Pharmaceutical Sciences & Analytical Research Journal
ISSN: 2640-6659

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Review Article *Volume 6 Issue 4*

A Review on Analytical Method for Estimation of Linagliptin and its Impurity

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Received Date: November 14, 2024; **Published Date:** December 10, 2024

Abstract

To facilitate future research on the medication and its contaminants, this study collects the essential data required to develop analytical methods for assessing linagliptin. Because it increases insulin secretion and controls blood sugar levels, linagliptin (DPP-IV inhibitor). The need for novel analytical methods is growing along with the quantity of newly manufactured pharmaceuticals, especially for those that are not yet listed in pharmacopoeias. The many analytical techniques for linagliptin, including HPLC, LC-MS, LC-PDA, UPLC, HPTLC, HILIC-UV, and UV spectrophotometry, are covered in this review.

Linagliptin is mostly measured using (RP-HPLC), either alone or in concoction with other drugs i.e., metformin or empagliflozin. A common RP-HPLC method for determining linagliptin uses a column: C18 (250 x 4.6 mm, 5µ), a mobile phase: 0.3% triethylamine & methanol (60:40 v/v) at a flow rate of 1 ml/min, & monitoring at 292 nm. This study highlights that more analytical advancements are required to examine the impurity profile of linagliptin, particularly 4-(Methylquinazoline-2-yl) methanol, which has not been examined in previous studies. When these methods are combined, this review provides a useful tool for researchers looking to improve Linagliptin analysis techniques, ensuring the effectiveness, security, and caliber of pharmaceutical items that contain this drug.

Keywords: Linagliptin; DPP-IV Inhibitors; Analytical Methods; UV Spectroscopy; Chromatography; Metformin; HPLC; Empagliflozin; Mobile Phase; Wavelength

Abbreviations

HPLCL: High-Performance Liquid Chromatography; ICH: International Council for Harmonisation; RSD: Relative Standard Deviation; CV: Coefficient of Variation; LOD: Detection Limit; LOQ: Quantitation Limit; DPP-4: Dipeptidyl peptidase-4; GIP: Glucose-Dependent Insulinotropic Peptide; UPLC: Ultra-Performance Liquid Chromatography; LC-MS: Liquid Chromatography-Mass Spectrometry; BP: British Pharmacopoeia; EP: European Pharmacopoeia; DAD: Diode-Array Detection; USP: United States Pharmacopeia; GLP-1: Glucagon-Like Peptide-1.

Literature Review

Sr. No.	Drug	Analytical Method	Description	References
1	Linagliptin	High-Performance Liquid Chromatography (HPLC)	Utilizes a C18 column and a phosphate buffer-acetonitrile mobile phase; commonly used for purity and assay determination.	[1]
2	Linagliptin	UV-Spectrophotometry	Absorbance is measured at 239 nm, providing a simple and quick method for quantifying linagliptin in bulk and tablet forms.	[2]
3	Linagliptin	LC-MS (Liquid Chromatography-Mass Spectrometry)	Highly sensitive and selective, suitable for identification and quantification in biological matrices and pharmacokinetic studies.	[3]
4	Linagliptin	Stability-Indicating HPLC	Analyzes linagliptin and its degradation products under stress conditions (heat, light, oxidation) for stability assessment.	[4]
5	Linagliptin	Ultra-Performance Liquid Chromatography (UPLC)	Offers fast analysis with high resolution, ideal for high-throughput testing in quality control settings.	[5]
6	Linagliptin	Capillary Electrophoresis	Separates compounds based on charge and size, an alternative method for linagliptin analysis in biological samples.	[6]
7	Linagliptin	HPLC with Fluorescence Detection	Enhances detection sensitivity in low concentrations, suitable for pharmacokinetic and bioanalytical studies.	[7]
8	Linagliptin	Derivative Spectrophotometry	Utilizes derivative techniques to enhance specificity when excipients are present in formulations.	[8,9]

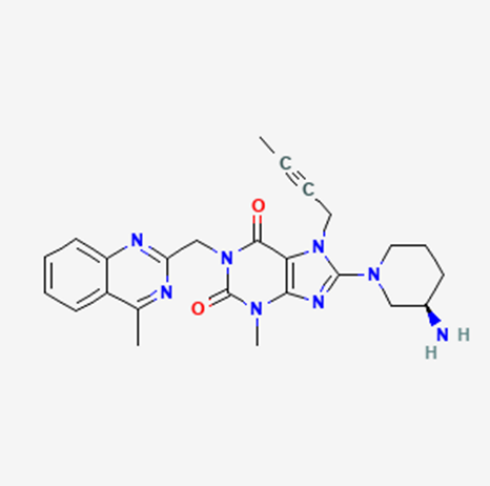
Table 1: Review of Reported Method of Linagliptin [1-9].

