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REVERSE PHASE HIGH-PERFORMANCE LIQUID CHROMATOGRAPHIC METHOD FOR SEPARATION AND ESTIMATION OF IMPURITIES PRESENT IN PHARMACEUTICAL FORMULATION OF CANAGLIFOZIN

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Keywords:

Canagliflozin, SGLT-2 inhibitor, Method development, Method validation, Stress condition, Impurities, ICH Q2(R1)

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ABSTRACT: Canagliflozin is sodium-glucose co-transporter-2 inhibitors work by inhibiting SGLT2 to prevent reabsorption of glucose and facilitate its excretion in urine. Impurities in pharmaceuticals which are unwanted chemicals that remain with the active pharmaceutical ingredients (APIs), or develop during stability testing, or develop during formulation or upon aging of both API and formulation. The presence of these unwanted chemicals, even in small amounts, may influence the efficacy and safety of the pharmaceutical products. A simple and very sensitive method developed for estimation of impurities present in Canaglifozin formulation by Reverse Phase High Performance Liquid Chromatographic method. A method is capable to detect impurities at very low level (0.1 µm/mL). Chromatographic separation of six different impurities was achieved on inertsil C8-3 (250 × 4.6) mm, 3 µm column using gradient elution method.

INTRODUCTION: Canagliflozin is a sodium-glucose co-transporter-2 inhibitor work by inhibiting SGLT2 in the PCT, to prevent reabsorption of glucose and facilitate its excretion in urine. As glucose is excreted, its plasma levels fall, leading to an improvement in all glycemic parameters. This mechanism of action is dependent on blood glucose levels and, unlike the actions of thiazolidinediones (mediated through GLUTs), is independent of the actions of insulin. Thus, there is minimal potential for hypoglycemia and no risk of overstimulation or fatigue of the beta cells. Because their mode of action relies upon normal renal glomerular-tubular function, SGLT2i efficacy is reduced in persons with renal impairment. Due to lots of advantages of canagliflozin, it is necessary to estimate related impurities present in this drug. So present investigation involves the development of RP-HPLC related substances method for pharmaceutical dosage form for canagliflozin. Possibly six impurities identified base on API source, so the separation was done on this impurities and validated developed method.

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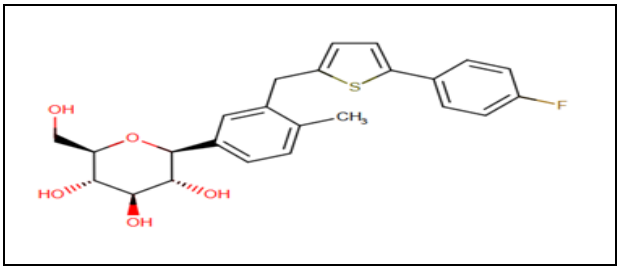


FIG. 1: CHEMICAL STRUCTURE OF CANAGLIFOZIN

TABLE 1: DETAILS OF IMPURITY-I TO III:

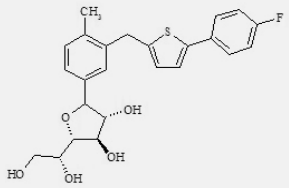
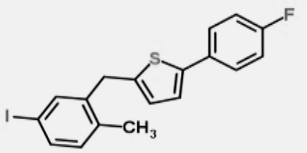
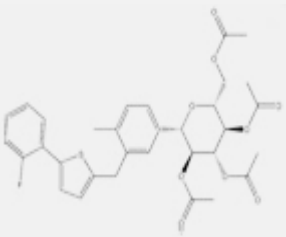
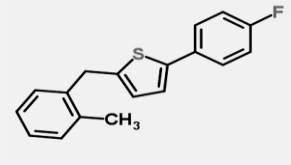
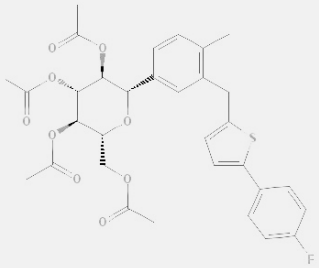
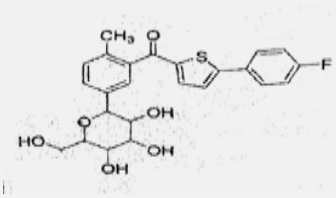
Impurity Name	Impurity-I	Impurity-II	Impurity-III
Chemical structure			
Chemical formula	$C_{24}H_{25}FO_5S$	$C_{18}H_{14}FIS$	$C_{32}H_{33}FO_9S$
Chemical name	(3R, 4R)-2-((S)-1, 2 dihyd roxyethyl)-5-(3-((5-(4-flurophenyl)thiopen-2-yl)methyl)-4-methyl phenyl) tetrahydrofuran-3, 4-diol	2-(4-flurophenyl)-5-(5-iodo-2-methyl benzyl) thiophene	(2R, 3R, 4R, 5S, 6S)-2-(acetoxymethyl)-6-(3-((5-(4-flurophenyl) thiopen-2-yl)methyl)-4-methyl phenyl) tetrahydro-2H-pyran-3, 4, 5-triyl triacetate
Molecular Weight	444.53 g/mol	408.27 g/mol	612.64 g/mol

