RESEARCH PAPER

Method Development and Validation for related Impurities of Dapagliflozin

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Abstract: The presence of related impurities in pharmaceutical formulations can significantly impact drug safety and efficacy, making their accurate determination essential. The present study focuses on the development and validation of a reverse-phase high-performance liquid chromatography (RP-HPLC) method for the analysis of related impurities in Dapagliflozin. Chromatographic separation was achieved using a C18 column with an optimized mobile phase under isocratic conditions, and detection was carried out using a UV detector. The developed method was validated in accordance with International Council for Harmonisation guidelines for parameters such as specificity, linearity, accuracy, precision, robustness, limit of detection, and limit of quantification. The results demonstrated that the method is precise, accurate, and capable of effectively separating the drug substances from their related impurities. Therefore, the proposed RP-HPLC method is suitable for routine quality control and stability studies of these antidiabetic drugs.

Key Words: C18 column, RP-HPLC, Dapagliflozin, UV detector
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Introduction:

In modern pharmaceutical analysis, ensuring the quality, safety, and efficacy of drug substances is of paramount importance. One critical aspect of quality control is the detection and quantification of related impurities, which may arise during synthesis, storage, or degradation of pharmaceutical compounds. These impurities can significantly affect the therapeutic performance and safety profile of the drug; hence, their identification and control are essential as per regulatory guidelines such as those issued by the International Council for Harmonisation.

Dapagliflozin are widely prescribed oral antidiabetic agents used in the management of type 2 diabetes mellitus. Dapagliflozin belongs to the class of sodium-glucose co-transporter-2 (SGLT2) inhibitors, Due to their widespread clinical use, stringent analytical methods are required to monitor their purity and impurity profile.

Reverse Phase High Performance Liquid Chromatography (RP-HPLC) is one of the most reliable and widely employed analytical techniques for the separation, identification, and quantification of pharmaceutical compounds and their related impurities. The technique offers high resolution, sensitivity, reproducibility, and suitability for routine quality control analysis.

Method development in RP-HPLC involves optimization of various parameters such as mobile phase composition, stationary phase selection, flow rate, detection wavelength, and column temperature to achieve efficient separation of the drug and its impurities. However, the developed method must be validated to demonstrate its suitability for intended use. Method validation is carried out according to ICH guidelines, particularly ICH Q2 (R1), and includes evaluation of parameters such as:

- Specificity
- Linearity
- Accuracy
- Precision
- Limit of Detection (LOD)
- Limit of Quantitation (LOQ)
- Robustness

The present study focuses on the development and validation of a simple, accurate, precise, and robust RP-HPLC method for the determination of related impurities in Dapagliflozin, Sitagliptin, and Vildagliptin. Such a validated method is essential for ensuring compliance with regulatory standards and for maintaining the quality and safety of pharmaceutical formulations.

Experimental Work

High-performance liquid chromatography (HPLC) analysis was carried out using an Agilent Technologies 1100 Gradient System equipped with an auto-injector. The system included a UV–DAD detector (Model G13148, S/N DE71365875) and a quaternary gradient pump (Model G130A, S/N DE9180834). Data acquisition and processing were performed using Chem Station version 10.1 software. Chromatographic separation was achieved on a reverse-phase C18 column (4.6 × 250 mm) packed with 5.0 µm particles, which served as the stationary phase throughout the analysis.

Chromatographic Condition

The chromatographic analysis was carried out using a mobile phase consisting of acetonitrile and 0.1% formic acid in water (50: 50, % v/v). The detection wavelength was set at 225 nm to ensure optimal sensitivity for the analyte. The mobile phase was delivered at a flow rate of 1.0 mL/min, and the column temperature was maintained at 25°C to ensure consistent chromatographic performance. A sample volume of 20 µL was injected for each run.

Preparation of stock standard solution and Working solution

A precisely weighed amount of 5 mg of DAPA standard was transferred into a clean, dry 10 mL volumetric flask. Methanol was added to dissolve the standard, and the solution was sonicated if necessary to ensure complete dissolution. The volume was then made up to the 10 mL mark with methanol, resulting in a stock solution with a final concentration of 500 µg/mL (Stock-I). This primary stock solution was stored in an amber vial to protect it from light and used for further dilutions during method development and analysis.

Preparation of Impurity Sample Solution

For Impurity 1

For impurity I (IMP-1), an accurately weighed quantity of 5 mg was transferred into a clean, dry 10 mL volumetric flask. Methanol was added to dissolve the weighed material, and the solution was gently mixed and sonicated, if necessary, to achieve complete dissolution. The volume in each flask was then brought up to the 10 mL mark with methanol, resulting in individual stock solutions with a concentration of 500 µg/mL for Impurity.

