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STABILITY INDICATING LC-ASSAY METHOD FOR METFORMIN HYDROCHLORIDE AND TENELIGLIPTIN HYDROBROMIDE FROM TABLET FORMULATIONS

Arindam Basu [1] and Jui Chakraborty [*2]

Department of Chemistry [1], Jadavpur University, Kolkata - 700032, West Bengal, India.
Bioceramics and Coating Division [2], CSIR Central Glass and Ceramics Research Institute, 196, Raja S.C. Mullick Road, Jadavpur, Kolkata - 700032, West Bengal, India.

Keywords:

High-Performance Liquid Chromatography, Metformin hydrochloride, Teneligliptin hydrobromide, Stability indicating assay, Reverse phase chromatography

Correspondence to Author:
Dr. Jui Chakraborty

Principal Scientist,
CSIR Central Glass and Ceramics Research Institute, 196, Raja S.C. Mullick Road, Jadavpur, Kolkata - 700 032, West Bengal, India.

E-mail: jui@cgcri.res.in

ABSTRACT: A simple, rapid, accurate, robust, and specific HPLC method was developed for the assay of metformin hydrochloride and teneligliptin hydrobromide from the oral tablet formulations. Stability-indicating reverse-phase chromatographic method was developed on a RP C18 column (250 mm × 4.6 mm, 5µm) using a mixture of 20 mM ammonium acetate of pH 5.5 and methanol in the ratio 50:50 v/v as mobile phase in an isocratic mode of elution at a flow rate of 1.0 ml/min at 35 ºC with a load of 20 µl. The detection was carried out at 255 nm. The method was validated with respect to linearity, robustness, precision, accuracy, specificity & stability as per ICH guidelines. The method produced excellent separation with good linear correlation coefficients (≥ 0.999) for both the components. The proposed method could be successfully applied for the assay of metformin hydrochloride and teneligliptin hydrobromide from tablet formulations.

INTRODUCTION: Metformin hydrochloride is chemically 1,1-Dimethylbiguanide hydrochloride [1] while teneligliptin hydrobromide hydrate is a Dipeptidyl peptidase-4 (DPP-4) inhibitor and chemically it is {(2S,4S)-4-[4-(3-methyl-1- phenyl-1H-pyrazol-5-yl) piperazin-1-yl] pyrrolidin-2-yl} (1,3-thiazolidin-3-yl) methanone hemipentahydro-bromide hydrate. Teneligliptin is used in the treat-ment of type-2 diabetes mellitus [2]. The chemical structures of both drugs metformin hydrochloride and teneligliptin hydrobromide are shown in **Fig. 1** and **Fig. 2,** respectively.

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A few UV methods are available for assay of metformin hydrochloride or teneligliptin alone or in their combination [3-6].

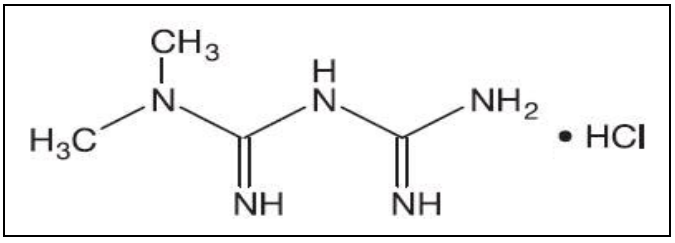

FIG. 1: CHEMICAL STRUCTURE OF METFORMIN HYDROCHLORIDE

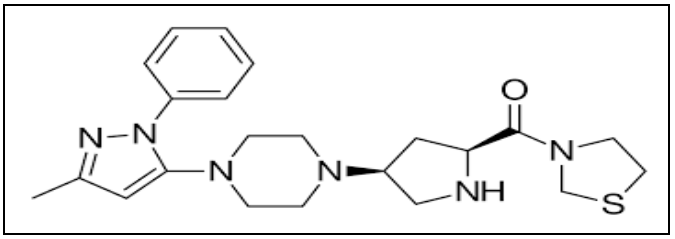

FIG. 2: CHEMICAL STRUCTURE OF TENELIGLIPTIN

RP-HPLC methods for only metformin or metformin hydrochloride with other drugs like linagliptin, glimepirde, and pioglitazone are also reported [7-9] while some HPLC methods for metformin hydrochloride with teneligliptin hydrobromide are also available [10-12]. The proposed method offers several advantages in terms of simple sample preparation technique with a very accurate, precise, and robust chromatographic system. The method was subsequently validated following ICH guidelines [13].

