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STABILITY INDICATING RP-UPLC-DAD METHOD FOR DETERMINATION OF METFORMIN AND CANAGLIFLOZIN IN BULK AND TABLET DOSAGE FORM

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Keywords:

Forced degradation, Metformin, Canagliflozin, RP-UPLC, Stability – indicating and Validation

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ABSTRACT: The objective of the present work is to develop and validate a novel stability-indicating RP-UPLC-DAD method for the simultaneous analysis of Metformin and Canagliflozin in bulk and tablet dosage form. The chromatographic separation was accomplished on a Waters UPLC system equipped with autosampler and PDA detector. A volume of 5 µL of sample or standard was injected into the column and the analytes were separated by using the mobile phase containing mixture of 0.1% orthophosphoric acid buffer (pH adjusted to 3.0 with 0.1 N NaOH) and acetonitrile in the ratio 30:70% v/v at a flow rate of 0.25ml/min through C18 BEH (Ethylene Bridged Hybrid) UPLC (100 mm × 2.1 mm 1.7 µm) at 55 °C column temperature and the detector wavelength was set at 260 nm. Peak area and retention time of Metformin and Canagliflozin were found to be 651341 & 332544, 0.994 & 1.508 respectively. Regression analysis shows r value greater than 0.999 for Metformin and Canagliflozin. Percent recovery of Metformin and Canagliflozin was found to be 99.94 %-100.16% & 100.17%-100.68%, respectively. The developed RP-UPLC method was validated with regard to system suitability, linearity, robustness, accuracy, precision, LOD, LOQ and forced degradation studies.

INTRODUCTION: Worldwide most of the patients with type 2 diabetes mellitus are commonly accomplished with singular-agent therapy, generally metformin. It is good and most commonly used antihyperglycemic agent which enhances the glucose margin in type 2 diabetes patients, lowering both basal plasma glucose and postprandial [1]. Metformin lowers abdominal absorption of glucose and reduces hepatic glucose output and enhances the insulin productivity by increasing peripheral glucose more.

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Metformin is a white crystalline compound with a Molecular formula $C_4H_{11}N_5$.HCl and molecular weight 165.62 **Fig. 1**.

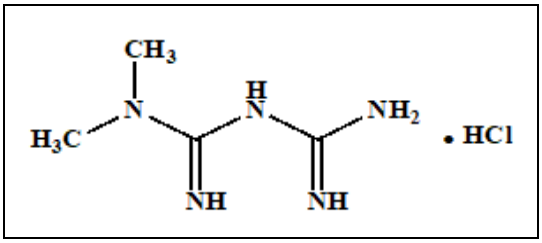

FIG. 1: CHEMICAL STRUCTURE OF METFORMIN

Canagliflozin is an inhibitor of SGLT2. SGLT2 is present in the proximal renal tubule especially in the kidney cortex, exactly in the S1 segment of the proximal tubule where it reuptakes the majority of glucose filtered by the glomerulus. Canagliflozin primarily transports glucose and sodium (Na) in a 1:1 ratio and it works as a low-attraction high-

capability transporter. Quelling of SGLT2 results in enhanced urinary glucose excretion (UGE) due to reduced glucose reabsorption. Canagliflozin is a white to off-white powder, normally insoluble in water and freely soluble in acetonitrile, methanol and it is non-hygroscopic. The chemical name of canagliflozin is, (1S)-1, 5-anhydro-1-[3-[[5-(4-fluorophenyl)-2-thienyl]-methyl]-4-methylphenyl]-D-glucitol hemihydrates [2-5] **Fig. 2.**

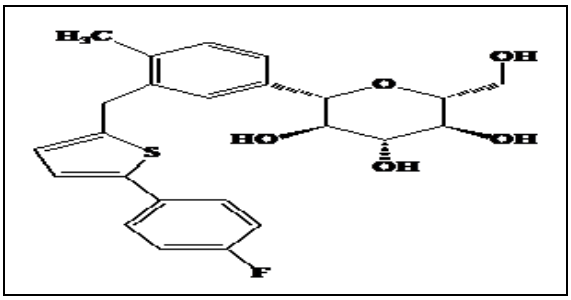

FIG. 2: CHEMICAL STRUCTURE OF CANAGLIFLOZIN

Literature survey reveals that canagliflozin is estimated by UV spectrophotometric method [6], human plasma by RP-HPLC [7], HPLC method [8], rat plasma by LC-MS/MS [9], HPTLC [10] and few chromatographic methods are available for the simultaneous determination of Metformin and Canagliflozin in tablet dosage form by using RP-HPLC [11-19].

