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Comprehensive Review Of Analytical Methodologies For Gliclazide And Sitagliptin

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ABSTRACT

This comprehensive review examines and critically evaluates the analytical methodologies developed for Gliclazide and Sitagliptin, two widely used antidiabetic drugs. It provides a detailed analysis of method development and validation parameters, such as linearity, accuracy, precision, and robustness, as defined by international guidelines. The review study highlights the strengths and limitations of each method for quantifying these drugs in various matrices, including bulk drug, pharmaceutical formulations, and biological fluids. Special emphasis is placed on approaches which offers a systematic and risk-based framework for method development, ensuring a more robust and rugged analytical procedure. By synthesizing a vast body of literature, this review aims to provide researchers and analysts with critical insights to select the most appropriate and efficient analytical method for a given application. The insights gained from this review can guide future research in developing more sensitive, rapid, and eco-friendly analytical methods for the quality control and therapeutic monitoring of Gliclazide and Sitagliptin. This extensive study critiques Gliclazide and Sitagliptin's analytical methods, two popular antidiabetics. Novel techniques like Analytical Quality by Design (AQbD), which provides a systematic and risk-based framework for method development, are prioritised to provide a more robust analytical procedure. This review synthesises a large amount of knowledge to help researchers and analysts choose the best analytical approach for a specific application. The findings of this study can help create more sensitive, fast, and environmentally friendly analytical procedures for Gliclazide and Sitagliptin quality control and therapeutic monitoring. The review covers spectrometry, HPLC, UPLC, and their hyphenated variants like LC-MS and LC-ESI-MS-MS. It analyses worldwide guidelines-defined method development and validation characteristics including linearity, accuracy, precision, and robustness..

Keywords: Gliclazide; Sitagliptin; Analytical Methodologies; RP-HPLC; LC-MS; Quality by Design

INTRODUCTION

Sitagliptin (Figure 1) is a widely prescribed oral medication used to manage type 2 diabetes, belonging to a class of drugs known as dipeptidyl peptidase-4 (DPP-4) inhibitors. Its therapeutic action is centered on enhancing the body's natural incretin system, a hormonal pathway crucial for regulating blood glucose levels. After a meal, the intestines naturally release incretin hormones, primarily glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) (1, 2).

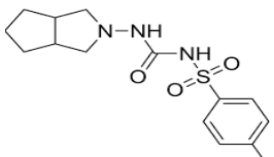


Figure 1: Chemical Structure of Gliclazide

These hormones signal the pancreas to increase insulin production and simultaneously decrease the release of glucagon, a hormone that raises blood sugar. Normally, these beneficial incretins are rapidly inactivated by the enzyme DPP-4. Sitagliptin works by inhibiting this very enzyme, thereby extending the action and increasing the levels of active incretin hormones. This results in a more efficient and glucose-dependent stimulation of insulin secretion and a suppression of glucagon, which effectively lowers blood sugar, particularly after meals, without causing the weight gain or high risk of hypoglycemia often associated with other antidiabetic agents (3, 4). Sitagliptin is typically taken as a once-daily tablet and can be used as a standalone treatment or in combination with other medications like metformin to achieve better glycemic control and reduce HbA1c levels. While generally well-tolerated, common side effects are usually mild and may include headaches or symptoms of a common cold. However, patients should be aware of rare but serious side effects, such as pancreatitis or severe allergic reactions, and should seek immediate medical attention if they experience severe abdominal pain or a rash (5-8).

Gliclazide (Figure 2) is an oral medication belonging to the sulfonylurea class, primarily used to manage type 2 diabetes mellitus. Its main mechanism of action involves stimulating the pancreas to produce and release more insulin. It achieves this by binding to and blocking the ATP-sensitive potassium channels on the beta cells of the pancreas, which leads to depolarization of the cell membrane. This depolarization opens voltage-gated calcium channels, allowing an influx of calcium ions. The increased intracellular calcium concentration triggers the release of insulin stored in secretory granules. This enhanced insulin secretion helps to lower blood glucose levels, particularly after meals, and improves the body's utilization of glucose (9-11).