For Impurity II

For the preparation of the impurity stock solution, accurately weighed quantities of Impurity-1 and Impurity-2 (IMP-2) (5 mg each) were transferred into separate clean and dry 10 mL volumetric flasks. Methanol was added to each flask to dissolve the impurities, and the solutions were gently mixed and sonicated, if required, to ensure complete dissolution. The volume in each flask was then made up to the 10 mL mark with methanol, yielding stock solutions with a concentration of 500 µg/mL for IMP-1 and IMP-2, respectively. These preparations were designated as Stock-III solutions and were stored appropriately until further dilution and analysis.

Preparation of working standard solutions

To prepare the mixed working solutions used in the study, graded concentrations of DAPA were combined with fixed levels of IMP-1 and IMP-2. The process began by taking 0.1 mL of the DAPA Stock-I solution together with 0.2 mL of the impurity Stock-III solution and diluting the mixture to 10 mL with the mobile phase, giving a final concentration of 5 µg/mL of DAPA along with 10 µg/mL each of IMP-1 and IMP-2. In the same manner, additional working solutions were prepared by increasing the volume of Stock-I to 0.2 mL, 0.3 mL, 0.4 mL, and 0.5 mL, respectively, while keeping the impurity volume constant at 0.2 mL. Each mixture was then made up to 10 mL with the mobile phase. These preparations resulted in solutions containing 10, 15, 20, and 25 µg/mL of DAPA, each consistently accompanied by 10 µg/mL of both impurities. All solutions were thoroughly mixed to ensure proper homogenization before use in calibration and analytical evaluation.

Preparation of sample solution

Preparation of Sample Stock Solution (Stock-II)

The marketed formulation selected for analysis was Cipdapla-10 (Cipla Ltd.). The combined weight of twenty tablets was found to be 0.700 g, giving an average tablet weight of 0.035 g. Based on this average weight and the label claim of 10 mg of DAPA per tablet, the amount of tablet powder equivalent to 5 mg of DAPA was calculated. From this calculation, 17.5 mg of the finely powdered tablet blend was accurately weighed and transferred into a clean 10 mL volumetric flask. Methanol was then added to dissolve the sample, and the volume was made up to the mark. This procedure yielded a sample stock solution containing 500 µg/mL of DAPA, which was designated as Stock-II and used for further analytical work.

Tablet Assay Preparation

For the assay of the tablet formulation, the powdered tablet sample was first extracted to obtain Sample Stock-I, followed by appropriate dilution to prepare Sample Stock-II. From this intermediate stock solution, 0.3 mL was accurately transferred to a 10 mL volumetric flask and the volume was made up with the mobile phase, yielding a final working concentration of 15 µg/mL of DAPA. The solution was mixed thoroughly to ensure uniformity and clarity before analysis. This final assay solution was then injected into the HPLC system under the optimized chromatographic conditions, and the peak area obtained was compared with that of the standard solution to determine the amount of DAPA present in the tablet formulation. This procedure ensured accurate dilution, appropriate sample handling, and reproducible quantification suitable for routine quality-control evaluation.

Method Validation

Specificity

Specificity is a critical performance characteristic of the HPLC method, referring to its ability to unequivocally assesses the analyte in the presence of components such as impurities, degradation products, and matrix constituents. In the present study, specificity was evaluated by comparing chromatograms of DAPA, IMP-1, and IMP-2, both individually and in combination, at the MQC level. The results confirmed that the analyte and impurity peaks were well resolved and free from interference from the solvent system or other components.

The specificity of the developed method was further established through forced degradation studies, thereby demonstrating its stability-indicating capability. DAPA, IMP-1, and IMP-2 samples were subjected to various stress conditions, including acidic, alkaline, neutral, oxidative, and photolytic degradation, in accordance with ICH guidelines. Known related impurities were spiked at concentrations corresponding to specification and qualification thresholds prior to stress exposure to assess impurity stability, potential co-degradation, and chromatographic resolution under stressed conditions. The method successfully resolved the analyte and impurities from all degradation products, confirming its specificity and suitability for stability studies.

Acid degradation study

For the acid degradation study, 0.3 mL of the API stock solution was transferred into a clean volumetric tube, followed by the addition of 5 mL of 0.1 N HCl. The mixture was then diluted to the required volume with diluent and allowed to stand for predetermined intervals of 1 hr, 4 hrs, and 24 hrs. At each time point, the sample was neutralized prior to injection, and the resulting solutions were analyzed by HPLC to assess the extent of degradation.