TABLE 2: DETAILS OF IMPURITY-IV TO VI

Impurity Name	Impurity-IV	Impurity-V	Impurity-VI
Chemical structure			
Chemical formula	$C_{18}H_{14}FS$	$C_{32}H_{33}FO_9S$	$C_{23}H_{35}FO_6S$
Chemical name	2-(4-flurophenyl)-5-(2-methyl benzyl) thiophene	(2R, 3R, 4R, 5S, 6S)-2-(acetoxymethyl)-6-(3-((5-(4-flurophenyl) thiopen-2-yl)methyl)-2-methy lphenyl) tetrahydro-2H-pyran-3, 4, 5-triyl triacetate	{{5-{4-Flurophenyl) thiopen-2-yl) (5-(tetrahydro-3, 4, 5-trihy droxy-6-{hydroxymethyl } -2H-pyran-2-yl}-2-methylphenyl) methanone
Molecular Weight	355.27 g/mol	612.64 g/mol	458.0 g/mol

MATERIALS AND METHODS:

Reagents and Chemicals: Canagliflozin and its impurities were the generous gifts from MSN Laboratories PVT Ltd, India. HPLC grade Acetonitrile was procured from Merck. Orthophosphoric acid (H_3PO_4) was purchased from Merck. All other chemicals and solvents used were of analytical grade. Water used in the HPLC analysis was prepared by the water purifier (Merck Millipore Milli-Q). The mobile phase and all the solutions were filtered through a 0.45 µm Merck HV membrane filter. The sample was filtered through a 0.45 µm millipore PVDF syringe filter.

Instruments: HPLC system (waters system, USA, e 2695 and Agilint 1200 series) with a PDA detector equipped with a quaternary pump, autosampler, column compartment, and empower and chrome eon software was employed during this study.

Chromatographic Condition: Chromatographic separation was achieved at 30 °C column temperature, and the detection was carried at 290 nm at a flow rate of 1.0 mL/min. Run time was kept at 80 min. Prior to the injection of drug solution, the column was equilibrated for 60 min with the mobile phase flowing through the system. The injection volume was 15 µL. The analysis has been performed by using Inertsil C8-3 (250 × 4.6 mm, 3 u). The mobile phase a containing 1 mL orthophosphoric acid in 1000 mL of purified water, and mobile phase B contains acetonitrile using following gradient.

TABLE 3: GRADIENT PROGRAMME

Time (min)	% Mobile phase-A	% Mobile phase-B
0	55	45
5	55	45
15	45	55
45	10	90
70	10	90
75	55	45
80	55	45

Standard Preparation: The standard stock solutions 200 ug/ml of canagliflozin were prepared by dissolving working standards in diluents and diluting with the same solvent to obtain a final concentration of 4 µg/mL.

Sample Preparation: Twenty tablets were weighed and finely powdered. Powder equivalent to 50 mg Canaglifozin was accurately weighed into a 25 ml volumetric flask, 20 ml of diluent was added and sonicated for 15 min with intermittent shaking, made up to the volume with diluent and mixed. Filter the solution through a 0.45 µm Millipore PVDF syringe filter.

Method Validation: After method development, validation of the current test method for canagliflozin tablets was performed in accordance with united states pharmacopeia requirements / ICH guidelines for related substance method the parameter includes precision, accuracy, linearity, LOD and LOQ, precision and accuracy at LOQ level, selectivity, specificity includes blank, placebo, known impurity interference and interference of degradants by degradation study. Robustness was also performed.

Specificity: To assess the method specificity, tablet powder without canagliflozin was prepared with the same excipients as those in the commercial formulation. For RP-HPLC, the solution was prepared using the same procedure as for the analytical sample. Placebo solution was injected into the HPLC system following test conditions; the chromatogram was recorded, and the responses of the peaks, if any, measured. The chromatogram of the placebo has not shown any interference at the retention time of both canagliflozin and its impurities. Blank, placebo, and impurity spiked sample preparation and impurities mixture chromatogram shown in **Fig. 2-6.**

