Review Article

SGVU Journal of Pharmaceutical Research & Education

ISSN: 2456-4508

JPRE

Journal homepage: http://www.gyanvihar.org/researchjournals/

A Review of Analytical Development Methods for the Determination of Vildagliptin

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ABSTRACT

Vildagliptin belongs to the novel dipeptidyl peptidase-4 (dpp-4) substance class of medications, which includes antihyperglycemic (anti-diabetic) drugs. Vildagliptin was approved by the USFDA in 2007. Pharmaceutical analysis plays an outstanding conspicuous role in quality assurance similarly to internal control of bulk medication and pharmaceutical formulations. Development of analytical methodologies has therefore emerged as the primary research focus. New drug molecules are being developed and the analysis is also gaining equal importance. A huge survey was conducted for the determination of Vildagliptin from the research articles published in various pharmaceutical and analytical chemistry Journals. The present paper accentuates the review of analytical methods including UV/Vis-Spectroscopy, HPLC, RP-HPLC, HPTLC, GC-MS, etc. procedures entail calculating Vildagliptin dosage in pharmaceutical form. The investigatory review may provide comprehensive details of various analytical techniques and their experimental condition to the researchers. The present studies revealed that the HPLC method combined with UV spectrophotometric has specific advantages and sensitivity for the analysis of vildagliptin in a pharmaceutical formulations and biological matrices.

Keywords: Vildagliptin, analytical method, RP-HPLC, GC-MS.

INTRODUCTION

The complexity and globalization of the pharmaceutical supply chain necessitate those standards be built into the creation and production procedures from raw materials to final goods. Standards are necessary to guarantee the authenticity, potency, purity 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 [1].

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. As such, there is a growing need for anti-hyperglycemic agents, along with their quality attributes [2].

Diabetes mellitus is a progressive disease characterized by deterioration of pancreatic islet cell function and increased insulin resistance. It is a multifactorial illness that impairs the quality of life for those who are afflicted. A novel family of antidiabetic medications for the management of type 2 diabetes is represented by inhibitors of dipeptidyl peptidase-4 (DPP-4), which improves glycemic control by preventing the degradation of intestinal peptides, also known as incretins [3]. 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 [4].

A novel family of antidiabetic medications for the management of type 2 diabetes is represented by inhibitors of dipeptidyl peptidase-4 (DPP-4). Vildagliptin, previously identified as LAF237, Vildagliptin [(2S)-1- {2- [(3-hydroxyadamantan-1-yl) amino] acetyl} pyrrolidine-2- carbonitrile (Figure no. 1) is a new oral antihyperglycemic agent of the new dipeptidyl peptidase-4 (DPP-4) inhibitor class of drugs. It is a solid powder that ranges in color from white to off-white and dissolves in both DMSO and water [5].

Vildagliptin prevents DPP-4 from inactivating GLP-1 and GIP, which enables GLP-1 and GIP to enhance insulin production in beta cells and decrease glucagon release by alpha cells in the pancreatic islets of Langerhans. It is currently in clinical trials in the U.S. and has been shown to reduce hyperglycemia in type 2 diabetes mellitus. Although the medicine remains unapproved for use in the United States, the European Medicines Agency approved it for use

in the EU in February 2008, and it is available on the Australian PBS with specific limitations [6]. Vildagliptin is a substrate-mimicking inhibitor containing a cyanopyrrolidine motif. Given that it is readily absorbed and removed from plasma, it must be taken twice daily, in contrast to certain other gliptins that only need to be taken once daily. Figure 1 shows the vildagliptin chemical structure [7].