The analysis of two drugs using GC/MS, LCMS and LC-MS/MS were very expensive and very delicate methods as compared to UPLC for general quality control analysis. Because of this purpose, we need to use this advanced technique (UPLC) for estimation of stability studies of these drugs by using the RP-UPLC method.

MATERIALS AND METHODS:

Chemicals and Reagents: Qualified Canagliflozin standard was kindly obtained from Manus akkteva (Ahmadabad, Gujarat, India) and Metformin was obtained from Aurobindo pharmaceuticals Ltd. (Hyderabad, India). Invokamet (Canagliflozin -50 mg and Metformin-500 mg film-coated tablets) (USA) were purchased from local market. Orthophosphoric acid (AR grade) purchased from Merck (Darmstadit, Germany). Acetonitrile (HPLC grade) was obtained from JVR fine chemicals Ltd (Hyderabad, India). Milli-Q ® type 1 ultrapure water system (Sartorius, Germany), vacuum pump, purchased from PCI Analytics Pvt., Ltd (Mumbai, India) were also used.

Instrumentation and Chromatographic Conditions: The UPLC waters system was used for the method development and method validation. It consists of a binary solvent manager with connected with photodiode array detector (MA, USA) controlled with Empower software and auto sampler and auto-injector. C18 BEH UPLC (100 mm × 2.1 mm 1.7 µm) column from waters was used. Photostability studies were performed in photo stability chamber (Osworld Scientific Equipment Pvt. Ltd, Mumbai, India). Thermal stability studies were carried out in a dry air oven (Newtronic lifecare, Mumbai, India). The mobile phase consists of mixture of 0.1% orthophosphoric acid buffer and acetonitrile in the ratio of 30:70% v/v at a flow rate of 0.25 ml/min. The column temperature was maintained at 55 °C with detection wavelength of 260 nm and it maintained at 35 °C with an injection volume of 5 µl.

Preparation of Solutions:

Preparation of Mobile Phase: 0.1% orthophosphoric acid buffer solution was prepared by taking 1 ml of orthophosphoric acid in a 1000 ml volumetric flask, dissolved in water, made up to the mark after adjusting the pH of solution equal to pH = 3.0 with 0.1 N NaOH solution. Then, the resulting solution was filtered through 0.45 µ filter under vacuum filtration. A mixture of buffer and acetonitrile in the ratio 30:70% v/v was degassed in an ultrasonic water bath for 5 min allowed to cool at room temperature and then filtered through 0.45 µ filter under vacuum filtration. This prepared mobile phase was used as diluent.

Preparation of Standard Solution: Accurately weighed 100 mg of Metformin and 10 mg of Canagliflozin working standard was taken into a 10 ml clean dry volumetric flask, added about 7 ml of diluent and sonicated to dissolve it totally and made volume up to the mark with the same solvent (Stock solution). After that, pipetted 0.3 ml of the above stock solutions into a 10 ml volumetric flask and dilute up to the mark with diluent.

Preparation of Sample Solution: Accurately weighed 100 mg of Metformin and 10 mg of Canagliflozin working standard was transferred into a 10 ml clean dry volumetric flask, and about 7 ml of diluent was added and sonicated to dissolve completely and make volume up to the mark with

the same solvent. After that 0.3 ml of the above stock solution was pipetted into a 10 ml volumetric flask and diluted up to the mark with diluent.

Method Validation: The developed method was validated as per ICH guidelines for its specificity, system suitability, linearity, accuracy, precision, LOQ, LOD, and robustness by using the following procedures [20-21].

