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Comparative Study of Method Performance (UV–Vis vs HPLC vs UPLC) for Stability-Indicating Assay of Selected Anti-Diabetic Drugs Under Forced-Degradation Conditions

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ABSTRACT

Forced-degradation (stress-testing) and stability-indicating assays are mandatory elements of modern pharmaceutical development. This review compares method performance of three common analytical techniques—UV–Vis spectrophotometry, conventional HPLC (RP-HPLC), and ultra-performance liquid chromatography (UPLC)—when applied as stability-indicating assays for representative antidiabetic drugs (Metformin, Glimepiride, Sitagliptin and Empagliflozin). We summarize the published literature, tabulate method parameters (column type, mobile phase, detection wavelength, linearity, LOD/LOQ, run time), summarize typical forced-degradation outcomes, compare strengths/weaknesses of the three techniques for stability work, and provide practical recommendations for selecting a suitable analytical approach depending on regulatory needs, matrix complexity, and throughput. Regulatory expectations (ICH Q1A, Q2) and chromatography fundamentals explain why HPLC/UPLC are usually required for true stability-indicating work while UV can be acceptable for simple assay/initial screening. Representative literature sources are cited throughout.

Keywords: Stability-Indicating, Forced Degradation, Anti-Diabetic Drugs, UV–Vis Spectrophotometry, RP-HPLC, UPLC, Metformin, Glimepiride, Sitagliptin, Empagliflozin.

1. INTRODUCTION

Stability testing and forced-degradation studies are intended to identify degradation pathways, generate potential degradation products, and demonstrate that the analytical method used can separate drug substance from its degradation products (i.e., is stability-indicating). Regulatory expectations are described by ICH guidelines (Q1A (R2) on stability testing and Q2(R1) on validation of analytical procedures), which emphasize stress testing to characterize intrinsic stability and the need for validated, specific assays[1].

Antidiabetic drugs are a chemically diverse class (biguanides, sulfonylureas, DPP-4 inhibitors, SGLT2 inhibitors, etc.), and their stability behaviour under acid/ base/ oxidative/ thermal/ photolytic stress can differ widely; thus, method selection must be tailored to the molecule and the formulation matrix.

This review focuses on four widely studied anti-diabetics with representative chemistries and an accessible literature base: metformin (biguanide, highly polar), glimepiride (sulfonylurea, lipophilic), Sitagliptin (DPP-4 inhibitor, polar but chromophoric), and Empagliflozin (SGLT2 inhibitor, relatively non-polar). We compare published performance of UV, HPLC and UPLC methods in forced-degradation contexts and extract practical guidance for analysts[2-3].

In recent years, the rapid growth in the use of anti-diabetic agents—particularly DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 analogues, and biguanides—has intensified the demand for highly reliable analytical methodologies capable of evaluating stability, impurity profiles, and degradation behavior. Many anti-diabetic drugs possess diverse physicochemical characteristics such as variable aqueous solubility, pKa values, and susceptibility to oxidative, thermal, or photolytic degradation. Hence, the selection of an appropriate analytical platform becomes crucial for ensuring accurate quantification during product development and quality control. Analytical scientists are increasingly comparing instrumental platforms such as UV-Visible spectrophotometry, HPLC, and UPLC to determine their suitability for stability-indicating applications[4]. Each method offers distinct advantages: UV-Vis provides simplicity and cost-effectiveness, HPLC offers robustness and established validation norms, while UPLC offers superior sensitivity,

peak resolution, and reduced solvent consumption. These characteristics justify a comparative evaluation under forced degradation conditions to determine the most effective technique for specific anti-diabetic agents.

Regulatory authorities such as the ICH, US-FDA, EMA, CDSCO, and WHO mandate the use of stability-indicating analytical methods to ensure that active pharmaceutical ingredients (APIs) and finished dosage forms remain safe, potent, and therapeutically effective throughout their lifecycle[5]. Forced degradation studies—covering hydrolysis (acid/alkaline), oxidation, photolysis, and thermal stress—are recommended to identify potential degradation pathways and to confirm that the analytical method can separate the drug from its degradants. While HPLC has long been regarded as the industry standard for SIAM (Stability-Indicating Analytical Methods), emerging technologies like UPLC and diode-array UV-Vis spectrophotometry have demonstrated improved speed, efficiency, and spectral clarity. Comparative studies of analytical platforms remain limited in the literature for several anti-diabetic drugs, creating a gap in understanding how method performance varies with molecular structure, degradation behavior, and chromatographic selectivity. This review addresses this gap by providing a systematic comparison of UV-Vis, HPLC, and UPLC performance for stability-indicating assessment under forced degradation conditions[6-7].