Sr. No.	Drugs Combination	Analytical Method	Description	References
1	Linagliptin and Metformin	High-Performance Liquid Chromatography (HPLC)	Analyzes both drugs simultaneously using a C18 column and a mobile phase with gradient elution; suitable for tablet dosage forms.	[10]
2	Linagliptin and Empagliflozin	Ultra-Performance Liquid Chromatography (UPLC)	Fast, high-resolution method for determining both compounds in combined dosage forms, useful for quality control in formulations.	[11,12]
3	Linagliptin and Glimepiride	Stability-Indicating HPLC	Detects both drugs along with any degradation products under stress conditions (e.g., light, heat, oxidation), ensuring stability.	[13]
4	Linagliptin and Pioglitazone	UV-Spectrophotometry	Simple, rapid absorbance-based method to quantify both drugs in pharmaceutical forms, using characteristic wavelengths for each drug.	[14]
5	Linagliptin and Vildagliptin	LC-MS (Liquid Chromatography-Mass Spectrometry)	Highly sensitive, suitable for simultaneous quantification in plasma for pharmacokinetic and bioavailability studies.	[15]
6	Linagliptin and Dapagliflozin	HPLC with Diode-Array Detection (DAD)	Employs DAD to identify both active ingredients, offering selectivity for quality control in pharmaceutical preparations.	[16,17]
7	Linagliptin and Sitagliptin	Capillary Electrophoresis	Separates both drugs in biological samples based on differences in charge, providing an alternative to chromatography for plasma analysis.	[18]

8	Linagliptin and Saxagliptin	Derivative Spectrophotometry	Uses derivative techniques to enhance the differentiation between both analytes in mixed formulations, improving specificity.	[19,20]

Table 2: Review of Reported Method of Linagliptin & other combination [10-20].

Drug Profile oF Linagliptin

Introduction	
Name	Linagliptin
Pharmacopoeia Status	Linagliptin is not listed in major pharmacopoeias, such as the United States Pharmacopeia (USP), European Pharmacopoeia (EP), British Pharmacopoeia (BP), or Indian Pharmacopoeia (IP).
Description	Linagliptin is a highly potent, orally bioavailable, and selective inhibitor of the enzyme dipeptidyl peptidase-4 (DPP-4), with primary use in the management of diabetes. This drug not only lowers blood sugar but may also have potential benefits in reducing arterial inflammation, which could help in treating atherosclerosis.
Structure	
Chemical Formula	$C_{25}H_{26}N_8O_2$
Mol. Weight	472.5 g/mol
IUPAC Name	8-[(3*R*)-3-aminopiperidin-1-yl]-7-but-2-ynyl-3-methyl-1-[(4-methylquinazolin-2-yl) methyl] purine-2,6-dione
Categories	Antidiabetic
Solubility	Soluble in methanol, sparingly soluble in ethanol, and only slightly soluble in isopropanol.
CDSCO Approved date	January 23, 2012
Pharmacology	
Classes	Dipeptidyl peptidase-4 (DPP-4) inhibitor, part of the gliptin class of antidiabetic drugs.
Mechanism of Action	Linagliptin inhibits DPP-4, an enzyme that degrades incretin hormones like glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). By preventing the breakdown of these hormones, linagliptin enhances their actions, leading to increased insulin secretion and reduced glucagon release from pancreatic beta cells
Properties	
State	Solid
CAS NO.	668270-12-0

Melting point	190-196°C
Nature	Basic
Log P (Partition coefficient)	2.8
Pka (Dissociation Constant)	9.86 (Strongest basic)

Table 3: Drug profile of Linagliptin [21,22].