Alkaline degradation

For the base degradation study, 0.3 mL of the API stock solution was taken into a 10 mL volumetric tube and mixed with 5 mL of 0.1 N NaOH. The solution was then diluted to the desired volume with the diluent and allowed to stand for 1 hr, 4 hrs, and 24 hrs. At each specified time point, the sample was neutralized prior to HPLC injection, and the resulting solutions were analyzed to evaluate the extent of degradation under basic conditions**.**

Neutral degradation study

For the hydrolytic degradation study, 0.5 mL of the API stock solution was taken into a 10 mL volumetric tube and mixed with 5 mL of water. The mixture was then diluted to the required volume with the diluent and allowed to stand for 1 hr, 4 hrs, and 24 hrs. At each time point, the sample was analyzed by HPLC to assess the extent of degradation under aqueous conditions**.**

Oxidative Degradation

For the oxidative degradation study, 0.5 mL of the API stock solution was taken into a 10 mL volumetric tube and mixed with 5 mL of 3% hydrogen peroxide (H_2O_2). The mixture was then diluted to the desired volume with the diluent and allowed to stand for 1 hr, 4 hrs, and 24 hrs. At each specified time point, the sample was neutralized before HPLC injection, and the solutions were analyzed to determine the extent of oxidative degradation of the API.

Photolytic Study

For the photolytic study, 100 mg of the sample was exposed to direct sunlight for 24 hrs. After the exposure period, a working solution containing 15 µg/mL of the sample was prepared and injected into the HPLC system to evaluate the effect of light on the stability of the compound.

Linearity and Range

A set of calibration standards was prepared in order to establish linear relationship between the concentration of analyte present in the sample and the detector response (peak area of the individual standards). Linearity studied by preparing five standard concentrations ranging from 5-25 µg/ml by diluting the standard stock solutions using diluents of DAPA in the presence of fixed impurity concentrations across all calibration points. 20 µl of each of these samples were

injected in duplicate into the HPLC system. Peak area corresponding to the concentration of each of the sample was recorded and a graph of concentration peak area was constructed. Slope, intercept and correlation coefficient value of the curve was calculated. This approach was adopted to assess the method's capability to selectively and accurately quantify the active pharmaceutical ingredient in the presence of its related impurities, thereby simulating real sample conditions.

Precision

The precision of an HPLC analytical system indicates the extent of harmony among multiple measurements of the same harmonized sample under consistent conditions. For calculating precision, intraday as well as interday precision was estimated, and the results were reported as % RSD. Additionally, the repeatability of the developed method was verified under the same experimental conditions. It was performed by preparing and injecting solutions of 25 µg//mL in duplicate, followed by the determination of the concentration found. For intraday precision, three different concentrations, including low, medium, and high, were analyzed on the same day. While estimating interday, samples were analyzed on three consecutive days. The acceptable range for the calculated % RSD must not exceed 2%.

Accuracy

Accuracy of the developed method was evaluated in terms of % recovery studies at three different levels 80, 100 and 120 % of the initial concentration (200 µg/mL). Working solutions of DAPA, with fixed concentrations of IMP-1, and IMP-2 were prepared in duplicate at each level to determine the respective recovery percentages. The mean % recovery at each concentration level was then calculated using following formula wherein the accepted range for it is 90−110% while it should not be more than 2% for % RSD and SD.

% Recovery = [(recovered concentration/injected concentration) × 100]

Robustness

Robustness signifies the reliability of the developed method under deliberate variations in the method parameters. Robustness of the method was established by changing mobile phase composition, wavelength, and flow rate. Robustness was evaluated by establishing system suitability parameters and by calculating % RSD of peak areas of duplicate injections. This ensures that the developed method is reliable and susceptible to the deliberate variations in the method parameters.

Ruggedness

Ruggedness was evaluated to determine the reproducibility of the method under normal but variable conditions such as a change in analyst. In the present study, a standard solution of DAPA (25 µg/mL) containing fixed concentrations of the related impurities IMP-1 and IMP-2 was analyzed independently by two different analysts, with each analyst performing two replicate determinations under identical chromatographic conditions. For each analyst, the mean peak area, SD, and % RSD were calculated.

Results and Discussion

Method Development

In the present methodology, an HPLC method was successfully employed for the quantification of DAPA, and its related impurities using an Agilent 1100 gradient HPLC system equipped with a PWD detector and controlled through CHEMSTATION 10.1 software. Chromatographic separation was carried out on a reversed-phase C18 column (4.6 × 250 mm, 5 µm; Agilent), which provided adequate retention and efficient resolution among all three analytes. A mobile phase consisting of acetonitrile and 0.1% formic acid (50:50, % *v/v*) was finalized after evaluating various solvent ratios, as it produced well-resolved, symmetrical peaks with minimal baseline noise. The method was operated at a flow rate of 1.0 mL/min and a column temperature of 25°C, which ensured reproducible retention times and system stability. Detection at 225 nm enabled optimal sensitivity for Dapagliflozin and its related impurities. An injection volume of 20 µL was used for standard and sample solutions.