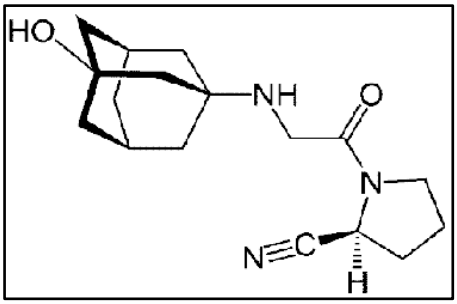

Figure no. 1: Structure of Vildagliptin

Adults with type 2 diabetes mellitus who are not achieving optimal glycemic control after monotherapy can use vildagliptin in combination with metformin, sulfonylurea, or thiazolidinedione to reduce hyperglycemia. It is marketed as Galvus. Vildagliptin is also available as Eucreas, a fixed-dose formulation with metformin for adults who do not adequately have glycemic control from monotherapy. Vildagliptin is currently under investigation in the US [8].

A review of the literature found that many analytical techniques, including GC-MS, HPTLC, and others, have been described for the estimate of vildagliptin. But given that the current approaches lack precision, accuracy, and sensitivity, and do not indicate stability. The goal of this work was to create an inexpensive, straightforward, precise, fast, and economical HPLC approach using UV spectrophotometry for the quantification of vildagliptin in tablet and bulk form [9].

Analytical Methods for the Determination of Vildagliptin in Pure Form or Dosage Form:

UV-Visible spectroscopy:

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. Single beam and double beam spectrometers are the two sorts of spectrometers that are based on the kind of beam utilized in UV sensors [10].

The UV-visible Spectrophotometric Method for the Estimation of Vildagliptin in a Gastric Medium was created and verified by Beena Kumari et al. Vildagliptin was measured in an acidic medium containing 0.1N HCl using a UV-visible double-beam spectrophotometer set to the wavelength of maximum absorption (210 nm). The ICH established criteria for the validation of analytical parameters such as linearity, precision, and accuracy. These parameters were used to validate the method.

The medication was discovered to have a melting point of 154°C, which is within its true melting range. In a similar vein, the medication was verified by spectrum interpretation. A regression coefficient of 0.999 was found for the linear response of vildagliptin throughout a concentration range of 5–60 µg/ml. The findings demonstrated that the intraday and interday precision, at 1.263 and 1.162, respectively, were within the limits. The limit of detection (LOD) and limit of quantification (LOQ), which were found to be 0.951µg/ml and 2.513µg/ml, respectively, were established in order to establish the sensitivity of the approach. It was discovered that the Vildagliptin drug's developed and validated UV approach was linear, accurate, exact, and cost-effective, and that it could be utilized to evaluate the drug's pharmaceutical formulations [11].

A novel visible Spectrophotometric analytical technique was created by Dayoub Loujain Anis and colleagues to measure vildagliptin in both bulk and prescription dosage forms. The process involves reacting the medication with p-dimethylaminobenzaldehyde (PDAB) in acidic ethanol to generate a Schiff base, which results in a vivid yellow color. The absorbance of the produced colored species was measured at 446 nm, which is its absorption maximum, or λmax. To optimize the reaction conditions, each variable was looked at. With a correlation coefficient of R2 = 0.9977, Beer's law has been followed in the concentration range of 75-175 µg/ml. The suggested method's LOD and LOQ were determined to be 10.633 (µg/ml) and 32.223 (µg/ml), respectively. When typical pharmaceutical excipients were present, there was no interference seen [12].

High-performance liquid chromatography (HPLC):

To evaluate drug products,HPLC is a crucial analytical instrument. 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.

Vildagliptin in tablet dose form was estimated using a high-performance liquid chromatographic approach that was developed and verified by K. Hanumantha Rao et al. A

150 mm x 4.6 mm internal diameter Altima C18 column with a 5 µm particle size was employed in an isocratic mode. The mobile phase included acetonitrile (72:28 v/v) and a diluted orthophosphoric acid solution with a pH of 2.6±0.5 as a buffer. The flow rate was 1.0 ml/min, and the effluents were measured at 266 nm. Vildagliptin had a 3.25-minute retention period. It was found that the process was simple, sensitive, exact, and accurate after validation. 1.28 was found to be the tailing factor. Vildagliptin was recovered from the tablet formulation with 99.73% accuracy, and the quantification and detection limits were 0.21µg/ml and 0.06µg/ml, respectively. These results suggest that the excipients employed in the formulation do not interfere with the method. Therefore, the recommended method of measuring the amount of vildagliptin in tablet formulation was successful[13].