MATERIALS AND METHODS: Metformin hydrochloride and teneligliptin hydrobromide standards were obtained as a gift from Macleods Pharmaceutical Private Limited. The commercially available finished formulations of metformin hydrochloride and teneligliptin hydrobromide used in the experiment, namely Tenecip M, Tenelimac M 500, and Zitamet plus containing 500 mg metformin hydrochloride and 20 mg teneligliptin were procured from the market for the analysis purposes. The ammonium acetate and ammonium hydroxide used were of AR grade from SRL; acetic acid used was of HPLC grade from Fisher Scientific for the experiment. Milli Q water was used for the preparation of buffer solution for the mobile phase. Glass wares used were of Borosil make. Miller Syringe filters of 0.45 µm, of Merck Millipore, were used to filter the sample solutions.

Instrumentation: The Lambda 45 UV visible spectrophotometer of Perkin Elmer make equipped with UV win Lab ES software version 6.0.4 was used for recording the UV spectrum. The Agilent 1200 series HPLC system with Quat Pump (Serial No G1311A), UV/VIS detector (1260 MWD VL G1365 D), EZchrome Elite software version (3.3.2 SP2), C18 column (Waters X Bridge 250 mm × 4.6 mm, 5 µm) and Ultrasound bath of PCI make were used in the experiment.

Chromatographic Condition: An isocratic mixture of 20 mM ammonium acetate solution of pH 5.5 and methanol in the ratio 50:50 v/v was chosen as the mobile phase. The buffer solution was filtered through a 0.45 µm membrane filter prior to the adjustment of pH. The pH of the buffer solution was adjusted to 5.5 with dilute acetic acid solution and was mixed with methanol in the ratio 50:50. The mobile phase was ultrasonicated for 5 min to degas the mixture and then used. The separation was achieved on a C18 column (Waters X Bridge 250 mm × 4.6 mm × 5 µm) at a flow rate of 1.0 ml/min in the isocratic mode of elution. All determinations were performed at a constant column temperature of 35 ºC with a load of 20 µl of the mobile phase. The detection was carried out at 255 nm. The mobile phase was used as a diluent for the preparation of standard and sample solutions. The finalized chromatographic condition is given in **Table 1**.

TABLE 1: CHROMATOGRAPHIC CONDITION

Parameters	Conditions
Column	C18 (4.6 × 250 mm, 5µm)
Mobile phase	20mM ammonium acetate pH 5.5 : methanol 50:50 v/v
Diluent	mobile phase
Flow rate	1.0 ml/min
Temperature	35 °C
Detection wavelength	255 nm
Injection volume	20 µl
Retention time	Metformin 2.52 min, Teneligliptin 7.9 min

Assay of Formulations: The working concentration for metformin and teneligliptin was selected as 250 µg/ml and 10 µg/ml, respectively. To assay the drug formulations, a mixed standard solution having a final concentration of 250 µg/ml metformin hydrochloride and 10 µg/ml teneligliptin was prepared in the mobile phase. Commercially available formulation, namely, Tenecip M, Tenelimac M 500, and Zitamet plus containing 500 mg metformin hydrochloride and 20 mg teneligliptin were taken for assay. Twenty tablets were weighed, and the average weight was determined for each brand. Sample powder equivalent to 25 mg metformin and 1 mg teneligliptin was weighed in a 100 ml volumetric flask. About 80 ml mobile phase was added, and the solution was ultrasonicated for 20 min. The resulting solutions were cooled to room temperature and volume was made up to the mark with mobile phase.

Method Validations: The proposed method was validated as per the ICH guidelines Q2 for Linearity, LOD, and LOQ, accuracy, precision, specificity, and robustness.

Linearity and Range: The linearity of a method is the ability to elicit test results that are directly

proportional to the concentration of the analyte in samples. To construct the calibration curve a standard stock solution of 1000 µg/ml metformin hydrochloride was prepared in the mobile phase. Subsequently, the stock solution was diluted in the mobile phase to obtain a concentration of 20, 100, 200, 300, 500, 600, 800 µg/ml in the mobile phase. Each solution was injected in triplicate, and the peak area was recorded. Similarly, for constructing a calibration curve of teneligliptin hydrobromide, a stock solution of containing 100 µg/ml teneligliptin was prepared in the mobile phase. The said solution was subsequently diluted in the mobile phase to obtain 2, 5, 10, 15, 20, 30, and 50 µg/ml of teneligliptin in the mobile phase. Each solution was injected to record the peak area. The obtained data were subjected to linear regression analysis using the least square method.