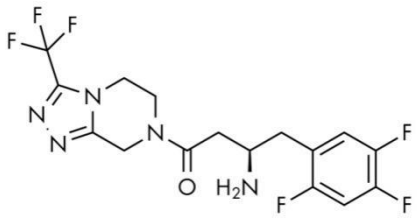


Figure 2: Chemical Structure of Sitagliptin

Beyond its insulinotropic effect, gliclazide also offers a potential benefit related to its vascular and platelet-modulating properties. It may help protect against the microvascular complications of diabetes, such as retinopathy and nephropathy. Some studies suggest it has antioxidant properties and can help reduce platelet aggregation, thereby potentially decreasing the risk of blood clots. This dual action on both glycemic control and vascular health makes it a valuable treatment option for many individuals with type 2 diabetes (12, 13). Gliclazide is typically taken once or twice daily, depending on the specific formulation (immediate-release or modified-release). It is important to take it with meals to help minimize the risk of hypoglycemia, a common side effect of sulfonylureas. Hypoglycemia occurs when blood sugar levels drop too low, and symptoms can include dizziness, sweating, and confusion. Due to this risk, careful monitoring of blood glucose is essential while on gliclazide therapy. It is often used as a monotherapy or in combination with other antidiabetic agents to achieve optimal blood sugar control. The dose is carefully titrated by a healthcare provider to balance effectiveness with safety (14-16).

2. LITERATURE REVIEW ON THE ANALYTICAL METHODOLOGIES FOR SITAGLIPTIN AND GLICLAZIDE

2.1 Literature Review of the Analytical Methodologies for Sitagliptin

Song Y et al., 2025 developed and validated a fast, sensitive, and novel LC–MS/MS assay to quantify plasma sitagliptin concentrations. We use sitagliptin-d4 as the internal standard in our analytical approach, which requires just 100 µL of plasma and a liquid-liquid extraction process using MTBE. A Kinetex® C18 column under isocratic elution, a 1:1 mix of 5 mM ammonium acetate (with 0.04% formic acid) and acetonitrile, and 0.2 mL/min flow rate yield excellent chromatographic separation. In positive ionisation mode, detection targets transitions at m/z 408.2 → 193.0 for sitagliptin and 412.2 → 239.1 for the IS using multiple reaction monitoring. It takes around 2 minutes to complete this experiment. Comprehensive validation according to MFDS and FDA requirements shows excellent linearity (5–1000 ng/mL, r2 > 0.998), accuracy, precision, recovery, and sample stability. The proven technique is ideal for sitagliptin pharmacokinetic and bioequivalence evaluations due to its low sample demand and high throughput (17).