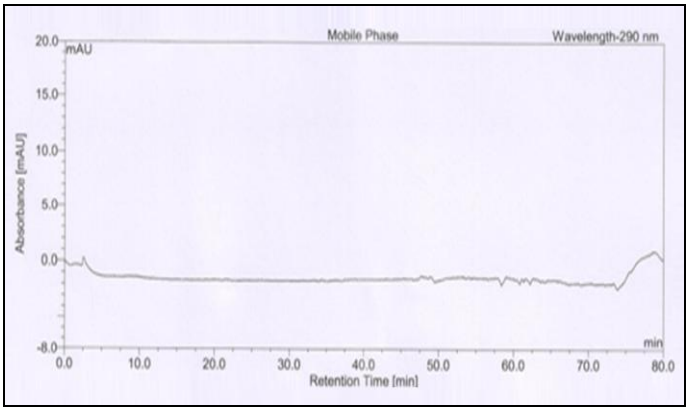


FIG. 2: CHROMATOGRAM OF DILUENT

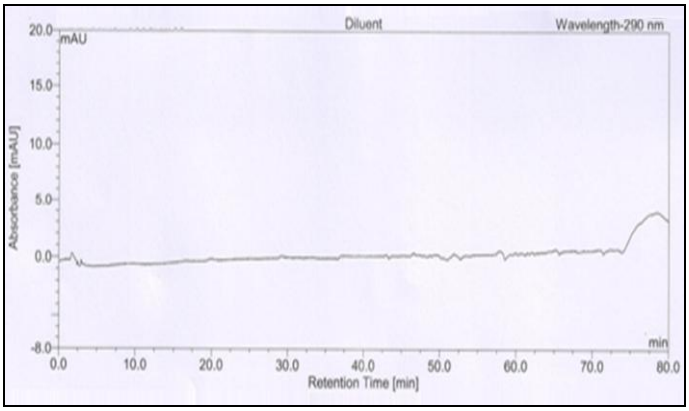


FIG. 3: CHROMATOGRAM OF PLACEBO

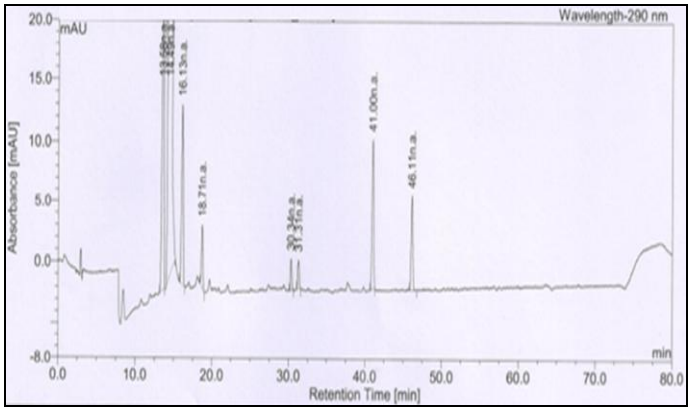


FIG. 4: CHROMATOGRAM OF IMPURITY SPIKED SAMPLE

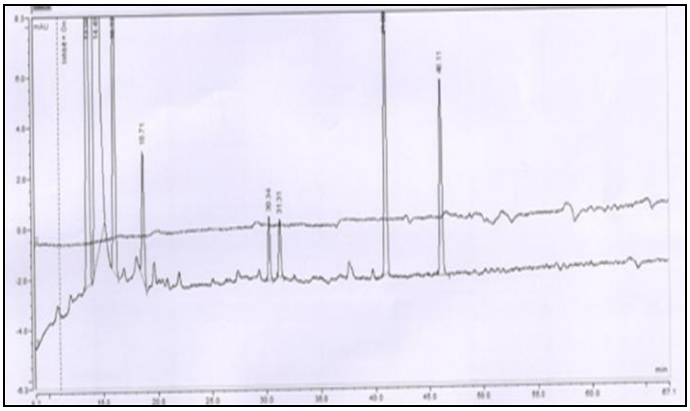


FIG. 5: CHROMATOGRAM OF OVERLAY OF DILUENT PLACEBO AND IMPURITY SPIKED SAMPLE

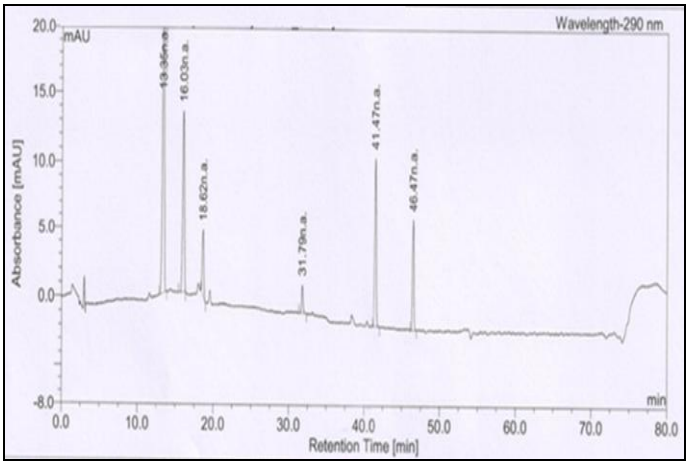


FIG. 6: CHROMATOGRAM OF IMPURITY MIXTURE SOLUTION

TABLE 4: SYSTEM SUITABILITY RESULT

Injection no	Peak area of canagliflozin	Theoretical plates	Tailing factor
1	66.511	29312	1.0
2	66.897	29874	1.0
3	65.234	29354	1.0
4	67.842	29541	1.0
5	66.325	29456	1.0
6	66.251	29328	1.0
Mean	66.510		
SD	0.9		
%RSD	1.3		

System Suitability: 15 µL of standard solution six times injected into HPLC and recorded the chromatogram; % RSD of canagliflozin, area was within the limit of 5.0%. The results summarized in **Table 4** and the standard solution chromatogram shown in **Fig. 7.**