LOD and LOQ: The limit of detection (LOD) and limit of quantitation (LOQ) were determined as per ICH guidelines using equations (1) and (2) from the standard deviation of y-intercepts of regression line

$$LOD = 3.3 \times \sigma/S \quad ...1$$

$$LOQ = 10 \times \sigma/S \quad ...2$$

Where σ = standard deviation of the response; S = slope of the regression line.

Accuracy: The accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted either as a true conventional value or an accepted reference value and the value found or measured. This is also termed trueness. Accuracy of the proposed method was determined using standard addition method or recovery study by spiking standard metformin hydrochloride and teneligliptin hydrobromide at three different levels of sample concentration (at 50%, 100%, and 150%) to the pre-analyzed sample of metformin-teneligliptin combination. Three different marketed formulations, namely Tencip M, Tenelimac M 500, and Zitamet plus (with the claim of metformin hydrochloride 500 mg and teneligliptin 20 mg) were taken as sample for accuracy. The target concentration for the proposed method was 250 µg/ml for metformin hydrochloride and 10 µg/ml for teneligliptin (100% level). For each of three brands, sample powder equivalent to 12.5 mg of metformin hydrochloride and 0.5 mg teneligliptin were weighed in separate 100 ml volumetric flasks. To each of the flasks, a measured amount of metformin hydrochloride and teneligliptin standards (at 50%, 100%, and 150% level of metformin hydrochloride and teneligliptin contributed from the sample) were added. About 80 ml of the mobile phase was added to each flask, and solutions were sonicated for 20 min. Finally, volume was made up to the mark with the same solvent and injected in replicate.

Precision: The precision of an analytical procedure expresses the closeness of agreement (degree of scattering) between a series of measurements under the prescribed conditions and is usually expressed as the variance, standard deviation or coefficient of variation of series of measurements. The precision and reproducibility of the proposed method were established from repeatability, inter-day, and inter-day assay.

For the repeatability test, six determinations of assay of pre-analyzed a sample of metformin hydrochloride-teneligliptin hydrobromide combination were carried out at the target concentration level (250µg/ml for metformin hydrochloride and 10 µg/ml for teneligliptin). The assay was done against a mixed standard solution of comparable concentration. The inter-day and intraday precisions were also carried out on three different commercially available formulations at the target concentration level.

Specificity: Specificity is the ability to assess the analyte unequivocally in the presence of components which may be expected to be present. Specificity analysis was carried out by subjecting 1 mg/ml solution of metformin hydrochloride and teneligliptin standard solutions separately to various stress conditions like exposure to water, heat, oxidative hydrolysis, UV light, acidic and alkaline hydrolysis for specified periods. Finally, each of stress-induced solution was diluted with the mobile phase in order to obtain a final concentration of 250 µg/ml of metformin and 10 µg/ml of teneligliptin. Each solution was injected, and the amount of degradation was calculated.

Robustness: The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small but deliberate variations in

method parameters and provides an indication of its reliability during normal usage. One consequence of the evaluation of robustness study should be that a series of system suitability parameters is established to ensure that the validity of the analytical procedure is maintained whenever used. A mixed standard solution containing 250 µg/ml of metformin hydrochloride and 10 µg/ml of teneligliptin was prepared, and replicate injections were given. To evaluate the robustness study, some small, deliberate variations in chromatographic parameters like change in flow rate (±0.1 ml/min), detection wavelength (± 2 nm), column temperature (±2 ºC), the ratio of buffer to methanol in the mobile phase and pH of buffer (±0.2 unit) used in a mobile phase were done. Under each varied condition, replicate injections of mixed standard and pre-analyzed sample solutions were given in order to assay the sample and to see the effect of such deliberate variation on the assay value of the sample.

