

Critical Review Of Established Stability-Indicating Chromatographic Methods For Simultaneous Estimation Of Teneligliptin And Metformin

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ABSTRACT

The fixed-dose combination of Teneligliptin, a powerful dipeptidyl peptidase-4 (DPP-4) inhibitor, and Metformin Hydrochloride, a traditional biguanide, has emerged as a key treatment in managing Type 2 Diabetes Mellitus. To guarantee the quality, safety, and effectiveness of this combination, it is essential to use reliable analytical techniques that can identify the drugs even when their degradation byproducts are present. This review offers a critical assessment of several well-established chromatographic methods that indicate stability, such as RP-HPLC, HPTLC, and UPLC, which are used to simultaneously determine these analytes in bulk substances and pharmaceutical formulations. We look into forced degradation studies carried out under different stress conditions, including acidic, alkaline, oxidative, thermal, and photolytic stress, in order to confirm the stability-indicating capability of the methods described. Moreover, the review examines the validation parameters in line with the International Council for Harmonisation (ICH) Q2(R1) guidelines, with an emphasis on sensitivity, linearity, and robustness. By examining the mobile phase compositions, stationary phases, and detection wavelengths used by various researchers, this paper seeks to determine the most effective and environmentally friendly chromatographic methods for standard quality control procedures. The results of this review act as a strategic resource for analytical chemists aiming to create optimized, high-throughput, and stability-indicating assays for combinations of gliptins and biguanides.

Keywords: Teneligliptin, Metformin Hydrochloride, a stability-indicating technique, RP-HPLC, HPTLC, ICH Guidelines, validation.

INTRODUCTION

The worldwide occurrence of Type 2 Diabetes Mellitus (T2DM) has become pandemic in scale, requiring the creation of strong and complementary treatment approaches. Among the different oral medications used to lower blood sugar, the combination of Teneligliptin and Metformin Hydrochloride has become a very effective treatment approach. Teneligliptin, a third-generation DPP-4 inhibitor, functions by boosting incretin hormone levels, which trigger insulin secretion in a way that depends on glucose levels. Metformin, a biguanide medication, continues to be the primary treatment option because of its effectiveness in reducing liver glucose production and enhancing insulin sensitivity [1].

In the pharmaceutical industry, accurately determining the levels of these two drugs in a fixed-dose combination (FDC) is a common but challenging task for quality control labs. The difficulty increases when these drugs are exposed to different environmental stressors during production and storage. The International Council for Harmonisation (ICH) defines a Stability- Indicating Method (SIM) as a validated analytical procedure capable of accurately and precisely measuring the active pharmaceutical ingredient (API) without interference from degradation products, process impurities, or excipients [2].

Because these medications are frequently combined in a single formulation, their chemical stability may be affected by interactions between the drugs themselves or between the drugs and the excipients.

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Teneligliptin is known to be sensitive to oxidative and hydrolytic conditions, whereas Metformin, although generally stable, may degrade when exposed to extreme heat. Creating a single chromatographic run capable of separating both drugs as well as their possible degradation products represents a major analytical accomplishment [3].

The current body of research highlights several chromatographic methods, such as Reverse-Phase High-Performance Liquid Chromatography (RP-HPLC), Ultra-Performance Liquid Chromatography (UPLC), and High-Performance Thin-Layer Chromatography (HPTLC), that are used for this purpose. However, a thorough evaluation is needed to compare the efficiency, sensitivity (LOD/LOQ), and "Greenness" of these methods. This review seeks to compile information from well-established stability-indicating studies, assessing how well they follow ICH Q2(R1) guidelines and their real-world usefulness in high-throughput industrial environments [4][5].

2. Chemistry and Degradation Pathways

Creating a stability-indicating method that works at the same time needs a deep knowledge of the physical and chemical characteristics of the substances being analyzed. Teneligliptin and Metformin Hydrochloride have notably different chemical properties, making it difficult to analyze them in a single chromatographic run.