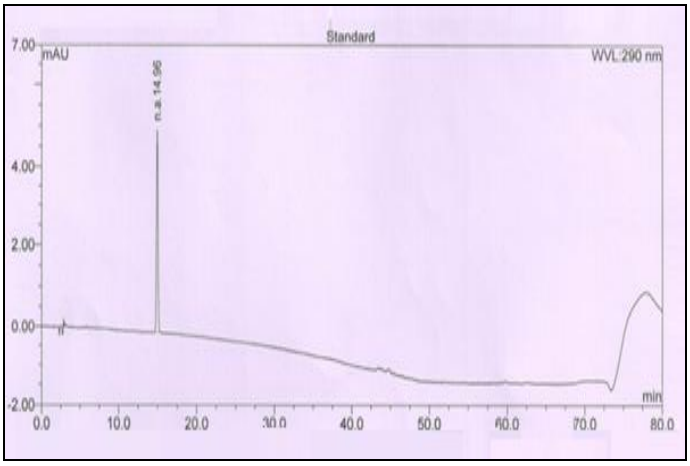


FIG. 7: CHROMATOGRAM OF STANDARD SOLUTION

Precision: Precision was measured in terms of repeatability of application and measurement. Repeatability of standard application (system precision).

Precision study of canagliflozin and its impurities were carried out by spiking known concentration in the sample and calculating % recovery of impurities in the sample. Intermediate precision carried out using the same manner but on another day using different columns and HPLC. The results summarized in **Tables 5** and **6.**

TABLE 5: METHOD PRECISION

	Method Precision							
S. no.	Impurity-1	Impurity-2	Impurity-3	Impurity-4	Impurity-5	Impurity-6	Single unk	Total Imp
1	0.64	0.48	0.63	0.50	0.58	0.46	0.00	3.29
2	0.62	0.49	0.64	0.52	0.59	0.48	0.00	3.34
3	0.62	0.48	0.63	0.51	0.56	0.46	0.00	3.26
4	0.62	0.47	0.63	0.51	0.60	0.47	0.00	3.30
5	0.62	0.48	0.63	0.50	0.61	0.45	0.00	3.29
6	0.63	0.47	0.65	0.51	0.61	0.46	0.00	3.33
Mean	0.63	0.48	0.64	0.51	0.59	0.46	0.00	3.30
SD	0.008	0.008	0.008	0.008	0.019	0.010	0.00	0.03
%RSD	1.3	1.6	1.3	1.5	3.3	2.2	0.0	0.9

TABLE 6: INTERMEDIATE PRECISION

S. no.	Impurity-1	Impurity-2	Impurity-3	Impurity-4	Impurity-5	Impurity-6	Single unk	Total Imp
1	0.50	0.52	0.61	0.55	0.49	0.60	0.00	3.27
2	0.50	0.52	0.61	0.54	0.50	0.62	0.00	3.29
3	0.51	0.51	0.61	0.55	0.49	0.61	0.00	3.28
4	0.49	0.53	0.62	0.52	0.50	0.60	0.00	3.26
5	0.50	0.52	0.61	0.55	0.49	0.60	0.00	3.27
6	0.50	0.51	0.61	0.55	0.49	0.60	0.00	3.26
Mean	0.50	0.52	0.61	0.54	0.47	0.61	0.00	3.27
SD	0.006	0.008	0.004	0.012	0.005	0.008	0.00	0.01
%RSD	1.3	1.5	0.7	2.2	1.1	1.4	0.0	0.4

Linearity: To evaluate the linearity of the method, six levels calibration curve made includes LOQ level. Signal to noise ratio was observed. The linearity of the method is obtained by the preparation of the calibration curve. The calibration curve for canagliflozin and its impurities were obtained by plotting the peak area of canagliflozin versus the concentration of canagliflozin over the range of 1-15 µg/ml. The results are summarized, and the overall linearity graph for canagliflozin and its impurities was shown in **Fig**.