RESULTS AND DISCUSSION:

Method Development: The HPLC method was developed and optimized after a series of trials in terms of selection of buffer for mobile phase, its pH, its exact composition for mobile phase, selection of organic solvent as the composition of the mobile phase, detection wavelength, choice of the stationary phase of column, flow rate and column temperature. To select the detection wavelength, UV spectrum of metformin hydrochloride (0.001% w/v), teneligliptin (0.001% w/v) and metformin-teneligliptin mixed standard (containing 0.0001% w/v each) in methanol were recorded. The overlay UV spectrum is represented in **Fig. 3**. Metformin hydrochloride showed absorption maxima at 233 nm while that for teneligliptin was found to be at 252 nm. 255 nm was chosen as the working wavelength for the HPLC method. Several buffers at different pH were tried as a component of the mobile phase; however, considering the pKa values for metformin hydrochloride (12.4) and teneligliptin (1.7, 3.8, and 7.3) the pH of 20mM ammonium acetate buffer was kept at 5.5. The optimum ratio for methanol to buffer was finalized at 50:50 v/v at a flow rate of 1.0 ml/min. The separation was achieved on a C18 column maintained at 35 ºC. 20 µl injections were given for both the sample and standard solutions. The mean retention time was found to be 2.52 min and 7.9 min for metformin hydrochloride and teneligliptin, respectively. A representative chromatogram of mixed standard for metformin hydrochloride and teneligliptin is shown in **Fig. 4**.

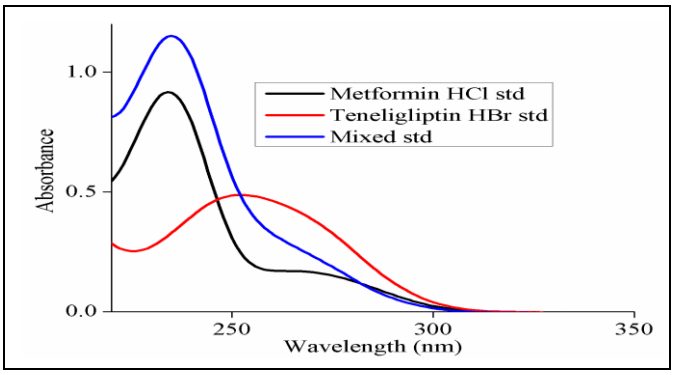

FIG. 3: OVERLAY UV SPECTRUM OF METFORMIN HYDROCHLORIDE, TENELIGLIPTIN STANDARD INDIVIDUALLY AND METFORMIN HYDROCHLORIDE – TENELIGLIPTIN MIXED STANDARD

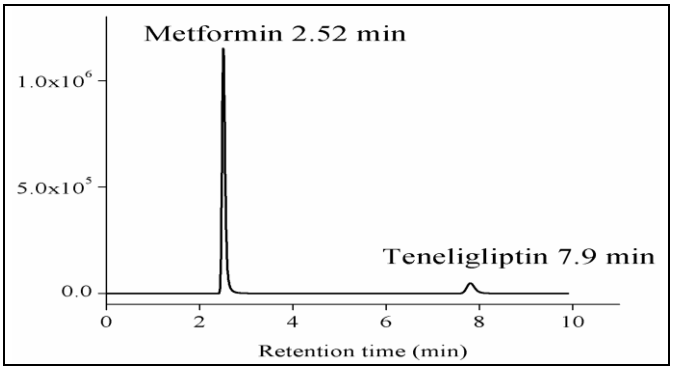

FIG. 4: REPRESENTATIVE CHROMATOGRAM OF METFORMIN HYDROCHLORIDE AND TENELIGLIPTIN MIXED STANDARD SOLUTION

Method Validation:

Linearity, Range and LOD-LOQ: The regression equations for metformin hydrochloride and teneligliptin were found to be y = 19357x + 270184 and y = 61730x-2179 respectively. The calibration curves were found to be linear within the concentration range of 20-1000 µg/ml for metformin hydrochloride, and 2-50 µg/ml for teneligliptin with correlation coefficient values 0.999 for both components. The calibration curves for metformin hydrochloride and teneligliptin are given in **Fig 5** and **Fig. 6,** respectively. The limit of detection (LOD) for metformin hydrochloride and teneligliptin are found to be 16.81 µg/ml and 0.044 µg/ml respectively while the limit of quantitation (LOQ) was found to be 50.94 µg/ml for metformin hydrochloride and 0.134 µg/ml for teneligliptin respectively. The linear regression results are reported in **Table 2**.

