(Research Article)

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A VALIDATED STABILITY INDICATING RP - HPLC METHOD FOR SIMULTANEOUS ESTIMATION OF METFORMIN AND TENELIGLIPTIN IN BULK AND PHARMACEUTICAL DOSAGE FORM

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ABSTRACT: This is a simple, economic, sensitive stability indicating RP-HPLC method for the simultaneous estimation of metformin and teneligliptin in bulk and pharmaceutical formulation. The method was carried out on octa-decyl C_{18} column (5 μm, 25 cm × 4.6 mm, i.d) using methanol: water in the ratio of 70:30 and pH of the mobile phase up to 3 was adjusted with OPA at a flow rate of 1.0 ml/min. The wavelength for metformin and teneligliptin at 235 nm was found to be appropriate. The linearity range was obtained in the concentration range of 25 - 150 μg/ml for MET, while 5 - 30 μg/ml for TNG respectively. The retention time of metformin and teneligliptin was found to be 2.45 and 6.68 min, respectively. The regression equation for MET and TNG were found to be as y = 8.288 x + 0.026 and y = 27.26 x + 38.28 with correlation coefficient (R^2) 0.999 and 0.999, respectively. The developed method was found to be robust, accurate and sensitive which can be used for estimation of combination of metformin and teneligliptin in pharmaceutical dosage forms.

INTRODUCTION: Metformin hydrochloride (MET), **Fig. 1** chemically is 1-carbamimidamido-N, N-dimethylmethanimidamide hydrochloride with a molecular formula of $C_4H_{11}N_5.HCl$ and a molecular weight of 165.63 [1]. It is white to pale white in colour which is freely soluble in water, and is practically insoluble in acetone, ether and chloroform. Metformin hydrochloride is the first-line medication for the treatment of type 2 diabetes [2], particularly in people who are overweight.

It is also used in the treatment of polycystic ovary syndrome [3]. Metformin inhibits hepatic gluconeo-genesis in mice independently of the LKB1/AMPK pathway *via* decrease in hepatic energy state [4].
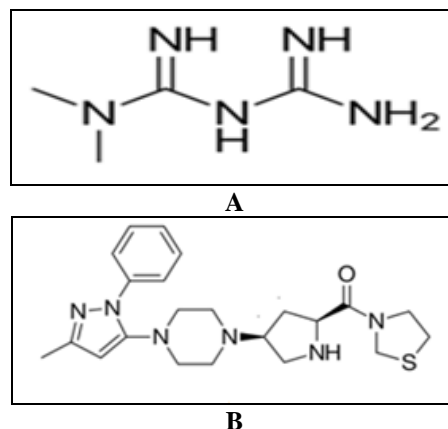

FIG. 1: CHEMICAL STRUCTURES OF MET (A) AND TNG (B)

QUICK RESPONSE CODE

Tenegliptin (TNG) chemically described as [(2S, 4S) - [- (3- methyl- 2- phenylpyrozol- 3- yl) piperazin- 1- yl] pyrrolidin- 2- [1, 3 thiazolidin- 3-yl) Methanone having molecular formula 426.58 [5]. It is white to pale white in colour which is freely soluble in water, sparingly soluble in alcohol and methanol. It is a highly potent, competitive and long-lasting DPP-4 inhibitor that improves postprandial hyperglycemia and dyslipidemia.

Literature survey revealed various analytical method validation for metformin including UV methods with empagliflozin [6 - 8] UV with alogliptin benzoate [9] UV with tenligliptin [10] HPLC [11] HPLC with saxagliptin [12] with rouvastatine [13] HPLC with pioglitazone [14 - 15] and other oral hypoglycaemic agents [16] with related compounds [17] while tenligliptin described HPLC [18] HPLC with UV [19] and stability study with LC-MS-MS [20].