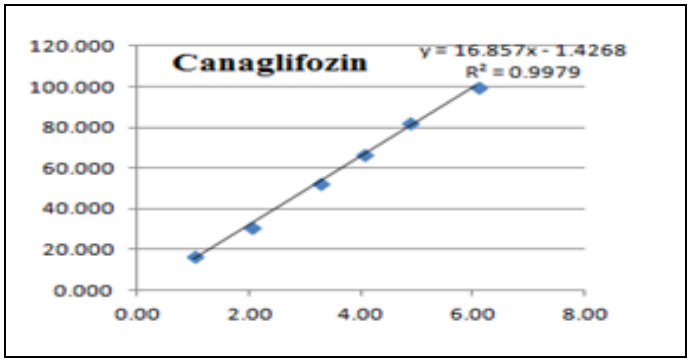


FIG. 8: LINEARITY CURVE OF CANAGLIFOZIN

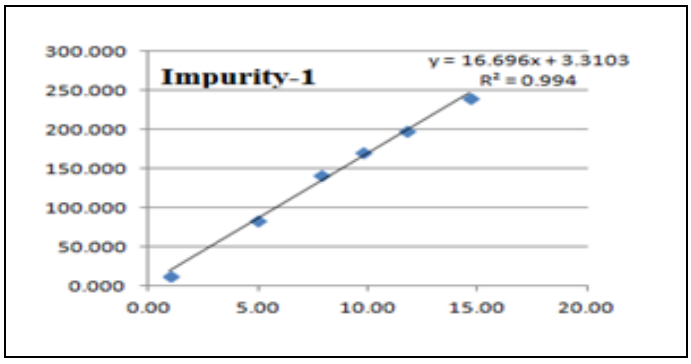


FIG. 9: LINEARITY CURVE OF IMPURITY-I

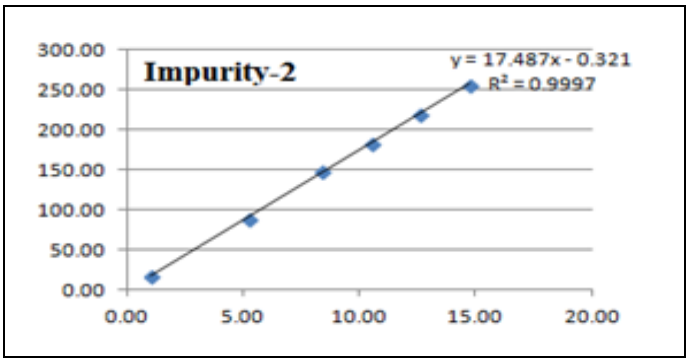


FIG. 10: LINEARITY CURVE OF IMPURITY-II

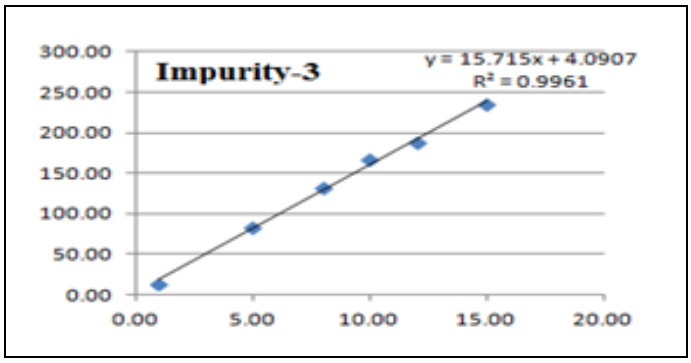


FIG. 11: LINEARITY CURVE OF IMPURITY-III

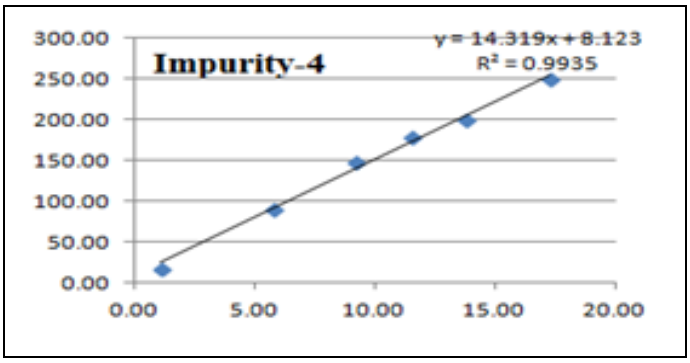


FIG. 12: LINEARITY CURVE OF IMPURITY-IV

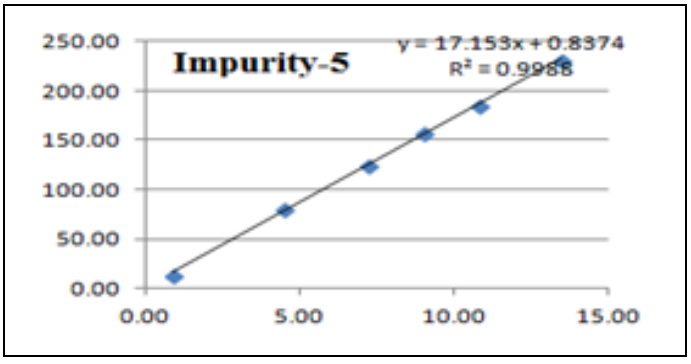


FIG.13: LINEARITY CURVE OF IMPURITY-V

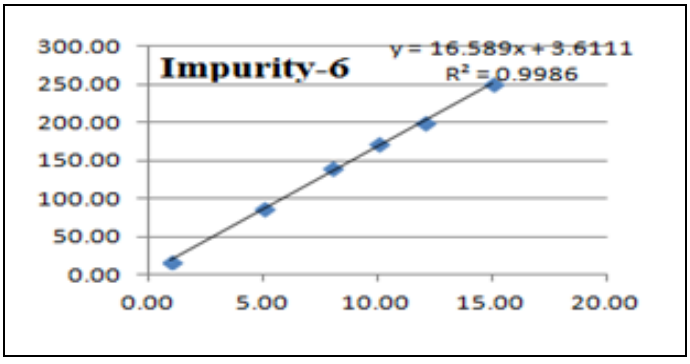


FIG. 14: LINEARITY CURVE OF IMPURITY-VI

Accuracy: Accuracy of the method was studied for three levels from 50% to 150% by spiking 0.05% for LOQ, and 0.25% for 50% level from the target concentration of canagliflozin impurities and 0.50%, 0.75% for 100%, 150% level from the target concentration of canagliflozin impurities spiked in sample preparation and analyzed with unspiked sample preparation, recorded the chromatogram. Six preparation for 50%, 150% level, and triplicate preparation of median level concentration was done. The results are summarized in **Table 7.**

