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ORIGINAL ARTICLE

Forced Degradation Studies and Stability-Indicating RP-HPLC Method Development for Simultaneous Estimation of Metformin HCl, Dapagliflozin, and Vildagliptin in Combined Dosage Forms

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ABSTRACT
Metformin HCl, Dapagliflozin, and Vildagliptin are commonly co-formulated antidiabetic agents. Accurate and reliable analytical methods are essential for simultaneous estimation and stability assessment of these drugs in combined dosage forms. To develop and validate a simple, sensitive, accurate, and robust stability-indicating reverse-phase high-performance liquid chromatography (RP-HPLC) method for the simultaneous estimation of Metformin HCl (MET), Dapagliflozin (DAPA), and Vildagliptin (VILDA) in bulk and combined pharmaceutical formulations. Chromatographic separation was carried out on a Cosmosil C18 column (250 mm × 4.6 mm, 5 µm) using a mobile phase of Methanol: 10 mM KH_2PO_4 buffer (80:20 v/v) at a flow rate of 0.8 mL/min and ambient temperature. Retention times for MET, DAPA, and VILDA were 3.6, 6.6, and 8.8 minutes, respectively. Forced degradation studies were conducted under acidic, basic, oxidative, thermal, and photolytic conditions. Validation was performed as per ICH guidelines. The method demonstrated linearity in the range of 50–250 µg/mL for MET, 10–50 µg/mL for VILDA, and 1–5 µg/mL for DAPA. Recovery values were 99.86% (MET), 99.53% (VILDA), and 100.25% (DAPA). The method showed excellent accuracy, precision, and robustness, with effective separation from degradation products. The developed RP-HPLC method is quick, cost-effective, and suitable for routine quality control analysis of MET, VILDA, and DAPA in combined dosage forms.
KEYWORDS: RP-HPLC, Forced Degradation Studies, Metformin HCl, Dapagliflozin, Stability-Indicating Method

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INTRODUCTION

In the current era of pharmaceutical development, the stability of drug substances and finished products holds paramount importance in ensuring the safety, efficacy, and quality of medicines throughout their shelf life.[1] Stability studies are essential components of the drug development process, as they offer critical insights into a drug's behaviour under the influence of various environmental stress conditions, including temperature fluctuations, humidity, light exposure, oxidation, and hydrolysis.[2] Such studies guide formulation strategies, establish appropriate storage conditions, determine shelf life, and support regulatory submissions. Internationally recognized regulatory bodies such as the United States Food and Drug Administration (FDA), the European Medicines Agency (EMA), and India's Central Drugs Standard Control Organization (CDSCO) have mandated comprehensive stability testing to be conducted before marketing approval of pharmaceutical products.[3] To harmonize stability testing procedures, the International Council for Harmonisation (ICH) has issued a series of guidelines, among which ICH Q1A (R2) stands out as a foundational document.[4] This guideline outlines standard protocols for accelerated and long-term stability studies, emphasizing the importance of forced degradation studies as a means to understand the intrinsic stability of drug molecules. Forced degradation, also referred to as stress testing, and involves subjecting the active pharmaceutical ingredients (APIs) to extreme conditions— acidic,

alkaline, oxidative, photolytic, and thermal stress— to identify degradation pathways and products.[5-6] These investigations serve as the scientific basis for the development of stability-indicating methods (SIMs), which are analytical tools capable of quantifying drugs while distinguishing them from their respective degradation products, impurities, and excipients.[7]

Stability-indicating methods are integral to ensuring that analytical procedures used in quality control are both selective and reliable. A stability-indicating RP-HPLC method is designed to detect any changes in a drug's purity profile during storage or stress exposure by separating, identifying, and quantifying the active components from degradation products.[8] Among the array of available analytical techniques, RP-HPLC remains the method of choice for pharmaceutical analysis due to its high resolution, reproducibility, and sensitivity.[9] RP-HPLC is particularly advantageous for the simultaneous estimation of multiple components in fixed-dose combinations (FDCs), offering rapid and accurate assessment in a single run, which is essential for cost-effective quality assurance.[10-11]