MATERIALS AND REAGENTS: Reference standards of metformin hydrochloride was obtained as gift sample from Dr. Reddy's laboratories, Hyderabad, India while tenegliptin was obtained as generous gift from Micro Labs Ltd., Bangalore, India. Pharmaceutical formulation was purchased from local market (Brand: tenglyn-M tablet labelled claim metformin 500 mg and tenligliptin 20 mg make Zydus). The HPLC grade solvents used were procured from E-Merck (India) Ltd., Mumbai. HPLC grade methanol and ortho phosphoric acid (Merck, Mumbai, India) were used in the analysis. HPLC grade water was prepared using millipore purification system.

Instrumentation: Younglin (S.K.) gradient system UV detector with autochro - 3000 database software, RP C_{18} column (250 × 4.6 mm), particle size 5µ) was used. Sonicator: PCi Mumbai, Model No. 3.5L 100H.

Chromatographic Conditions: Various combinations of mobile phases were screened with respect to resolution, theoretical plate capacity factors and other system suitability parameters. Finally the separation was performed with freshly prepared mobile phase consist of methanol: water in the ration of 70:30 and pH up to 3 was adjusted with OPA with isocratic programming at a flow rate of 1.0 ml/min. 235 nm wavelength, injection volume of 20 µL and ambient temperature was

maintained during the entire process to obtain symmetric peaks of MET and TNG.

Preparation of Standard Solutions: All solutions were prepared on a weight basis and solution concentrations were also measured on weight basis to avoid the use of an internal standard pharmaceutical formulation which is available in the market has the proportion of 1:25. For the ease of quantification, proportion of MET and TNG was reduced to 1:5 by using standard addition method. Standard stock solution was prepared by dissolving separately 50 mg of MET and 10 mg of TNG in 100 ml clean dry volumetric flask. Dissolved and diluted with methanol up to the mark and filtered through 0.45 µm membrane filter. This gives the concentration of stock solution 500 µg/ml for MET and 100 µg/ml for TNG.

Linearity Study: From the prepared standard stock solutions of both, 0.5 ml, 1.0, 1.5, 2.0, 2.5 and 3.0 ml were transferred to 10 ml volumetric flask and volume made up to the mark with the optimised mobile phase to obtain concentration of 25 - 150 µg/ml for MET, while 5 to 30 µg/ml for TNG respectively. Volume of 20 µL of each sample was injected with the help of Hamilton Syringe. All measurements were repeated three times for each concentration and calibration curve was constructed by plotting the peak area *vs* the drug concentration.

Validation of Proposed Method: The proposed method was validated as per ICH guidelines. The solutions of the drugs were prepared as per the earlier adopted procedure given in the experiment.

Accuracy: It was done by recovery study using standard addition method at 80%, 100% and 120% level; known amount of standard MET and TNG were added to pre-analyzed sample (75 µg/ml of MET; 15 µg/ml of TNG) and subjected them to the proposed HPLC method.

Precision: Precision is the measure of how close the data values are to each other for a number of measurements under the same analytical conditions.

Intraday and Interday Precision: Intraday precision were determined by analyzing, the three different concentrations 50 µg/ml, 75 µg/ml and

100 µg/ml of MET, while 10 µg/ml, 15 µg/ml and 20 µg/ml of TNG for three times in the same day. Day to day variability was assessed using above mentioned three concentrations analyzed on three different days, over a period of one week.

Repeatability: It is measured by multiple injections of a homogenous sample of 75 µg/ml of MET and 15 µg/ml of TNG that indicates the performance of the HPLC instrument under chromatographic conditions.

Robustness: To evaluate robustness few parameters were deliberately varied. The parameters include variation of flow rate, percentage of methanol using 75 µg/ml solution of MET and 15 µg/ml of TNG.

Sensitivity: Sensitivity of the proposed method was estimated in terms of limit of detection (LOD) and limit of quantitation (LOQ). LOD = 3.3 SD/S and LOQ = 10 SD/S, where SD is the residual standard deviation and S is the slope of the line.