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

Hydrophobicity-based molecular separation is achieved via a process called reversed-phase high-performance liquid chromatography (RP-HPLC). The solute molecule from the mobile phase binds hydrophobically to immobilized hydrophobic ligands situated on the stationary phase, or the sorbent, to cause the separation[14].

For the purpose of analyzing vildagliptin in bulk medication and its pharmaceutical formulation, Meetali M. Chaphekar et al. developed the Reverse Phase-High Performance Liquid Chromatography (RP-HPLC) method by QbD methodology using the Design of Experiments and subsequent validation. Quality by design, or QbD, is a concept that has gained prominence recently in the field of analytical method development. It entails using a desired set of trials to understand the essential components and their interactions. The paper offered an effective experimental strategy that relies on a methodical assessment of the three essential elements of the RP-HPLC method: buffer pH, organic phase-% acetonitrile, and organic modifier-methanol.The significance and interaction effects of these parameters on the response variables (Retention time and tailing factor) were evaluated through the use of statistical analysis techniques such as Analysis of Variance (ANOVA) and plots that displayed the final chromatographic conditions of the procedure. In order to ascertain the suggested method's stability-indicating character, forced degradation studies were conducted in addition to validation. The Jasco CrestPack RP C18 (250 × 4.6 mm, 5µ) column was utilized to accomplish the chromatographic separation with the aid of Buffer (pH 6). Acetonitrile was detected at 210 nm using a Photo-Diode Array (PDA) detector with methanol (70:10:20 v/v) as the mobile phase. With a correlation coefficient R2 value of 0.999, the Vildagliptin developed method is linear over a range of 5-15µg/ml. The accuracy and precision %RSD of

the approach was found to be less than 2%. By gradually lowering the vildagliptin concentration while maintaining a signal-to-noise ratio of at least 3:1 and 10:1, respectively, the LOD and LOQ were determined.Vildagliptin was shown to have a LOD of 200 ng/ml. Vildagliptin's LOQ was discovered to be 600 ng/ml. As a result, the validation results clearly show that the RP-HPLC assay technique for vildagliptin created using the QbD approach is linear, accurate, precise, repeatable, and specific. The discovered approach can be easily applied for quality control to ascertain the assay in routine Vildagliptin product development, production, and stability samples. It is also stability-indicating. The findings shown that the suggested approach is appropriate for the exact and accurate formulation of vildagliptin and its determination in bulk[15].

Vildagliptin test using RP-HPLC was developed and validated by Pragati Ranjan Satpathy et al. This involved the use of a Waters HPLC in conjunction with an Autosampler, empower 2.0 software, Symmetry C18 (4.6 x 150mm, 5mm, make: Thermosil), and Galvus (Manufactured by NOVARTIS) tablets for the preparation of the sample solution for chromatographic separation.

An indirect UV detection technique based on RP-HPLC was created to measure vildagliptin in pharmaceutical dose forms. Vildagliptin is a dipeptidyl peptidase IV inhibitor that is effective in treating diabetes.In under 4 minutes, reverse phase separation was achieved, and its linearity was seen within the 50–90 µg/mL range (r^2 = 0.999). A combination of pH 8.2 buffer, acetonitrile, and methanol in the ratio of 450:480:70 was used for separation on a C18 column.

Prior to usage, a 0.22 µ PVDF filter was used to filter the solvent combination, and it was then Sonicated. The flow rate through the column was 0.5 milliliters per minute. At 254 nm, the drug's detection was tracked. This method's resilience, LOD, LOQ, linearity, accuracy, precision, and robustness were all evaluated as part of its validation.The LOD was 2.98 g/m and The LOQ was 9.94 g/mL for Vildagliptin.

A more quick, accurate, specific, sensitive, repeatable, cost-effective, isocratic reverse phase HPLC technique was created and validated for the quantitative determination of vildagliptin, according to the results of the contemporary analytical investigation.