In the context of chronic diseases like Type 2 Diabetes Mellitus (T2DM), combination therapies are increasingly favoured due to their ability to address various pathophysiological targets simultaneously.[12] A prominent example is the fixed-dose combination of Metformin Hydrochloride (MET),Vildagliptin (VILDA) and Dapagliflozin (DAPA)—three pharmacologically distinct yet synergistic agents used in the management of T2DM.[13] Metformin, a biguanide derivative, is a first-line antihyperglycemic agent that suppresses hepatic glucose production and enhances insulin sensitivity.[14] Dapagliflozin, a selective sodium-glucose cotransporter-2 (SGLT2) inhibitor, lowers blood glucose by promoting renal glucose excretion.[15] Vildagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, prolongs the activity of incretin hormones, enhancing glucose-dependent insulin release and reducing glucagon secretion.[16] The combination of MET, DAPA, and VILDA offers enhanced glycemic control by leveraging different mechanisms of action, making it particularly beneficial for patients inadequately managed on monotherapy.[17] However, the analytical estimation of these three compounds in a combined dosage form is challenging due to their divergent chemical structures, polarities, solubility's, and degradation behaviours. These challenges necessitate the development of a robust, reliable, and validated RP-HPLC method that can effectively resolve each component from its degradation products under various stress conditions.[18] The implementation of such a method is crucial not only for regulatory compliance but also for routine quality control and post-marketing surveillance. Several analytical methods have been developed for the individual or dual estimation of MET, DAPA, and VILDA using techniques such as UV-Visible spectroscopy**,** mass spectrometry**,** HPTLC, and RP-HPLC. However, there is a notable lack of comprehensive studies focusing on the simultaneous estimation of this triple-drug combination using a validated stability-indicating RP-HPLC method.

Most existing methods do not fully adhere to the ICH guidelines for method validation or fail to account for forced degradation conditions, making them less suitable for regulatory submissions and routine quality control. Furthermore, previously reported methods often lack the sensitivity or resolution required to distinctly quantify each analyte in the presence of degradation products, which compromises their applicability in stability studies.

To bridge this gap, forced degradation studies must be incorporated during method development to expose the drug substances to stressors such as acidic and basic hydrolysis, oxidative degradation, photolysis, and thermal exposure.[19] These studies reveal the degradation behaviour and potential impurities that may arise during manufacturing, storage, or usage. This knowledge is critical in developing a stability-indicating method that can selectively analyze the active compounds in the presence of these degradant's, ensuring the safety and efficacy of the drug product throughout its shelf life.[20] In addition, identifying degradation products enables better understanding of the molecule's stability profile and supports formulation scientists in optimizing excipient compatibility and manufacturing conditions.[21] In the present study, a well-defined research gap is addressed. Despite the therapeutic significance of the MET-DAPA-VILDA combination, no existing RP-HPLC method has been reported in the literature that simultaneously estimates all three drugs under forced degradation conditions in a single, validated assay. Thus, this research aims to develop and validate a simple, accurate, sensitive, economical, and stability-indicating RP-HPLC method for the simultaneous estimation of Metformin HCl, Dapagliflozin, and Vildagliptin in fixed-dose combination formulations.[22] The method is designed to meet all critical validation parameters as per ICH Q2 (R1) guidelines, including linearity, accuracy, precision, specificity, robustness, limit of detection (LOD), and limit of quantitation (LOQ). Furthermore, the method is subjected to a comprehensive forced degradation protocol to evaluate its ability to effectively separate the APIs from their degradation products under various stress conditions.[23] The final validated method is expected to demonstrate suitability for routine

pharmaceutical quality control, ensuring batch-to-batch consistency and aiding in the detection of potential stability-related issues.