These chromatographic conditions were optimized to ensure adequate retention, sharp peak shape, and reproducible quantification of the analytes.

Table 1: Chromatographic Conditions for DAPA and Related Impurities

Chromatographic Modes	Chromatographic Conditions
Instrument	HPLC-Agilent 1100 gradient system; PWD detector
Software	CHEMSTATION 10.1 software
Column	C18 reversed-phase column (4.6 × 250 mm, 5 µm; Agilent)

Mobile phase	Acetonitrile and 0.1% formic acid (50:50, % *v/v*)
Detection wavelength	225 nm
Column temperature	25°C
Flow rate	1 mL/min
Sample volume	20 µl

In the optimized conditions it has been observed that the DAPA, IMP-1 and IMP-2 were well separated with a resolution greater than 6. Peak symmetry was assessed using the asymmetry factor. All peaks exhibited acceptable symmetry. The system suitability results are tabulated in **Table 2**. The optimized final system suitability chromatogram in the developed HPLC method for SITA in presence of impurities is captured in **Fig 1**.

Table 2: System Suitability Parameters for Optimized Chromatographic Condition

Name	Retention Time (min)	Area	Resolution	No. of Theoretical plates
DAPA	4.167	250.44284	8.68	6934
IMP-1	2.574	46.24896	-	3839
IMP-2	5.645	57.75891	6.82	9387

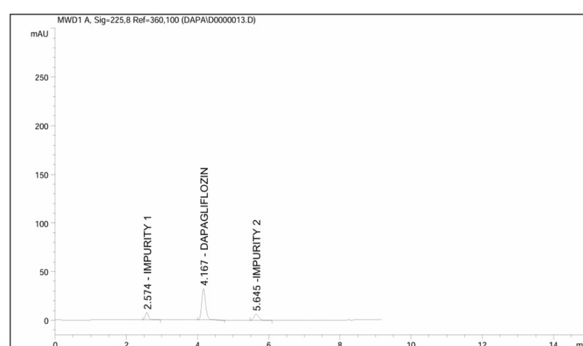


Figure 1: Chromatogram showing the separation of DAPA, IMP-1 and IMP-2

Tablet Assay Preparation

Table 3: Analysis of Drug from Tablet Formulation

Conc.	Peak Area-I	Peak Area-II	Mean Peak Area	SD	% RSD
15.00 µg/mL	617.43	618.08	617.76	0.460	0.074

Method Validation

Specificity

Table 4: Specificity

Name	Retention Time (min)	Area	Resolution	No. of Theoretical plates
DAPA	4.115	1051.07910	7.91	6950
IMP-1	2.548	34.22297	-	2643
IMP-2	5.637	57.28020	7.04	9274