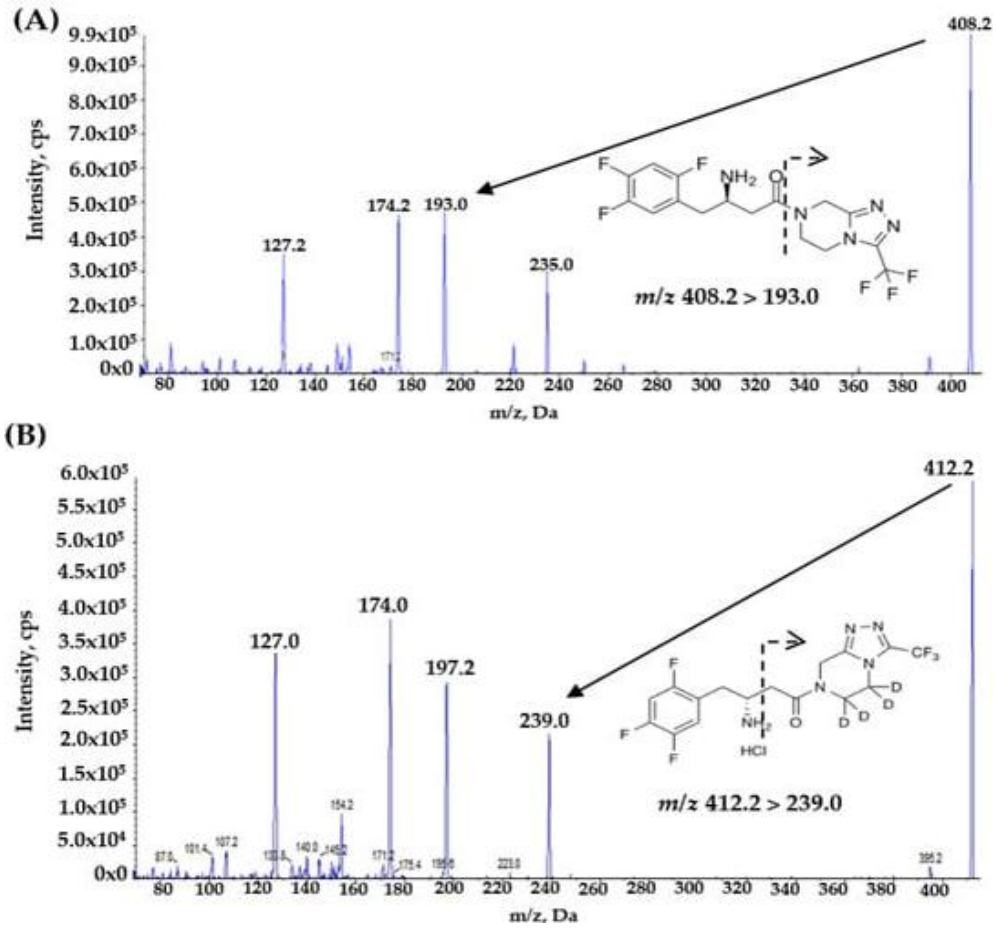


Figure 3: LC–MS/ assay to quantify plasma sitagliptin concentrations

Manukonda V et al., 2025 developed and tested a sensitive, accurate, and precise uplc-ms technique to measure ert and sit in bulk and mixed tablet forms and evaluate the greenness profile was the study's main goal. the separation on an agilent zorbax eclipse xdb-c18 column (50 × 2.1 mm, 5 µm) used acetonitrile and 2 mm ammonium formate (85:15 v/v) at 0.1 ml/min, with 2.5 min per sample. isocratic elution was used. the technique was verified for linearity, precision, accuracy, lod, and lq. in positive ionisation mode employing electrospray ionisation, the tandem mass spectrometer discovered ert at 437.36/415.41 and sit at 408.11/235.05 in multiple reaction monitoring (mrm). a linear range of ert 5–22.5 ng/ml and sit 10–150 ng/ml was determined, with a r^2 value over 0.99. precision data indicates ert and SIT % RSD values of 0.83 and 1.14. The ERT and SIT recovery rate was 98–104.9%. The suggested approach quantifying the two medicinal chemicals simultaneously was verified and approved by the ICH and USFDA (18).

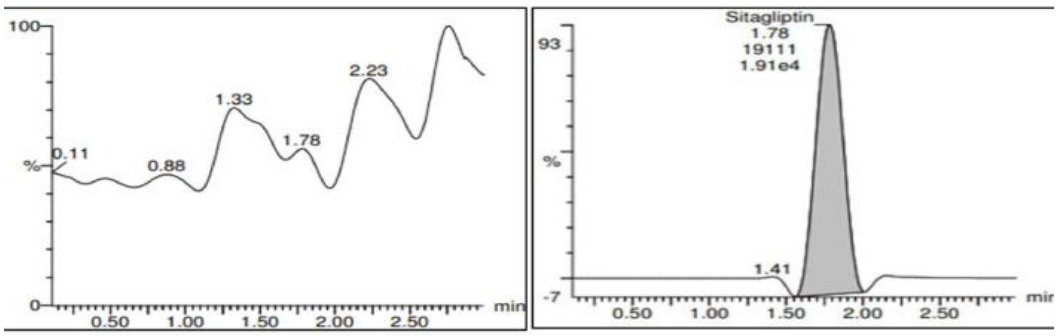


Figure 4: UPLC-MS technique to measure SIT in bulk and mixed tablet forms

Alshora D et al., 2025 worked on response surface approach to build an ultraperformance liquid chromatography method for simultaneous metformin and sitagliptin estimation in a short run time. To evaluate the effects of three independent factors—aqueous phase concentration in the mobile phase (5–15%), mobile phase flow rate (0.4–1 mL/min), and ammonium formate buffer strength (5–20 mM), a Box–Behnken design was used. Data analysis indicated that flow rate significantly reduced retention time and peak area. The optimised analytical condition was 15% aqueous phase concentration, 0.52 mL/min flow, and 5 mM buffer strength. According to ICH criteria, the analytical procedure was legitimate. In 2 min, SG and MF were separated. SG and MF retained times of 0.73 and 1.36 min, respectively, were reliable for separating and extracting Janumet tablets (19).