2. Overview of Analytical Techniques

UV–Vis Spectrophotometry is low-cost, simple, and high-throughput for routine assay. However, it lacks inherent separation capability and cannot distinguish parent drug from co-eluting degradation products unless the degradants are non-absorbing or derivative/chemometric approaches are used. It's useful for initial screening and routine assay when excipients and degradants do not interfere. (Multiple method papers use UV for glimepiride & metformin screening).

UV–Visible spectrophotometry is one of the most widely used analytical techniques for routine quantitative analysis due to its simplicity, cost-effectiveness, and rapid operation. It measures the absorption of ultraviolet or visible light by a substance at specific wavelengths associated with electronic transitions. For many anti-diabetic drugs, UV-Vis enables quick assay determination, provided the API has suitable chromophores[8]. However, its major limitations include poor selectivity in the presence of degradation products and matrix interference, making it less suitable as a stand-alone stability-indicating method. Despite this, UV-Vis remains valuable for preliminary screening, dissolution studies, and quality control applications.

RP-HPLC (with UV/PDA or MS detection) is the backbone of stability-indicating assays. It separates parent from degradants and, with diode-array or MS detection, can provide peak purity and mass information. Well-validated HPLC methods are routinely used in regulatory filings[9]. Representative stability-indicating HPLC methods exist for Sitagliptin, Empagliflozin, glimepiride, and metformin (often in combination formulations).

HPLC is a robust, highly selective, and widely regulatory-accepted analytical technique used for quantitative and qualitative drug analysis. It separates analytes based on interactions with a stationary phase (commonly C18) and a mobile phase under controlled pressure. HPLC is the traditional gold standard for stability-indicating assays due to its ability to resolve the parent compound from multiple degradation products formed under forced conditions. Although more resource-intensive than UV-Vis—requiring longer run times and higher solvent volumes—it provides excellent precision, reproducibility, and versatility for diverse anti-diabetic drugs with varied chemical structures[10].

UPLC (or UPLC–PDA/MS) uses sub-2-µm particles and higher pressures to deliver increased resolution, sensitivity, and dramatically reduced run times and solvent consumption versus conventional HPLC. UPLC is particularly advantageous when high throughput and improved peak capacity is needed, or when critical separation of closely related degradation products is required. Several stability-indicating UPLC methods have been published for combinations of antidiabetics and single agents.

UPLC represents an advanced chromatography technology designed to achieve faster, more efficient separations using smaller particle-size columns (<2 µm) and higher pressures. It significantly reduces analysis time, improves resolution, and enhances sensitivity compared to traditional HPLC[11-12]. UPLC is particularly advantageous in stability-indicating studies where early detection of minor degradant peaks is essential. Its superior peak sharpness, reduced solvent consumption, and improved signal-to-noise ratios make UPLC ideal for method optimization and high-throughput pharmaceutical analysis. Although the equipment cost is higher, UPLC offers unmatched performance and reliability for modern drug stability testing.

3. Regulatory Context for Forced-Degradation & Validation

ICH Q1A(R2) requires that stress testing be "sufficient to indicate the likely degradation products, and the intrinsic stability of the molecule," and that analytical procedures used be capable of quantifying the active substance in presence of its degradation products. ICH Q2(R1) defines validation characteristics (specificity, accuracy, precision, linearity, LOD/LOQ, robustness) to be demonstrated for analytical methods. These guidelines together make HPLC/UPLC plus PDA/MS the preferred routes to produce scientific

evidence of specificity and stability-indicating capability; UV methods may be acceptable when validated for specificity (e.g., by demonstrating non-interference after stress) and when degradants do not absorb at assay wavelength[13].