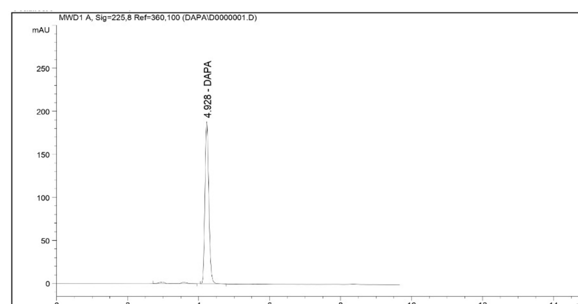


Figure 2a: Representative chromatogram of DAPA

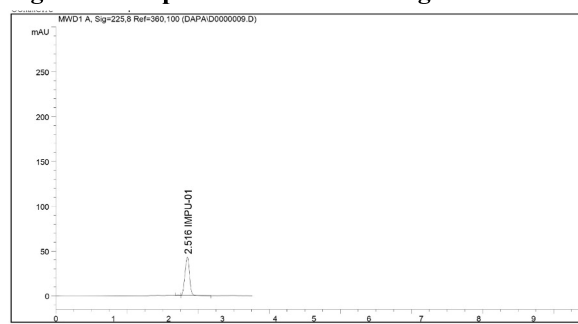


Figure 2b: Representative chromatogram of IMP-1

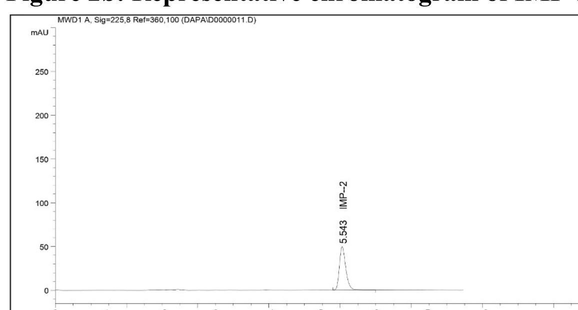


Figure 2c: Representative chromatogram of IMP-2

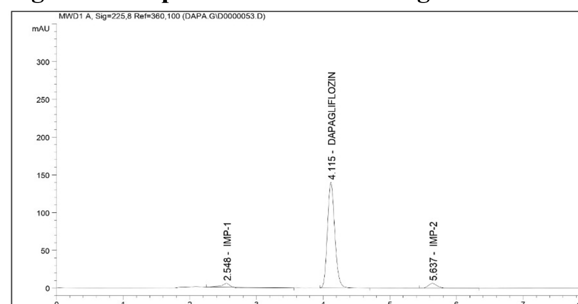
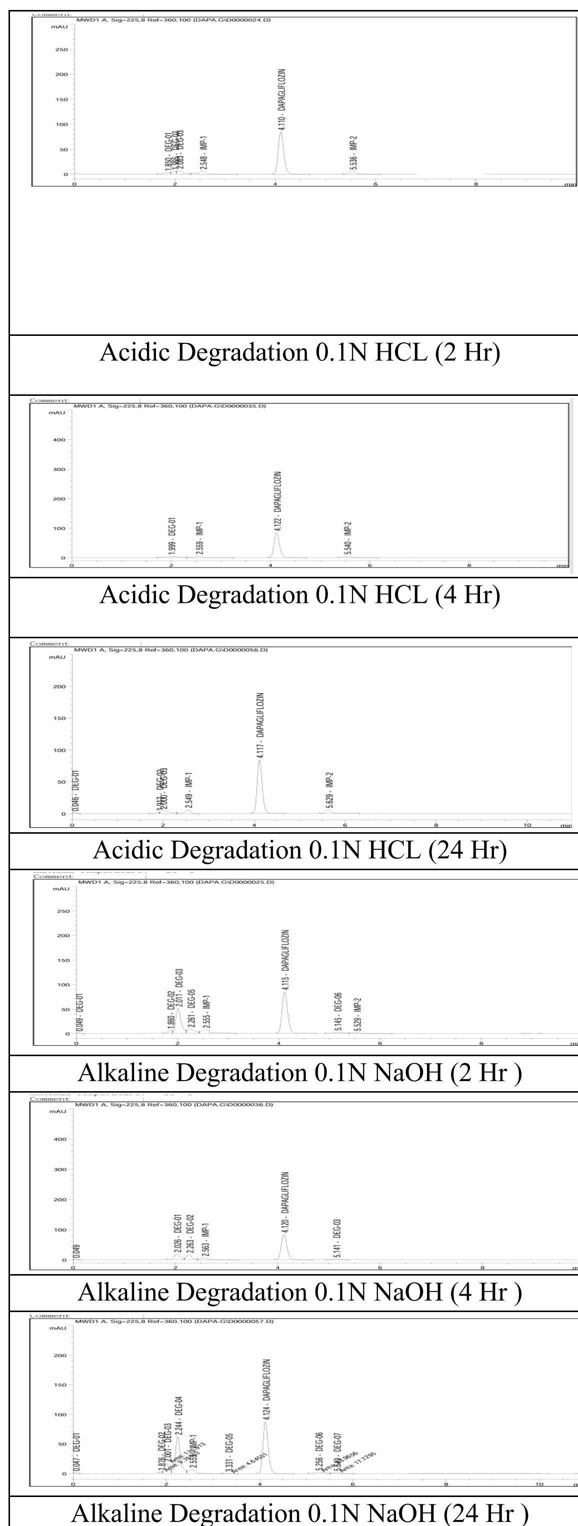


Figure 2d: Representative chromatogram of Combination of DAPA, IMP-1 and IMP-2

Table 5: Forced degradation data

DAPA					
Sr. No.	**Degradation**	**Area of Standard**	**Area of degraded Sample**	**Degraded upto %**	**Actual % degradation**
AFTER 2 HR					
1	Acid Degradation	612.18	603.07	98.51	1.49
2	Basic Degradation	612.18	598.95	97.84	2.16
3	H_2O_2 Degradation	612.18	559.97	91.47	8.53
4	Neutral	612.18	610.97	99.80	0.20
AFTER 4 HR					
1	Acid Degradation	612.18	598.05	97.69	2.31
2	Basic Degradation	612.18	549.05	89.69	9.61
3	H_2O_2 Degradation	612.18	511	83.47	16.53
4	Neutral	612.18	609.72	99.60	0.40
AFTER 24 HR					
1	Acid Degradation	612.18	497.73	81.30	18.70
2	Basic Degradation	612.18	447.88	73.16	26.84
3	H_2O_2 Degradation	612.18	411.24	67.18	32.82
4	Neutral	612.18	600.95	98.17	1.83
5	Photolytic	612.18	606.89	99.14	0.86