Hadawale S et al., 2025 discusses a review on spectroscopic, chromatographic, and hyphenated DPP-4 inhibitor analytical and bioanalytical procedures. There is no comprehensive DPP-4 inhibitor evaluation. This study aims to teach analysts how to quantify and estimate DPP-4 inhibitors in diverse matrices using analytical and bioanalytical approaches. A database of pre-existing studies from ScienceDirect and PubMed was created to aid comprehension. The literature selection flowchart shows the methods. Researchers and clinicians can benefit from a complete DPP-4 inhibitor analysis review. No comprehensive DPP-4 inhibitor review has been published. Thus, to gather data on a construct, subject-specific data gaps must be needed. This evaluation reveals that chromatographic methods were mostly employed for analysis, using solvents including acetonitrile, methanol, and buffer solutions as mobile phases that might damage HPLC columns and equipment. Scientists might test DPP-4 inhibitors using greener solvents (20).

2.2 Literature Review on the Analytical Methodologies for Gliclazide

Demir İ et al., 2025 used acetonitrile as an organic modifier in the mobile phase, while the green method used ethanol. Mobile phases were 0.1% formic acid solution in ultrapure water and 40/60 acetonitrile. The isocratic elution was done at 1.0 mL/min, with 10 µL of active material injected into the column and monitored at 226 nm UV detector. All requirements of the classical approach were followed in the green method, which employed ethanol as an organic modifier. Both chromatographic methods were tested for robustness, selectivity, accuracy, linearity, detection, and quantification limits using ICH principles. Chromatographic correlation coefficients exceeded 0.999 at 5–30 mg mL-1. The chromatographic procedures were used on pharmaceuticals. Comparisons using the Student's (t) test for means and the Fischer (F) test for standard deviations showed no significant difference. The AGREE greenness evaluation program assessed these two techniques. Gliclazide quantification in pharmaceutical formulations might be done more sustainably and analytically with the green technique (21).

Hassouni N et al., 2025 carried out a project involves developing a sensitive, cost-effective, and specific spectroscopic analytical technique to evaluate ligands as raw materials and pharmaceutical formulations. The recommended method creates an orange-red compound with 450 nm absorbance via nucleophilic substitution. The optimum experimental conditions for the reaction were 1.4 ml of reagent at 2.2% w/v, methanol as a solvent, and 90°C in a water bath for 22 minutes. Job and molar ratio methods were used to study product stability and reactant ratios. The compound was stable for two hours and had a one-to-one reaction ratio for each reagent. ICH-compliant analytical methods were tested under optimal reaction circumstances. Within concentrations (30-110 M), Lambert-Beer's law has a correlation coefficient of R=0.99 and recovery values of 99.39-99.59%. Tablet ligands were successfully determined using the approach since no hindrance was seen from excipients or metformin in the participating pharmaceutical forms. Using t-test and F-test, the findings were not significantly different from HPLC and UV-vis absorption assays. The finding results of the docked compound Gliclazide with binding affinity – 7.7 kcal/mol, the results show us the compound's ability to inhibit the enzyme UNC, which promises to inhibit and treat inflammation in the udder of cows, thus achieving the highest possible levels of milk production (22).

Trailokya AA et al., 2025 reviewed the Type 2 diabetic mellitus (T2DM) treatment has shifted towards streamlined dose and new drugs. Sulfonylureas, notably gliclazide, are still necessary for T2DM management, especially in resource-constrained settings. The second-generation sulfonylurea Gliclazide and its modified variant Gliclazide MR are recommended because to its long-acting, once-daily formulation, superior safety profile, and success in decreasing HbA1c levels. Due to its low hypoglycaemia risk and renal impairment compatibility, it works in many patients, including elderly and chronic kidney disease patients. Due to its specific targeting of pancreatic SUR1 receptors without cardiac receptors, gliclazide has a reduced risk of cardiovascular adverse effects than other sulfonylureas. Its use in fixed-dose combinations (FDCs) with other antidiabetic medicines like metformin improves adherence and glycaemic control. In India, where pricing and accessibility are issues, gliclazide is seen as a promising, effective, and cost-effective choice as diabetes guidelines emphasise individualised therapy. They emphasise the need of alerting healthcare professionals about gliclazide's clinical value to promote its incorporation into T2DM therapy frameworks that balance efficacy, safety, and patient demands (23).