MATERIAL AND METHODS

Material and Reagents

Metformin HCl, Vildagliptin, and Dapagliflozin were kindly provided as gift samples by Harman Finochem Ltd., Maharashtra, India. "Daparyl VM 500"(Intas Pharmaceuticals Ltd, Gujrat, India),were purchased from a pharmacy shop.All solvents and reagents used in the study—including methanol, hydrochloric acid, sodium hydroxide, potassium dihydrogen phosphate (ortho-phosphoric acid, and hydrogen peroxide—were of analytical grade and procured from certified suppliers. These chemicals were used without further purification to ensure consistency, accuracy, and reproducibility throughout the experimental procedures.

Instrumentation

The analytical procedures were conducted using a Shimadzu Prominence HPLC Binary Gradient System (Shimadzu Analytical Pvt. Ltd., India), comprising an LC-20AD UFLC pump capable of withstanding a maximum pressure of 40 MPa, along with an SPD-20A UV detector. Chromatographic separation was achieved using a Cosmosil C18 column (250 mm × 4.6 mm i.d., 5 µm particle size). Data acquisition, processing, and system control were managed using LC Solution software. All samples and reagents were weighed with precision using a Wenser High Precision Analytical Balance (Model PGB 100), with a capacity of 100 g and a readability of 0.001 g. Sample preparation and degassing were facilitated by a Wenser Ultra Sonicator(Model WUC-4L).

METHODS

Preparation of Solvents:

A 10 mM KH_2PO_4 buffer was prepared by dissolving 0.136 g of KH_2PO_4 in 100 mL of HPLC-grade water, sonicated, and filtered through a 0.45 µm membrane. To adjust pH, 0.1% o-phosphoric acid was prepared by diluting 0.1 mL of concentrated o-phosphoric acid to 100 mL with HPLC water. The final mobile phase consisted of methanol and 10 mM KH_2PO_4 buffer in an 80:20 (v/v) ratio, filtered and degassed using an ultra-sonicator before use.[24]

Sample and Stock Solution Preparation:

Twenty marketed tablets were weighed, crushed, and homogenized; the average weight was 1262.1 mg. A quantity equivalent to 10 mg of Metformin HCl (25.242 mg of powder) was accurately weighed and dissolved in 10 mL of mobile phase to obtain a 1000 ppm stock solution. The same solution contained 200 ppm of Vildagliptin and 20 ppm of Dapagliflozin. All sample preparations were conducted under standardized laboratory conditions to ensure reproducibility.[24]

Forced Degradation Study

Forced degradation studies were conducted under ICH Q_1A (R2) recommended conditions to evaluate the stability-indicating capability of the developed RP-HPLC method.[25]

- **Acidic Hydrolysis**: The formulation was exposed to 0.1 N HCl and heated at 60 °C for 30 minutes, followed by neutralization.
- **Basic Hydrolysis**: Samples were treated with 0.1 N NaOH under similar thermal conditions and then neutralized.
- **Oxidative Degradation**: Oxidative stress was induced using 3% hydrogen peroxide (H_2O_2) at room temperature for 30 minutes.
- **Thermal Degradation**: Dry powder samples were heated in an oven at 105 °C for 6 hours.
- **Photolytic Degradation**: Samples were exposed to UV light at 254 nm in a photostability chamber for 24 hours.

Chromatographic Method Parameters

The chromatographic analysis was carried out using a Cosmosil C18 column (250 mm × 4.6 mm, 5 µm particle size) which provided efficient separation of the analytes. The mobile phase consisted of Methanol and 10 mM potassium dihydrogen phosphate (KH2PO4) in an 80:20 v/v ratio, with the pH adjusted to 3.0 using 0.1% o-phosphoric acid to enhance peak symmetry and resolution. The flow rate was maintained at 0.8 mL/min, ensuring optimal elution of the components. Detection was performed at a wavelength of 210 nm using a UV detector, and the injection volume for each run was set at 20 µL to maintain sensitivity and reproducibility throughout the analysis.