Acidic Degradation 0.1N HCL (2 Hr)

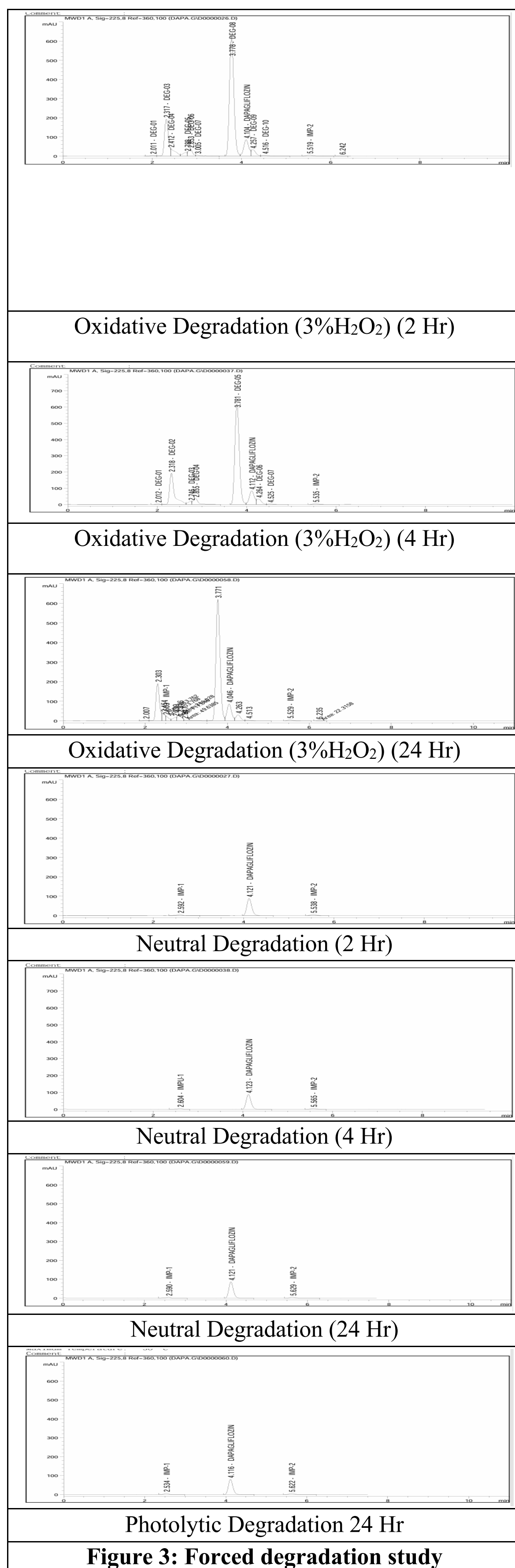
Acidic Degradation 0.1N HCL (4 Hr)

Acidic Degradation 0.1N HCL (24 Hr)

Alkaline Degradation 0.1N NaOH (2 Hr)

Alkaline Degradation 0.1N NaOH (4 Hr)

Alkaline Degradation 0.1N NaOH (24 Hr)



Oxidative Degradation (3%H_2O_2) (2 Hr)

Oxidative Degradation (3%H_2O_2) (4 Hr)

Oxidative Degradation (3%H_2O_2) (24 Hr)

Neutral Degradation (2 Hr)

Neutral Degradation (4 Hr)

Neutral Degradation (24 Hr)

Photolytic Degradation 24 Hr

Figure 3: Forced degradation study

Linearity and Range

Table 6: Linearity Parameters for DAPA

Compound	Linearity Range (µg/mL)	Correlation Coefficient (R^2)	Slope	Y-Intercept
DAPA	5.00-25.00	0.9993	42.578	15.806

