reference standard [36].

Single-crystal and Powder X-ray Diffraction (XRD): X-ray diffraction methods comprise the predominant tool used for the characterization of pharmaceutical powders.

Single-crystal X-ray diffraction (SXRD) is a technique used for the determination of the solid-state structures at an atomic level, while powder X-ray diffraction (PXRD) is mainly used for identification purposes since crystalline powders exhibit characteristic sharp peaks.

Currently, software programs such as Malvern Panalytical's XRD software suite and Diffrac. Suite Topas (Bruker AXS, Karlsruhe, Germany) allow structural determination and refinement based on Rietvield refinement.

They are also routinely used to assess the yield of the product by being able to quantify the percentage of crystals and their components in a mixture.

A drawback is that a single pharmaceutical crystal that is qualified for SXRD testing cannot always be produced. Therefore, powder X-ray diffraction (PXRD) is utilized more frequently to verification **Fig. 6** [37-39].

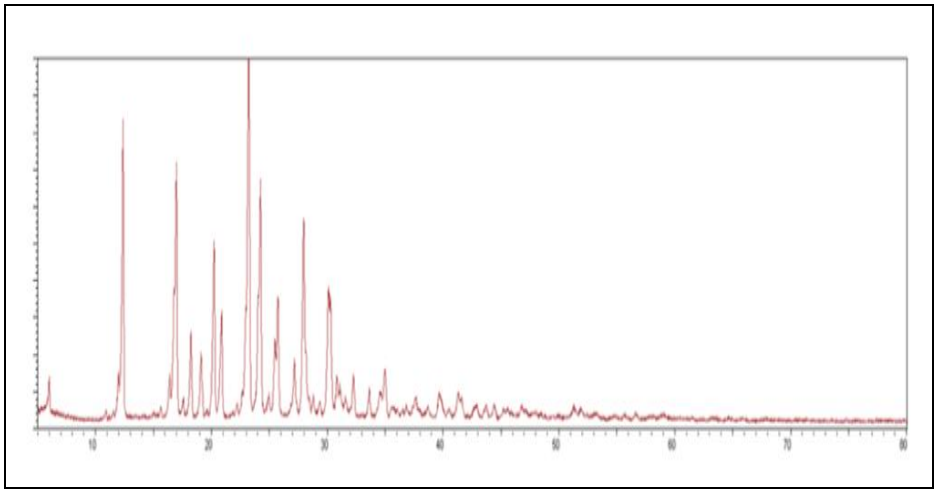

FIG. 6: POWDERED X-RAY DIFFRACTOGRAM OF PURE ONDANSETRON

Raman Spectroscopy: In the year 1928, Raman and Krishnan invented Raman spectroscopy. This technique involves exposure of monochromatic radiation to samples resulting in the molecular vibration of chemical structures of a substance [40-41]. In the pharmaceutical industry, it is an excellent tool for the identification of drugs. This including product development and the real-time monitoring of the production process by Process Analytical Technology [40, 42-43]. This technique has advantages such as it is non-invasive, solvents are not required, ease of handling, analysis can be performed without any preparations, and availability of portable equipment can produce results in seconds [41-43]. Along with the conventional Raman dispersion phenomenon, various variants are available with diverse applications **Table 1** [44-54].

TABLE 1: VARIANTS OF RAMAN SPECTROSCOPY AND THEIR APPLICATIONS

Variants	Advantages	Applications
Conventional Raman scattering	Non-destructive, little or no sample preparations, short analysis time	API quantification and characterization of tablets
Fourier transform-Raman	Simultaneous measurement at all wavelengths, improved sensitivity	API quantification in powder mixture
Resonance Raman spectroscopy	Required less sample	API with less concentration
Surface enhanced Raman spectroscopy	Sensitive, can determine the concentration of target molecules in unknown systems	Quantifies highly complex samples and target molecules in unknown systems.
Spatially offset Raman spectroscopy	Isolation of chemically rich spectral data from sub surfaces, substructures, layers and through other types of barriers. Quantifies chemical markers. Readings can penetrate container	Samples inside packs and samples for medical diagnostics
Coherent anti-Stokes Raman spectroscopy	Label-free, chemically specific signal, fast data-acquisition time and inherent non-destructive “confocal”- like imaging.	Characterizes raw materials, tablets and powder mixtures
Stimulated Raman Scattering	Increased sensitivity, because it is free of limitations from labeling and applicable to spot reduction effect	Characterizes multiple excipients distributions in tablets. Mapping of samples as cells and tissues
Tipenhanced Raman scattering	Spatial resolution required for nanoscale characterization. Ability to spectroscopically map surfaces	Characterization of materials at nanoscale
Raman Micro spectroscopy	Acquire more representative spectra of the sample mixtures; The wide area illumination and/or reduced particle size allows for more accurate measurements of polymorphs	Quantification of polymorphic mixtures, API content in tablets and powder mixtures
Low-frequency Raman	Low-maintenance cost, flexible experimental setup and rapid measurement time	Characterization of solid-state forms and their transformations, Imaging of solid dosage forms, Monitoring of solubilization/dissolution processes

CONCLUSION: Drugs are used to treat or prevent disease or illness in humans. Therefore, drugs must be free from impurities, which can be harmful to humans. Nowadays, it is a mandatory requirement in various pharmacopeias to know the impurities present in APIs. The current review was aimed to study the recent trends in pharmaceutical analysis instruments. It describes the titrimetric techniques methods, HPLC, RP-HPLC, UHPLC, Supercritical Fluid Chromatography (SFC), Hydrophilic interaction Chromatography, LC-MS, XRD, Raman Spectroscopy. The review also highlights the sources of impurities and modern, modified techniques for the analysis of pharmaceuticals.

ACKNOWLEDGEMENT: Nil

CONFLICTS OF INTEREST: Nil

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How to cite this article:
Chavan A and Gandhimathi R: Modern analytical tools for the determination of the active pharmaceutical ingredients: a review. Int J Pharm Sci & Res 2022; 13(1): 61-69. doi: 10.13040/IJPSR.0975-8232.13(1).61-69.