Identification and Quantification of Degradation Products

Chromatograms of degraded samples were compared with those of the standard solution. Additional peaks (apart from the retention times of MET, DAPA, and VILDA) were interpreted as degradation

products. Quantitative comparison was made by calculating the peak areas, percentage degradation, and retention shifts.

RESULTS AND DISCUSSION

Stress Testing Results

Forced degradation studies were successful in demonstrating that the developed RP-HPLC method can distinguish between the active ingredients and their degradation products. Chromatograms from each stress condition confirmed well-resolved peaks with no interference at the retention times of the analytes.

Separation and Resolution of Degradation Products

Chromatograms (Figures 1–3) for each degradation condition displayed baseline-separated peaks for MET, DAPA, and VILDA. The resolution between drug peaks and degradation products was above 2.0 in all cases, satisfying system suitability requirements. No co-elution or interference was observed.

Validation of Stability-Indicating Method

The developed RP-HPLC method was validated following the guidelines of ICH Q2 (R1), covering key parameters such as specificity, linearity, precision (intra-day and inter-day), accuracy and percent recovery, limit of detection (LOD), limit of quantification (LOQ), system suitability, and robustness. Each parameter was evaluated to confirm the method's reliability, reproducibility, and suitability for routine pharmaceutical analysis of metformin hydrochloride (MET), dapagliflozin (DAPA), and vildagliptin (VILDA) in combination dosage forms.[26]

Specificity

Specificity was assessed to ensure the method could distinctly identify and quantify the analytes in the presence of excipients and potential degradation products. The chromatographic method successfully separated all analytes from each other and from any interfering peaks, confirming that structurally similar compounds did not interfere. A representative chromatogram showed complete peak resolution, demonstrating the method's suitability for both qualitative and quantitative analysis.

Linearity

Linearity was established by analyzing six concentration levels for each drug: 50–250 µg/mL for MET, 10–50 µg/mL for VILDA, and 1–5 µg/mL for DAPA. Calibration curves were plotted between peak area and concentration, yielding correlation coefficients (R^2) of 0.9995 for MET, 0.9997 for VILDA, and 0.9997 for DAPA. These values confirm excellent linearity in accordance with ICH Q2 (R1), supporting the method's reliability for quantitative estimation.

Precision

Precision was evaluated through intra-day and inter-day studies. For intra-day precision, the %RSD values were 0.0673% for MET, 0.4481% for VILDA, and 0.1233% for DAPA. Inter-day precision produced %RSD values of 0.1312% for MET, 0.1567% for VILDA, and 0.3064% for DAPA. All values were well below the ICH acceptance limit of 2%, indicating excellent repeatability and intermediate precision.

Accuracy

Accuracy was determined through recovery studies conducted at three levels: 50%, 100%, and 150%. Known quantities of standard drugs were spiked into the sample matrix and analyzed in triplicate. The mean percentage recoveries were 100.41% for MET, 100.94% for VILDA, and 100.11% for DAPA, with %RSDs below 0.5% in all cases. These results confirmed that the method is accurate, with negligible matrix effects or analyte loss.

Percent Recovery

Percent Recovery is a critical indicator of analytical method accuracy. In this study, recoveries within the 98–102% range affirmed the method’s reliability for quantifying each drug in the dosage matrix. High and consistent recovery results validate the method’s trueness and analytical precision.

Limit of Detection (LOD) and Limit of Quantification (LOQ)

Limit of Detection (LOD) and Limit of Quantification (LOQ) were calculated using the standard deviation of the response (σ) and the slope of the calibration curve (S) with the formulas LOD = 3.3σ/S and LOQ = 10σ/S. The LODs were 1.2543 µg/mL for MET, 0.1386 µg/mL for VILDA, and 0.0191 µg/mL for DAPA, while the LOQs were 3.8011 µg/mL, 0.4202 µg/mL, and 0.0580 µg/mL, respectively. These values confirm the method’s high sensitivity and its capability for detecting analytes at low concentrations.

