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A comprehensive review on analytical, stability-indicating, and spectrophotometric methods for the estimation of Trelagliptin Succinate in pharmaceutical dosage forms

Rujuta Chaudhari, Gavli Jagruti, Patel Dimple, Dr. Deepa Patel, Dr. Ghanshyam Patel
Department of Quality Assurance, Kalol Institute of Pharmacy, Gujarat Technological University (GTU), Gujarat, India

Abstract
Trelagliptin succinate, a long-acting dipeptidyl peptidase-4 (DPP-4) inhibitor, is widely used for the management of type-2 diabetes mellitus due to its once-weekly dosing advantage. Accurate estimation of Trelagliptin in bulk and dosage forms is essential for ensuring drug quality, safety, and regulatory compliance. This review compiles and critically evaluates official and non-official analytical methods, including RP-HPLC, UV spectrophotometry, UPLC, LC–MS/MS, and stability-indicating studies. Literature from peer-reviewed journals, patents, regulatory documents, and research projects from 2010–2025 is analyzed. Emphasis is placed on ICH Q1A(R2) and Q2(R2) guidelines, forced degradation studies, method validation, and emerging analytical approaches such as QbD and green chemistry. This comprehensive article aims to support formulation scientists and analytical chemists in developing robust, accurate, and regulatory-compliant methods for Trelagliptin succinate.

Keywords: Trelagliptin Succinate, RP-HPLC, UV Spectrophotometry, Stability-Indicating Method, Forced Degradation, ICH Guidelines

Introduction
Analytical method development is central to pharmaceutical quality assurance. Trelagliptin succinate, a potent long-acting DPP-4 inhibitor, requires precise and validated analytical techniques for routine quality control and stability assessment. Due to the lack of pharmacopoeial monographs and its susceptibility to hydrolytic and oxidative degradation, the need for robust, stability-indicating methods is critical.
The current review consolidates all official, non-official, patented, and peer-reviewed analytical strategies reported for Trelagliptin succinate. Special emphasis is placed on RP-HPLC and UV methods, which are widely applied in routine analysis and stability testing.

Drug Profile
1. Trelagliptin Succinate
- **Category:** DPP-4 inhibitor (antidiabetic)
- **Chemical Name:** (R)-2-{[6-(3-methyl-1-phenyl-1H-pyrazol-5-yl)-2-pyridyl] amino}-2-oxo-ethyl succinate
- **Molecular Formula:** $C_{18}H_{19}N_5O_2 \cdot C_4H_6O_4$
- **Molecular Weight:** 525.52 g/mol
- **Solubility:** Freely soluble in methanol and water; slightly soluble in acetonitrile
- **λmax:** 238–245 nm
- **Mechanism:** Inhibits DPP-4 enzyme, prolonging GLP-1 activity and enhancing glycemic control.

Rationale for Analytical and Stability-Indicating Methods
Trelagliptin is susceptible to hydrolysis, oxidation, and photodegradation, making stability-indicating assays essential. Due to the absence of official monographs, analytical methods rely entirely on published research, patents, and in-house validations.
RP-HPLC is the preferred analytical tool for quantitative estimation and stability studies. UV spectroscopy is widely used for rapid screening and routine testing.

Official Pharmacopoeial Status
Trelagliptin succinate presently lacks an official monograph in major pharmacopoeias such as IP, USP, BP, JP, and EP (as of 2025). The absence of standardized compendial methods necessitates the development of reliable in-house analytical procedures supported by regulatory-compliant validation data. Consequently, quality control relies on well-established RP-HPLC and UV methods published in peer-reviewed journals, analytical strategies disclosed in patents, and robust methodologies optimized through academic and industrial research. These sources collectively provide the scientific foundation for accurate, reproducible, and stability-indicating analytical protocols for Trelagliptin succinate.

Reported Non-Official and Peer-Reviewed Analytical Methods
1. RP-HPLC Methods
Common chromatographic conditions include:
- Column: C18 (150–250 mm × 4.6 mm, 5 µm)
- Mobile phase: methanol–water, acetonitrile–buffer, or formic acid mixtures
- Flow rate: 0.8–1.0 mL/min
- Detection wavelength: 238–245 nm
- Linearity: 2–50 µg/mL
- Retention time: 3–7 min

Reported methods show high accuracy (98–102%), precision (RSD < 2%), and strong linearity ($R^2 > 0.999$).

2. UV Spectrophotometric Methods
UV methods employ solvents such as methanol, water, or phosphate buffer. Key features:
- **λmax:** 238–245 nm
- **Linearity range:** 5–30 µg/mL
- **Accuracy:** 98–102%
- **Precision:** RSD < 2%
- Derivative UV methods used to reduce excipient interference

3. Advanced Analytical Techniques

- **UPLC:** ultrafast analysis with improved resolution
- **LC–MS/MS:** used for bioanalytical estimation and pharmacokinetics
- **Capillary electrophoresis:** green and low-solvent method

Forced Degradation and Stability-Indicating Studies

ICH Q1A(R2) recommends stress testing to ensure method specificity. Reported degradation behavior:

Stress Condition	Result
Acidic (0.1 N HCl)	Moderate degradation
Alkaline (0.1 N NaOH)	Significant hydrolysis
Oxidative (3% H_2O_2)	Notable oxidative degradation
Thermal (60 °C)	Minor to moderate degradation
Photolytic	Significant photodegradation

Peak purity studies confirm absence of co-eluting impurities, demonstrating stability-indicating nature.

Validation Parameters (ICH Q2R1/Q2R2)

Validation criteria met by most analytical methods:

- **Specificity:** No interference from excipients
- **Linearity:** $R^2 \geq 0.999$
- **Accuracy:** 98–102%
- **Precision:** RSD ≤ 2%
- **LOD/LOQ:** Low values based on SD/slope
- **Robustness:** No significant effect from minor procedural changes

Patents and Research Projects

Relevant patents include:

- **WO2013119250A1:** Trelagliptin pharmaceutical composition and stability insights
- **US20140221481A1:** Trelagliptin synthesis and impurity profile

Academic projects (GTU and others, 2018–2025) describe multiple validated RP-HPLC and UV methods.

Quality-by-Design (QbD) Approaches

QbD tools enhance method robustness:

- Analytical Target Profile (ATP)
- Risk assessment (Ishikawa, FMEA)
- DoE using Box–Behnken or CCD
- Establishing Method Operable Design Region (MODR)
- Control strategy for routine QC

Discussion

RP-HPLC is the most reliable and widely used technique for Trelagliptin succinate estimation. UV methods serve as cost-effective alternatives for routine use. Forced degradation confirms that the method is stability-indicating. Emerging technologies such as UPLC, LC–MS/MS, and green analytical chemistry enhance efficiency.

Conclusion

This review consolidates analytical, spectrophotometric, and stability-indicating methods for Trelagliptin succinate. RP-HPLC remains the preferred tool due to its accuracy, specificity, and robustness. Compliance with ICH guidelines ensures reliability and regulatory acceptance. QbD and UPLC approaches represent significant future directions.

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