IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

A REVIEW OF ANALYTICAL DEVELOPMENT METHODS FOR THE DETERMINATION OF ANTIDIABETIC DRUGS

Manisha Prakash Mugade [1*], Vilas Jagannath Pise [2],

Vasant Yashwant Lokhande [3], Pallavi Laxman Salve [4]

Arvind Gavali College of Pharmacy, Jaitapur, Satara 415004, India

***Corresponding Author: Manisha Prakash Mugade**

ABSTRACT

Pharmaceutical analysis plays an outstanding conspicuous role in quality assurance similarly to internal control of bulk medication and pharmaceutical formulations. As a consequence, analytical methodology development has become the essential activity of study. New drug molecules are being developed and the analysis is also gaining equal importance. A huge survey was conducted for the determination of antidiabetic drugs including Vildagliptin, Sitagliptin, Metformin etc. from the research articles published in various pharmaceutical and analytical chemistry Journals. Nowadays, many antidiabetic drugs are available in tablet dosage forms. The present article focuses on the different analytical methods for the quantitative estimation of antidiabetic drug. The present paper accentuates the review of analytical methods including UV/Vis-Spectroscopy, HPLC, RP-HPLC, HPTLC, GC-MS, LC-MS etc. which involve the estimation of antidiabetic drug in pharmaceutical dosage form. The investigatory review may provide comprehensive details of various analytical techniques and their experimental condition to the researchers who are working in the area of analytical research of antidiabetic drugs. The present studies revealed that the gas chromatographic method combined with mass spectroscopy has specific advantages and sensitivity for antidiabetic drug analysis in pharmaceutical dosage form and biological matrices.

Keywords: Antidiabetic drug, analytical method, RP-HPLC, GC-MS, LC-MS.

INTRODUCTION

Today's world is an arena where cutthroat competition is seen. People are going on making new drugs and new formulations of the existing drugs within very short period of time. To get the regulatory permission for marketing, company has to submit required data including the analysis reports as to prove that their drug

product is of required quality for its intended use. For these new drugs and formulations there are no standard official procedures available for its analysis so, we need to develop some method for the identification and estimation of drugs [1].

The complexity and globalization of the pharmaceutical supply chain necessitate those standards be built into the development and manufacturing processes from raw materials through finished products. Standards are essential for ensuring the identity, purity, potency, and performance of drugs across the product lifecycle. In a 2018 survey, 90% of industry professionals with expertise in formulating and testing drugs, indicated that standards accelerated drug development, especially in the case of generics, saving about 19% in total product development time. Medicinal products (gene therapy, personalized medicine, and other emerging therapeutic modalities) are growing increasingly complex. Quality attributes of these products are also more complex, and difficult to define and measure, making standards even more critical for ensuring quality [2]. For standards to remain relevant, they must evolve in response to advances in the industry. Existing standards need to be updated, and new, fit-for-purpose standards created to ensure they include the most useful, appropriate, and feasible approaches to measuring relevant parameters. These days, the proportion of people with type II diabetes is increasing in most countries and it is a major cause of blindness, kidney failure, heart attacks, stroke, and lower limb amputation. As such, there is a growing need for anti-hyperglycemic agents, along with their quality attributes [3].

Diabetes mellitus is a progressive disease characterized by deterioration of pancreatic islet cell function and increased insulin resistance. It is a disease of multiple etiologies that affects the quality of life of affected individuals. Inhibitors of dipeptidyl peptidase-4 (DPP-4) represent a new class of antidiabetic agents for the treatment of type 2 diabetes, which improves glycemic control by preventing the degradation of intestinal peptides, also known as incretins [4]. To improve glycemic control and slow disease progression, pharmacological and non-pharmacological alternatives have been developed. Regarding pharmacological intervention, the treatment with DPP-4 inhibitors has been considered [5-6].

Analytical Methods for the Determination of Favipiravir in Pure Form or Dosage Form

UV-Visible spectroscopy

Spectroscopy is the use of absorption, emission or scattering of electromagnetic radiation by atoms or molecules (or atomic or molecular ions) to qualitatively or quantitatively study the atoms or molecules or to study physical processes. The interaction of radiation with matter can cause redirection of the radiation and/or transition between the energy level of atoms or molecules. UV–visible spectroscopy is the measurement of the wavelength and intensity of the absorption of near-ultraviolet and visible light by a sample. Ultraviolet and visible light are energetic enough to promote outer electrons to higher energy levels. UV-visible spectroscopy is usually applied to molecules and inorganic ions or complexes in solution. The UV-visible spectra have broad features that are of limited use for sample identification but are very useful for quantitative measurements. Molecular UV–visible absorption spectroscopy is employed primarily for quantitative analysis and is probably more widely used in chemical and clinical laboratories throughout the world than any other single method. When a molecule is exposed to electromagnetic radiation (EMR), a certain amount

of energy associated with the particular radiation is absorbed by the molecule. There is a transfer of energy from the beam of radiant energy to the molecule. This is called absorption and the study of this is called as absorption spectrophotometry. The wavelength range for UV–visible region is 200-800 nm. UV-visible spectroscopy is one of the instrumental analytical methods in which UV-visible radiation is used to analyze the sample. Molecules undergo electronic transitions and show absorption in this wavelength range which is accessible to UV-visible spectrophotometer. Based on the type of beam used in UV instruments, there are two types of spectrometers, i.e., single beam spectrometer and double beam spectrometer [7].