System Suitability: A system suitability test was defined based on the analytical results obtained in various representative chromatograms. The concentration of the standard solution was found to be 300 µg/mL for Metformin and 30 µg/mL for Canagliflozin respectively. The column efficiency resolute from the sample peak >20,000, the tailing factor <5.0% and resolution between peaks of two drugs should be >1.5.

Precision: Precision was evaluated by studying the repeatability and intermediate precision. The precision of each level was determined by three replicate of concentrations (25, 50, and 75µg/mL) of Metformin and (5, 10, and 15 µg/mL) of Canagliflozin respectively.

Accuracy: The accuracy of the assay method was evaluated in triplicate by a recovery experiment using three different levels (50, 100, and 150% of the normal assay concentration). The standard solutions of Metformin (120, 240 and 360 µg/mL) and Canagliflozin (4.0, 8.0 and 12.0 µg/mL) were injected in triplicate (n=3) into UPLC system.

Linearity: Calibration curve of Metformin and Canagliflozin solutions was constructed by plotting peak area *vs*. concentration. The least-square regression equation was applied, and the calibration curve was plotted over the concentration range of 100-500 µg/mL for Metformin and 10-50 µg/mL for Canagliflozin.

Limit of Quantitation (LOQ) and Limit of Detection (LOD): The quantitation limit of an analytical procedure is the lowest amount of analyte in a sample, which can be quantitatively determined with suitable precision and accuracy. The detection limit of an individual analytical procedure is the lowest amount of analyte in a sample, which can be detected but not necessarily quantitated as an exact value.

Robustness: To determine the robustness of the method, system suitability parameters were verified by making deliberate changes in the chromate-graphic conditions, *viz*., changing flow rate by ± 0.04 mL/min, column temperature (± 5 °C) and changing the organic phase in the mobile phase from 100% to 90% and 110% during the development stage itself using 4 µg/mL of Metformin and 24 µg/mL of Canagliflozin solutions respectively.

Degradation Study: The forced degradation studies were performed to establish the stability-indicating nature of the assay method and to observe any degraded compounds [21]. In this study, Metformin and Canagliflozin were exposed to different chemical and physical conditions such as 0.1 N HCl (acid hydrolysis), 0.1 N NaOH (base hydrolysis), 30% H_2O_2 (oxidation), heat (thermal decay) and UV-light (radiation decay) for specified time then diluted similar as standard stock solution and chromatograms were obtained. The percentage of degradation of compounds were calculated from the peak area of the chromatograms. In the study of base or acid hydrolysis, an amount of fine powdered sample equivalent to 100 mg Metformin and 10 mg of Canagliflozin was transferred into 10 ml of volumetric flask and added 3 ml of freshly prepared 0.1 N NaOH or 0.1N HCl shaken well and allowed for 12 h at a temperature of 60 °C. Then the solution was filtered through 0.45µ filter into 10 ml standard flasks and neutralized the unreacted acid or base with 0.1 N HCl or 0.1N NaOH and was made up to the mark. In case of peroxide degradation same amount of sample was transferred into a 10 ml volumetric flask, added 3 ml of freshly prepared 30% H_2O_2 and kept at 75 °C for 24 h and filtered the solution through 0.45µ filter and made up to the mark. In the study of thermal degradation same amount of sample was transferred into clean and dry watch glass, placed in an oven over a period of 24 h at 110 °C. In case of photodegradation same amount of sample was exposed to UV light of 254 nm for 10 days.

RESULTS AND DISCUSSION:

Method Development and Optimization of Chromatographic Conditions:

Wavelength Selection: The standard Metformin and Canagliflozin solutions were scanned in UV spectrophotometer, and isoabsorptive wavelength

was found at 260 nm. Hence, a wavelength at 260 nm is selected for the method development purpose and it is shown in **Fig. 3**.