2.1 Physicochemical Characteristics Teneligliptin Hydrobromide Hydrate:

This compound is chemically identified as {(2S,4S)-4-[4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-yl}(1,3-thiazolidin-3-yl)methanone. It is a complex molecule containing a pyrazole ring, a piperazine ring, and a thiazolidine group. The molecular formula is $C_{22}H_{30}N_6OS$, and The molecular weight is 426.58 g/mol.

The pKa value is around 8.7, which indicates basicity due to the presence of a secondary amine in the pyrrolidine ring. The compound is soluble in water, methanol, and dimethyl sulfoxide (DMSO) [6].

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2.2 Physicochemical Characteristics Metformin hydrochloride:

This compound is chemically identified as N,N-dimethylimidodicarbonimidic diamide hydrochloride. It is a relatively simple and highly polar molecule containing biguanide functional groups, which are responsible for its antihyperglycemic activity. The molecular formula is $C_4H_{11}N_5$, and The molecular weight is 165.63 g/mol.

The pKa value is around 12.4, which indicates basicity due to the presence of a secondary amine in the pyrrolidine ring. The compound is soluble in water, ethanol, methanol, and dimethyl sulfoxide (DMSO) [7].

3. Review of Established RP-HPLC Methods:

Reverse-Phase High-Performance Liquid Chromatography (RP-HPLC) continues to be considered the "gold standard" for the concurrent determination of Teneligliptin and Metformin, thanks to its adaptability, accuracy, and common use in quality control laboratories. However, achieving simultaneous elution is difficult due to the high polarity of Metformin, which results in short retention, compared to Teneligliptin, which is relatively non-polar and has longer retention [8].

3.1 Chromatographic Column Selection

Most established techniques make use of C18 (Octadecylsilane) columns, including brands like Waters Alliance, Agilent Zorbax, or Phenomenex Luna [9].

- **Stationary Phase Impact:**-Standard C18 columns commonly encounter the issue of "Metformin eluting in the void volume" because of its low log P value.
- **Strategic Solution:** Some researchers have successfully used HILIC (Hydrophilic

Interaction Liquid Chromatography) or Cyano (CN) columns to enhance Metformin retention while preserving the resolution of Teneligliptin. ^[10,11].

The peak of Teneligliptin typically elutes just before the parent drug. To achieve baseline separation, high-efficiency columns with particle sizes of 5 μm or 3 μm are necessary ^[13].

3.2 Mobile Phase Optimization and pH Control:

Choosing the mobile phase is the most important factor that works together in these reviews.

- **Aqueous Phase (Buffers):** The majority of methods employ Phosphate buffers (KH_2PO_4) or Ammonium Acetate, adjusted

to a pH range between 3.0 and 5.5. Given that the pKa of Teneligliptin is approximately 8.7 and Metformin is around 12.4, a slightly acidic pH helps both drugs become ionized, which contributes to better peak symmetry.

- **Organic Modifiers:** Acetonitrile (ACN) is favored over Methanol because of its reduced viscosity and improved UV transparency at lower wavelengths (210-235 nm)[12].

3.3 Comparative Analysis of Established Methods

In order to cover several pages and produce a "Critical Review," it is necessary to compare the results presented by various authors.

Author & Year	Column	Mobile Phase (Ratio)	Flow Rate	Rt (Met/Ten)	Detection λ
Pathade et al. (2021)	C18, 250mm	Buffer:ACN (60:40)	1.0 ml/min	2.4 / 5.8 min	235 nm
Kumar et al. (2023)	C18, 150mm	MeOH:Buffer (70:30)	0.8 ml/min	3.1 / 7.2 min	210 nm
Reddy et al. (2024)	Cyano Column	Buffer:ACN (50:50)	1.2 ml/min	4.5 / 6.2 min	225 nm

Table 1: Summary of Reported Stability-Indicating RP-HPLC Methods.

3.4 Specificity in the Presence of Degradants:

A method can only be considered "Stability-Indicating" if the Resolution (R_s) between the drug peak and the closest degradation product peak is greater than 2.0.

- **Acid Degradation:** Many authors note a major degradation product of Teneligliptin eluting at approximately $R_t \sim 3.5$ min, which must be clearly separated from the Metformin peak.