Forced Degradation (Stress Testing) is a regulatory-mandated procedure used to intentionally degrade the drug substance or product under accelerated conditions such as acid/base hydrolysis, oxidation, photolysis, and thermal stress. As recommended by ICH Q1A(R2) and ICH Q1B, these studies help identify potential degradation pathways, structural vulnerabilities, and degradation products that may form during shelf life. The primary objective is to ensure that the analytical method can distinctly separate the active drug from its degradants, demonstrating its stability-indicating capability. Forced degradation typically aims for 5–20% degradation to avoid complete destruction while ensuring meaningful peak separation[14].

Analytical Method Validation, as outlined under ICH Q2(R1) and the updated Q2(R2) guidelines, confirms that an analytical procedure is suitable for its intended purpose. Stability-indicating methods must be validated for key parameters including specificity, linearity, accuracy, precision, robustness, limit of detection (LOD), limit of quantification (LOQ), and system suitability. In the context of forced degradation, specificity is crucial, requiring clear resolution between the drug peak and all degradants. Validation ensures reliability of the method throughout the drug lifecycle, forming an essential requirement for regulatory submissions, quality control testing, and stability studies[15-17].

4. Literature Review — Representative Stability-Indicating Methods

Below are concise literature summary tables for the four selected drugs. Each row lists the reference (full citation in References), technique, key chromatographic/detection details, linearity/LOD/LOQ if reported, principal stress/degradation findings, and run time. These examples illustrate typical performance differences between UV, HPLC and UPLC approaches[18-20].

Table-1: Metformin (Selected Reports)

Reference	Technique	Key Method Details	Linearity / LOD-LOQ	Forced Degradation Results	Run time
Narasimha Rao et al., IJPCBS (2013).	UV–Vis spectrophotometry (stability-indicating UV method)	UV at λmax ~232 nm; pH and H_2O_2 stress evaluated	Reported linearity; LOD/LOQ reported in paper	Observed hydrolytic and oxidative degradation (not fully separated chromatographically — assay based on spectral changes)	Rapid (minutes)
Ramesh et al., RP-HPLC simultaneous with other APIs (2014).	RP-HPLC (C18), UV detection	Standard RP-HPLC separation conditions for multi-API analysis	Good linearity & precision reported	HPLC allowed separation of metformin from degradation products under forced conditions	Typical HPLC run (e.g., 6–12 min)

Table-2: Glimepiride (Selected Reports)

Reference	Technique	Key Method Details	Linearity / LOD-LOQ	Forced Degradation Results	Run time
ResearchGate (2016) Stability-Indicating UV for Glimepiride	UV Spectrophotometry	UV method validated; derivative UV used to improve selectivity	Linearity & validation parameters reported	Moderate degradation under acid/base/oxidative stress; UV can indicate loss but cannot separate co-eluting degradants	Minutes
Kovaříková et al. (2004) hydrolytic stress, RP-HPLC.	RP-HPLC; Detailed Forced-Degradation HPLC study	HPLC separation with LC conditions optimized for glimepiride	Validated LOD/LOQ; specificity demonstrated	Clear separation of primary degradation products; HPLC shows kinetics under hydrolytic stress	Typical HPLC run ~10–15 min

Table-3: Sitagliptin (Selected Reports)

Reference	Technique	Key Method Details	Linearity / LOD-LOQ	Forced Degradation Results	Run time
Gumieniczek et al. (2019) LC-UV determination of Sitagliptin (stability).	LC-UV (RP-HPLC), PDA used for peak purity	C18 columns; LC-UV method for Sitagliptin in presence of degradants	Good linearity; LOD/LOQ reported	Sitagliptin degraded under acidic & oxidative stress; LC-UV allowed quantitation in presence of degradants	~6–12 min
Ramalingam et al. (2014) Sitagliptin + simvastatin stability method.	RP-HPLC, stability-indicating method	PDA detection, peak purity checks	Validated	HPLC resolved Sitagliptin and degradation products	HPLC run times typical

Table-4: Empagliflozin (Selected Reports)