The run time was set at ten minutes. With optimal chromatographic conditions, a retention time of approximately 3.9 ± 0.1 min enables the rapid examination of several samples. Using metrics including accuracy, precision, linearity, LOD, LOQ, and robustness, the approach was effectively validated.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 recommended method worked well for the quantitative examination of VLG in tablet dose form, which would enhance quality assurance and support investigations into the stability of pharmaceutical tablets containing this medication [16].

The RP-HPLC method was developed and verified by Jagdale Ramkrishna Raosaheb et al. to estimate the dosage and bulk form of Vildagliptin. Vildagliptin was prepared for use in the RP-HPLC method with a stationary phase of Phenomenex C18 column (5µm, 250mm × 4.6mm) and a mobile phase of methanol: water (60:40 v/v) (pH 4.5 adjusted with OPA). The injection volume was 20 µl, and the mobile phase was kept at a flow rate of 0.8 ml/min. At 207 nm, detection was performed. ICH guidelines were used to validate the procedure.

A good linear relationship (R^2 = 0.999) was observed between the concentration of Vildagliptin and the individual mean peak area. Vildagliptin's percentage assay result for the commercial formulation was determined to be between 98.65 and 100%, respectively. A recovery study was conducted to evaluate the method's accuracy; the findings showed that Vildagliptin's w/w ranged from 99.56 to 102.25%, respectively. Vildagliptin's retention time was found to be 3.58 minutes.At 0.98µg/ml, the LOD and LOQ were determinedand 2.98µg/ml respectively for Vildagliptin, indicating the method sensitivity. The precision study's percent RSD for these medications was less than 2%, indicating that the devised method's precision was good.The HPLC process that was created was straightforward, quick, easy, precise, and accurate. Thus, the technique can be effectively used for the regular analysis of Vildagliptin in pharmaceutical dosage forms and bulk in the pharmaceutical business[17].

Vildagliptin estimate from tablet dose form using RP-HPLC method developed and validated by Aparajita Malakar et al. A combination of an aqueous phase (1 ml of 25% ammonium hydroxide was dissolved in 1000 ml of water for chromatography; the pH of the solution was adjusted to the value of 9.5 using a 50% solution of phosphoric acid) and an organic phase (methanol) was used to achieve the separation on an Xterra® Waters C18 column (150 mm x 4.6 mm, 5µm). The flow rate of the mixture was 1.0 milliliters per minute at a ratio of 60:40 v/v. The wavelength of detection was 210 nm. Vildagliptin was shown to have a retention duration of 6.3 minutes. Between 5 and 200µg/ml, the calibration curve was determined to be linear (r2 = 0.9997).

The respective limits of detection and quantitation were 1.47µg/mL and 4.90µg/mL. The percentages of vildagliptin recovery were found to range from 99.11 to 100.62%. The International Conference on Harmonization accepted criteria for specificity, linearity,

accuracy, robustness, precision, and system applicability, which validated the approach. The excipients have no effect on Vildagliptin's determination. Vildagliptin dosage form quantitative analysis was successfully conducted using the suggested method, which will enhance quality control[18].

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 the sample's separation.

The stability-indicating HPTLC method for determining the concentrations of metformin hydrochloride and vildagliptin in pharmaceutical dosage forms was developed and verified by Atul R. Bendale et al. Vildagliptin and metformin hydrochloride were determined using a validated HPTLC technique. With this method, one parameter is optimized while the other parameterssuch as the organic solvent, the make-up of the mobile phase, and any used acid or base modifiersremain constant. TLC plates were coated with 10 µl of the Metformin stock solution (500 ng/band) and 2 µl of the Vildagliptin stock solution (100 ng/band). The final solutions were applied to the HPTLC plates after being developed under optimal densitometry conditions.