Specificity and Selectivity: The analyte should have no interference from other extraneous components and be well resolved from them. Specificity is a procedure to detect quantitatively the analyte in presence of component that may be expected to be present in the sample matrix, while selectivity is the procedure to detect qualitatively the analyte in presence of components that may be expected to be present in the sample matrix.

Ruggedness: From stock solutions, sample solutions of MET (75 µg/ml) and TNG (15 µg/ml) were prepared and analyzed by two different analysts using similar operational and environmental conditions. Peak area was measured for same concentration solutions, six times.

System Suitability Test: System suitability testing is essential for the assurance of the quality performance of the chromatographic system. Earlier prepared solutions for chromatographic conditions were tested for system suitability testing.

Analysis of Pharmaceutical Formulation: To determine the contents of drugs in conventional tablets (Brand: tenglyn-M tablet labelled claim metformin hydrochloride 500 mg and teneligliptin

20 mg per tablet make zydus). Twenty tablets were weighed, their mean weight determined and they were finely powered. Powder equivalent to 500 mg MET was transferred into a 100 ml volumetric flask containing 50 ml methanol. In that solution standard teneligliptin was added to have the concentration proportion 1:5.The resulting solution was sonicated for 30 min and diluted to 100 ml with methanol. The solution was filtered, using 0.45 µm filter (Millifilter, Milford, MA). Excipients were separated by filtration. The solution was further diluted with optimised mobile phase to get concentration75 µg/ml of MET and 15 µg/ml of TNG which were subjected to proposed method and amount of MET and TNG were determined.

RESULTS AND DISCUSSION:
Optimization of Chromatographic Conditions: The primary target in developing this stability indicating HPLC method is to achieve the resolution between metformin hydrochloride, teneligliptin and its degradation products. To achieve the separation of degradation products, octadecyl silane C_{18} stationary phase and freshly prepared mobile phase consist of methanol: water in the ration of 70:30 and pH up to 3 was adjusted with OPA with isocratic programming at a flow rate of 1.0 ml/min. 235 nm wavelength, injection volume of 20 µL and ambient temperature was maintained during the entire process to obtain symmetric peaks of MET and TNG. The tailing factor obtained was less than two and retention time was about 2.93 and 6.966 min for MET and TNG **Fig. 2**.
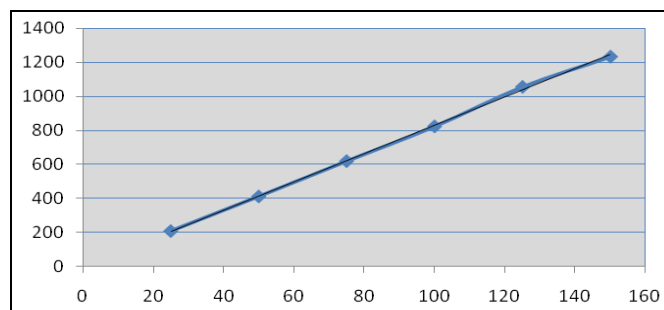

FIG. 2: CALIBRATION CURVE OF METFORMIN HYDROCHLORIDE

This developed method was found to be specific and method was validated as per international guideline.

Linearity Study: Linearity was studied by preparing standard solutions at different concentration levels. The linearity range for metformin hydrochloride and tenegliptin were found to be as 25 - 150 µg/ml and 5 - 30 µg/ml respectively **Table 1**. The regression equation for MET and TNG were found to be as y = 8.288 x + 0.026 and y = 27.26 x + 38.28 with correlation coefficient (R^2) 0.999 and 0.999, respectively **Fig. 3** and **4**.