Pharmaceutical Dosage Form

Sr.No.	Brand Name	Manufacturer	Dose
1	Trajenta Tablet	Boehringer Ingelheim	5mg
2	Ondero Tablet	Lupin Ltd.	5mg
3	Emlinz Tablet	Emcure Pharmaceuticals Ltd.	5mg
4	Linapil Tablet	Alkem Laboratories Ltd	5mg
5	Linapride 5 Tablet	Micro Labs Ltd.	5mg
6	Linares Tablet	Eris Lifesciences Ltd	5mg
7	Renolina Tablet	Sidhbali Formulations	5mg
8	Linanext Tablet	MSN Laboratories	5mg
9	Linanat Tablet	Natco Pharma Ltd.	5mg
10	Linaone	Adonis Laboratories Pvt Ltd.	5mg

Table 4: Linagliptin Drug [23].

Introduction [24-30]

Introduction to Diabetes

Definition: The word diabetes mellitus refers to a faction of metabolic disease wherein an entity have eminent blood glucose either because of inadequate insulin manufacture, an inappropriate cell response to insulin, or both [24-25].

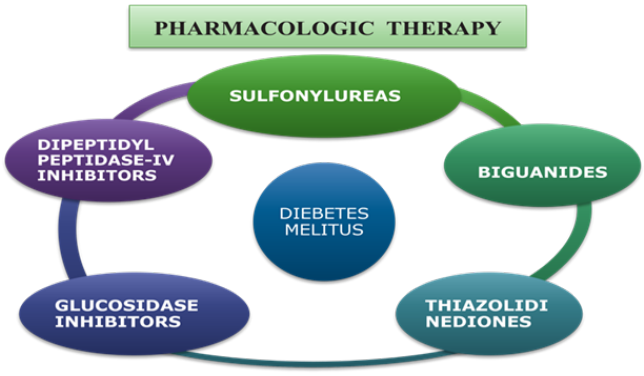


Figure 1: Pharmacologic Therapy.

DPP-IV inhibitors:

- They function by preventing the breakdown of incretins, a class of gastrointestinal hormones, by the enzyme DPP-IV. When necessary (such as after eating), incretins help the liver produce more insulin; when not needed (such as during digestion), they help the liver produce less glucagon.
- They also slow down digestion and reduce hunger. As a result, DPP-IV inhibitors aid in blood glucose regulation by protecting incretins [26].

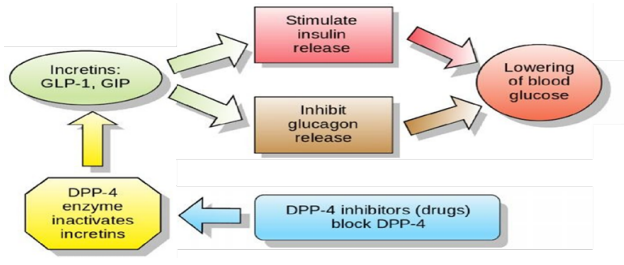


Figure 2: Mechanism of DPP-4inhibitors.

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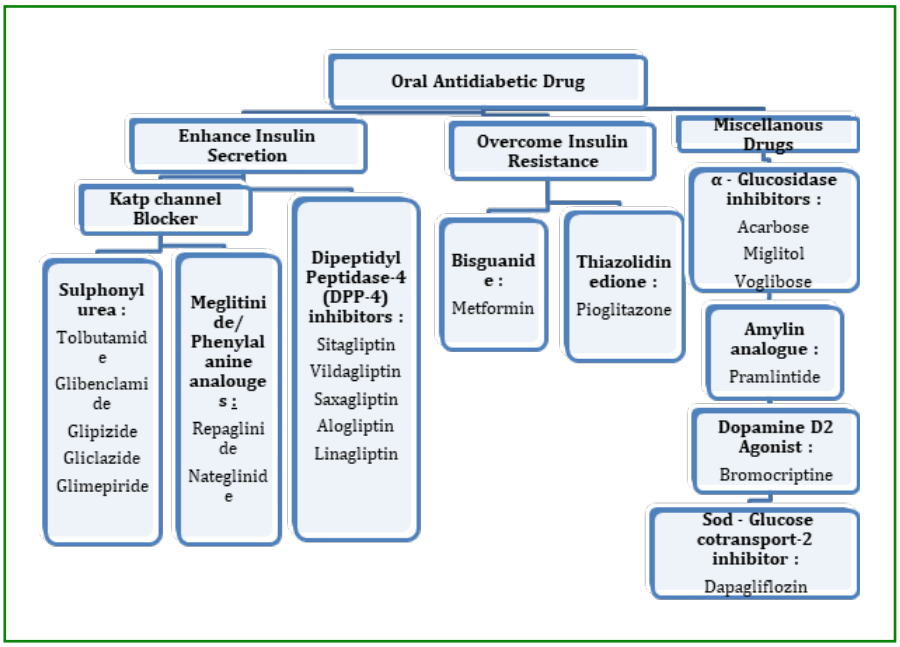
Classification of Diabetes [27]