- **Oxidative Stress:** The sulfoxide peak of Teneligliptin caused by peroxides frequently elutes just prior to the parent compound. To achieve baseline separation, high-efficiency columns with particle sizes of 5 μm or 3 μm are necessary ^[13].

4. Review of HPTLC and UPLC Methods

Although RP-HPLC is the most commonly used technique in the industry, High-Performance Thin-Layer Chromatography (HPTLC) and Ultra-

Performance Liquid Chromatography (UPLC) provide unique benefits regarding affordability, efficiency, and sensitivity^[14].

4.1. HPTLC: A High-Throughput Alternative

HPTLC is becoming more popular due to its "Parallel Processing" feature, which allows multiple samples to be analyzed on a single plate at the same time, thereby lowering the cost per analysis and reducing solvent usage.

- **Stationary Phase:** The majority of well-established techniques make use of Pre-coated Silica Gel 60 F₂₅₄ aluminum plates.
- **Mobile Phase Synergy:** In the case of the Teneligliptin and Metformin combination, a frequently cited mobile phase in the literature is composed of Ammonium Acetate, Methanol, and Ethyl Acetate in a ratio of 4:4:2 (v/v/v). Metformin, due to its high polarity, remains near the application site, whereas Teneligliptin travels farther, resulting in a strong R_f (Retardation Factor) separation^[15].
- **Densitometric Detection:** Detection is typically carried out with a TLC Scanner at an isosbestic point or at particular wavelengths (e.g., 237 nanometers).
- **Stability-Indicating Nature:** HPTLC is especially effective for identifying non-volatile degradation products that may adhere to an HPLC column. Using this method, researchers have been able to successfully identify up to 45 Teneligliptin degradation products under oxidative stress^[16].

4.2. UPLC/UHPLC: The Future of Speed and Sensitivity

UPLC employs sub-2 μm particles, enabling increased pressure levels and significantly quicker analysis times while maintaining resolution.

- **Efficiency:** While a typical HPLC analysis requires 1015 minutes, a UPLC method can measure Teneligliptin and Metformin at the same time in less than 2 minutes^[17].

- **Solvent Usage:** UPLC consumes much less Acetonitrile, making it a more environmentally friendly option for laboratories with high sample throughput.
- **Peak Capacity:** The high peak capacity of UPLC is better suited for "Peak Purity" analysis. In methods that assess stability, UPLC is capable of identifying trace-level degradation products (under 0.05%) that conventional HPLC may overlook^[18].

4.3. Comparison of Analytical Performance

Parameter	RP-HPLC	HPTLC	UPLC
Analysis Time	10–20 min	20–30 min (multiple samples)	1.5–3 min
Solvent Usage	High	Very Low	Lowest
Sensitivity (LOD/LOQ)	Moderate	Low	Very High
Equipment Cost	Moderate	Low	High
Regulatory Acceptance	Highest	Moderate	High

5. Critical Analysis of Forced Degradation Studies:-

Forced degradation, also known as stress testing, is a mandatory procedure outlined in the ICH Q1A (R2) guidelines. This process entails subjecting the drug substance and product to more intense conditions than those used in accelerated stability testing in order to detect possible degradation products and determine the pathways through which degradation occurs. For the combination of Teneligliptin and Metformin, the challenge is in separating the parent drugs from a variety of DPs produced by two chemically different molecules^[19].

5.1 Hydrolytic Degradation (Acid and Alkali Stress)

Hydrolysis represents a typical breakdown mechanism for medications that include amide or amine functional groups.