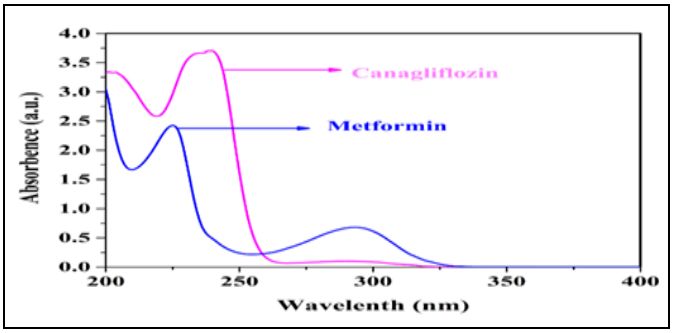

FIG. 3: UV SPECTRA OF CANAGLIFLOZIN AND METFORMIN

Optimized Method: After trying different columns like, cyano, PFP, C8 the final chance of the stationary phase that gave a good resolution and eluting all peaks with better separation was reverse phase C18 BEH UPLC (100mm × 2.1mm, 1.7µm particle size) column, this column was only showing elution time less than 2 min. Compare to methanol; acetonitrile was showing good separations and less column backpressure. In acidic conditions, drugs were showing good peak shape. Finally, the best results were obtained by use of mixture of 0.1% orthophosphoric acid buffer (pH adjusted to 3.0 with 0.1 N NaOH) and acetonitrile in the ratio 30:70% v/v at a flow rate of 0.25ml/min through C18 BEH UPLC (100mm × 2.1mm, 1.7µm) at 55 °C column temperature and the detector wavelength was set at 260 nm. Optimized UPLC chromatogram of Metformin and Canagliflozin was shown in **Fig. 4** and optimized chromatographic conditions are finalized in **Table 1**.

TABLE 1: OPTIMIZED CHROMATOGRAPHIC CONDITIONS

Optimized chromatographic conditions	
Column	BEH UPLC C_{18} (100 × 2.1mm × 1.7µm)
Mobile phase	0.1% orthophosphoric acid buffer and acetonitrile in the ratio 30:70% (v/v)
UPLC program	Isocratic
Flow rate	0.25mL/min
Wavelength of detection	260 nm
Column temperature	35°C
Injection volume	5 µL
Diluent	Mobile phase
Retention time	1.017 min (Metformin) 1.556 min (Canagliflozin)

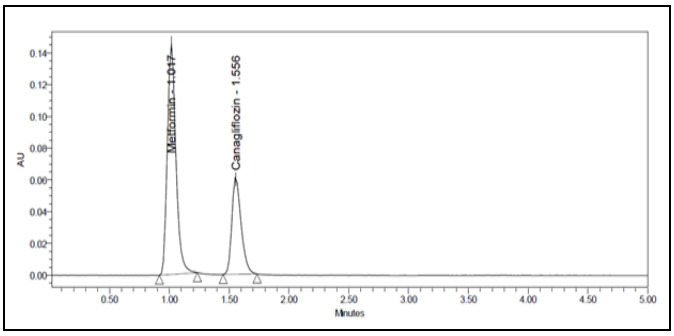

FIG. 4: OPTIMIZED UPLC CHROMATOGRAM OF METFORMIN AND CANAGLIFLOZIN

Method Validation:

System Suitability: The concentration of the standard solution was found to be 300 µg/mL for Metformin and 30 µg/mL for Canagliflozin, respectively. The column efficiency resolute from the sample peak >20,000, the tailing factor <5.0% and resolution between peaks of two drugs should be >1.5. The results of system suitability were expressed in **Table 2.**

TABLE 2: SYSTEM SUITABILITY PARAMETERS

Name	Peak area (µV* sec)	Theoretical plate (N)	Tailing factor (T_f)	Retention Time	Resolution
Metformin	651341	3871.59	1.26	0.994	3.67
Canagliflozin	332544	3711.90	1.30	1.508	

Precision: All the samples exhibited RSD values < 2% confirming that the analytical method was precise. The results of precision were expressed in **Table 3**.