TABLE 1: LINEARITY STUDY OF MET AND TNG

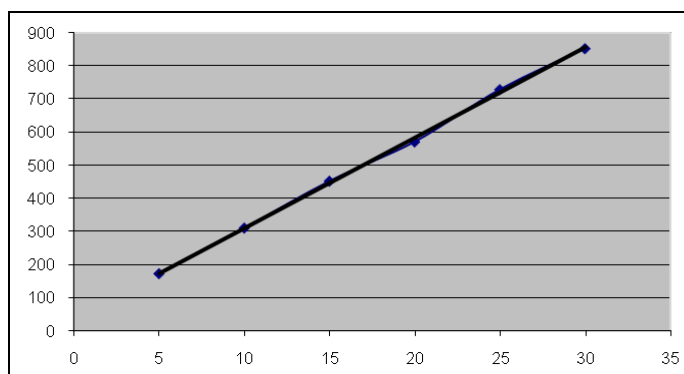| S. no.	MET			TNG		
	Concentration (µg/ml)	Mean peak area ± SD (n = 5)	% RSD	Concentration of (µg/ml)	Mean peak area ± SD (n = 5)	% RSD
1	25	208.8±3.70	1.77	5	173.6±3.05	1.76
2	50	412.2±6.87	1.67	10	311.4±5.98	1.92
3	75	619.4±5.81	0.94	15	453.0±7.28	1.61
4	100	823.2±7.12	0.86	20	571.6±4.83	0.84
5	125	1055.4±9.34	0.89	25	729.6±5.90	0.81
6	150	1231.6±13.24	1.07	30	853.2±8.87	10.04

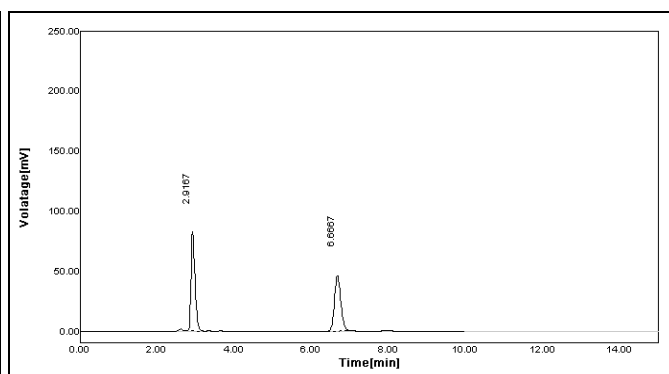**FIG. 3: CALIBRATION CURVE OF TENELIGLIPTIN**

FIG. 4: CHROMATOGRAM OF STANDARD METFORMIN HYDROCHLORIDE AND TENELIGLIPTIN AT 235 nm

Method Validation:

Accuracy: To check the degree of accuracy of the method, recovery studies were performed in triplet by standard addition method at 80%, 100% and 120% concentration levels. Known amounts of standard MET and TNG were added to the pre-analyzed samples and were subjected to the proposed HPLC method. The % recovery was found to be within the limits of the acceptance criteria with average recovery of 99.58 - 100.55% for MET and 99.11 - 100.99% for TNG. Result of recovery studies is shown in **Table 2**.

TABLE 2: RESULTS OF RECOVERY STUDIES OF MET AND TNG

Drug	Initial amount (µg/ml)	Amount added (µg/ml)	Amount recovered ± S.D. (µg/ml, n = 3)	% Recovery	% RSD
MET	75	0	75.29 ± 0.67	100.39	0.89
	75	60	59.89 ± 0.89	99.81	1.49
	75	75	74.69 ± 1.09	99.58	1.45
	75	90	90.49 ± 1.28	100.55	1.42
TNG	15	0	15.15 ± 0.27	100.99	1.83
	15	12	12.07 ± 0.20	100.57	1.67
	15	15	15.08 ± 0.24	100.51	1.58
	15	18	17.84 ± 0.18	99.11	1.02

Precision: Precision was evaluated by carrying out six independent sample preparations of a single sample by intra-day and inter-day precision. The sample preparation was carried out in same manner as described in sample preparation. Percentage relative standard deviation (% RSD) was found to be less than 2 % that proves method is precise shown in **Table 3**.