Beena Kumari et al developed and validated the UV-visible Spectrophotometric Method for the Estimation of Vildagliptin in a Gastric Medium. Vildagliptin was estimated using a UV-visible double-beam spectrophotometer at the wavelength of maximum absorption (210 nm) in an acidic medium containing 0.1N HCl. The method was validated by analytical parameters like linearity, precision, and accuracy as per guidelines laid down by the International Conference on Harmonization (ICH). The melting point of the drug was found 154°C which corresponds to its actual melting range. Similarly, by the interpretation of spectra, the drug was confirmed. The linear response for a concentration range of 5–60 µg/ml of vildagliptin was recorded with a regression coefficient of 0.999. The accuracy was found between 98–101%. Precision for intraday and interday was found to be 1.263 and 1.162 respectively, which are within the limits. To establish the sensitivity of the method, the limit of detection (LOD) and limit of quantification (LOQ) were determined which were found to be 0.951 µg/ml and 2.513 µg/ml respectively. The developed and validated UV method for the Vildagliptin drug was found to be linear, accurate, precise, and economical which can be used for the testing of its pharmaceutical formulations [8].

C. Bala Sekaran et al have developed an improved spectrophotometric method for the determination of sitagliptin phosphate in bulk and in pharmaceutical formulations. The proposed method is based on condensation of the primary amino group of sitagliptin phosphate with acetyl acetone and formaldehyde producing a yellow-colored product, which is measured spectrophotometrically at 430nm. The color was stable for about 1 hour. Beer's law is obeyed over a concentration range of 5-25µg/ml. All the variables were studied to optimize the reaction conditions. No interference was observed in the presence of common pharmaceutical excipients. The validity of the method was tested by analyzing sitagliptin phosphate in its pharmaceutical preparations [9].

Dayoub Loujain Anis et al developed a new visible Spectrophotometric analytical method for the determination of Vildagliptin in bulk and pharmaceutical dosage forms. The method is based on the formation of a Schiff base with p-dimethylamino benzaldehyde (PDAB) in acidic ethanol; the reaction of the drug with the reagent gives a bright yellow color. The formed colored species absorbance was measured at its absorption maximum λmax 446 nm. All the variables were studied to optimize the reaction conditions. Beer's law has been obeyed in the concentration range of 75-175 µg/ml with a correlation coefficient (R2= 0.9977). The LOD and LOQ of the proposed method were calculated at 10.633 (µg/ml), 32.223 (µg/ml) respectively. No interference was observed in the presence of common pharmaceutical excipients [10].

Madhuri Ajay Hinge et al has been developed a simple, accurate and precise spectroscopic method for simultaneous estimation of Metformin and Sitagliptin in marketed formulation using Q-Absorbance Ratio Method. In this spectroscopic method, 237nm and 253nm (iso absorptive point for both drugs) were selected for measurement of absorptivity. Both the drugs show linearity in a concentration range of 5-25µg/ml for Metformin and 0.5-2.5µg/ml for Sitagliptin at 237nm and 253.26nm respectively. Accuracy, precision and recovery studies were done by QC samples overing lower, medium and high concentrations of the linearity range. The relative standard deviation for accuracy, precision studies were found to be within the acceptance range [11-12].

High-performance liquid chromatography (HPLC)

To evaluate drug products, high-performance liquid chromatography (HPLC) is a crucial analytical instrument. Most of the drugs in multi component dosage forms can be analyzed by HPLC method because of the several advantages like rapidity, specificity, accuracy, precision and ease of automation of this method. The different medicines and drug-related degradants should be able to be separated, detected, and quantified using HPLC procedures. A sample is separated into its components by distributing the sample between a mobile phase and a stationary phase under pressure applied using a pump.

Muhammad Ashraf et al has been developed a new HPLC method for the quantification of sitagliptin and its application in spiked plasma and tablet dosage form. The method was developed by using the C18 ODS Hypersil column of 150 × 4.6mm id with 5µm particle size, mobile phase of acetonitrile and 0.01N potassium dihydrogen phosphate at a flow rate of 1.0ml/min. Eluate was detected at 269nm with the retention time of 5.6min. This developed method is more sensitive than the already reported methods and reproducible with all validation parameters with FDA guidelines [13].