For both metformin and vildagliptin, the range of concentration was plotted against peak area in mix standard, yielding calibration curves of 50–500 ng/band and 10-150 ng/band, respectively.Vildagliptin and metformin were shown to have good absorbance at roughly 217 nm based on the spectrum analysis. Degradation of both medications was evident, with further peaks appearing at Rf values of 0.81 for Vildagliptin and 0.16 for Metformin. With retardation factor (Rf) values of 0.22±0.01 for metformin and 0.73±0.02 for vildagliptin, good separation was accomplished using the following mobile phase: hexane, methanol, acetonitrile, and glacial acetic acid (2:3.5:2.5:0.2 v/v/v/v).

The levels of exposure (LOD) and limit of quantification (LOQ) for metformin and vildagliptin were determined to be 8.2 ng/band and 1.74 ng/band, respectively. It was discovered that the suggested approach for determining the pure and dose forms of metformin and vildagliptin was straightforward, exact, accurate, fast, and specific. The mobile phase is affordable and easy to prepare. The formulation's sample recoveries showed that the excipients did not affect the estimate and that they performed very well in line with the

statements stated on their separate labels. Therefore, this technique is simple to use and handy for routine examination of both the dose form and pure forms of Vildagliptin and Metformin[19].

Gas Chromatography-Mass Spectrometry (GC-MS):

Chemical mixtures can be separated using the Gas Chromatography-Mass Spectrometry (GC/MS) system, which is also used to identify components at the molecular level (the MS component). It is one of the most accurate tools for analyzing data from environmental samples that is currently accessible. Heat is thought to induce a mixture to split into its component parts, which is how the GC works.

An inert gas columnsuch as heliumis used to send the heated gases. After leaving the column aperture, the separated materials enter the MS. Using mass spectrometry, compounds are identified by their analyte molecule's mass.

On a computer is kept a "library" of known mass spectra for thousands of different compounds. It is believed that mass spectrometry is the sole reliable analytical detector.The sophisticated hyphenated technique known as gas chromatography–mass spectrometry (GC–MS) is used to identify compounds by combining the mass spectral fragmentation patterns, which are indicative of the chemical structures of the compounds, with the relative gas chromatographic retention times and elution patterns of mixture constituents.

The Gas Chromatography-Mass Spectrometry technique for Sensitive and Specific Analysis of Vildagliptin in Pharmaceutical Formulation was developed and verified by Ebru Uçaktürk et al.Vildagliptin was effectively derivatized using MSTFA/NH4I/β-mercaptoethanol at 60°C for 30 minutes prior to GC-MS analysis.

Using the diagnostic ions m/z 223 and 252, the resulting O-TMS derivative of Vildagliptin was detected by selected ion monitoring mode. The internal standard that was selected was nandrolone. The linearity, precision, accuracy, specificity, stability, robustness, and ruggedness of the GC-MS method were all completely validated. The LOD and LOQ were found to be 1.5 and 3.5 ng/mL^{-1}, respectively.

The GC-MS method has a linear range of 3.5–300 ng/mL−1. Less than ≤3.62% was found in the intraday and interday precision values. Results showed that the accuracy values for both intraday and interday ranged from -0.26 to 2.06%.As a result, compared to previous documented approaches that use UV or PDA detection, the suggested GC-MS method would be far more sensitive and specific. The validation studies evaluated the new GCMS method

and found it to be sensitive, selective, precise, accurate, robust, and rugged. Finally, Vildagliptin in pharmaceutical formulation was identified through the successful application of the GC-MS method[20].

CONCLUSION

The present review discusseddifferent analytical approaches employed for the assessment of Vildagliptin. Extensive examinations have been accomplished includingadvanced techniques like UV/Vis-Spectroscopy, HPLC, RP-HPLC, HPTLC, GC-MS,etc. for evaluation of Vildagliptin in bulk and when used with additional medications from pharmaceutical formulas.However, the RP-HPLC analysis method is often used in research because it can detect samples with low concentrations. The HPLC method combined with UV spectrophotometric has specific advantages and sensitivity of Vildagliptin analysis in biological matrices and pharmacological dose forms.These compiled data may be of use for research for further studies in the analysis of Vildagliptin or otherdrugs.

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