Introduction to Analytical Method

Analytical methods are systematic approaches for examining and interpreting data, aiding researchers and professionals in making informed decisions. These methods work by breaking down complex information into smaller, more manageable components, allowing for a deeper understanding of various phenomena. Widely used in fields such as chemistry, finance, engineering, and social sciences, analytical methods help test hypotheses, validate results, and uncover patterns. These methods typically follow a structured process that begins with data collection and progresses through data processing, analysis, and interpretation. Advanced techniques, including regression analysis, spectroscopy and content analysis, enable specialized applications across diverse fields. By applying analytical methods, organizations and researchers can make predictions, assess effectiveness, and enhance decision-making. The accuracy and rigor of these methods are essential for producing reliable, reproducible insights, establishing analytical methods as foundational in scientific research and practical applications [25].

Introduction to UV Spectroscopy: UV spectroscopy is an analytical technique used to measure the absorption of ultraviolet light by a substance to reveal its chemical composition. As UV light passes through sample, specific wavelengths are absorbed based on the molecular structure of the substance. This absorption produces a unique spectrum, aiding in the identification of compounds and concentration analysis. Widely applied in chemistry, biology, and pharmaceuticals, UV spectroscopy is vital for quality control, molecular analysis, and impurity detection. Its precision and non-destructive nature makes it invaluable for both research and industrial purposes [28].

Principle of UV Spectrophotometer: The principle behind UV spectroscopy involves molecules absorbing ultraviolet (UV) light, which causes electronic transitions within the molecule. As UV light passes through a sample, specific wavelengths are absorbed, causing electrons to shift from lower-energy ground states to higher-energy excited states. The particular wavelengths and intensity of absorbed light depend on the molecular structure, especially the presence of conjugated double bonds and functional groups that influence the energy needed for these transitions [28].

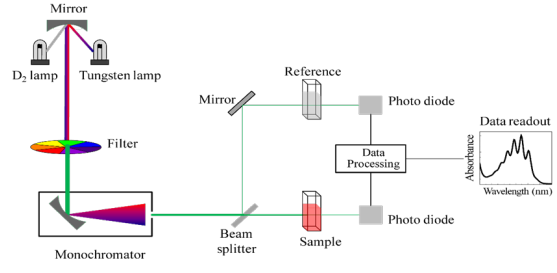


Figure 3: Instrumentation of UV.

Copyright information for Figure 4: Schematic illustration of UV-Vis spectrophotometer (Source: Kumar et al. 2019 with permission from Elsevier)

Instrumentation [28]: The instrumentation of UV spectroscopy consists of several key components designed to generate, measure, and analyze UV light interactions with samples.

- **UV Light Source:** Typically, a deuterium or tungsten lamp produces a continuous UV spectrum covering a range of wavelengths required for analysis.
- **Monochromator:** This device separates the light into individual wavelengths and directs the selected wavelength to the sample. Commonly, prisms or diffraction gratings are used to achieve precise wavelength selection.
- **Sample Holder:** The sample is placed in a cuvette, typically made of quartz, which allows the UV light to pass through without interference.
- **Detector:** A photodetector, such as a photomultiplier tube or photodiode array, captures and measures the intensity of light that passes through or is absorbed by the sample.
- **Data Processor:** The detected signals are converted into an absorption spectrum by a computer or data processor, enabling analysis of the sample's properties [28].

Figure 4: Instrumentation of UV Spectrophotometer.

These components work together to produce a spectrum that reflects the molecular structure of the sample, making it possible to identify compounds and analyze concentrations.

Applications: UV spectroscopy has a range of applications across various fields due to its ability to provide insights into molecular composition and concentration.