TABLE 3: PRECISION STUDIES OF METFORMIN AND CANAGLIFLOZIN

Name of drug	Amount applied(µg/mL)	Repeatability (Mean peak area ±SD) n=3	% RSD	Intermediate precision (Mean peak area ±SD) n=3	% RSD
Metformin	25	659181 ± 3993.20	0.605	661892 ± 3696.75	0.569
	50	661942 ± 3696.75	0.547	661892 ± 3626.04	0.547
	75	661992 ± 3484.62	0.526	662042 ± 3555.33	0.537
Canagliflozin	5	334705 ± 3837.46	1.146	334752 ± 4044.65	1.208
	10	334741 ± 3887.67	1.161	334742 ± 3903.22	1.160
	15	334842 ± 3973.94	1.186	334445.3 ± 3123.3	0.933

Accuracy: The acceptable percentage recovery of Metformin and Canagliflozin in bulk and pharmaceutical dosage form ranges from 99.94%-100.16% and 100.17%-100.68%, respectively. The results are tabulated in **Table 4.**

TABLE 4: PERCENTAGE RECOVERY OF METFORMIN AND CANAGLIFLOZIN

Name of drug	Spiked level (%)	Amount added	Amount recovered	% Recovery	% RSD
Metformin	50	48.51	49.08	100.16	0.61
	100	98.5	99.02	100.09	0.42
	150	147.1	148.32	99.94	0.65
Canagliflozin	80	4.62	4.95	100.58	0.62
	100	9.82	9.94	100.68	0.45
	120	14.24	14.56	100.17	0.24

Linearity: The least square regression equation was applied, and the calibration curve was plotted over the concentration range of 100-500 µg/ml for Metformin and 10-50 µg/ml for Canagliflozin. The linear regression equations for Metformin and Canagliflozin were y = 2341.5x –13257 and y = 12416x – 9952.6 with correlation coefficient (r) being 0.999 for Metformin and Canagliflozin. The results of linearity were shown in **Table 5.** The linearity graphs were shown in **Fig. 5** and **6.**

TABLE 5: LINEARITY DATA OF METFORMIN AND CANAGLIFLOZIN

S. no.	Metformin Conc. (µg/mL)	Peak area (µV* sec)	Canagliflozin Conc. (µg/mL)	Peak area (µV* sec)
1	0	0	0	0
2	100	209137	10	109847
3	200	449696	20	229695
4	300	683462	30	356543
5	400	931615	40	492390
6	500	1158818	50	614238
Slope	2341.5		12416	
Y-intercept	13257		9952.6	
Correlation coefficient	0.999		0.999	

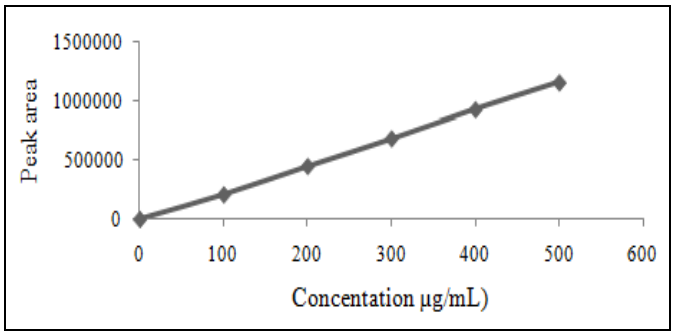

FIG. 5: CALIBRATION CURVE OF METFORMIN

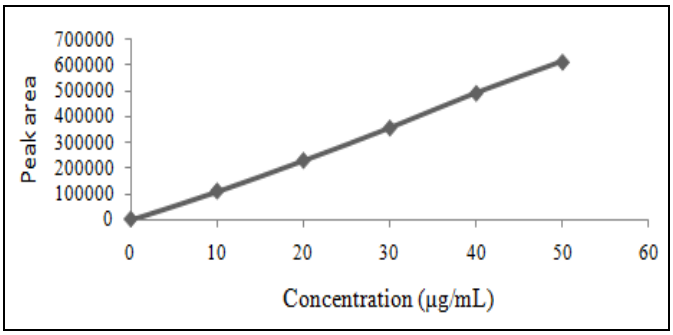

FIG. 6: CALIBRATION CURVE OF CANAGLIFLOZIN

Limit of Quantitation (LOQ): The quantification limit of Metformin and Canagliflozin was found to be 1.536 µg/mL and 1.962 µg/mL.