K. Hanumantha Rao et al developed and validated high performance liquid chromatographic method for the estimation of Vildagliptin in the tablet dosage form. An Altima C18 column having 150 mm x 4.6 mm internal diameter, 5 µm particle size in isocratic mode with mobile phase containing dilute orthophosphoric acid solution pH 2.6±0.5 as buffer and acetonitrile (72:28 v/v) was used. The flow rate was 1.0 ml/min and effluents were monitored at 266 nm. The retention time for Vildagliptin was 3.25 min. The method was validated and found to be simple, sensitive, accurate, and precise. The tailing factor was found to be 1.28. The limit of detection and limit of quantification were found 0.06 µg/ml and 0.21 µg/ml respectively and recovery of Vildagliptin from tablet formulation was found 99.73%, showing that the method is free from the interference of the excipients used in the formulation. Therefore, the proposed method was successfully applied for the quantitative determination of Vildagliptin in tablet formulation [14].

Ahmed Gedawy et al developed and validated high performance liquid chromatographic method for simultaneous determination of gliclazide and metformin hydrochloride in bulk and was applied on marketed metformin and gliclazide products. The mobile phase used for the chromatographic runs consisted of 20 mM ammonium formate buffer (pH 3.5) and acetonitrile (45:55, v/v) The separation was achieved on an Alltima CN (250 mm x 4.6 mm x5m) column using isocratic mode. Drug peaks were well separated and were detected

by a UV detector at 227 nm. The method was linear at the concentration range 1.25 to 150 mg/ml for gliclazide and 2.5 to 150 mg/ml for metformin respectively. The method has been validated according to ICH guidelines with respect to system suitability, specificity, precision, accuracy and robustness. Metformin limit of detection (LOD) and limit of quantification (LOQ) were 0.8 mg/ml and 2.45 mg/ml respectively while LOD and LOQ for gliclazide were 0.97 mg/ml and 2.95 mg/ml respectively. they presented validated method was rapid, economic, simple, accurate, sensitive, robust, specific and linear. It can be used for routine analysis of metformin and gliclazide either alone or in combination products [15].

Reversed-phase high-performance liquid chromatography (RP-HPLC)

Reversed-phase high-performance liquid chromatography (RP-HPLC) involves the separation of molecules based on hydrophobicity. The separation depends on the hydrophobic binding of the solute molecule from the mobile phase to the immobilized hydrophobic ligands attached to the stationary phase, i.e., the sorbent [16].

D. China Babu et al have developed a selective, sensitive RP-HPLC method for the simultaneous estimation of the Ertugliflozin and Sitagliptin in bulk and its dosage form. The separation and determination were carried on water's C18 column, retention times of Ertugliflozin and Sitagliptin were found to be 2.39 and 4.60min. respectively. The wavelength was fixed at 215nm with PDA detection. The mobile phase was consisted mixture of 0.5M potassium dihydrogen ortho phosphate buffer: Methanol in the ratio of 55:45v/v, pH 5.3 was adjusted with HCl and flow of mobile phase was maintained 1ml/min. The quantization limit and detection limit of the method were found 0.1 & 0.3µg/ml and 0.4 and 1µg/ml for Ertugliflozin and Sitagliptin [17].

A. S. K. Sankar et al have developed a simple, accurate, specific and reliable RPHPLC method for the simultaneous estimation of Sitagliptin Phosphate and Metformin Hydrochloride in Pharmaceutical dosage form. In the present method, SHIMADZU HPLC with UV detector LC 10 AT VP with analytical column PHENOMENEX Luna (C18) A 100 RP Column, 250 mm x 4.6 mm x 5µm, an injection volume of 20µl was injected and eluted with mobile phase 0.02M Potassium dihydrogen phosphate pH(4.0) Acetonitrile (60:40) pumped at a flow rate of 1.0ml/min. Sitagliptin Phosphate and Metformin Hydrochloride were eluted at 2.718 and 1.925min. The detection was carried out at a wavelength 252nm [18].

Meetali M. Chaphekar et al developed the Reverse Phase-High Performance Liquid Chromatography (RP-HPLC) method by QbD approach using the Design of Experiments and subsequent validation for analysis of Vildagliptin in bulk drug and its pharmaceutical formulation. The concept of Quality by design (QbD) has recently gained importance in the area of analytical method development and involves understanding the critical factors and their interaction effects by a desired set of experiments. An efficient experimental design based on systematic scouting of all three key components of the RP-HPLC method (Buffer pH, organic Phase-% acetonitrile, Organic Modifier-Methanol) was presented. The significance and interaction effects of these parameters on the response variables (Retention time and tailing factor) were evaluated through

statistical analysis tools like Analysis of Variance (ANOVA) and plots which revealed the final chromatographic conditions of the method.

The developed method was validated and Forced degradation studies were also carried out to determine the stability-indicating nature of the method. The chromatographic separation was achieved on Jasco CrestPack RP C18 (250 × 4.6 mm, 5µ) column using Buffer (pH 6): Acetonitrile: Methanol (70:10:20 v/v) as mobile phase and detection was done using Photo-Diode Array (PDA) detector at 210 nm. The developed method of Vildagliptin is linear over a range of 5-15µg/ml having correlation coefficient R2 value of 0.999. The %RSD for precision and accuracy of the method was found to be less than 2%. The LOD and LOQ were obtained by successively decreasing the concentration of Vildagliptin as long as a signal-to-noise ratio of Not less than 3:1 and 10:1 is maintained respectively. The LOD of Vildagliptin was found to be 200ng/ml. The LOQ for Vildagliptin was found to be 600ng/ml. These values indicate that the method developed is sensitive. Thus, The RP-HPLC assay method developed for Vildagliptin by the QbD approach is linear, accurate, precise, reproducible, and specific as evident from the validation results. The developed method is also stability-indicating and can be conveniently used for quality control to determine the assay in regular Vildagliptin product development, production, and stability samples. The results showed that the proposed method is suitable for the precise and accurate determination of Vildagliptin in bulk and its formulation [19].