- **Chemical Analysis:** In chemistry, UV spectroscopy is widely used to identify organic compounds and study molecular structures by analyzing electronic transitions, especially in molecules with conjugated systems.
- **Pharmaceuticals:** It is essential for quality control, enabling the detection of impurities and ensuring drug purity and potency. It also aids in quantifying active ingredients in formulations.
- **Biochemistry:** UV spectroscopy helps analyze biomolecules like proteins and nucleic acids. By measuring absorbance at specific wavelengths, researchers can estimate concentrations and study protein folding and enzyme reactions.
- **Environmental Monitoring:** UV spectroscopy is used to detect pollutants in water, such as nitrates and organic contaminants, by identifying characteristic absorption patterns.
- **Food and Beverage Industry:** The technique helps in assessing food quality and detecting additives or contaminants, ensuring products meet safety standards.

UV spectroscopy's versatility and sensitivity make it valuable for qualitative and quantitative analysis across these and many other applications [29].

Introduction to HPLC Method

Introduction to HPLC: High-Performance Liquid Chromatography (HPLC) is an advanced analytical technique widely used for separating, identifying, and quantifying components in complex mixtures. In HPLC, liquid samples are forced through a column packed with a stationary phase under high pressure. This method is highly effective for analyzing compounds that are heat-sensitive or non-volatile, making it essential in fields like pharmaceuticals, food science, environmental monitoring, and biochemistry. Due to its precision, speed, and adaptability, HPLC has become a valuable tool in both research and industry [29].

Figure 5: Block diagram of HPLC.

Instrumentation of HPLC: The HPLC system comprises several key components that work together to ensure accurate separation and detection of sample components:

- **Solvent Reservoir:** Contains the mobile phase, typically a mixture of water, organic solvents, or buffers, which is used to transport the sample through the system.
- **Pump:** Generates high pressure to push the mobile phase and sample through the system at a consistent flow rate, ensuring accurate and reproducible results.
- **Injector:** Introduces the sample into the mobile phase stream, often through an autosampler for precision and efficiency.
- **Column:** The heart of the HPLC system, packed with a stationary phase (e.g., silica particles). As the sample moves through, different components interact with the stationary phase to varying degrees, causing separation [28].
- **Detector:** Monitors and records the separated components as they exit the column, often using UV, fluorescence, or mass spectrometry detection, depending on the application.
- **Data Processor:** Converts the detector signals into readable data, typically displayed as chromatograms, showing each component's retention time and concentration [29].