Robustness: Robustness of the current method was investigated by analyzing the standard solution and established system suitability with the deliberate variation of flow rate and column temperature at 10 percentage levels from the original value. RSD of six replicate injections of the standard solution was found below 5.0% for all the chromatographic conditions and all peaks in standard solutions. The conditions with the variation and the results are presented in **Table 8-9.**

TABLE 7: RECOVERY/ACCURACY

Name	Level	% Recovery	% RSD
Impurity-1	LOQ	93.2	1.8
	50%	92.5	2.7
	100%	99.7	2.4
	150%	96.8	2.9
Impurity-2	LOQ	97.7	2.3
	50%	99.4	0.7
	100%	99.7	2.4
	150%	95.9	3.5
Impurity-3	LOQ	100.8	1.5
	50%	99.6	0.5
	100%	102.2	2.7
	150%	99.0	1.2
Impurity-4	LOQ	96.9	1.3
	50%	94.9	3.5
	100%	96.0	2.7
	150%	96.8	1.4
Impurity-5	LOQ	100.7	0.6
	50%	99.8	0.5
	100%	102.9	0.4
	150%	99.8	0.5
Impurity-6	LOQ	96.6	2.0
	50%	98.7	1.3
	100%	99.3	2.6
	150%	98.4	1.1

TABLE 8: ROBUSTNESS (FLOW RATE)

Normal Condition			Flow +		Flow -	
	RT	RRT	RT	RRT	RT	RRT
Impurity - VI	13.35	0.92	12.06	0.92	14.23	0.93
Canaglifozin	14.49	1.00	13.15	1.00	15.32	1.00
Impurity - I	16.03	1.11	14.45	1.10	17.89	1.17
Impurity - V	18.62	1.29	16.81	1.28	21.52	1.40
Impurity - III	31.79	2.19	28.65	2.18	35.83	2.34
Impurity - VI	41.47	2.86	37.81	2.88	44.87	2.93
Impurity -II	46.47	3.21	42.32	3.22	52.36	3.42

TABLE 9: ROBUSTNESS (COLUMN TEMPERATURE)

Normal condition			Column temp +		Column temp -	
	RT	RRT	RT	RRT	RT	RRT
Impurity - VI	13.35	0.92	13.25	0.93	13.68	0.89
Canaglifozin	14.49	1.00	14.31	1.00	15.36	1.00
Impurity - I	16.03	1.11	15.48	1.08	17.02	1.11
Impurity - V	18.62	1.29	17.36	1.21	19.25	1.25
Impurity - III	31.79	2.19	30.17	2.11	33.1	2.15
Impurity - VI	41.47	2.86	39.51	2.76	44.05	2.87
Impurity -II	46.47	3.21	44.03	3.08	48.36	3.15

TABLE 10: LOD AND LOQ OF CANAGLIFOZIN AND ITS IMPURITIES

Name	LOD	LOQ
Canaglifozin	0.02%	0.05%
Impurity-I	0.02%	0.05%
Impurity-II	0.02%	0.05%
Impurity-III	0.02%	0.05%
Impurity-IV	0.02%	0.05%
Impurity-V	0.02%	0.05%
Impurity-VI	0.02%	0.05%

TABLE 11: FORCE DEGRADATION SAMPLE CONDITION

Sample	Condition
Acid	5N HCL (5 mL) 80 °C , 3H
Base	5N NaOH (5 mL) 80 °C , 1H
Peroxide	0.1M $KmnO_4$(5 mL) RT,1H
Thermal	40 °C, 10 Days
Photo	Sun Tester, 1.2 Lux/H, 24H
Humidity	75% RH, 10Days

LOD and LOQ: LOD and LOQ were calculated by using the formula 3.3 S.D / S and 10 S.D / S where S.D is the standard deviation of Y-intercept, and S is the slope of the calibration curve.