Robustness

Robustness was tested by introducing deliberate minor variations in method parameters, including pH changes (±0.3 units) and detection wavelength shifts (±3 nm). The standard deviations under these changes remained acceptable: for pH, they were 0.3706% (MET), 0.4003% (VILDA), and 0.5962%

(DAPA); for wavelength, they were 0.7179% (MET), 0.5358% (VILDA), and 1.0120% (DAPA). These results indicate the method's stability under varied analytical conditions.

System Suitability

System Suitability was confirmed by evaluating chromatographic parameters such as theoretical plates, resolution, asymmetry, and retention time for each analyte. All values were within acceptable ICH limits, affirming that the system is suitable for consistent and reproducible analysis.

Assay of Commercial Tablet Formulation

The validated RP-HPLC method was successfully applied to the assay of a commercially available fixed-dose combination tablet formulation containing 500 mg of Metformin HCl (MET), 100 mg of Vildagliptin (VILDA), and 10 mg of Dapagliflozin (DAPA). The analysis was carried out using the optimized and validated chromatographic conditions established during method development and validation.The assay results demonstrated excellent agreement with the labelled claims, confirming the method's precision, accuracy, and reliability for quantitative estimation of the active pharmaceutical ingredients in the formulation. The observed assay values were 99.86% for MET, 99.53% for VILDA, and 100.25% for DAPA. These values fall well within the pharmacopeia and ICH-accepted range of 98–102%, indicating the method's suitability for accurate drug content determination.

The findings validate the applicability of the developed stability-indicating RP-HPLC method for routine quality control, batch release, and stability testing of the fixed-dose combination product, even in the presence of potential degradation products.[27]