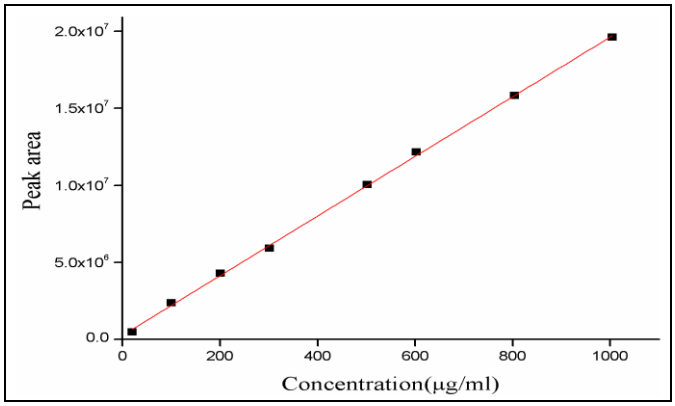

FIG. 5: CALIBRATION CURVE OF METFORMIN HYDROCHLORIDE

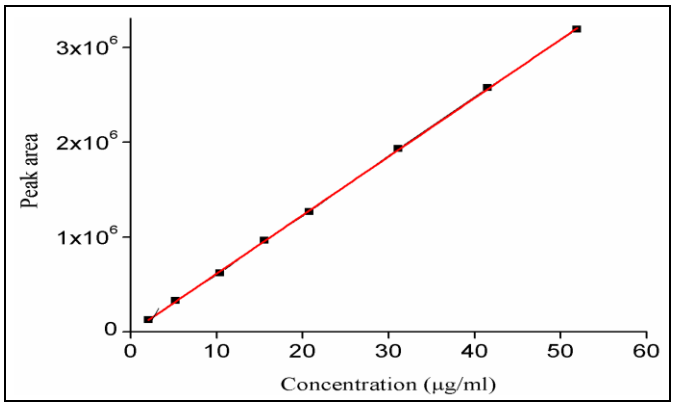

FIG. 6: CALIBRATION CURVE OF TENELIGLIPTIN

TABLE 2: LINEAR REGRESSION DATA FOR METFORMIN HYDROCHLORIDE AND TENELIGLIPTIN HYDROBROMIDE

Parameter	Metformin	Teneligliptin
Regression equation	Y = 19357x +270184	Y =61730x -2179
Concentration range (µg/ml)	20-1000	2-50
Slope	19357	61730
Intercept	270184	- 2179
R^2	0.999	0.999

Accuracy: The amount of drug recovered was calculated in each case. The percentage of recovery was calculated by using the following formula = (Amount of drug recovered in mg/ Amount of drug added) in mg × 100, and the result for all the nine determinations is presented in **Table 3** for metformin hydrochloride and teneligliptin. The method was proved to be very accurate as the recovery for metformin hydrochloride was 98.54%-101.08% while that for teneligliptin was 98.81-101.72% for all the three levels *i.e.*, 50%, 100%, and 150%.

TABLE 3: ACCURACY RESULTS FOR METFORMIN HYDROCHLORIDE AND TENELIGLIPTIN

% of standard spiked	Sets	Metformin HCl standard			Teneligliptin standard		
		Added (mg)	Recovered (mg)	Recovery (%)	Added (mg)	Recovered (mg)	Recovery (%)
50%	Rec. 1	6.5	6.43	98.92	0.252	0.249	98.81
	Rec. 2	6.5	6.45	99.23	0.252	0.25	99.21
	Rec. 3	6.5	6.57	101.08	0.252	0.252	100
100%	Rec. 1	12.5	12.53	100.24	0.504	0.508	100.79
	Rec. 2	12.5	12.41	99.28	0.504	0.503	99.8
	Rec. 3	12.5	12.35	98.8	0.504	0.502	99.6
150%	Rec. 1	18.5	18.43	99.62	0.756	0.769	101.72
	Rec. 2	18.5	18.23	98.54	0.756	0.754	99.74
	Rec. 3	18.5	18.51	100.05	0.756	0.751	99.34

Precision: The results of five replicate injections of mixed standard solutions showed very low %RSD for retention time, area of both components, and also for system suitability parameters. In repeatability test assay (in %) of metformin hydrochloride was found to be 97.81 ± 0.37 confidence interval while teneligliptin showed 98.85 ± 0.78 confidence interval. The % RSDs for six determinations were found to be 0.47% for metformin hydrochloride and 0.98% for teneligliptin, and results are reported in **Table 4**. The inter-day and intraday precisions results for assay were found to be very precise with low %RSD for both components of all three brands, and results were summarised in **Table 5**.