Patel B et al., 2025 carried out a study in which chromatographic separation was obtained using a Cosmosil CN column (150 x 4.6 mm, 5 µm) and an isocratic elution pattern with a mobile phase of 10 mM ammonium formate (pH 5.0) and 30:70 v/v methanol. A positive ion electrospray ionisation (ESI) source and mass spectrometer were employed for detection. The MRM collection mode was used to collect data. In the experiment, metformin D6 and vildagliptin D7 were utilised as

internal standards at 1.0 mL/min. The medicines were extracted using Phenomenex Strata-X-packed SPE. Equal parts methanol and 5 mM sodium lauryl sulphate were used to extract the medication. The MET and VLG retention times were 3.2 and 3.8 minutes. SPE extracted metformin and ISTD with 89.44% and 87.57% recovery, and vildagliptin and ISTD with 92.26% and 89.58% recovery. Solid phase extraction (SPE) created clean, high-recovery extracts from samples. The liner calibration curve for MET was 0.5-400 ng/mL and for VLG, 0.2-160 ng/mL, with a correlation coefficient r2 > 0.99 (24).

2.3 Analytical Methodologies for Sitagliptin and Gliclazide

Qin M et al., 2025 compared the efficacy and safety of sitagliptin and gliclazide, combined with metformin, in treatment-naive patients with type 2 diabetes mellitus (T2DM) and glucotoxicity. 129 patients were randomized to receive sitagliptin plus metformin or gliclazide plus metformin for 12 weeks. The study found that sitagliptin achieved faster glycemic targets, greater FPG and body weight reductions, and higher rates of FPG < 6.1 mmol/L (26.2% vs. 5.7%). No significant differences were observed in β-cell function or hypoglycemia incidence. Genetic analysis showed specific single-nucleotide polymorphisms affected drug efficacy, with dipeptidyl peptidase-4 and rs4664443 GG genotypes showing lower efficacy with sitagliptin, while GLP1R and KCNJ11 genotypes responded better to sitagliptin. The study concluded that sitagliptin combined with metformin is noninferior to gliclazide combined with metformin in treatment-naive patients with T2DM with glucotoxicity. Genetic polymorphisms significantly affect drug efficacy, highlighting the importance of personalized medicine. The sitagliptin group achieved glycemic targets more quickly and had greater weight reductions without increased adverse effects (25).

Jadhav S et al., 2025 examines the role of internal standards (ISs) in ensuring accurate quantification of antidiabetic drugs within biological matrices. It identifies trends in IS selection, extraction techniques, biological fluid distribution, and analytical methodologies used for quantifying these drugs. The study highlights the importance of using stable isotope-labeled compounds, structurally related drugs, and deuterated analogs for IS selection, as well as optimizing sample preparation techniques like protein precipitation, liquid-liquid extraction, and solid-phase extraction. Advanced chromatographic and mass spectrometric techniques, such as LC–MS/MS and HPLC/UPLC–MS/MS, provide high sensitivity and specificity, facilitating precise drug concentration measurements. The findings underscore the need for standardized IS selection criteria and refined bioanalytical methodologies to ensure reliable quantification across diverse biological fluids. This review contributes to the advancement of bioanalytical research in diabetes management, optimizing pharmacokinetic studies and therapeutic monitoring (26).