Reference	Technique	Key Method Details	Linearity / LOD-LOQ	Forced Degradation Results	Run time
Patil et al. (2016) validated stability-indicating RP-HPLC.	RP-HPLC (Phenomenex C18), UV detection at 224–265 nm	Validated linearity (2–14 µg/mL etc.)	Reported LOD/LOQ and specificity	Empagliflozin degraded under oxidative, thermal stress; HPLC resolved degradants	~6–10 min
Pathak et al. (2021) RP-HPLC-DAD stability method.	RP-HPLC with DAD	Short retention (peak at ~2.5 min reported), sensitive	Validated	HPLC/DAD used to demonstrate specificity and to observe degradation profiles	Short HPLC runs (fast method)
Addanki et al. (2021) RP-UPLC for Sitagliptin + Ertugliflozin (example UPLC).	RP-UPLC (2.1×100 mm, 2 µm), flow 0.2 mL/min	Very short run, high resolution	High sensitivity and precision	UPLC resolved APIs & impurities rapidly	Run times <3 min typical

5. Comparative Performance: Metrics & Discussion

Below we compare the three techniques across key performance metrics relevant to forced-degradation stability work[21].

5.1 Specificity & Peak Purity

* **UV–Vis:** No chromatographic separation — specificity depends on uniqueness of absorption bands or use of derivative/chemometric methods. If degradants absorb at the same λ, UV cannot differentiate them. For true stability-indicating claims, regulators expect separation unless demonstrably unnecessary.

* **HPLC (RP-HPLC + PDA/DAD):** Can separate parent and degradants; PDA allows peak purity assessment and identification of co-eluting peaks. Widely accepted for stability-indicating assays.

* UPLC + PDA/MS: Highest resolving power; more likely to separate very closely related degradants and offer better peak purity metrics; MS provides direct mass information for degradant identification[22].

5.2 Sensitivity (LOD/LOQ)

* **UV:** Moderate sensitivity; LOD/LOQ depend on chromophore strength and path length. May be insufficient for low-level degradant detection.

* **HPLC:** Good sensitivity, particularly with low-noise detectors (PDA) or MS.

* **UPLC:** Often improved sensitivity relative to HPLC because of narrower peaks (higher signal/ noise) and more efficient columns. Multiple comparative studies document performance gains in sensitivity for UPLC[23].

5.3 Resolution & Separation Efficiency

* **HPLC:** Adequate in most cases; method development may require gradient optimization and column selection.

* **UPLC:** Superior resolution due to sub-2-µm particles and higher pressures — enables shorter columns and faster separations without loss of resolution. Studies report several-fold reductions in run time with equal or improved resolution vs HPLC[24].

5.4 Throughput & Solvent Consumption

* **UV:** Highest practical throughput for single-wavelength assays (no separation) and minimal solvent use. However, cannot provide degradant separation.

* **HPLC:** Moderate throughput; solvent consumption higher due to longer runs.

* **UPLC:** Highest throughput among chromatographic methods and significantly lower solvent consumption per analysis (shorter runs, smaller columns).

5.5 Robustness & Cost

* **UV:** Low equipment cost, low maintenance, high robustness.

* **HPLC:** Moderate cost, robust; widely available in QC labs.

* **UPLC:** Higher capital & maintenance cost and requires UHPLC-capable systems/columns, but gives operational savings via solvent/time and improved information per run[25].

Below is a **clear, descriptive, publication-quality Discussion section** focusing on **UV spectroscopy, HPLC, and UPLC** for stability-indicating assays under forced degradation conditions.

6. Discussion on UV Spectroscopy, HPLC, and UPLC Methods

1. UV–Visible Spectroscopy: Strengths, Limitations, and Performance in Forced Degradation

UV–Visible spectrophotometry remains one of the simplest and most economical techniques for routine assay determination of anti-diabetic drugs. In forced degradation studies, UV methods are often used as preliminary screening tools to monitor overall degradation trends because they offer rapid quantitation without the need for complex sample preparation. However, UV absorbance depends entirely on the presence of chromophores and provides only **bulk absorbance information** without the ability to distinguish the parent drug from its degradation products. This lack of chromatographic separation presents a major limitation in stability-indicating applications[26].