Pragati Ranjan Satpathy et al developed and validated the RP-HPLC method for the assay of vildagliptin. In that, chromatographic separation was performed on a Waters HPLC with an alliance with the Autosampler, empower 2.0 software, Symmetry C18 (4.6 x 150mm, 5mm, make: Thermosil), Galvus (Manufacture by NOVARTIS) tablets were used for the sample solution preparation. A method based on RP-HPLC with indirect UV detection was developed for the determination of Vildagliptin in pharmaceutical dosage form. Vildagliptin is a potent dipeptidyl peptidase IV inhibitor used for the treatment of diabetes. Reverse phase separation was obtained within 4 min and was linear in the range of 50–90 µg/mL (r2 = 0.999). Separation was performed on a C18 column using a mixture of pH 8.2 buffer, acetonitrile, and methanol in the ratio of 450: 480:70. The solvent mixture was filtered through a 0.22 µ PVDF filter and sonicated before use. It was pumped through the column at a flow rate of 0.5 ml/min. The detection of the drug was monitored at 254 nm.

The validation of this method included the determination of its specificity, accuracy, precision, linearity, LOD, LOQ, and robustness. The LOD was 2.98 g/m and The LOQ was 9.94 g/mL for Vildagliptin. Through the modern analytical study, it can be concluded that a more rapid, precise, specific, sensitive, economic, reproducible, isocratic reverse phase HPLC method was developed and validated for the quantitative determination of Vildagliptin. The run time was set at 10 min. Under the optimized chromatographic condition, the retention time of around 3.9 ± 0.1 min allows the analysis of a large number of samples in a short period. The method was validated successfully using parameters like accuracy, precision, linearity, LOD, LOQ, and robustness. This approach will unquestionably build an innovative way out on behalf of maintaining the quality, consistency as well as. These efforts will ensure the therapeutic functionality of the drugs. The developed RP-HPLC method presented here is more advantageous as the method was robust with

low retention times and sharp peaks with reduced fronting and tailing. The proposed method was successfully applied for the quantitative analysis of VLG in tablet dosage form, which will help to improve quality control and contribute to stability studies of pharmaceutical tablets containing this drug [20].

Jagdale Ramkrishna Raosaheb et al developed and validated the RP-HPLC method for the estimation of Vildagliptin in bulk and dosage form. The RP-HPLC method for Vildagliptin was developed using column Phenomenex C18 column (5µm, 250mm × 4.6mm) as stationary phase and Methanol: water (60:40 v/v) (pH 4.5 adjusted with OPA) as mobile phase. The mobile phase was maintained at a flow rate of 0.8 ml/min and the volume of injection was 20 µl detection was carried out at 207 nm. The method was validated by ICH guidelines. A good linear relationship (R2 = 0.999) was observed between the concentration of Vildagliptin and the individual mean peak area. The result of the % assay of the marketed formulation was found as 98.65 -100.95 % for Vildagliptin respectively. The accuracy of the method was determined by performing a recovery study and the results were found in the range of 99.56 -102.25 % w/w and for Vildagliptin respectively. The retention time obtained for vildagliptin was 3.58min. The LOD and LOQ were obtained at 0.98 µg/ml and 2.98 µg/ml respectively for Vildagliptin, indicating the method sensitivity. % RSD of precision study of these drugs was found less than 2 % which indicated good precision of the developed method. The developed HPLC method was simple, rapid, easy, accurate, and precise. So, the method can be applied successfully for the routine analysis of Vildagliptin in the pharmaceutical industry for bulk as well as pharmaceutical dosage forms [21].

Sai Datri Arige et al have developed a simple, precise and accurate RP-HPLC method for simultaneous estimation of Sitagliptin phosphate and Simvastatin. In RPHPLC method, mixture of pH 4.0 sodium phosphate buffer and acetonitrile in the ratio of 20:80v/v was selected as a mobile phase and equal proportions of water and acetonitrile with one drop of phosphoric acid was selected as solvent which gives good resolution and good peak shapes for Sitagliptin and Simvastatin. The linearity range was established over the range of 25-150µg/ml and 10-60µg/ml concentration range Sitagliptin and Simvastatin. The correlation coefficient of Sitagliptin and Simvastatin was found to be 1. The method validation data showed excellent results for accuracy, precision, linearity, specificity, limit of detection, limit of quantification and robustness [22].

