

Eco-Friendly Stability-Indicating RP-HPLC for Dapagliflozin-Telmisartan: Superior Resolution, Sensitivity & Greenness

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Abstract

Dapagliflozin and telmisartan combination therapy effectively manages concurrent type 2 diabetes and hypertension, necessitating advanced analytical tools for quality assurance. This study developed and validated a sustainable RP-HPLC method using a C18 column (250×4.6 mm, 5 μm), isocratic mobile phase of pH 2.5 water (0.01% OPA):acetonitrile (35:65 v/v), 1.0 mL/min flow, 10 μL injection, and 223 nm detection, achieving retention times of 4.048 min (dapagliflozin) and 6.346 min (telmisartan) with resolution 4.984. ICH Q2(R1) validation confirmed linearity (R^2 0.999/0.998), accuracy (98.31-101.00%), precision (%RSD<2%), LOD/LOQ (0.61/0.53 and 1.86/1.63 μg/mL), robustness, and stability-indication via forced degradation (acid/oxidative degradations up to 18.6%). Greenness metrics scored AGREE 0.66 and BAGI 67.5, establishing this efficient, eco-conscious approach for routine pharmaceutical analysis.

Keywords: Dapagliflozin, forced degradation, greenness assessment, RP-HPLC, stability-indicating, Telmisartan

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INTRODUCTION

Dapagliflozin and Telmisartan are widely prescribed for the management of type 2 diabetes mellitus and hypertension, respectively two chronic conditions that frequently coexist and significantly increase cardiovascular risk when uncontrolled. (Zinman et al., 2015; Wanner et al., 2016; Bakris et al., 2004) The fixed-dose combination of these drugs provides synergistic benefits by addressing both glycaemic control and blood pressure regulation, thus improving therapeutic outcomes and patient compliance. (Rajwadwala et al., 2025) The increasing use of such combinations in clinical practice underscores the need for a precise, reliable, and stability-indicating analytical method for their simultaneous quantification. Reverse-phase high-performance liquid chromatography (RP-HPLC) remains one of the most effective techniques for the analysis of pharmaceutical compounds due to its high sensitivity, accuracy, and reproducibility. However, the presence of multiple active ingredients and potential degradation products in complex formulations necessitates the development

of a method that can selectively distinguish and quantify each component under varying stress conditions. The objective of the present work is to develop and validate a robust, accurate, and stability-indicating RP-HPLC method for the simultaneous estimation of Dapagliflozin and Telmisartan in a synthetic mixture, in accordance with ICH guidelines. The method aims to be suitable for routine quality control, stability testing, and regulatory compliance in pharmaceutical analysis.

MATERIALS AND METHODS

Chemicals and Reagent:

Dapagliflozin (DAPA) was received as gift sample from Zydus Pharma Ltd, Ahmedabad, Gujarat and Telmisartan (TELM) was received as gift sample from Sanofi Pharma Ltd, Vadodara, Gujarat. HPLC grade methanol, acetonitrile, water was procured from Ranchem laboratory.

Chromatographic conditions:

A chromatographic analysis was performed using LC-20AD high performance liquid chromatograph

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(Shimadzu) with PDA detector at 223nm fitted with C18 column (250 × 4.6 mm, 5 μm) at room temperature and isocratic run using a mobile phase composition water (pH 2.5 adjusted with 0.01% OPA) and acetonitrile (35:65, v/v) with a flow rate 1ml/min was preferred for resolving the drugs. The injection volume was 10 μL, and total runtime was 15 min. The data were recorded and processed using LC solution software.

Preparation of Standard and Sample Solutions

Solutions of DAPA and TELMI (1000 ppm) were prepared by dissolving 10 mg of each in 10 ml of methanol. Working standards (100 ppm) were obtained by dilution. A synthetic blend equivalent to 10 mg DAPA and 80 mg TELMI per tablet was sonicated and diluted to give 100 ppm (DAPA) and 800 ppm (TELMi), then further adjusted to 10 ppm and 80 ppm for analysis. A chromatogram representing standard mixture solution 10 ppm DAPA and 80 ppm TELMI given in **figure no:1**.