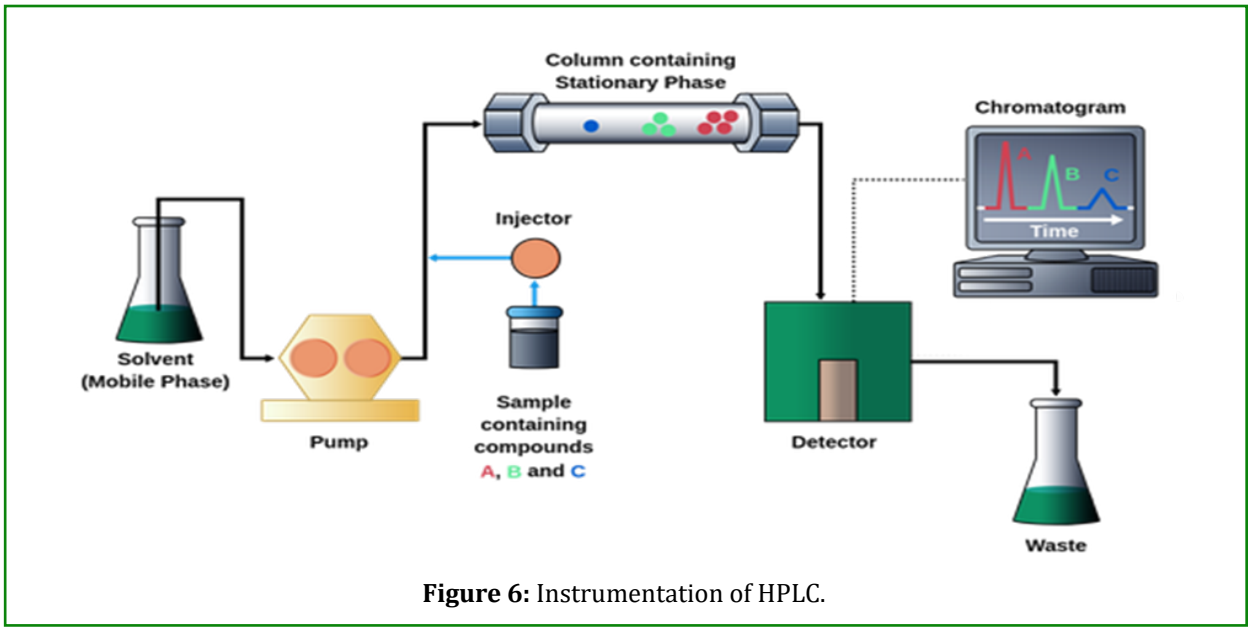


Figure 6: Instrumentation of HPLC.

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Applications of HPLC: HPLC is widely applicable in various fields due to its high precision and versatility:

- **Pharmaceuticals:** It is essential for drug formulation, purity testing, and stability studies, ensuring product safety and efficacy by identifying and quantifying active ingredients and impurities.
- **Environmental Science:** HPLC helps detect and measure contaminants in water, soil, and air samples, aiding in pollution control and environmental protection.
- **Food and Beverage Analysis:** The method is used to test food additives, preservatives, and vitamins, as well as to monitor quality and detect contaminants in products.
- **Clinical and Biomedical Research:** HPLC allows for the analysis of biological samples, such as blood or urine, to study metabolites, drugs, and biomarkers, supporting diagnostic and therapeutic research.
- **Chemical and Petrochemical Industries:** It helps in quality control by analyzing the composition of chemicals and petroleum products, ensuring product consistency and safety.

HPLC's high sensitivity, accuracy, and ability to handle complex samples make it indispensable across a broad range of applications [28].

Analytical Method Validation [30-34]

Analytical method validation is a systematic process to confirm that an analytical method is suitable for its intended purpose. It is essential for regulatory compliance, especially in pharmaceutical contexts, to ensure consistent, reliable, and accurate measurement of analytes in drugs or biological samples. The International Council for Harmonisation (ICH) provides standardized guidelines for method validation under ICH Q2 (R1), specifying key validation parameters that should be assessed during this process.

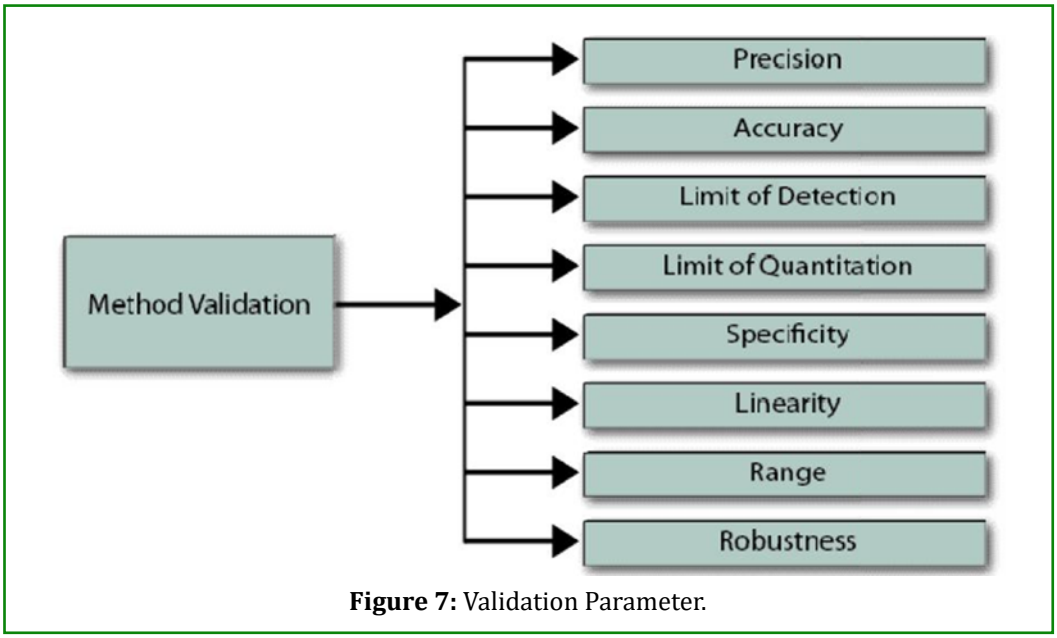

Figure 7: Validation Parameter.