TABLE 3: RESULTS OF PRECISION STUDIES OF MET AND TNG (INTRA-DAY AND INTER-DAY)

Drug	Conc. (µg/ml)	Intraday Amount Found (µg/ml)		Inter day Amount Found (µg/ml)	
		Mean ± S.D.	% RSD (n = 3)	Mean ± S.D.	% RSD (n = 3)
MET	50	49.87 ± 4.16	0.34	49.51 ± 8.50	0.69
	75	74.37 ± 10.21	0.55	74.77 ± 7.64	0.41
	100	99.50 ± 6.66	0.27	99.50 ± 9.45	0.38
TNG	10	9.77 ± 2.00	0.29	10.13 ± 2.00	0.28
	15	15.25 ± 3.06	0.27	15.09 ± 5.57	0.50
	20	20.39 ± 5.51	0.35	19.65 ± 5.03	0.34

Repeatability: It is measured by multiple injections of a homogenous sample of 150 µg/ml of MET and 15 µg/ml of TNG and the % R.S.D. was found to be less than 2 **Table 4**.

TABLE 4: RESULTS OF REPEATABILITY STUDY OF MET AND TNG

Drug	Concentration (µg/ml) (n = 6)	Peak Area	Mean (µg/ml) ± SD	% RSD
MET	75	622.833	75.15 ± 0.94	1.26
TNG	15	377.677	15.25 ± 0.255	1.677

Robustness of the Method: To evaluate the robustness of the developed RP-HPLC method, small deliberate variations in optimized method parameters were done. The effects of change in flow rate, pH retention time, and in mobile phase ratio were studied. The method was found to be unaffected by small changes like ± 10 % in flow rate, ± 0.2 change in pH, shown in **Table 5**.

TABLE 5: ROBUSTNESS EVALUATION OF THE HPLC METHOD FOR TMS

Chromatographic conditions	MET			TNG		
	Tailing (T')	Capacity Factor (K')	Theoretical Plate (N)	Tailing (T')	Capacity Factor (K')	Theoretical Plate (N)
A: Mobile phase pH						
2.8	1.26	1.23	2683.9	1.28	0.99	7591.4
3.0	1.22	1.27	2683.5	1.23	1.09	7632.5
3.2	1.21	1.33	2625.5	1.25	1.15	7414.7
Mean ± SD	1.23 ± 0.02	1.27 ± 0.05	2687.63 ± 36.80	1.25 ± 0.02	1.07 ± 0.02	7546.2 ± 115.72
B: Flow rate (ml/min.)						
0.9 ml	1.23	0.98	2723.8	1.26	0.76	7587.3
1.0 ml	1.16	1.08	2818.9	1.29	1.10	7668.8
1.1 ml	1.15	1.09	2768.7	1.22	0.88	7423.5
Mean ± SD	1.18 ± 0.04	1.05 ± 0.06	2770.47 ± 47.57	1.25 ± 0.03	0.91 ± 0.17	7593.2 ± 7282
C: Percentage methanol in mobile phase (v/v)						
60	1.09	1.22	2646.2	1.18	0.87	7623.8
70	1.06	1.13	2687.4	0.94	0.95	7667.3
80	1.19	1.18	2638.3	1.23	0.87	7433.2
Mean ± SD	1.11 ± 0.06	1.17 ± 0.04	2657.3 ± 26.36	1.11 ± 0.15	0.89 ± 0.04	7574.77 ± 124.51

Sensitivity: LOQ and LOD can be determined based on visual evaluation, signal-to-noise approach and standard deviation of the response and slope. Limit of detection of MET and TNG was determined 1.656 and 0.617, respectively. Limit of quantitation of MET and TNG was determined 5.019 and 1.869, respectively.

Specificity and Selectivity: The method is quite selective. There were no other interfering peak around the retention time of MET and TNG; also the base line did not show any significant noise.