TABLE 12: RESULT OF FORCED DEGRADATION STUDY

Sample	Furanose	Oxidative	Methyl phenyl	Unk-1	Unk-2	Unk-3	Total im.	Assay	Mass balan.	Peak purity
Acid	0.02	ND	0.01	0.04	0.07	0.02	0.44	100.2	98.9	995
Base	ND	ND	0.01	0.11	0.05	0.04	0.27	99.8	99.4	996
Peroxide	ND	9.80	0.01	1.30	0.07	0.25	11.53	86.3	102.3	996
Thermal	ND	ND	0.01	0.04	0.04	0.04	0.22	98.7	100.6	997
Photo	ND	0.09	0.01	0.13	0.09	0.06	0.45	99.0	100.1	998
Humidity	ND	ND	BQL	0.05	0.04	0.07	0.16	98.8	100.5	998

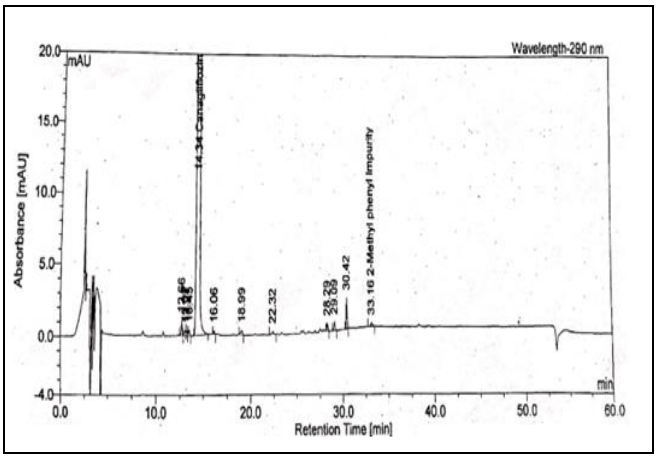


FIG. 15: BASE DEGRADATION SAMPLE

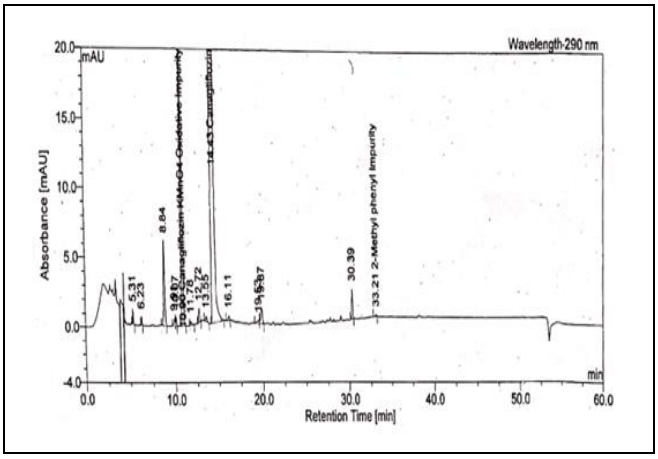


FIG. 16: PEROXIDE DEGRADATION SAMPLE

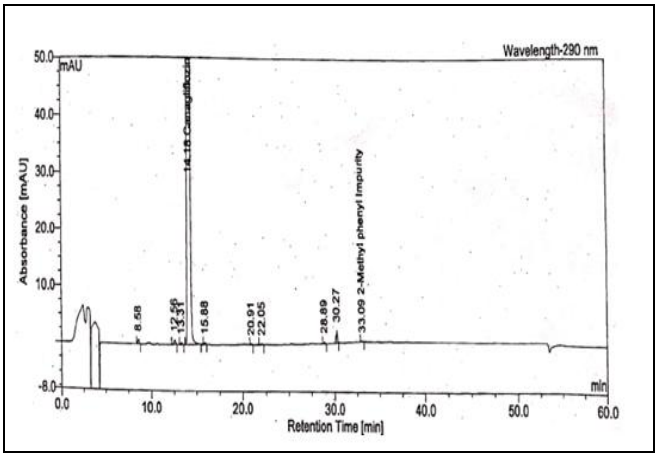


FIG. 17: THERMAL DEGRADATION SAMPLE

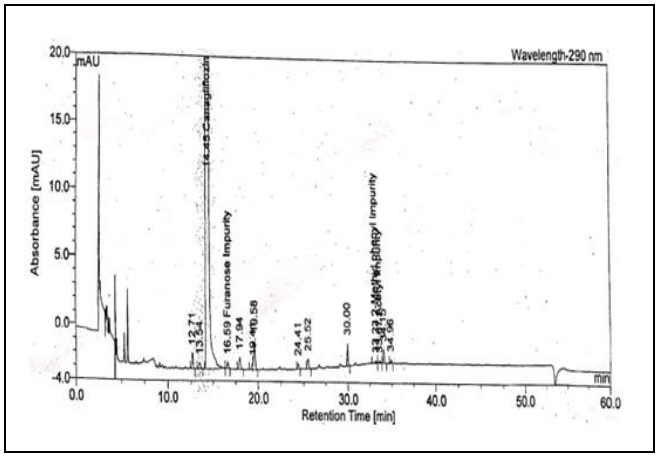


FIG. 18: ACID DEGRADATION SAMPLE

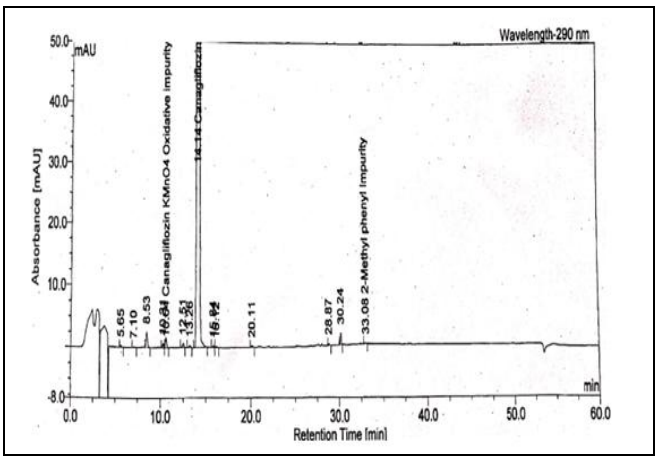


FIG. 19: PHOTO/UV DEGRADATION SAMPLE

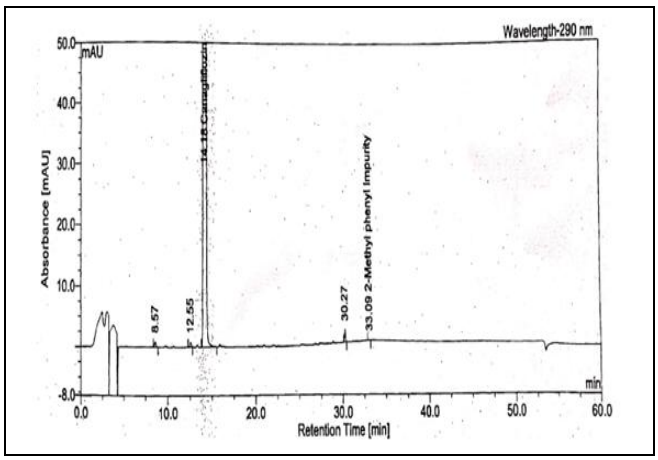


FIG. 20: HUMIDITY DEGRADATION SAMPLE

TABLE 13: RESULT OF STABILITY OF STANDARD SOLUTION

Standard Solution		
Time (h)	**Area**	**% Deviation**
Initial	66.511	-
18	66.200	-0.47
24	66.897	0.58
36	67.847	2.01
48	68.500	2.99
54	69.874	5.06

Solution Stability: Solution stability optimized by injected standard solution and sample at a different time interval and calculated % deviation against the initial area of the standard solution.

It was found that standard and sample were stable upto 54 h. The results are presented in **Table.**

TABLE 14: RESULT OF STABILITY OF SAMPLE SOLUTION

Time (HR)	Impurity-1	Impurity-2	Impurity-3	Impurity-4	Impurity-5	Impurity-6	Single unk	Total im.
Initial	0.64	0.48	0.63	0.50	0.58	0.46	0.00	3.29
18	0.65	0.48	0.63	0.48	0.58	0.46	0.00	3.28
24	0.64	0.48	0.63	0.50	0.58	0.46	0.00	3.29
36	0.64	0.48	0.63	0.50	0.57	0.46	0.00	3.28
48	0.63	0.48	0.63	0.49	0.58	0.46	0.00	3.27
54	0.64	0.48	0.63	0.50	0.59	0.47	0.00	3.31
Time (HR)	**Impurity-1**	**Impurity-2**	**Impurity-3**	**Impurity-4**	**Impurity-5**	**Impurity-6**	**Single unk**	**Total Im.**
Initial	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
18	0.01	0.00	0.00	0.02	0.00	0.00	0.00	0.01