TABLE 4: REPEATABILITY SUMMARY

Sets	Metformin HCl		Teneligliptin	
	mg/ tab	Assay (%)	mg/ tab	Assay (%)
Set 1	489.69	97.94	20	100
Set 2	490.91	98.18	19.57	97.85
Set 3	491.21	98.24	19.89	99.45
Set 4	486.12	97.22	19.51	97.55
Set 5	486.25	97.25	19.76	98.8
Set 6	490.08	98.02	19.89	99.45
Mean	489.04	97.81	19.77	98.85
SD	2.28	0.46	0.19	0.97
%RSD	0.47	0.47	0.98	0.98
Confidence Interval	489.04 ±1.8	97.81 ±0.37	19.77 ±0.15	98.85 ±0.78

TABLE 5: INTER DAY AND INTRADAY PRECISION

Brand	Days	Sets	Metformin HCl		Teneligliptin	
			Assay (mg)	Assay (%)	Assay (mg)	Assay (%)
Brand 1		Set 1	500.07	100.01	19.76	98.8
	Day 1	Set 2	496.8	99.36	19.9	99.5
		Set 3	486.63	97.33	19.96	99.8
		Set 1	500.2	100.04	19.77	98.85
	Day 2	Set 2	497.34	99.47	19.79	98.95
		Set 3	496.64	99.33	19.82	99.1
Mean ± SD			496.28±4.98	99.26±0.99	19.83±0.08	99.17±0.4
Confidence interval			3.99	0.8	0.06	0.35
Brand 2		Set 1	494.26	98.85	19.75	98.75
	Day 1	Set 2	504.85	100.97	20.04	100.2
		Set 3	501.13	100.23	19.69	98.45
		Set 1	499.89	99.98	19.72	98.6
	Day 2	Set 2	492.5	98.5	19.77	98.85
		Set 3	493.05	98.61	19.66	98.3
Mean ± SD			497.61±5.06	99.52±1.01	19.77±0.14	98.86±0.68
Confidence interval			4.05	0.81	0.11	0.55
Brand 3		Set 1	490.8	98.16	19.43	97.15
	Day 1	Set 2	490.32	98.06	19.82	99.1
		Set 3	508.18	101.64	19.68	98.4
		Set 1	498.76	99.75	19.67	98.35
	Day 2	Set 2	496.29	99.26	19.86	99.3
		Set 3	493.15	98.63	19.9	99.5
Mean ± SD			496.25±6.68	99.25±1.34	19.73±0.17	98.63±0.87
Confidence interval			5.35	1.07	0.14	0.69

Specificity: Metformin hydrochloride was found to be degraded under the influence of 0.1 N NaOH, showing a total degradation of about 10.8% degradation with two degradation products at retention time 1.6min and 1.697 min, respectively. The UV light had also produced about 8% degradation with degradation products at retention time of 3.77 min and 5.78 min respectively. Other forced degradation agents like 0.1 N HCl or heat or H_2O_2 did not have much impact on metformin hydrochloride. However, teneligliptin was found to be quite stable under all conditions showing no major degradation products. The chromatogram for forced degradation of metformin hydrochloride by 0.1N NaOH and UV light are represented in **Fig. 7** and **Fig. 8** respectively.