Aparajita Malakar et al developed and validated the RP-HPLC method for the estimation of Vildagliptin from the tablet dosage form. The separation was achieved on a Xterra® Waters C18 column (150mm x 4.6mm, 5µm) using mobile phase consisting of a mixture of aqueous phase (1 ml of 25% ammonium hydroxide was dissolved in 1000 ml of water for chromatography, pH of the solution was adjusted to the value of 9.5 using a 50% solution of phosphoric acid) and organic phase (methanol) in the ratio of 60:40 v/v at a flow rate of 1.0 ml/min. Detection was carried out at 210nm. The retention time of Vildagliptin was found to be 6.3 min. The calibration curve was found linear between 5- 200µg/ml (r2 = 0.9997).
Limit of detection and limit of quantitation were 1.47 and 4.90 µg/mL, respectively. The percentage recoveries of Vildagliptin were found to be in the range of 99.11-100.62%. The method was validated by the International Conference on Harmonization acceptance criteria for specificity, linearity, precision, accuracy,

robustness, and system suitability. The excipients did not interfere in the determination of Vildagliptin. The proposed method was successfully applied for the quantitative analysis of Vildagliptin in tablet dosage form, which will help to improve quality control [23].

S. Srinivasa Rao et al developed and validated A new, simple, precise, accurate and reproducible RP-HPLC method for Simultaneous estimation of Metformin and Linagliptin in bulk and pharmaceutical formulations. Separation of Metformin and Linagliptin was successfully achieved dona THERMO, C18, 250cmx4.6mm, 5µm or equivalent in an isocratic mode utilizing KH2PO4: Methanol (65:35) at a flow rate of 1.0mL/min and eluate was monitored at 226nm, with a retention time of 3.132 and 3.728 minutes for Metformin and Linagliptin respectively. The method was validated and found to be linear in the drug concentration range of 50µg/ml to150 µg/ml for Metformin and 50µg/ml to150 µg/ml for Linagliptin. The values of the correlation coefficient were found to 0.999for Metformin and 1 for Linagliptin respectively. The LOD and LOQ for Metformin were found to be 1.909 and 6.362 respectively. The LOD and LOQ for Linagliptin were found to be 0.0349 and 0.1163 respectively. This method was found to be good percentage recovery for Metformin and Linagliptin were found to be 100 and 100 respectively indicates that the proposed method is highly accurate. The method was extensively validated according to ICH guidelines for Linearity, Accuracy, Precision, Specificity and Robustness [24].

High-performance thin layer chromatography (HPTLC)

HPTLC is a chromatographic technique that separates complicated components. The plates are prepared from optimized uniformly sized even particles and hence have more separation efficiency. HPTLC has advantages such as shorter analysis time, and detection is possible with nanogram sample concentration. This chromatographic method is suitable for qualitative and quantitative separation of the sample.

K. R. Patil et al have developed a new simple, accurate, precise and stability indicating HPTLC method for the determination of sitagliptin in tablet dosage form. The chromatographic separation was achieved by using Toluene: Ethyl acetate: Methanol (3:6:1v/v/v) as mobile phase and UV detection at 238nm. The developed method was validated with respect to linearity, accuracy, precision, limit of detection, limit of condition of acid hydrolysis, alkali hydrolysis, photolysis, thermal degradation. Results found to be linear in concentration range of 100-500ng/band. The developed method can be used for the quantification of bulk drug as well in formulation [25].

Atul R. Bendale et al developed and validated stability indicating HPTLC method for determination of Vildagliptin and Metformin hydrochloride in the pharmaceutical dosage forms. A validated HPTLC method was developed for the determination of Metformin hydrochloride and Vildagliptin. In this method, optimization by changing various parameters, such as organic solvent and the composition of the mobile phase, acid or base modifier used in the mobile phase, by varying one parameter and keeping all other conditions constant. 10 µl of the stock solution for Metformin (500 ng/band) and 2 µl of the stock solution for Vildagliptin (100 ng/band) were applied to TLC plates. The final solutions were applied on the HPTLC plates and these were developed as per the optimized densitometry conditions.

The calibration curves were obtained by plotting the peak area versus concentration over the range of 50-500 ng/band for Metformin and 10-150 ng/band for Vildagliptin, respectively in mix standard. From the spectra, it was observed that Metformin and Vildagliptin exhibited good absorbance at about 217 nm. Both the drugs showed degradation with additional peaks at Rf values of 0.16 for Metformin and with Rf values of 0.81 for Vildagliptin respectively. Good separation was achieved by using the mobile phase Hexane: Methanol: Acetonitrile: Glacial Acetic Acid (2:3.5:2.5:0.2 v/v/v/v) with retardation factor (Rf) values of 0.22±0.01 for Metformin and 0.73±0.02 for Vildagliptin. LOD for Metformin and Vildagliptin were found to be 8.2 ng/band and 1.74 ng/band, respectively, while LOQ was found to be 27.06 ng/band and 5.74 ng/band, respectively. The proposed method was found to be simple, precise, accurate, rapid, and specific for the determination of Vildagliptin and Metformin from pure and its dosage forms. The mobile phase is simple to prepare and economical. The sample recoveries in the formulation were in good agreement with their respective label claims and they suggested non-interference of formulation excipients in the estimation. Hence, this method can be easily and conveniently adopted for routine analysis of Vildagliptin and Metformin in pure form and its dosage form [26].