Ruggedness: Different analyst carried out precision studies in a similar manner carried out by first analyst. The % Assay was found to be 99.40 - 99.58%, and 99.60 - 99.80% of MET and TNG, respectively. Percentage relative standard deviation (% RSD) was found to be less than 2% that proves method is rugged, shown in **Table 6**.

System Suitability Test: System suitability testing is essential for the assurance of the quality performance of the chromatographic system. The tailing factor, capacity factor, and theoretical plates for MET and TNG were in the acceptance criteria as per the ICH guidelines **Table 7**.

Analysis of Pharmaceutical Formulation: The assay procedure was repeated for six times; the

percentage content of MET and TNG in the tablet formulation was determined as 98.76 - 101.77% and 98.36 - 101.79% respectively **Table 8**.

TABLE 6: RUGGUDDNESS EVALUATION OF THE HPLC METHOD

Analyst	Amount found of MET [%]	Amount found of TNG [%]	%RSD [n=3]	%RSD [n=3]
I	99.40	99.60	0.98	1.27
II	99.58	99.80	1.13	1.31

TABLE 7: SYSTEM SUITABILITY TEST FOR MET AND TNG

MET		TNG	
System suitability parameters	Proposed method	System suitability parameters	Proposed method
Retention time (R_t)	2.9333	Retention time (R_t)	6.9167
Capacity factor (K')	1.18	Capacity factor (K')	0.98
Theoretical plate (N)	2838.7	Theoretical plate (N)	7465.8
Tailing factor (T)	1.16	Tailing factor (T)	0.95

TABLE 8: ANALYSIS OF TABLET FORMULATION

Drug	Label claim (mg)	Amount found (mg)	Amount found (%) ± SD	% RSD
MET	500	499.67	99.93 ± 0.46	0.46
TNG	20	20.06	100.3 ± 1.13	1.13

Procedure for Forced Degradation Study: Forced degradation of each drug substances and the drug product was carried out under acidic, basic, oxidative stress, thermolytic and photolytic, conditions. Thermal degradation of drug was carried out in solid state. While remaining all studies were carried out in solution form. Solutions were prepared by dissolving drug with either distilled water, aqueous hydrochloric acid, aqueous sodium hydroxide, or aqueous hydrogen peroxide solution, which is further diluted with mobile phase to achieve a concentration of 150 µg/ml each of MET and 30 µg/ml for TNG. These solutions were kept for 1 hr. For thermal stress, samples of drug was placed in a controlled-temperature oven at 50°C for 1 hr. Solutions of drug substances and drug product were also kept at 80 °C for 48 hr. For photolytic stress, samples of drug in solution state, was irradiated with UV radiation having peak intensity at 254 and 366 nm. The degradation studies **Fig. 5 - 8** were tabulated in **Table 9**.
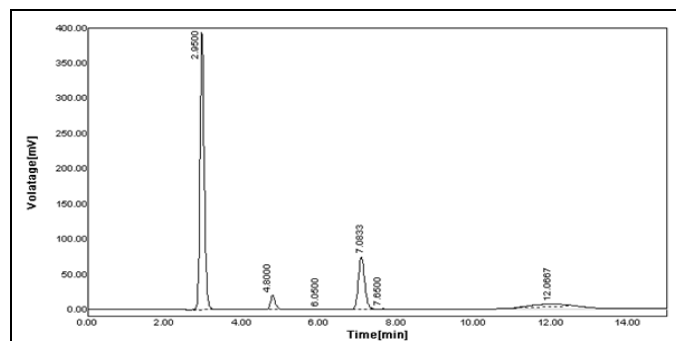