Table 1. Summary of 2025 Analytical Studies on Sitagliptin & Gliclazide

Study (2025)	Drug	Method	Core Condition
Song Y	Sitagliptin	LC-MS/MS	Kinetex C18; MTBE LLE; 1:1 ammonium acetate: ACN; 0.2 mL/min
Manukonda V	Ertugliflozin + Sitagliptin	UPLC–MS/MS	Zorbax XDB-C18; ACN: ammonium formate 85:15; 0.1 mL/min
Alshora D	Metformin + Sitagliptin	UPLC (QbD)	Box–Behnken optimized; 15% aqueous; 0.52 mL/min
Hadawale S	DPP-4 inhibitors	Review	Overview of chromatographic & spectroscopic techniques
Demir İ	Gliclazide	HPLC (Classical vs Green)	ACN vs ethanol; 1 mL/min; 226 nm UV

3. Various Analytical Methodologies

For determining active pharmaceutical ingredients (APIs) highlights the essential role these techniques play in ensuring drug quality, safety, and efficacy. These methods, which fall into major categories like chromatography, spectroscopy, and electrochemistry, are vital throughout the entire drug lifecycle, from initial research and development to manufacturing and

quality control. The choice of method depends on the API's chemical properties and the sample matrix, with an emphasis on achieving high selectivity, sensitivity, accuracy, and precision. Analyzing active pharmaceutical ingredients (APIs) is crucial in drug development and quality control to ensure a drug's identity, purity, and concentration. A wide range of analytical methodologies are used, each with unique advantages. They can generally be categorized into three main groups: chromatographic, spectroscopic, and electrochemical methods (27, 28).

3.1. Chromatographic Methods

Chromatographic methods are paramount for separating and quantifying APIs from complex mixtures. High-Performance Liquid Chromatography (HPLC) is the industry's workhorse, offering exceptional resolution and versatility for a vast range of APIs, including those that are not volatile. It identifies compounds by their retention time and quantifies them based on peak area, often coupled with detectors like UV-Vis or mass spectrometers to enhance sensitivity. Gas Chromatography (GC) is reserved for volatile APIs and is particularly useful for analyzing residual solvents and impurities. Meanwhile, Thin-Layer Chromatography (TLC) serves as a simple, cost-effective screening tool for quick purity checks. These methods are based on the separation of compounds within a mixture based on their differential distribution between a stationary phase and a mobile phase (29, 30).

3.1.1 High-Performance Liquid Chromatography (HPLC):

This is the most common and versatile technique for API analysis. It's used for both qualitative identification (by retention time) and quantitative analysis (by peak area). It's highly sensitive, accurate, and can be easily automated (31, 32).

3.1.2 Gas Chromatography (GC):

Used for volatile or thermally stable APIs. The sample is vaporized and carried by a gas mobile phase through a column. It's excellent for analyzing drug-related impurities and residual solvents (33, 34).

3.1.3 Thin-Layer Chromatography (TLC):

A simple, low-cost technique for qualitative analysis and purity checking. It provides a quick way to confirm the presence of an API and to detect impurities, often used as a preliminary screening tool (35).

3.2. Spectroscopic Methods

Spectroscopic techniques exploit the interaction of light with matter to identify and quantify APIs. UV-Visible (UV-Vis) Spectroscopy is a rapid and straightforward method for determining the concentration of APIs that absorb light in the UV or visible range. Infrared (IR) Spectroscopy provides a molecular "fingerprint" and is used for API identification and structural confirmation. Mass Spectrometry (MS), often hyphenated with chromatography (e.g., LC-MS), is unparalleled in its ability to provide definitive structural information and detect trace amounts of impurities. Newer techniques like Near-Infrared (NIR) Spectroscopy are increasingly used as process analytical technology (PAT) tools for real-time monitoring of API content in manufacturing. Spectroscopic methods rely on the interaction of matter with electromagnetic radiation. They provide information about the molecular structure and concentration of the API (36, 37).

3.2.1 UV-Visible (UV-Vis) Spectroscopy:

Measures the absorbance of UV or visible light by a compound. It's a simple, fast, and cost-effective method for quantifying APIs that have a chromophore (a part of the molecule that absorbs light) (38).

3.2.2 Infrared (IR) Spectroscopy:

Provides a unique "fingerprint" spectrum for a molecule based on its vibrational frequencies. It's primarily used for API identification and structural confirmation (39).

3.2.3 Mass Spectrometry (MS):

This technique measures the mass-to-charge ratio of ions, allowing for the definitive identification of a compound and its impurities. It is often coupled with chromatographic methods (e.g., LC-MS) for highly sensitive and specific analysis (40).