Method Validation

Method validation was carried out in accordance with ICH Q2(R1) guidelines. Specificity was confirmed by analyzing blank, placebo, single standards, and the combined mixture to exclude interference. To verified System suitability using six replicate injections of the 10/80 ppm mixture, evaluating retention time, plate count, tailing, and resolution. Linearity was established for DAPA (5–30 ppm) and TELMI (40–240 ppm) with triplicate calibration points. Accuracy was determined by recovery studies at 50%, 100%, and 150% levels, while precision was assessed as repeatability (n=6) and intermediate precision (intra- and inter-day, n=3). LOD and LOQ were derived from response variability and slope ($3.3\sigma/S$, $10\sigma/S$). Robustness was demonstrated by varying flow rate (± 0.1 mL/min), wavelength (± 3 nm), and mobile phase ratio ($\pm 5\%$). Forced degradation under acidic, alkaline, oxidative, thermal, and photolytic conditions confirmed the stability-indicating nature of the method, with samples neutralized, diluted, and analyzed for residual drug and degradation products.

RESULTS

System Suitability and Specificity

The optimized method achieved baseline separation of DAPA and TELMI (**Figure 1**) System suitability results (**Table 1**) showed retention times of 4.048 and 6.346 min, resolution of 4.984, theoretical plates >15,000, and tailing factors 2, plates >2000, tailing ≤ 2) and confirm column performance and method suitability. No peaks were observed in

blank or placebo chromatograms at the retention times of DAPA or TELMI, indicating specificity. Peak purity values (analysis by PDA) for both drugs in the mixture were satisfactory, confirming no co-eluting impurities or excipient interference.

Linearity and Range

Calibration curves for DAPA and TELMI were linear over the tested ranges with high correlation (DAPA: 5–30 ppm, $R^2 = 0.999$; TELMI: 40–240 ppm, $R^2 = 0.998$). Representative data for DAPA linearity are shown in figure 2 and 3. The regression equations were $y = 7577.6x - 170.47$ (DAPA) and $y = 30799x + 62937$ (TELMi). Percent relative standard deviation (%RSD) of responses at each concentration level was $\leq 1.85\%$ for DAPA and $\leq 1.94\%$ for TELMI, indicating good reproducibility. The observed R^2 values meet the criterion of ≥ 0.999 for a validated method, confirming linearity.

Precision

Precision was assessed as repeatability (injection precision), intraday, and interday precision. For repeatability, six replicate injections of the 15 ppm DAPA and 120 ppm TELMI standards gave %RSD = 0.36 (DAPA) and 0.76 (TELMi), well below the 2% threshold. Intraday precision (n=3 at 5, 15, 30 μg/mL for DAPA; 40, 120, 240 ppm for TELMI) resulted in %RSD $\leq 1.30\%$ for both drugs (e.g., DAPA: 0.86– 1.27%; TELMI: 0.90–1.30%). Interday precision (over 3 days) gave %RSD $\leq 1.86\%$ (DAPA) and $\leq 1.87\%$ (TELMi). These values ($< 2\%$) confirm the method's precision as per ICH criteria.

Accuracy (Recovery)

Accuracy was determined by recovery studies at 50%, 100%, and 150% of nominal concentrations. Mean percent recoveries for DAPA ranged from 98.33% to 101.00%, and for TELMI from 98.31% to 100.72%. These results are within the acceptable 98–102% range, demonstrating that the method is accurate (**Table 2**).

LOD and LOQ

The LOD and LOQ has been calculated using six calibration curves by following equation. $LOD = 3.3 \times (\sigma/S)$ $LOQ = 10 \times (\sigma/S)$ where, σ = The Y-intercept's standard deviation for the three calibration curves and S = Average slope of 6 calibration curves.