24	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
36	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.01
48	0.01	0.00	0.00	0.01	0.00	0.00	0.00	0.01
54	0.00	0.00	0.00	0.00	0.02	0.01	0.00	0.01

RESULTS AND DISCUSSION: The main objective of the chromatographic method development was to separate canagliflozin from the impurities that were carried out for accurate and precise method development, and impurities were coeluted.

After using several columns and buffers, suitable column chemistry and good peak shape were obtained with inertsil C8-3 (250 × 4.6) mm 3 µ particle size, column temperature was adjusted at 30 °C, with gradient mobile phase system consisting the mobile phase A containing 0.1% orthophosphoric acid solution in water and mobile phase B contains acetonitrile and water in a ratio of 80: 20% v/v using an above-mentioned gradient.

HPLC method has been the development and validated for the determination of related substances of canagliflozin in tablets with gradient elution. The method is selective because we have very good separation between impurities. The method described in this study is suitable to determine impurities at a very low level.

These parameters showed good linearity with correlation coefficients. We have shown that the method is robust, with little change in critical chromatographic parameters. Validation parameters have proved that our method can use as a stability-indicating method for the determination of related substances of canagliflozin in the tablet.

CONCLUSION: A novel, reverse phase liquid chromatographic method has been developed and validated for the estimation of canagliflozin and its impurities with a very recent and advanced HPLC method. The proposed method is found to be simple, accurate, precise, sensitive, specific, and robust. Hence, it can be successfully used for the routine analysis of canagliflozin in pharmaceutical dosage forms.

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CONFLICTS OF INTEREST: The authors declare no conflicts of interest.

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