Limit of Detection (LOD): The detection limit of Metformin and Canagliflozin was found to be 0.612 µg/Ml and 0.458 µg/mL. The low value of LOQ and LOD indicates the high sensitivity of the method.

Robustness: The analysis of Metformin and Canagliflozin was carried out at different conditions of flow rate by ±0.04 mL/min, column temperature (±5 °C) and change in composition of the mobile phase. Robustness was expressed by % RSD values of Metformin and Empagliflozin peak areas as quantitative responses. All values were found to be less than 2%, indicating the robustness of the method. The results are shown in **Table 6**.

Degradation Studies: The drug substances were exposed to 0.1N HCl at 60 °C for 12 h. The drugs gradually underwent degradation with time and got degraded. No degradation took place over 12 h in basic conditions.

The drug substances were not degraded by oxidative conditions. The drug substances were subjected to thermal degradation at 110 °C for 24 h and no degradation was observed. The drug substances were stable on the effect of photolysis. Drugs did not undergo any degradation with time. The results of forced degradation studies are given in **Table 7,** and chromatograms were shown in **Fig. 7-11.**

TABLE 6: ROBUSTNESS OF METFORMIN AND CANAGLIFLOZIN

S. no.	Metformin peak area ± SD	%RSD	Theoretical plates	Canagliflozin peak area ± SD	% RSD	Theoretical plates
Flow rate (mL/min)						
0.80	651974 ± 895.1	0.13	3762.62	331689 ± 1209.1	0.36	361.80
1.00	652474 ± 1602.3	0.24	3785.12	331189 ± 502.0	0.15	3618.05
Mobile phase composition (v/v/v)						
40:60	654474 ± 1226.1	0.18	3761.24	333389 ± 2043.5	0.61	3625.52
30:70	654874 ± 1367.5	0.28	3808.12	333889 ± 2750.6	0.82	3705.50
Column temperature						
50 °C	654624 ± 1013.9	0.15	3901.46	334889 ± 1336.4	0.39	3874.84
55 °C	653874 ± 2781.7	0.42	3912.74	335389 ± 2043.5	0.60	3625.88