Degradants formed under oxidative or photolytic stress often display overlapping absorbance spectra with the parent molecule, resulting in reduced specificity. Even with derivative or multi-wavelength approaches, UV spectroscopy typically cannot achieve the resolution needed to satisfy regulatory expectations for a stability-indicating method. Thus, although UV-Vis is advantageous for speed, simplicity, and low solvent consumption, its limited selectivity restricts its use to supportive analysis, preliminary degradation assessment, and routine QC, rather than as a primary tool for detailed stability profiling.

2. High-Performance Liquid Chromatography (HPLC): Reliability and Analytical Suitability

HPLC has long been regarded as the industry standard for stability-indicating assay development, particularly for drugs susceptible to multiple degradation pathways. Using columns such as C18 and flexible mobile-phase compositions, HPLC provides robust chromatographic separation of the active drug from impurities, degradants, and excipients. In forced degradation conditions (acid/base hydrolysis, oxidative stress, and dry heat), HPLC consistently demonstrates the capacity to resolve minor degradant peaks with acceptable resolution ($Rs \geq 2.0$), fulfilling ICH specificity criteria[27].

HPLC also provides repeatable retention behavior, making it suitable for long-term stability studies and real-time QC applications. However, the technique has limitations: longer run times, higher solvent consumption, and lower peak efficiency compared to newer chromatographic systems. For drugs with multiple close-eluting degradants (e.g., metformin, gliptins), achieving sufficient resolution may require gradient systems, longer run times, or fine-tuning of pH and ionic strength of buffers. Nevertheless, HPLC

remains the backbone of regulatory submissions because of its proven reliability, method versatility, and broad acceptance across pharmacopeias.

3. Ultra-Performance Liquid Chromatography (UPLC): Enhanced Sensitivity and Separation Efficiency

UPLC represents a significant evolution over HPLC, offering markedly enhanced performance through the use of <2 µm particle-size columns and high-pressure capabilities. In stability-indicating methods, UPLC demonstrates superior peak resolution, sharper peak shapes, and reduced retention times—often compressing a 15–20 min HPLC run into 3–5 minutes. This reduction in analysis time is particularly beneficial during forced degradation studies, where multiple stress samples require rapid evaluation.

The improved efficiency of UPLC also allows detection of minor degradation products at lower concentrations, making the technique suitable for detailed impurity profiling. For structurally complex anti-diabetic drugs such as SGLT2 inhibitors and incretin-based agents, UPLC enables clearer separation of closely related degradants that may co-elute in HPLC. The technique also reduces solvent usage, increasing its suitability for modern green-analytical approaches. The major drawbacks include higher instrument cost, column fragility, and the need for well-filtered samples to protect sub-2 µm columns. Nevertheless, UPLC offers unmatched analytical performance, making it the preferred platform for advanced stability studies, method optimization, and high-throughput workflows[28].

Integrated Comparative Perspective

Overall, UV spectroscopy offers rapid but non-selective analysis; HPLC delivers reliable separation suitable for regulatory acceptance; and UPLC provides fast, highly efficient separations ideal for complex degradation mixtures. The performance of each technique is inherently linked to its resolving power and ability to differentiate degradants formed under forced stress conditions. As regulatory expectations emphasize specificity, precision, and degradant resolution, UPLC tends to outperform, followed by HPLC as the conventional gold standard, with UV spectroscopy serving as a supportive but non-primary tool.

7. Forced-Degradation Practicality

Forced-degradation studies typically include acid/base hydrolysis, oxidative stress (H_2O_2), thermal stress, and photolytic stress. To demonstrate a stability-indicating method, the following are generally expected: (1) the method separates degradants generated under stress from parent, (2) peak purity is confirmed (PDA/MS), and (3) mass balance/identification when possible. HPLC/UPLC methods are thus the standard for forced-degradation work; UV can be used adjunctively or for preliminary screening but rarely suffices alone for definitive stability-indicating claims.

8. Practical Experimental Design for Comparative Forced-Degradation Testing

If a laboratory wants to directly compare UV, HPLC and UPLC as stability-indicating assays for an anti-diabetic compound, a recommended experimental plan is:

1. Select a Single API (e.g., Glimepiride or Sitagliptin) and, if relevant, the finished dosage form. Prepare a validated reference standard.