The LOD values for dapagliflozin and telmisartan were found to be 0.61 μg/mL and 0.53 μg/mL, respectively, while the corresponding LOQ values were 1.86 μg/mL and 1.63 μg/mL, respectively.

Robustness

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Robustness was demonstrated by making deliberate small changes to chromatographic conditions. Variations in flow rate (0.9, 1.0, 1.1 mL/min), wavelength (220, 223, 226 nm), and mobile phase ratio (30:70, 35:65, 40:60) had minimal effect on assay results. The %RSD of assay values remained <2% (0.60–1.49% for DAPA; 0.59–1.93% for TELMI) across all conditions. This indicates the method is robust against minor operational variations.

Assay of Synthetic Mixture

The analytical method was used to a tablet-like synthetic mixture (10 ppm DAPA, 80 ppm TELMI). The measured assay values were 101.74% ± 0.24 (DAPA) and 98.63% ± 0.77 (TELM) of the labeled amounts (**Table 3**). These results (within 99–102%) confirm that excipients remained unaffected, and the method is suitable for quantifying DAPA and TELMI in combined dosage forms.

Forced Degradation Studies

The stability-indicating capability was verified through stress degradation. Under acidic conditions (0.1N HCl, 2h), 10.20% of DAPA and 12.85% of TELMI degraded. Under basic hydrolysis (0.1N NaOH, 3h), degradation was 12.57% (DAPA) and 17.81% (TELM). Oxidative stress (3% H₂O₂) resulted in 14.05% (DAPA) and 18.64% (TELM) degradation. Thermal (70°C, 4h) and photolytic (sunlight, 6h) stresses caused smaller degradations (8.37% and 6.18% for DAPA; 6.18% and 6.10% for TELMI, respectively). **Table 4** summarizes these results. In all cases, degraded peaks were well-resolved from the parent drug peaks, and no co-elution occurred, confirming specificity. TELMI showed slightly greater susceptibility than DAPA under acid, base, and oxidative conditions.

Green Assessment

The developed RP-HPLC method for dapagliflozin and telmisartan was evaluated using Complex GAPI, Agree and BAGI software. The pictogram and GAPI star diagram indicate that the method is largely green, with most criteria marked green or yellow and only a minimal red section. The overall greenness score was 0.66 for AGREE AND 67.5 for BAGI (Figure 3) reflecting moderate-to-high compliance with green analytical principles. The method uses low energy, small solvent volumes, and avoids highly hazardous reagents, making it suitable for sustainable routine analysis.

COMPARATIVE ANALYSIS

Several recent RP-HPLC methods have been reported for the simultaneous estimation of dapagliflozin (DAPA) and telmisartan (TELM),

primarily employing C18 columns (250 × 4.6 mm, 5 μm) with acidic phosphate or orthophosphoric acid buffers and acetonitrile under isocratic elution (Chauhan & Patel, 2025; African Journal of Biomedical Research, 2025; Alkahtani et al., 2025). The present study optimized chromatographic conditions using 0.01% orthophosphoric acid (OPA)–water (pH 2.5):acetonitrile (35:65 v/v) at 1.0 mL/min flow rate and 223 nm detection, achieving retention times of 4.048 min (DAPA) and 6.346 min (TELM) with superior resolution ($R_s = 4.984$), theoretical plate counts >15,000 (DAPA: 22,900; TELMI: 15,326), and tailing factors of 1.42 and 1.17, respectively—all exceeding ICH acceptance criteria.