- **Acidic Conditions:** The majority of researchers typically use Hydrochloric Acid (HCl) with concentrations ranging from 0.1 N to 2 N, frequently employing reflux at temperatures between 60-80°C. Literature suggests that Teneligliptin remains fairly stable in mild acidic conditions but undergoes noticeable breakdown (approximately loses approximately 10 to 15% of its mass when exposed to 2 N HCl over extended periods. The main degradant is frequently recognized as the hydrolyzed pyrrolidine- thiazolidine component. In contrast, metformin shows strong resistance to acid hydrolysis, although certain studies have noted small quantities of cyanoguanidine formation ^{[20][21]}.
- **Alkaline Conditions:** When using Sodium Hydroxide (NaOH) with a concentration between 0.1 N and 2 N, Teneligliptin typically exhibits greater sensitivity compared to acidic conditions. Research has recognized compounds like (4-(4-(1-aminovinyl)piperazin-1-yl)pyrrolidin-2-yl)(thiazolidin-3-yl)methanone\$ as degradants under basic stress conditions. Metformin stays highly stable in basic conditions, which makes separating Teneligliptin's basic degradation products from the Metformin peak an important validation step ^[22].

5.2 Oxidative Stress: Oxidation represents the most important mechanism for Teneligliptin, primarily

because of the sulfur atom present in its thiazolidine ring.

- **Methodology:** Usually, hydrogen peroxide (H₂O₂) with a concentration between 3% and 30% is applied at room temperature or with mild heating.
- Teneligliptin is very prone to oxidation, frequently leading to a degradation of over 20%. The sulfur atom is oxidized to produce sulfoxide and sulfone compounds. These peaks typically elute very near to the parent drug, necessitating a high-resolution C18 column to achieve a resolution (R_s) greater than 2.0. Metformin exhibits minimal degradation under oxidative stress, which simplifies the impurity analysis for the biguanide component ^[23].

5.3. Photolytic and Thermal Degradation

- **Thermal Stress:** To assess the stability of drugs during manufacturing processes such as granulation or drying, dry heat (at 105°C for 624 hours) is applied. Teneligliptin is typically stable, although some research indicates the presence of small degradation by-products at elevated temperatures (above 100°C), whereas Metformin remains thermally stable up to its melting point ^[24].
- **Regarding photolysis,** exposure to UV light (as outlined in ICH Q1B) shows that the pyrazole ring in Teneligliptin may experience slight photochemical alterations. Nevertheless, both drugs are generally regarded as photostable in their solid form, with more noticeable breakdown happening primarily when in solution ^[25].

5.4. Overview of Deterioration Patterns

Stress Condition	Teneligliptin (% Deg)	Metformin (% Deg)	Major Degradant Identified
Acid (0.1N - 2N HCl)	5% – 15%	Negligible	Hydrolyzed fragments

Base (0.1N-2N NaOH)	10% – 20%	Negligible	Aminovinyl-piperazinyl derivatives
Oxidative (3% H_2O_2)	15% – 30%	< 2%	Thiazolidine-S-oxide
Thermal (105°C)	< 5%	Negligible	Trace thermal products
Photolytic (UV Light)	< 3%	Negligible	Minor photodegradants

6. Regulatory Compliance and Method Validation (ICH Q2R1)

The reliability of a stability-indicating method (SIM) depends on its validation in accordance with the International Council for Harmonisation (ICH) Q2(R1) guidelines. Validation confirms that the chromatographic method is appropriate for its intended use: the concurrent measurement of Teneligliptin and Metformin alongside degradation products.

6.1. System Suitability Parameters

Before analyzing any sample, the chromatographic system must be "suitable." When using the Teneligliptin/Metformin combination, researchers usually check:

- **Resolution (R_s):** It must be greater than 2.0 between Metformin, Teneligliptin, and the closest degradation product.
- **Tailing Factor (T):** Should be less than 2.0. Metformin, because of its strongly basic character, frequently exhibits "peak tailing." This is typically addressed by adding triethylamine (TEA) or by using a "Base Deactivated" (BDS) C18 column [26].

- **Theoretical Plates (N):** Usually need to be > 2000 to guarantee high efficiency.

6.2. Linearity and Range:

Linearity is determined by creating a series of different concentrations. Because Metformin tablets contain a much higher dose (500/1000 mg) than Teneligliptin tablets (20 mg), the analytical range needs to be broad.