Copyright information for Figure 7: ICH technical requirements for pharmaceuticals for human use.

Accuracy

- **Definition:** Accuracy refers to the closeness between the observed measurement and the actual or true value of the analyte [30].
- **Evaluation:** It is commonly assessed by comparing test results to a known reference standard or by spiking the analyte at known concentrations into a blank matrix. Accuracy is often expressed as a percentage and may be calculated across different levels (e.g., low, medium, and high concentrations).

Precision

Definition: Precision describes the reproducibility of the method when it is repeated under specific conditions, showing the degree of variability in the results.

Types:

- **Repeatability:** Assesses precision under the same conditions within a short period (intra-assay).
- **Intermediate Precision:** Evaluates precision under varying conditions such as different days, analysts, or instruments within a laboratory.
- **Reproducibility:** Determines precision across different laboratories (inter-laboratory studies), useful in collaborative studies or method transfers.

Evaluation: Precision is generally quantified as the relative standard deviation (RSD) or coefficient of variation (CV) across multiple measurements.

Specificity (or Selectivity)

- **Definition:** Specificity refers to the method's ability to measure the analyte accurately and unambiguously in the presence of other components, such as impurities, degradation products, or matrix components [30]
- **Evaluation:** For specificity, each component must be assessed to ensure that the analyte is distinct from other substances in the sample matrix. This is often performed by comparing test results of the analyte in the presence and absence of potential interfering substances.

Linearity

- **Definition:** Linearity is the method's ability to obtain test results directly proportional to the concentration of analyte over a specified range [30].
- **Evaluation:** The linearity range is often confirmed by analyzing samples at various concentrations, plotting the concentration against the response, and calculating the correlation coefficient (r). ICH suggests that the r-value should typically be above 0.99 for acceptable linearity.

Range

- **Definition:** Range is the interval between the highest and lowest concentrations of the analyte that the method can accurately and precisely measure.
- **Evaluation:** The range is usually derived based on the linearity, accuracy, and precision of the method. It is expressed as a concentration range and should be appropriate for the intended application, whether for potency, purity, or impurity measurements.

Detection Limit (LOD)

- **Definition:** LOD refers to the lowest concentration of an analyte that can be detected (but not necessarily

quantified) by the method.

- **Evaluation:** LOD can be estimated based on the signal-to-noise ratio or calculated from the standard deviation of the response and the slope of the calibration curve, typically using a ratio of 3:1 (signal-to-noise) or 3.3 times the standard deviation divided by the slope.

Quantitation Limit (LOQ)

- **Definition:** LOQ is the lowest concentration of the analyte that can be quantitatively determined with acceptable precision and accuracy.
- **Evaluation:** Similar to LOD, the LOQ can be calculated from the standard deviation and slope of the calibration curve but typically uses a signal-to-noise ratio of 10:1 or a 10 times standard deviation-to-slope ratio.

Robustness

- **Definition:** Robustness measures the method's reliability against small variations in procedural or environmental conditions, such as temperature, pH, or equipment.
- **Evaluation:** Robustness is assessed by deliberately introducing minor variations in method parameters and observing the effect on test results. A method that remains consistent across these changes is considered robust [30-36].

Conclusion

In conclusion, existing analytical methods have been reported for the estimation of Linagliptin and its combinations with other drugs, such as Linagliptin & Empagliflozin, Linagliptin & Metformin, and Linagliptin & Empagliflozin. However, there are no analytical methods specifically designed for the estimation of Linagliptin and its impurity, 4-(Methylquinazoline-2-yl) methanol. Future research could focus on analyzing its impurities in combination with other drugs using UV Spectroscopy. This technique could improve the reliability of quality control processes and enable a more comprehensive analysis of Linagliptin. By integrating UV spectroscopy with current methods, we can create a more complete analytical framework that will support ongoing research and development efforts for Linagliptin.

Acknowledgement

The Authors would like to thanks Dept. of Pharmachemistry and Quality Assurance, School of Pharmacy, Rai University, Ahmedabad & Saraswati Institute of Pharmaceutical Sciences, Dhanap, Gandhinagar for continuous assistance and support.

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