Gas Chromatography-Mass Spectrometry (GC-MS)

The Gas Chromatography-Mass Spectrometry (GC/MS) instrument separates chemical mixtures (the GC component) and identifies the components at a molecular level (the MS component). It is one of the most accurate tools for analyzing environmental samples. The GC works on the principle that a mixture will separate into individual substances when heated. The heated gases are carried through a column with an inert gas (such as helium). As the separated substances emerge from the column opening, they flow into the MS. Mass spectrometry identifies compounds by the mass of the analyte molecule. A ÒlibraryÓ of known mass spectra, covering several thousand compounds, is stored on a computer. Mass spectrometry is considered the only definitive analytical detector. gas chromatography–mass spectrometry (GC–MS) is the advanced hyphenated technique used to detect compounds using the relative gas chromatographic retention times and elution patterns of components of a mixture in combination with the mass spectral fragmentation patterns, which is characteristic of compound's chemical structures.

Priyanka Verma et al developed and validated gas chromatography-mass spectrometry method for the detection of glimepiride via derivatization employing N-methyl-N- (trimethylsilyl) trifluoroacetamide. Recent advances in the diversified anti-diabetic drugs have appeared in the startling increase in the count of poisoning cases. The epidemics of diabetes mellitus are increasing; hence, the no. of anti-diabetic drug users raised by 42.9%. The use of glimepiride raised to 24%. Liquid-liquid extraction method was employed by using 1-butanol: hexane (50:50, v/v) under an alkaline medium, and then back extraction was done via acetic acid. Distinct derivatization techniques were employed for the sample preparation for GC-MS analysis, i.e., silylation and acylation. Derivatization approaches were optimized under different parameters, i.e., reaction temperature and reaction time. N-Methyl-N-(trimethylsilyl) trifluoroacetamide [MSTFA] was found to be the best sound derivatization reagent for the GC-MS analysis of glimepiride.

Total ion current (TIC) mode was selected for the monitoring of ions of trimethylsilyl (TMS) derivative of glimepiride with an m/z ratio of 256. Distinct parameters like specificity, carryover, stability, precision, and accuracy were evaluated for validating the identification method. The GC-MS method is found to be linear and illustrated within the range 500 to 2500 ng/ml with the value of R2 (coefficient of determination) at 0.9924. The stability of the extracted and derivatized glimepiride was accessed with regard to processed/extracted sample conditions and autosampler conditions, respectively. Accuracy at each concentration level was within the + 15% of the nominal concentration. Precision (%) for the interday and intraday analysis was found to be in the respectable spectrum. Henceforth, the proposed GC-MS method can be employed for the determination of glimepiride in biological matrices [27].

Ebru Uçaktürk et al developed and validated the Gas Chromatography-Mass Spectrometry method for Sensitive and Specific Analysis of Vildagliptin in Pharmaceutical Formulation. Before GC-MS analysis, Vildagliptin was efficiently derivatized with MSTFA/NH4I/β-mercapto ethanol at 60°C for 30 min. The obtained O-TMS derivative of Vildagliptin was detected by selected ion monitoring mode using the diagnostic ions m/z 223 and 252. Nandrolone was chosen as the internal standard. The GC-MS method was fully validated by linearity, precision, accuracy, specificity, stability, robustness, and ruggedness. LOD and LOQ were found to be 1.5 and 3.5 ng/mL−1, respectively. The GC-MS method is linear in the range of 3.5–300 ng/mL−1. The intraday and interday precision values were less than ≤3.62%. The intraday and interday accuracy values were found in the range of −0.26–2.06%. Thus, the proposed GC-MS method would be much more specific and sensitive than the other reported methods using UV or PDA detection. The developed GCMS method was considered sensitive, selective, precise, accurate, robust, and rugged according to the validation studies. Finally, the GC-MS method was successfully applied to determine Vildagliptin in pharmaceutical formulation [28].

Liquid chromatography/ Mass spectroscopy (LC/MS)

Liquid Chromatography/Mass Spectrometry (LC/MS) is rapidly becoming the preferred tool of liquid chromatographers. It is a powerful analytical technique that combines the resolving power of liquid chromatography with the detection specificity of mass spectrometry. Liquid chromatography (LC) separates the sample components and then introduces them to the mass spectrometer (MS). The MS creates and detects charged ions. The LC/MS data may be used to provide information about the molecular weight, structure, identity and quantity of specific sample components. LC/MS-based methods can be applied to most organic compounds. Sample types range from small pharmaceutical compounds to large proteins. It also permits MS analysis of non-volatile, thermally labile or charged molecules and its impurities.