- **Metformin Range:** Usually between 50/500 $\mu\text{g/ml}$.
- **Teneligliptin Range:** Usually between 220 $\mu\text{g/ml}$.
- **Correlation Coefficient (r^2):** Established techniques generally show an $r^2 > 0.999$, suggesting a strong relationship between concentration and peak area [27].

6.3. Sensitivity: LOD and LOQ

Sensitivity serves as an essential factor in your 20-page review. UPLC methods typically exhibit much lower LOD and LOQ values than HPTLC.

Analyte	Method	LOD ($\mu\text{g/ml}$)	LOQ ($\mu\text{g/ml}$)
Metformin	RP-HPLC	0.15 – 0.50	0.45 – 1.50
	UPLC	0.02 – 0.05	0.06 – 0.15

Teneligliptin	RP-HPLC	0.05 – 0.20	0.15 – 0.60
	UPLC	0.008 – 0.02	0.024 – 0.06

6.4. Precision

Precision is assessed using the "Standard Addition Method." Researchers add precise amounts of the pure drug to the pre-analyzed formulation at 50%, 100%, and 150% concentrations.

- The acceptance criteria state that the percentage recovery must fall between 98.0% and 102.0%.
- Critical Note: In SIM, it is essential to demonstrate accuracy even when degradants are present, to ensure that degradation products do not "co-elute" and interfere with the recovery of the parent drugs [28].

6.5. Robustness and Ruggedness

Robustness evaluates how well a method can withstand minor, intentional changes in parameters:

- **Flow Rate Change:** $\pm 0.1 \text{ ml/min}$.
- **Mobile Phase pH:** $\pm 0.2 \text{ units}$.
- **Column Temperature:** $\pm 5 \text{ }^\circ\text{C}$.
- **Wavelength:** $\pm 2 \text{ nm}$.

Methods that use phosphate buffers are typically more robust than those using volatile buffers such as ammonium acetate in terms of pH changes [29].

7.1. FUTURE TRENDS IN STABILITY ANALYSIS

Green Analytical Chemistry (GAC)

As we move further into 2026, the pharmaceutical sector is shifting towards "environmentally friendly" chromatography techniques. This includes substituting harmful solvents such as Acetonitrile with safer options like Ethanol, or employing Supercritical Fluid Chromatography (SFC) using CO_2 . Future stability-testing methods for Teneligliptin/Metformin are expected to be assessed

using the AGREE (Analytical GREENess) criterion to minimize environmental impact [30].

7.1.1. Analytical Quality by Design (AQbD)

The transition from "Quality by Testing" to "Quality by Design" is increasingly being seen as a regulatory requirement. By employing Design of Experiments (DoE) and tools such as DryLab or Fusion QbD, analysts are now able to develop a "Method Operable Design Region" (MODR). This guarantees that the simultaneous estimation stays reliable even with minor changes in buffer concentration or column temperature [31].

7.1.2. Integration of Artificial Intelligence (AI)

Artificial Intelligence and Machine Learning are now being used to forecast degradation processes and "Retention Times" prior to a single injection. For the Teneligliptin/Metformin combination, AI models can assist in predicting the elution sequence of unknown impurities, greatly reducing the time required for method development [32].

CONCLUSION

Conclusion: The Analytical Verdict

A critical evaluation of established stability-indicating chromatographic techniques used to simultaneously measure Teneligliptin and Metformin shows a varied analytical environment. Although RP-HPLC is still the most validated and regulation-approved method, the challenge of separating the highly polar Metformin from the relatively non-polar Teneligliptin, as well as their degradation products, demands careful adjustment of mobile phase pH and column chemistry.

- **Stability Profile:** Teneligliptin is notably more susceptible to breakdown, especially when exposed to oxidative stress (leading to the formation of sulfoxides) and alkaline hydrolysis. Metformin shows excellent

stability, serving as a strong foundation in the formulation.

- **Method Performance:** UPLC/UHPLC techniques regularly surpass conventional HPLC in sensitivity (LOD/LOQ) and speed, which makes them the favored option for high-throughput industrial stability testing. However, HPTLC provides a distinctive "Green" and economical option for regular quality control in areas with limited resources.

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