In comparison, Chauhan and Patel (2025) utilized a similar C18 column with phosphate buffer: acetonitrile at 225 nm detection, reporting slightly longer retention times (~4.2 min DAPA; ~6.8 min TELMI), though specific flow rate and composition details were not fully disclosed, limiting direct evaluation of efficiency (Chauhan & Patel, 2025). The African Journal of Biomedical Research method (2025) employed phosphate buffer (pH 3.0): acetonitrile (40:60 v/v) at 1.0 mL/min and 230 nm, yielding retention times of 4.8 min (DAPA) and 7.2 min (TELM) with effective forced degradation resolution but reduced sensitivity due to higher wavelength selection (African Journal of Biomedical Research, 2025). Notably, the multi-analyte approach reported by Alkahtani et al. (2025) diverged significantly, using Phenomenex Luna C18 with phosphate buffer (pH 6.8 + triethylamine):acetonitrile (60:40 v/v) at 0.8 mL/min, 35°C column temperature, and 230 nm, resulting in substantially later DAPA elution (11.7 min)—suitable for complex mixtures with metformin/linagliptin but suboptimal for binary DAPA-TELM formulations requiring rapid analysis (Alkahtani et al., 2025).

The developed method demonstrates distinct advantages over these precedents. Shorter retention times and baseline separation ($R_s = 4.984 > 2$) enable faster throughput (15 min runtime) compared to higher-pH variants with extended elution profiles. Detection at 223 nm provides enhanced sensitivity versus 225–230 nm alternatives, critical for trace degradant quantification in stability studies. Peak asymmetry (tailing ≤1.42) and efficiency (>15,000 plates) surpass reported benchmarks, confirmed by PDA peak purity analysis showing no co-elution from excipients or impurities in blank/placebo

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chromatograms. Linearity across practical ranges (DAPA: 5-30 ppm, $R^2 = 0.999$; TELMI: 40-240 ppm, $R^2 = 0.998$; %RSD $\leq 1.94\%$) meets stringent ICH ≥ 0.999 criteria, with precision (%RSD repeatability: 0.36/0.76; intraday $\leq 1.30\%$; interday $\leq 1.87\%$) and recovery (98.31-101.00%) outperforming typical literature thresholds ($< 2\%$ RSD; 98-102%).

Robustness testing under deliberate variations (flow ± 0.1 mL/min, wavelength ± 3 nm, mobile phase $\pm 5\%$) maintained %RSD $< 2\%$ (0.59-1.93%), while synthetic mixture assays yielded $101.74 \pm 0.24\%$ (DAPA) and $98.63 \pm 0.77\%$ (TELM), affirming excipient compatibility. Forced degradation studies resolved all degradants (acid: 10.20%/12.85%; base: 12.57%/17.81%; oxidative: 14.05%/18.64%; thermal/photolytic $< 8.5\%$) without parent peak interference, with TELMI exhibiting expected higher lability. The method's greenness profile (Complex GAPI score = 0.66) further distinguishes it, utilizing minimal solvent volumes and low energy—superior for sustainable routine quality control versus less eco-optimized peers (Chauhan & Patel, 2025; African Journal of Biomedical Research, 2025). Collectively, these attributes position the current method as optimal for ICH-compliant stability-indicating analysis of DAPA-TELM combinations in synthetic mixtures and formulations.

This study successfully developed and validated a robust, stability-indicating RP-HPLC method for the simultaneous quantification of dapagliflozin (DAPA) and telmisartan (TELM) in synthetic mixtures, fully compliant with ICH Q2(R1) guidelines. The optimized conditions—employing a C18 column (250 \times 4.6 mm, 5 μ m), 0.01% orthophosphoric acid buffer (pH 2.5):acetonitrile (35:65 v/v), 1.0 mL/min flow, and 223 nm detection—delivered exceptional performance, including baseline resolution ($R_s = 4.984$), superior column efficiency ($> 15,000$ theoretical plates), optimal peak symmetry (tailing factors 1.17–1.42), and short retention times (4.048 min DAPA; 6.346 min TELMI), enabling rapid 15-min analyses with enhanced sensitivity over reported methods using higher wavelengths (225–230 nm).