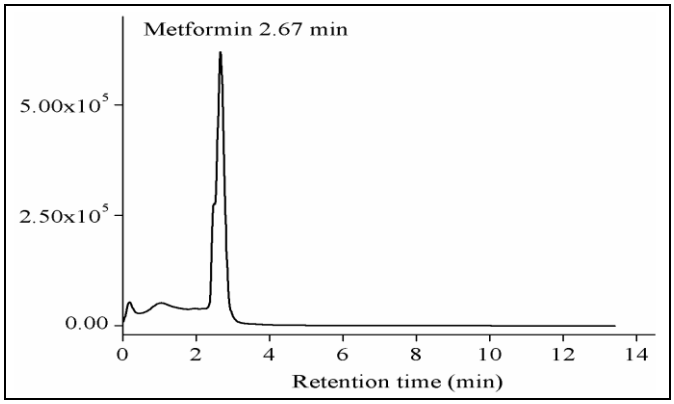

FIG. 7: FORCED DEGRADATION OF METFORMIN HYDROCHLORIDE BY 0.1 N NaOH

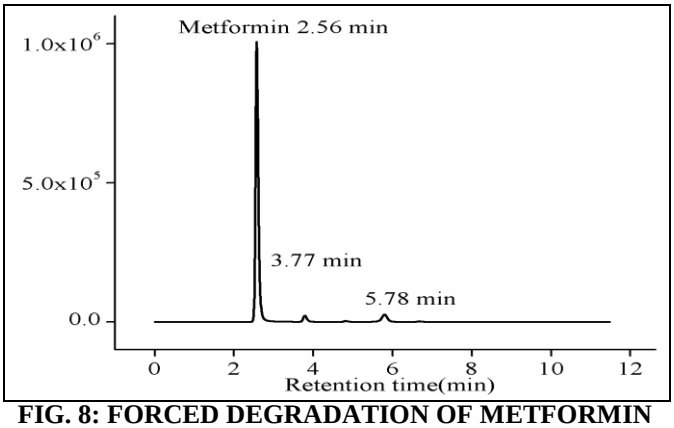

FIG. 8: FORCED DEGRADATION OF METFORMIN BY UV LIGHT

Robustness: The method was found to be very robust as deliberate variations did not lead to an appreciable change in peak shape, system suitability parameters like tailing factor, plate count, and resolution. The summary of the assay of the sample under deliberately varied conditions is given in **Table 6**.

TABLE 6: ROBUSTNESS DATA FOR ASSAY UNDER VARIED CONDITIONS

Parameters	Experimental conditions	Metformin HCl		Teneligliptin	
		Assay (mg)	Assay (%)	Assay (mg)	Assay (%)
Wavelength	253	490.8	98.16	19.59	97.95
	255	498.02	99.6	19.76	98.8
	257	503.26	100.65	19.93	99.65
Flow rate	0.9	492.77	98.55	19.89	99.45
	1.0	498.02	99.6	19.76	98.8
	1.1	492.19	98.44	19.87	99.35
Temperature	33ºC	490.81	98.16	19.78	98.9
	35ºC	498.02	99.6	19.76	98.8
	37ºC	491.09	98.22	19.81	99.05
CH_3OH :buffer	52:48	489.12	97.82	20.1	100.5
	50:50	498.02	99.6	19.76	98.8
	48:52	490.68	98.14	19.92	99.6
pH	5.3	492.88	98.58	19.98	99.9
	5.5	498.02	99.6	19.76	98.8
	5.7	499.55	99.91	19.87	99.35
Mean± SD		494.88±4.27	98.98±0.853	19.84±0.121	99.18±0.605
%RSD		0.86	0.86	0.61	0.61
Confidence interval		2.16	0.43	0.06	0.31

System Suitability Testing: System suitability is an integral part of the method validation study. System suitability testing is used to verify that the reproducibility of the system is adequate for the analysis to be performed. System suitability was assessed from the replicate injections of a mixed standard solution of 250 µg/ml metformin hydrochloride and 10 µg/ml teneligliptin under optimized chromatographic condition. Parameters such as theoretical plates, tailing factor, capacity factor were determined and summarized in **Table 7**.

TABLE 7: SYSTEM SUITABILITY PARAMETERS

Parameters	Metformin HCl	Teneligliptin
Concentration range (µg/ml)	20-1000	2-50
Retention time (min)	2.52	7.9
Theoretical plate	6500	8100
Tailing factor	1.5	1.2
Capacity factor (*k'*)	4.07	14.8
Resolution	-	22.2
LOD (µg/ml)	16.81	0.044
LOQ (µg/ml)	50.94	0.134

CONCLUSION: The proposed method is supported by full validation parameters and proved to be very specific as all degradants produced during forced degradation study are found to be well separated from the peaks of interests. The robustness is established from precise assay results (low % RSD) obtained under varied chromatographic conditions. The method offers simplicity in terms of short analysis time, isocratic mode of elution, easy sample preparation technique and wide concentration range, low LOD-LOQ values for both components, the effective resolution with reproducible system suitability parameters. The method has produced good accurate results for finished product formulations without any interference from the excipients or any degradation products. So, these advantages make this method reliable for the intended purpose.

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CONFLICTS OF INTEREST: The authors have declared no conflicts of interest.

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