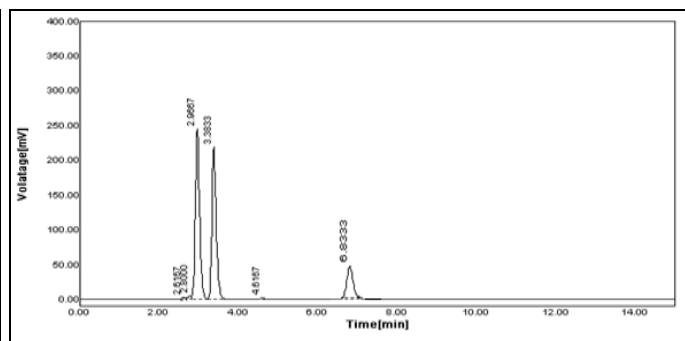**FIG. 5: ACIDIC DEGRADATION (1N, HCl) AFTER 1 h**
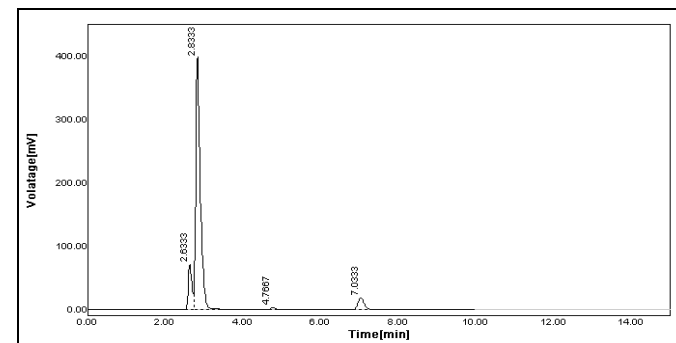

FIG. 6: ALKALINE DEGRADATION (1N NaOH) AFTER 1 h

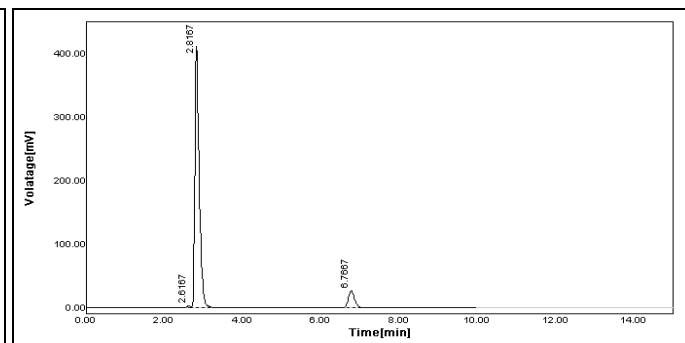**FIG. 7: PER OXIDE DEGRADATION (30% H_2O_2) AFTER 1 h**

FIG. 8: HEAT DEGRADATION AT 50 °C FOR 1 h

TABLE 9: FORCED DEGRADATION OF MET AND TNG

Sample Exposure condition	Total Number of products with their R_t	MET		TNG	
		Degradation remained (150 µg/ml)	Recovery (%)	Degradation remained (30 µg/ml)	Recovery (%)
Acidic, 1N, 1 h	5 (2.95, 4.80, 6.05, 7.08, 7.65)	136.224	90.81	28.25	94.18
Basic, 1N, 1 h	6 (2.61, 2.80, 2.95, 3.38, 4.51, 7.20)	122.22	81.48	13.28	44.29
Per oxide, 30 %, 1 h	4 (2.63, 2.83, 4.76, 7.03)	128.50	85.67	20.92	69.73
Heat, 50 °C, 1 h	3 (2.61, 2.81, 6.766)	136.58	91.05	22.20	74.01

CONCLUSION: The present study was conducted to develop and validate a simple, sensitive and reproducible RP-HPLC method for quantitative determination of metformin hydrochloride and teneligliptin with stressed stability studies under different conditions. The developed chromatographic assay fulfilled all the requirements to be identified as simple, specific, selective and reliable method, including accuracy, linearity, recovery and precision data. Furthermore, this simple and rapid RP-HPLC method can also be used successfully for the determination of metformin hydrochloride and teneligliptin in pharmaceutical formulations without any interference from the excipients and degraded peaks.

CONFLICT OF INTEREST: There is no conflict of interest. The authors alone are responsible for content and writing of this article.

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