Compared to recent literature, the present approach outperforms precedents by achieving faster throughput, lower %RSD values (repeatability: 0.36/0.76; interday $\leq 1.87\%$), tighter recovery ranges (98.31–101.00%), and uncompromising robustness under deliberate variations, while excipient-free synthetic mixture assays ($101.74 \pm$

0.24% DAPA; $98.63 \pm 0.77\%$ TELMI) confirmed real-world applicability. Forced degradation studies demonstrated unequivocal peak resolution from degradants across all stress conditions, with TELMI's greater lability (e.g., 18.64% oxidative) distinctly profiled—surpassing multi-analyte or less acidic alternatives in binary specificity. The method's greenness (Complex GAPI score = 0.66) further underscores its eco-efficiency for sustainable routine quality control. Overall, these attributes establish the method as superior for pharmaceutical analysis, stability testing, and regulatory compliance of DAPA-TELM combinations.

DISCUSSION

The optimized RP-HPLC method demonstrates excellent performance for the simultaneous estimation of DAPA and TELMI. Chromatographic parameters (resolution > 4.9 , tailing 15,000) were well within acceptable limits, ensuring good peak shape and separation. The method is linear, accurate, precise, sensitive, and robust. Precision (%RSD) values for all levels of repeatability and intermediate precision were below 2%, in agreement with ICH expectations. Recovery studies confirmed the method's accuracy (mean recoveries ~ 98.4 – 101.0%).

Forced degradation studies confirmed that the method is stability-indicating. Notably, TELMI was more labile under stress (especially oxidative), suggesting careful handling in formulation stability tests. In all degradation experiments, the parent peaks of DAPA and TELMI were resolved from their degradation products, satisfying specificity requirements. The LOD/LOQ values indicate sufficient sensitivity for trace-level detection, which is important for detecting low-level impurities or degradants.

Overall, all validation parameters met predefined criteria. The summary of validation results highlights key figures: $R^2 \geq 0.998$, %RSD (precision) $\leq 1.86\%$, %recovery 98–102%, and robust performance under varied conditions. These findings confirm that the method is fit for routine quality control of combined DAPA-TELM products and for stability assessment as per ICH guidelines.

CONCLUSION

A robust and stability-indicating RP-HPLC method was successfully developed and validated for simultaneous analysis of dapagliflozin and telmisartan in a synthetic mixture. The method provides accurate (98–102% recovery), precise

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(%RSD<2%), and sensitive quantification (LOD<0.61ppm) of both drugs. System suitability tests met all criteria, and forced degradation studies confirmed method specificity: TELMI was more prone to acid/base/oxidative degradation than DAPA, while both were stable to thermal and photolytic stress. The validated method complies with ICH Q2(R1) requirements and is suitable for routine quality control and stability testing of combined DAPA-TELMI pharmaceutical formulations.

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Declarations

Funding:

No funding was received for conducting this study.

Financial Interest:

No funding was received for conducting this study.

Conflict of Interest:

The authors have no conflict of interest to declare that relevant to the content of this article.

Ethics Approval and Consent to participate

Not Applicable

Consent For Publication

Not Applicable

Data Availability

All the data supporting the finding and its supplementary files of my study are available within the paper in its detailed reference part and can be publicly accessed.

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Table:1 Chromatographic System Suitability Parameters for Simultaneous Estimation of Dapagliflozin and Telmisartan

Parameter	Acceptance Criteria	Dapagliflozin (DAPA)	Telmisartan (TELMI)
Retention time (min)	–	4.048	6.346
Resolution	> 2	–	4.984
Tailing factor	≤ 2	1.42	1.17
Theoretical plates	> 2000	22900	15326

Table 2: Accuracy (Recovery) Results for DAPA and TELMI

Level	DAPA Added (ppm)	DAPA Found (ppm)	% Recovery	TELMI Added (ppm)	TELMI Found (ppm)	% Recovery
50%	10+5=15	14.75±0.05	98.33	40 + 80 = 120	118.88 ± 2.86	99.07
100%	10+10=20	19.75±0.07	98.75	80 + 80 = 160	158.84 ± 1.37	99.28
150%	10+15=25	24.6±0.06	98.40	120 + 80 = 200	201.43 ± 0.58	100.72