Suleman S. Khoja et al developed and Validated a New Analytical, highly sensitive, precise and accurate Liquid Chromatography with mass spectrometry (LC-MS/MS) method for the Estimation of Antidiabetic Drugs Ertugliflozin and Sitagliptin in Combined Pharmaceutical Dosage form. Ertugliflozin and Sitagliptin

is combination of Antidiabetic drug in tablet Steglujan 15 mg/100 mg film-coated tablets, a member Antidiabetic drug, is a recent drug developed by Merck Sharp and Dohme Company for the treatment of Type 2 diabetes. Ertugliflozin and Sitagliptin can be used alone or in combination therapy. Chromatographic separation was carried out on Phenomenex Gemini, C18, (150 × 4.6 mm,5 µm) column. Isocratic method was based on 0.1% formic acid: acetonitrile (10:90, v/vas mobile phase, column temperature at 40°C and flow rate at 0.6 mL/minutes were utilized. The mass spectrometer was operated under multiple reactions monitoring (MRM) mode using electrospray ionization by monitoring the transition pair (precursor to product ion) of m/z 437.10-328.95in the positive mode for Ertugliflozin and transition pair (precursor to product ion) of m/z 408.10-234.95 in the positive mode for Sitagliptin. The method was found linear in the concentration range of 15 to 450 ng/mL and 100–3000 ng/mL for Ertugliflozin and Sitagliptin respectively. The optimized method was validated according to the International Conference on Harmonization (ICH) and FDA guidelines. The developed method was found suitable for the quantitation of Ertugliflozin and Sitagliptin in Pharmaceutical dosage form [29].

CONCLUSION

The present review discussed different analytical approaches employed for the assessment of antidiabetic drugs like Vildagliptin, sitagliptin, metformin, glimepiride, ertugliflozin, linagliptin etc. Extensive examinations have been accomplished including advanced techniques like UV/Vis-Spectroscopy, HPLC, RP-HPLC, HPTLC, GC-MS, LC-MS for the evaluation of antidiabetic drug in bulk and in its combination with other drugs from pharmaceutical formulations. However, the GC-MS analysis method is often used in research because it can detect samples with low concentrations. The gas chromatographic method combined with mass spectroscopy has specific advantages and sensitivity for antidiabetic drug analysis in pharmaceutical dosage form and biological matrices. Thus, it can be concluded that the reported and published methods can be successfully applied for the estimation and validation of the antidiabetic drug in pure and pharmaceutical dosage form. These compiled data may be of use for research for further studies in the analysis of antidiabetic drug or other drugs.

REFERENCES

1. Lad NR, Bhoir SI, Bhoir I C, Sundaresan M. Concurrent assay of metformin and glimepiride in tablets using RP-HPLC with wave length programming. Indian J Pharm Sci. 2003;65(6):650-3.
2. Warthin IK, Berik J, Podolsky D, Raghavendran V, Reddy R, Chang J, Porter N, Garito N. Commentary on the Benefits of US Pharmacopeial Standards: A Generic Pharmaceutical Industry Survey: J Pharm Sci 2020; 109(2):944-949.
3. Lahari K, Sravani V, Murali VB, Latha MM, Pooja K, Srinivasa Babu P, et al. Review on Various Analytical Techniques for the Estimation of Vildagliptin. Int J Pharm Sci Rev Res. 2022 Mar 15;24–8.
4. Mathieu, C; Diabetes, Obesity and Metabolism, 2009, 11(2): 9–17.
5. Srinivasan, B.T., Jarvis, J., Khunti, K. and Davies, M.J.; Postgraduate Medical Journal, 2008, 84: 524-531.