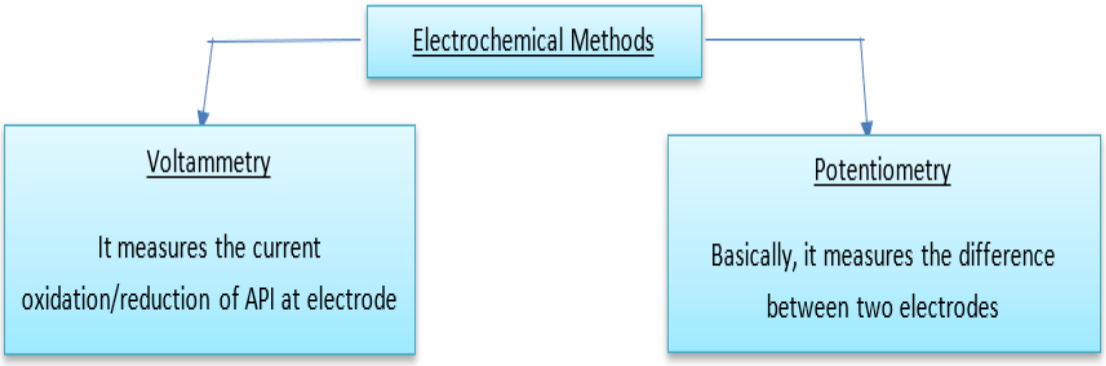
3.2.4 Nuclear Magnetic Resonance (NMR) Spectroscopy:

Provides detailed information about a molecule's chemical structure and composition. It's an invaluable tool for structural elucidation of new drug candidates and for confirming the identity and purity of an API (41, 42).

3.3. Electrochemical Methods

Electrochemical methods offer high sensitivity and selectivity for APIs that can be oxidized or reduced. Techniques such as voltammetry and potentiometry measure electrical properties of a solution to quantify APIs (43, 44). They are particularly valuable for their low sample volume requirement, rapid analysis time, and cost-effectiveness. These methodologies collectively form the foundation of pharmaceutical analysis, each contributing a specialized function to ensure the robust characterization and quality of active pharmaceutical ingredients (45, 46). These methods measure an electrical property

(like potential, current, or charge) of a solution containing the API. They are known for their high sensitivity and selectivity (47, 48).



A potentiodynamic technique that measures the current as a function of the applied potential. It's used for quantifying APIs that can be oxidized or reduced at an electrode (49, 50).

3.3.2 Potentiometry:

Measures the potential difference between two electrodes. It's used in potentiometric titrations to determine the concentration of an API by monitoring the potential changes during the titration (51).

Table 2: Analytical Methods Used for Determining Active Pharmaceutical Ingredients

Technique	Principle	Key advantages
HPLC	Separates APIs based on interaction with stationary & mobile phases	High sensitivity, accurate, versatile, widely used
GC	Vaporizes sample; separates volatile/thermally stable APIs	Excellent for volatile compounds & residual solvents
TLC	Separation on a plate by differential migration	Low-cost, fast, good for screening & purity checks
UV-Vis	Measures absorbance of UV/visible light	Simple, rapid, cost-effective for chromophore-containing APIs
IR	Detects molecular vibrations to create fingerprint spectra	Ideal for identification & structural confirmation.

4. Conclusion

This review evaluates the analytical methodologies for Gliclazide and Sitagliptin, two popular antidiabetic drugs. It analyzes method development and validation parameters, such as linearity, accuracy, precision, and robustness, as defined by international guidelines. The study highlights the strengths and limitations of each method for quantifying these drugs in various matrices, including bulk drug, pharmaceutical formulations, and biological fluids. The review emphasizes approaches that offer a systematic and risk-based framework for method development, ensuring a more robust and rugged analytical procedure. The insights gained from this review can guide future research in developing more sensitive, rapid, and eco-friendly analytical methods for Gliclazide and Sitagliptin quality control and therapeutic monitoring. The review covers spectrometry, HPLC, UPLC, and their hyphenated variants like LC-MS and LC-ESI-MS-MS. The findings can help create more sensitive, fast, and environmentally friendly analytical procedures for Gliclazide and Sitagliptin quality control and therapeutic monitoring.

5. Conflict of Interest

No Conflict of Interest was found..

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