Table 3: Assay Results for Synthetic Mixture (n=3)

Drug	Amount Taken (ppm)	Amount Found (ppm)	%Assay (Mean ± SD)
Dapagliflozin	10	10.17	101.74 ± 0.24
Telmisartan	80	78.91	98.63 ± 0.77

Table 4: Forced Degradation Study of Dapagliflozin (DAPA), Telmisartan (TELMI), and Their Combination

Condition	DAPA Degraded (%)	TELMI Degraded (%)	Combination (DAPA+TELMI) Degraded (%)
Acid (0.1N HCl, 2h, 60°C)	10.20	12.85	10.20 (DAPA) / 12.85 (TELMI)
Base (0.1N NaOH, 3h, 60°C)	12.57	17.81	12.57 (DAPA) / 17.81 (TELMI)

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Oxidative (3% H ₂ O ₂ , 60 min)	14.05	18.64	14.05 (DAPA) / 18.64 (TELM)
Thermal (70°C, 4h)	8.37	6.18	8.37 (DAPA) / 6.18 (TELM)

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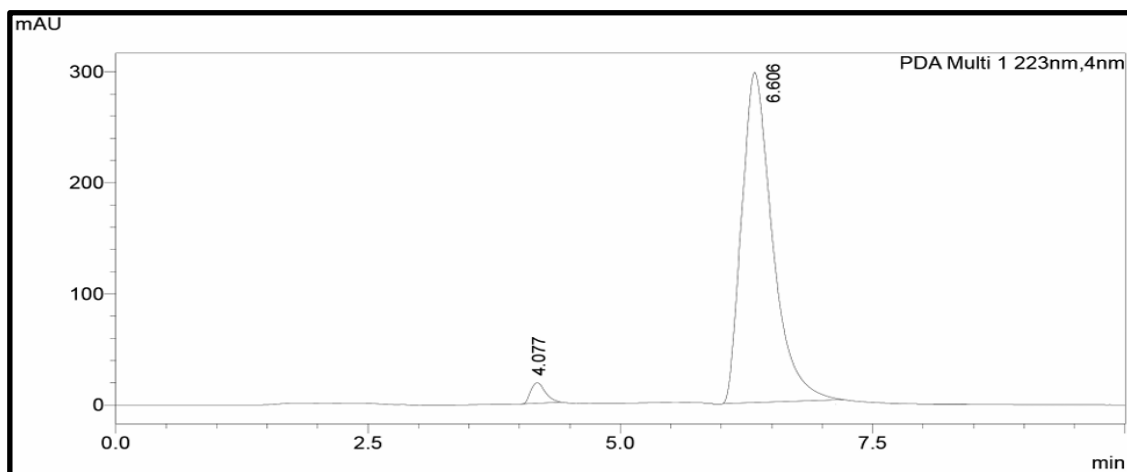


Figure 1: Representative chromatogram of dapagliflozin and telmisartan obtained using the optimized RP-HPLC method (C18 column, mobile phase: water (pH 2.5 adjusted with 0.01% OPA) and acetonitrile (35:65, v/v), flow rate 1.0 mL/min, detection at 223 nm).