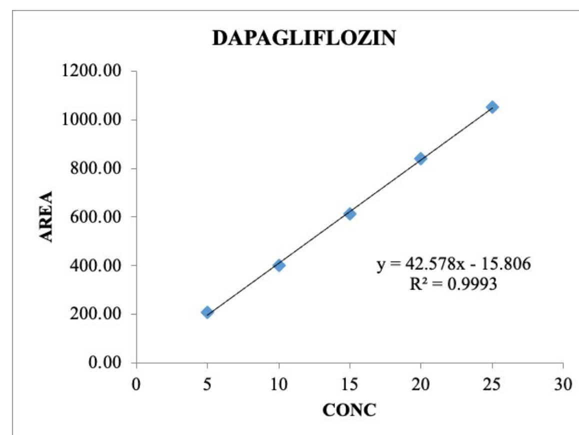


Figure 4: Linearity assessment of DAPA

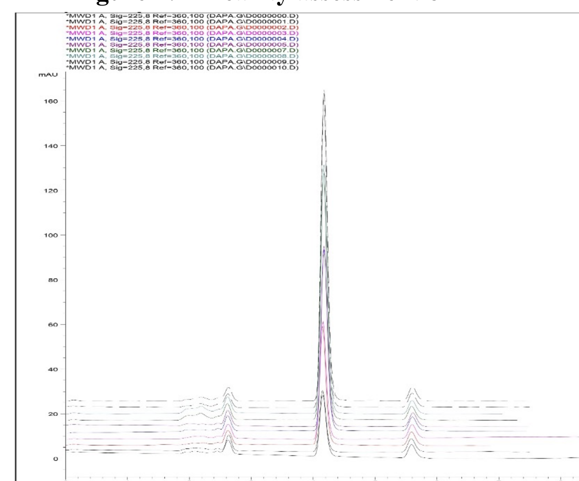


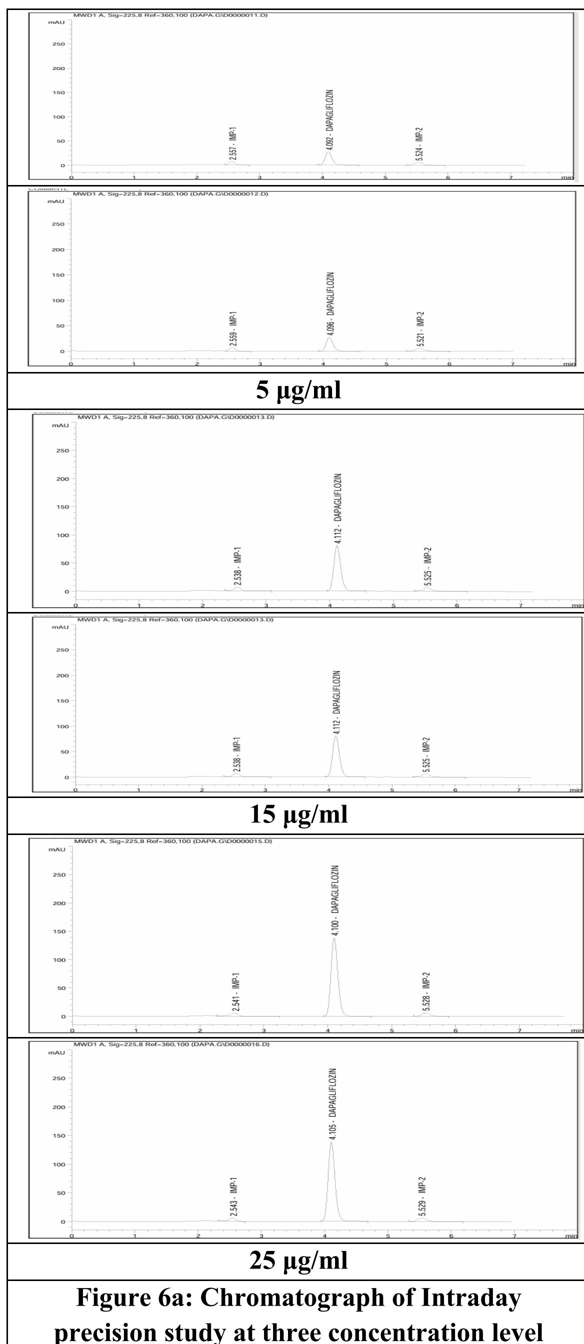
Figure 5: Typical overlay chromatogram of linearity

Precision

Table 7.i: Intra-day precision

Sample	Conc. (µg/ml)	Peak Area 1	Peak Area 2	Mean	SD	%RSD
DAPA	5	201.3791	200.906	201.3791	0.33	0.17
	15	624.3381	626.8038	624.3381	1.74	0.28
	25	1065.1021	1066.4648	1065.1021	0.96	0.09
IMP-1	10	41.84122	41.32074	41.58	0.37	0.89

	10	46.976	46.0198	46.50	0.68	1.45
	10	47.9057	48.98217	48.44	0.76	1.57
IMP-2	10	54.68895	54.97577	54.83	0.20	0.37
	10	59.04468	58.7543	58.90	0.21	0.35
	10	56.08571	57.13139	56.61	0.74	1.31