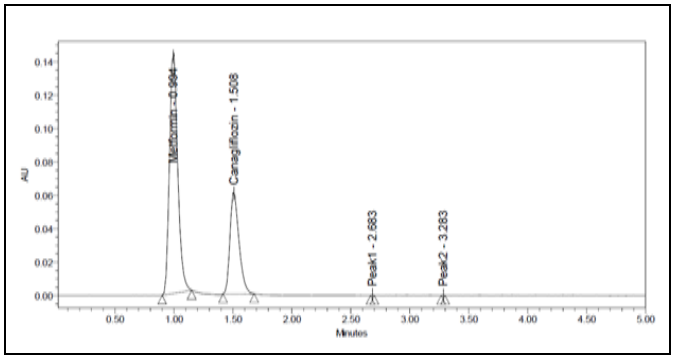

FIG. 7: TYPICAL UPLC CHROMATOGRAM OF ACID DEGRADATION

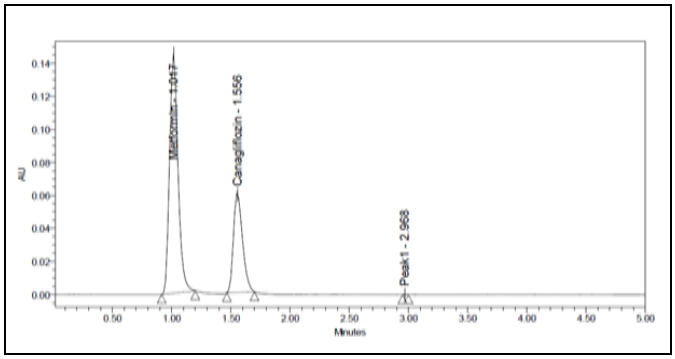

FIG. 8: TYPICAL UPLC CHROMATOGRAM OF BASE DEGRADATION

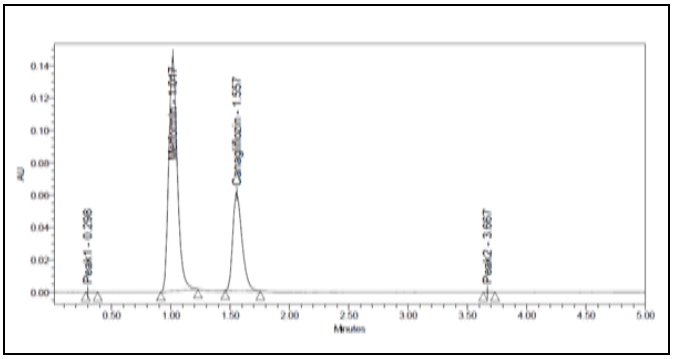

FIG. 9: TYPICAL UPLC CHROMATOGRAM OF OXIDATIVE DEGRADATION

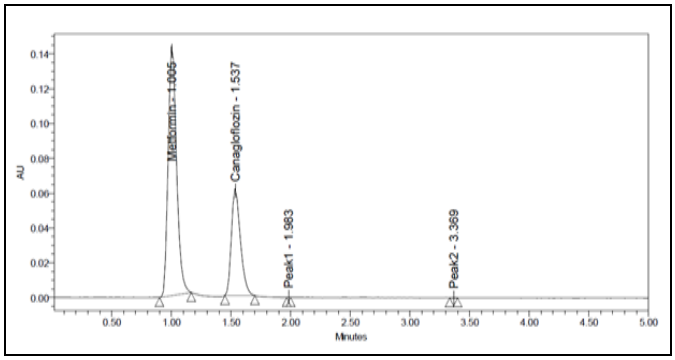

FIG. 10: TYPICAL UPLC CHROMATOGRAM OF THERMAL DEGRADATION

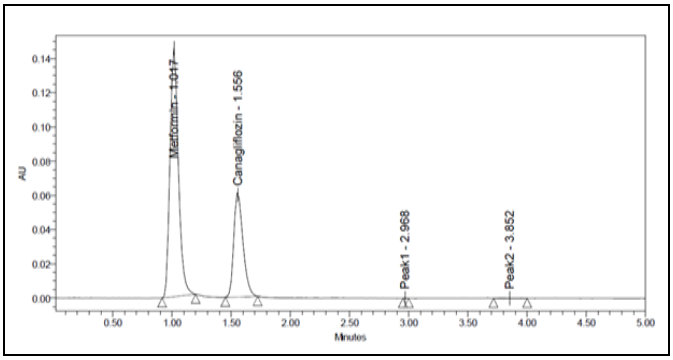

FIG. 11: TYPICAL HPLC CHROMATOGRAM OF PHOTO DEGRADATION

TABLE 7: DEGRADATION STUDIES OF METFORMIN AND CANAGLIFLOZIN

Type of degradation	Metformin Peak area	% Recovery	% Degraded	Canagliflozin Peak area	% Recovery	% Degraded
Acid	622195	91.45	8.55	305160	91.94	8.06
Base	612185	94.04	5.96	318326	95.90	4.10
Peroxide	624049	95.86	4.14	309199	93.15	6.85
Thermal	628411	96.53	3.47	319758	96.34	3.66
Photo	612185	94.04	5.96	318326	95.90	4.10

CONCLUSION: A new RP-UPLC method was developed and validated for the determination of Metformin and Canagliflozin in bulk and tablet dosage form. The developed method was simple, accurate, precise, and satisfactory results were obtained through the analytical method validation data.

The current method can be easily applied for routine drug analysis in the pharmaceutical industry and laboratories. Forced degradation studies were performed to assess the stability of the compound and prove the stability-indicating nature of the developed chromatographic method. The method was validated as per ICH guidelines.

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CONFLICTS OF INTEREST: The authors did not report any conflict of interest

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