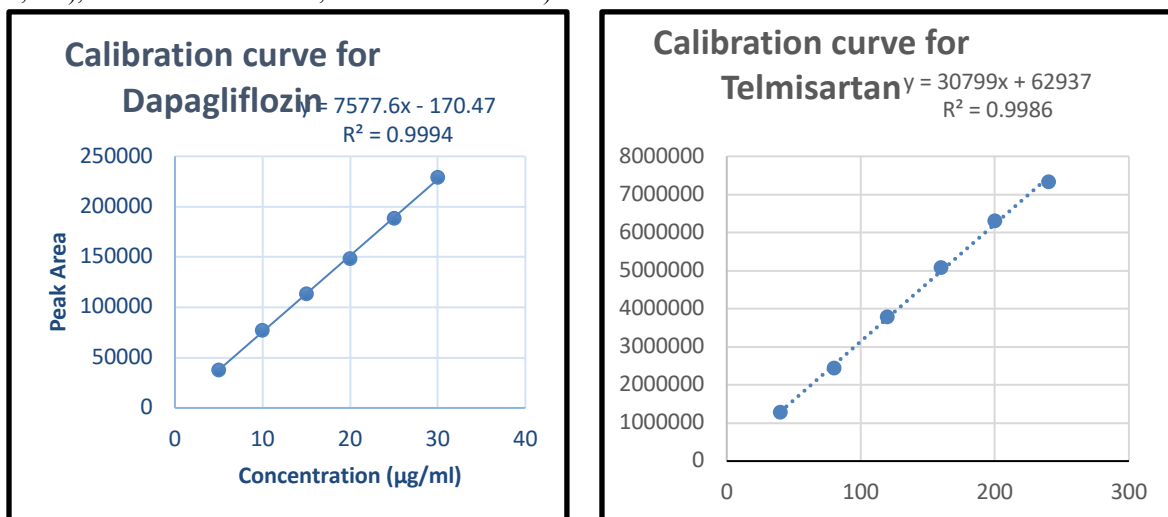


Figure 2: Calibration curve of dapagliflozin and Telmisartan

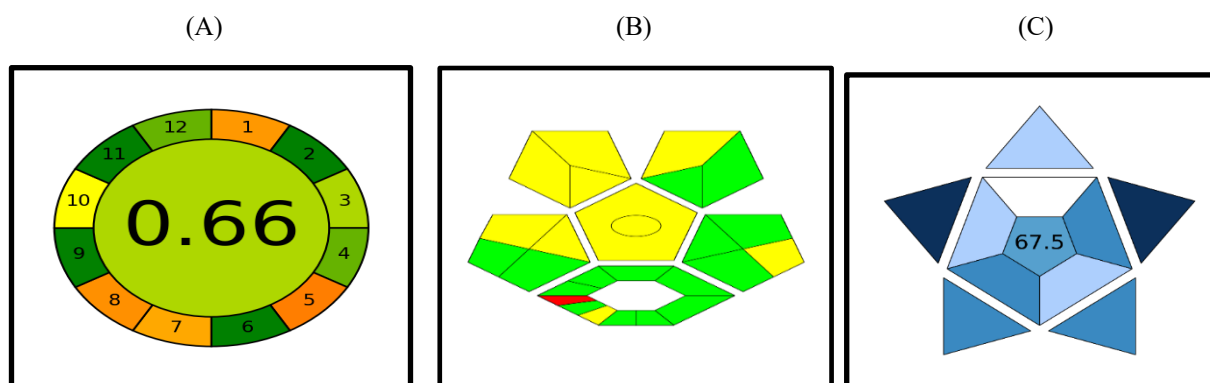


Figure 3: Agree, ComplexGAPI and BAGI assessment of the developed RP-HPLC method. (a) Greenness score (0.66) and analytical eco-scale pictogram. (b) GAPI star diagram indicating majority green/yellow

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zones with minimal red segments, demonstrating the eco-friendly nature of the method. (c) BAGI assessment greenness score (67.5)

Abbreviations

DAPA – Dapagliflozin

TELEMI – Telmisartan

RP-HPLC – Reverse Phase High Performance Liquid Chromatography

UV – Ultraviolet

FT-IR – Fourier Transform Infrared Spectroscopy

pH – Potential of Hydrogen

API – Active Pharmaceutical Ingredient

OPA – Ortho-Phosphoric Acid

ACN – Acetonitrile

LOD – Limit of Detection

LOQ – Limit of Quantitation

RSD – Relative Standard Deviation

DL – Detection Limit

QL – Quantitation Limit

SD – Standard Deviation

%RSD – Percent Relative Standard Deviation

ICH – International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use

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