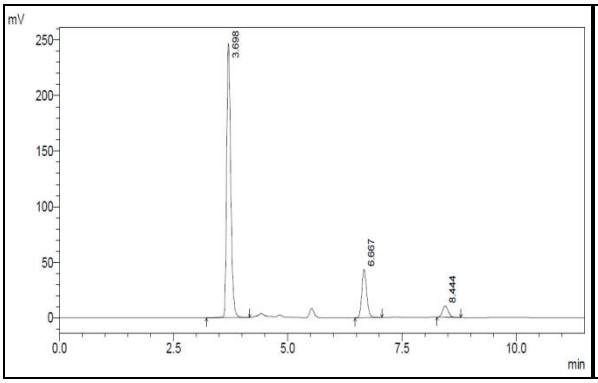

Fig.1. A- Acid Degradation

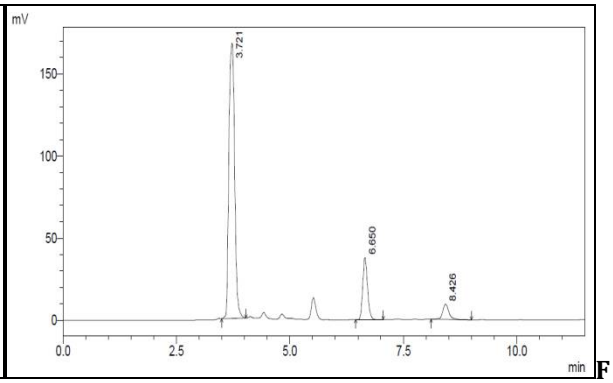

Fig.1. B- Base Degradation

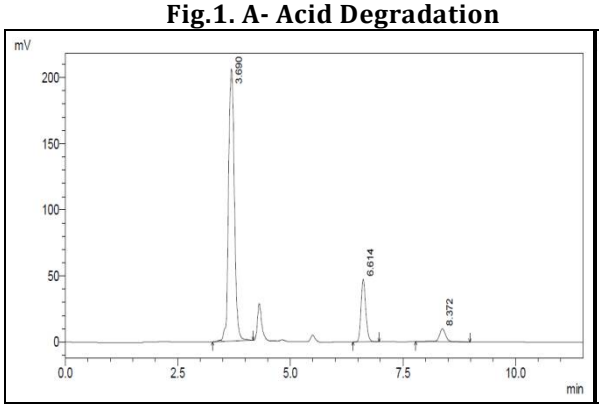

Fig.2. A- Oxidation **Degradation**

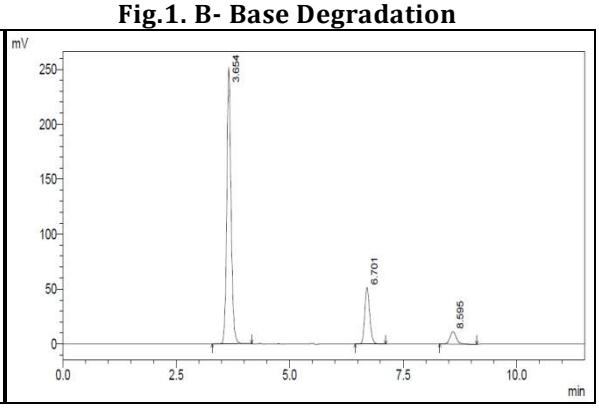

Fig.2. B- Photolytic **Degradation**

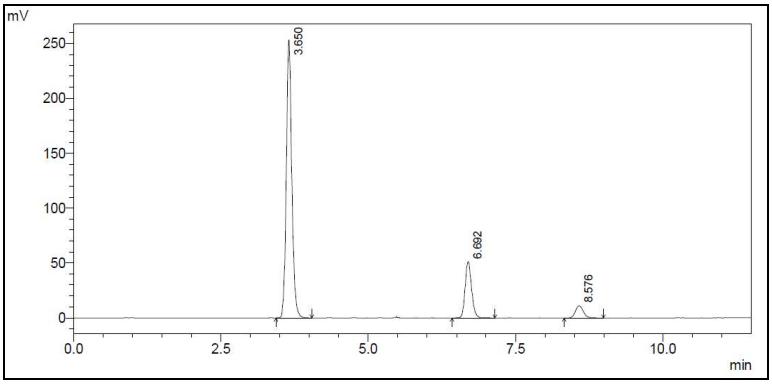

Fig.3. Thermal Degradation

Table 1. % Degradation of Drugs under Stress Conditions

Stress Condition	% Degradation		
Drug	**MET**	**VILDA**	**DAPA**
Acid	13.57%	12.01%	6.74%
Base	10.98%	15.49%	12.47%
Oxidative (H_2O_2)	0.97%	2.73%	6.49%
Photolytic	0.71%	1.36%	3.72%
Thermal	0.38%	0.30%	6.49%

Metformin showed higher degradation in acidic conditions; Vildagliptin was most sensitive to base degradation, and Dapagliflozin displayed moderate degradation under both base and thermal conditions. Oxidative and photolytic stresses had comparatively lower impact on all three drugs. These patterns are indicative of their respective chemical stability profiles and can guide formulation adjustments and packaging considerations.

CONCLUSION

The present study successfully demonstrates the development and validation of a stability-indicating RP-HPLC method for the simultaneous estimation of Metformin HCl, Vildagliptin, and Dapagliflozin in combined dosage forms. Forced degradation studies confirmed the susceptibility of the active pharmaceutical ingredients (APIs) to various stress conditions including acidic, basic, oxidative, photolytic, and thermal environments. The developed method effectively separated the parent drugs from their respective degradation products with high resolution and specificity. Validation parameters, as per ICH guidelines, confirmed the method's accuracy, precision, robustness, and linearity. These findings affirm that the proposed method is reliable and suitable for routine quality control and stability testing of the combined formulation.

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ETHICAL STATEMENT: Nil.

ABBREVIATIONS

ICH: International Council For Harmonization; RP-HPLC: Reverse Phase High Performance Liquid Chromatography; API: Active Pharmaceutical Ingredient; LOD: Limit of Detection; LOQ: Limit of Quantification; RSD: Relative Standard Deviation; KH2 PO4: Potassium Dihydrogen Ortho Phosphate Buffer; MET: Metformin HCL; VILDA: Vildagliptin; DAPA: Dapagliflozin

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