2. Apply Forced-Degradation Conditions per ICH/Q1A Guidance:

- Acid hydrolysis (e.g., 0.1–1.0 N HCl, 1–24 h, RT or reflux as required)
- Base hydrolysis (0.1–1.0 N NaOH)
- Oxidation (3–10% H_2O_2, short exposure)
- Thermal (40–80 °C, dry heat)
- Photolytic (sunlight/UV per ICH photostability)

Adjust severity so ~5–20% degradation is observed (avoid complete destruction).

3. Measure Stressed Samples By:

* **UV–Vis:** record spectra (190–400 nm), attempt derivative or chemometric deconvolution if needed. Evaluate whether absorbance changes can be uniquely assigned to parent loss.

* **RP-HPLC-PDA:** develop a stability-indicating isocratic or gradient method; perform peak purity checks.

* **UPLC-PDA/MS:** develop UPLC method for shorter run times and higher resolution; collect MS data for degradant ID where possible.

4. Compare method performance using the following metrics: specificity (peak purity), resolution between parent and nearest degradant, sensitivity (LOD/LOQ), and linearity, accuracy/precision on stressed and non-stressed samples, runtime, solvent use, and ability to identify degradants (MS). Report full validation (ICH Q2) results for each method.

9. Case Summaries and Lessons from Literature

* **Metformin:** Because metformin is highly polar and sometimes lacks strong chromophores, UV can detect assay changes but chromatographic methods (HPLC) are preferred to resolve polar degradation products, often using ion-pairing or HILIC variants in some reports. UV-only approaches have been published for some formulations but require careful specificity demonstration.

* **Glimepiride:** Hydrolysis and oxidative degradation produce products that can co-absorb with the parent. HPLC forced-degradation studies (including DoE approaches) have produced clear degradant profiles and allow kinetics determination — HPLC is the recommended approach for stability-indicating assays here.

* **Sitagliptin:** Several validated HPLC methods with PDA have been reported to separate Sitagliptin from degradants; LC-UV/PDA is adequate for most stability studies, while UPLC gives faster separations if throughput is important.

* **Empagliflozin:** Stability-indicating RP-HPLC methods (some very rapid) and UPLC methods for combinations have been reported; DAD/PDA detection plus MS is useful to characterize degradation.

10. Recommendations

1. My primary objective is regulatory submission / demonstration of stability-indicating capability: use RP-HPLC with PDA (and MS if identification is required). HPLC remains the standard and is broadly accepted by regulators for stability studies.

2. If you need high throughput, faster runs, reduced solvent use, and improved resolution for complex impurity profiles: use UPLC (UPLC-PDA/MS). Consider costs and instrument availability. UPLC often shortens run times dramatically while improving separation and sensitivity.

3. If the molecule has a unique strong chromophore, few degradants, and the formulation matrix is simple: a rigorously validated UV method (with forced-degradation checks demonstrating no interference) can be acceptable for routine assay but usually not the primary stability-indicating method.

4. Always document forced-degradation studies in accordance with ICH Q1A(R2) and validate analytical methods per ICH Q2(R1). Demonstrate specificity, peak purity, and mass balance when possible.

11. Limitations of Existing Literature & Research Gaps

- Many published UV-based stability studies do not provide full separation evidence or MS-based identification of degradants — limiting confidence for regulatory filing.

- Comparative head-to-head studies that run the *same* stressed samples through UV, HPLC and UPLC and report quantitative comparative metrics are relatively scarce; most papers present single-technique validation. A systematic experimental comparison (identical stress samples analyzed by all three methods) would provide more definitive, quantitative guidance.

- Heterogeneity in reported HPLC/UPLC conditions and reporting standards (LOD/LOQ formats, run time reporting) makes cross-paper comparisons challenging.

12. Conclusion

➢ For forced-degradation / stability-indicating work, chromatographic separation is essential in most cases to unequivocally demonstrate specificity; RP-HPLC with PDA (and MS if necessary) is the established standard. ICH guidelines explicitly require stress testing and validated specificity.

➢ UPLC frequently offers practical advantages (speed, sensitivity, resolution, solvent economy) and is recommended when throughput and peak capacity are priorities, provided an UHPLC-capable system is available.

➢ UV–Vis methods can be used for initial screening and for routine assays where demonstrated specificity holds, but they usually cannot replace chromatographic stability-indicating methods for regulatory submissions.

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