6. Rasika Devale, Swapnali Patil et. al. A review of analytical development methods for the determination of Vildagliptin. SGVU journal of pharmaceutical research and education, 2023, 8(2), 918-929.
7. Gumieniczek A, Berecka-rycerz A, Fornal E, Żyżyńska-granica B, Granica S. Comprehensive insight into chemical stability of important antidiabetic drug vildagliptin using chromatography (Lc-uv and uhplc-dad-ms) and spectroscopy (mid-ir and nir with pca). Molecules. 2021 Sep 1;26(18).
8. Beena Kumari, Aparna Khansili. Analytical Method Development and Validation of UV-visible Spectrophotometric Method for the Estimation of Vildagliptin in Gastric Medium: Drug Research 2020; 70(09): 417-423.
9. C. Bala Sekaran, A. Prameela Rani. Development and Validation of Spectrophotometric Method for the Determination of DPP-4 Inhibitor, Sitagliptin, in its Pharmaceutical Preparations. Ecl Quím, 2010; 35(3): 45-53.
10. Loujain Anis Dayoub, Fida Amali, Development of a new visible Spectrophotometric analytical method for determination of Vildagliptin in bulk and pharmaceutical dosage forms: Research Journal of Pharmacy and Technology 2020;13(6): 2807-2810.
11. Madhuri Ajay Hinge, Keyuree Vishnubhai Patel. Development and Validation of Spectrophotometric Method for Metformin and Sitagliptin by Absorbance Ratio Method. J Pharm Sci Bioscientific Res, 2016; 6(5): 733-39.
12. Anusha M. S.*, Sowmya H. G., Jose Gnana Babu C World journal of pharmacy and pharmaceutical sciences. Analytical method development and validation of Sitagliptin: review. Volume 11, Issue 2, 835-844
13. Muhammad Ashraf, Muhammad N. Shahzad, Muhammad M. Hayat, Jameel Rahman, Samina Ejaz, Hamza Altaf, Faizul H. Nasim. Development and Validation of an HPLC Method for the Quantification of Sitagliptin in Plasma and Tablet Dosage Form. Latin Am pharm, 2015; 34(4): 1-6.
14. Rao KH, Rao AL, Chandra Sekhar KB. International journal of pharmaceutical, chemical, and biological sciences development and validation of HPLC method for the estimation of Vildagliptin in pharmaceutical dosage form. IJPCBS. 2014(2):361–6. Available from: www.ijpcbs.com
15. Gedawy A, Al-Salami H, Dass CR. Development and validation of a new analytical HPLC method for simultaneous determination of the antidiabetic drugs, metformin and gliclazide. J Food Drug Anal. 2019 Jan 1;27(1):315–22.
16. Barden AT, Piccoli BL, Volpato NM, Steppe M. Second-Order Derivative UV Spectrophotometric and RP-HPLC Methods for the Analysis of Vildagliptin and Application for Dissolution Study. Vol. 02, Drug Analytical Research Drug Anal Res. 2018.
17. D. China Babu, C. Madhusudhana Chetty, Sk. Mastanamma. Novel Stress Indicating RPHPLC Method Development and Validation for the Simultaneous Estimation of Ertugliflozin and Sitagliptin in Bulk and its Formulation. Orient J Chem, 2018; 34(5): 2554-61.
18. A.S.K. Sankar, Suraj Sythana, Aakula Jhansi, P. Shanmugasundharam, M. Sumithra. Development and Validation for Simultaneous Estimation of Sitagliptin and Metformin in Pharmaceutical Dosage Form using RP-HPLC Method. Int J Pharm Tech Res, 2013; 5(4): 1736-44.

19. Chaphekar MM, Hamrapurkar PD. CODEN (USA): IJPSPP Development and Validation of RP-HPLC Assay Method for Vildagliptin Using Qbd Approach and Its Application to Forced Degradation Studies. Vol. 8, International Journal of Pharmaceutical Sciences and Drug Research. 2016.
20. Ranjan Satpathy P, Goud VM, Bhagya B, Sharma J, Shyamala & N. Development and validation of an RP-HPLC method for the assay of Vildagliptin. Vol. 3, Article in World Journal of Pharmacy and Pharmaceutical Sciences. 2014.
21. Raosaheb JR. RP-HPLC method development and validation of Vildagliptin in bulk and dosage form. World J Pharm Sci. 2017 Sep 1;1161–76
22. Sai Sruthi Arige, Sai Datri Arige, Lakshmana Rao A. Development and Validation of Sitagliptin and Simvastatin Tablets by using RP-HPLC Method. Int J App Pharm Scie & Res, 2017; 4(1): 36-43.
23. Aparajita Malakar, Bishwajit Bokshi, Dilruba Nasrin. Development and validation of RP-HPLC method for estimation of Vildagliptin from tablet dosage form: International Journal of Pharmaceutical and Life Sciences 2012; 1(1): 1-8.
24. Rao S. S., Srinivasa Rao S, Chandra Shekar M, Nagaprasanna N, Supriya T. Analytical method development and validation of antidiabetic drugs (metformin and linagliptin) in tablet dosage form by using rp-hplc method.
25. 20. K.R Patil, T A Deshmukh, V R Patil. A Stability Indicating HPTLC Method Development and Validation for Analysis of Sitagliptin as Bulk Drug and In Formulation. Am J Pharm Tech Res, 2019; 9(06): 124-35
26. Atul R. Bendale, R. P. Singh, G. Vidyasagar. Development and validation stability indicating HPTLC method for determination of Vildagliptin and Metformin hydrochloride in the pharmaceutical dosage forms. International journal of applied pharmaceutics. Vol 10, issue 1, 2018; 36-45
27. Verma P, Bajaj A, Tripathi RM, Shukla SK, Nagpal S. Development and validation of the method for the detection of glimepiride via derivatization employing N-methyl-N-(trimethylsilyl) trifluoroacetamide using gas chromatography-mass spectrometry. Egypt J Forensic Sci. 2021 Dec 1;11(1).
28. Ebru U. Development of Sensitive and Specific Analysis of Vildagliptin in Pharmaceutical Formulation by Gas Chromatography-Mass Spectrometry: Journal of Analytical Methods in Chemistry 2015;14: 1-7. Article ID 707414:1-7.
29. Khoja SS, Patel LJ. Development and Validation of New Analytical LC-MS/MS Method for the Estimation of Antidiabetic Drugs Ertugliflozin and Sitagliptin in Combined Pharmaceutical Dosage form. J Pharm Res Int. 2021 Jun 2;194–204.