5 µg/ml

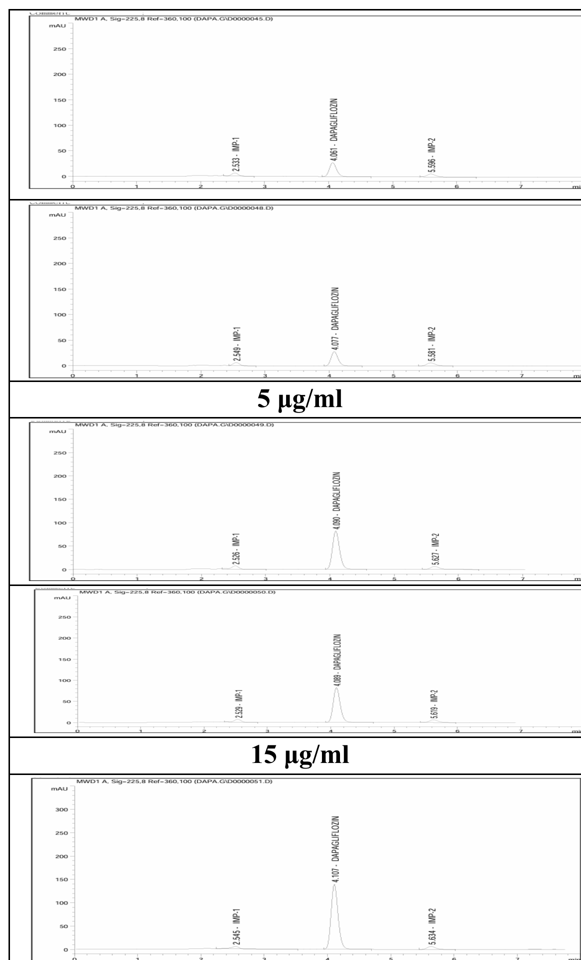
15 µg/ml

25 µg/ml

Figure 6a: Chromatograph of Intraday precision study at three concentration level

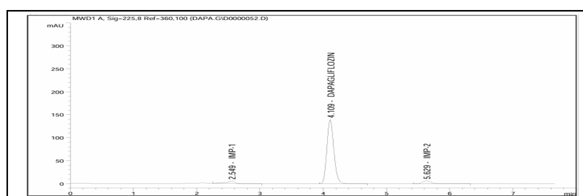
Table 7.ii: Inter-day precision

Conc. (µg/mL)	Conc. (µg/mL)	Peak Area 1	Peak Area 2	Mean	SD	%RSD
DAPA	5	200.1999	201.4693	200.83	0.90	0.45
	15	613.841	613.1881	613.51	0.46	0.08
	25	1051.1477	1052.9261	1052.04	1.26	0.12
IMP-1	10	39.16767	38.95107	39.06	0.15	0.39
	10	52.14208	53.35846	52.75	0.86	1.63
	10	43.53972	44.63898	44.09	0.78	1.76
IMP-2	10	52.50472	53.9073	53.21	0.99	1.86
	10	57.43845	59.01778	58.23	1.12	1.92
	10	57.7387	57.71685	57.73	0.02	0.03



5 µg/ml

15 µg/ml

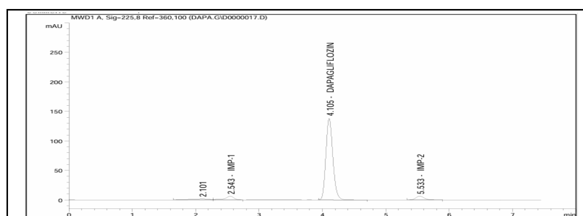


25 µg/ml

Figure 6b: Chromatograph of Interday precision study at three concentration level

Table 7.iii: Repeatability study

Sample	Conc. (µg/ml)	Peak Area 1	Peak Area 2	Mean Peak Area	SD	%RSD
DAPA	25	1051.955	1051.249	1051.60	0.50	0.05
IMP-1	10	60.86117	59.66668	60.26	0.84	1.40
IMP-2	10	55.82856	56.54564	56.19	0.51	0.90



25 µg/ml

Figure6c: Chromatograph of Repeatability study

Accuracy

Table 8.i: Recovery results of IMP-1

Level (%)	% Recovery	Mean % Recovery	SD	% RSD
80	98.2	99.9	1.81	1.81
	101.8			
	99.7			
100	100.3	100.7	1.44	1.43
	99.5			
	102.3			
120	101	101.4	1.83	1.81
	99.8			
	103.4			

Table 8.ii: Recovery results of IMP-2

Level (%)	% Recovery	Mean % Recovery	SD	% RSD
80	98.2	99.83	1.82	1.83
	99.5			
	101.8			
100	99.7	101.12	1.45	1.43
	101.2			
	102.6			
120	99.2	100.9	1.81	1.79

Conclusion:

A novel, simple, precise, accurate, robust, and stability-indicating RP-HPLC method has been successfully developed and validated for the estimation of DAPA in the presence of its related impurities, IMP-1 and IMP-2, in tablet dosage forms. The method demonstrated excellent specificity, linearity, accuracy, precision, and robustness in accordance with ICH guidelines.

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