IJBPAS, September, 2024, 13(9): 4210-4224

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

STABILITY INDICATING HPLC METHOD FOR SIMULTANEOUS ESTIMATION OF REMOGLIFLOZIN ETABONATE AND TENELIGLIPTIN IN TABLET DOSAGE FORM

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Received 18th July 2023; Revised 20th Sept. 2023; Accepted 1st Dec. 2023; Available online 1st Sept. 2024

https://doi.org/10.31032/IJBPAS/2024/13.9.8280

ABSTRACT

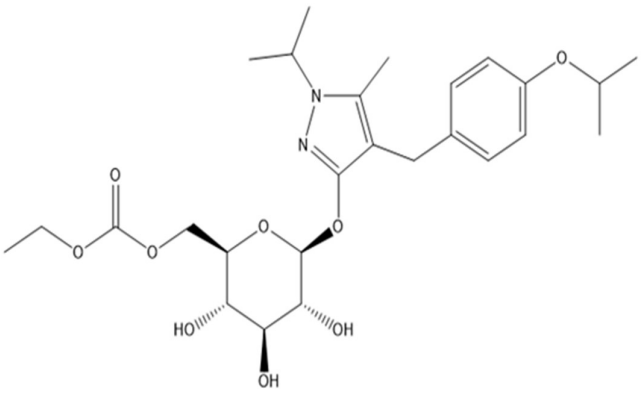
Remogliflozin etabonate (REMO) and Teneligliptin (TNG) have been simultaneously estimated using reliable and accurate reverse phase liquid chromatographic technique in tablet dose form. The stationary phase used was BDS Hypersil C18 column (250 x 4.6 mm, 5µ), while the mobile phase was a 75:25 (% v/v) Methanol: Potassium Dihydrogen Phosphate buffer combination. The analysis was conducted at 242 nm with a mobile phase flow rate of 1 mL/min. The method was linear in the concentration range of 100-200 µg/mL for Remogliflozin Etabonate and 10-20 µg/mL for Teneligliptin with correlation coefficient (r^2) 0.998 and 0.996 respectively. Teneligliptin and Remogliflozin etabonate had retention times of 3.20 and 5.71 minutes, respectively. The limit of detection was 1.392 µg/mL (REMO) and 0.288 µg/mL (TNG). The limit of quantification was 4.22 µg/mL (REMO) and 0.874 µg/mL (TNG). It was discovered that the percent recoveries at 80%, 100%, and 120% were within the range of 98-102%. According to the ICH Q2 (R2) guideline, the suggested method's linearity, accuracy, precision, and robustness all were verified. Studies on forced degradation were carried out to determine the potential degradation mechanism. With a noticeable difference in their retention time values, the deteriorated product peaks were clearly separated from the peak of the pure medication. In both

medications, greatest degradation was seen with hydrogen peroxide during the stress assay with acid, base, peroxide, and temperature, suggesting the susceptibility of the molecule towards oxidative stress. Remogliflozin etabonate and Teneligliptin can be evaluated and stability samples can be analyzed using the established approach.

Keywords: Remogliflozin etabonate, Teneligliptin, Liquid chromatography, Forced degradation, validation

INTRODUCTION

It's safe to state that one of the most ancient conditions affecting people is diabetes mellitus (DM). Type 2 diabetes is brought on by the interaction of genetic, environmental, and behavioral risk factors. Teneligliptin and Remogliflozin etabonate are both anti-diabetic medications **[1-3]**. REMO causes the body to expel excess sugar through the urine. On the other hand, TNG functions by increasing the pancreas' synthesis of insulin and lowering the hormones that raise blood sugar levels. The chemical name for remogliflozin etabonate is 5-Methyl-4-[4-(1-methylethoxy)benzyl]. 1-(1-methylethyl)-1H-pyrazol-3-yl-6-O-(ethoxycarbonyl)-β-D-glucopyranoside **[4-6]**. For the treatment of Type 2 Diabetes Mellitus, SGLT-2 inhibitors are employed. Remogliflozin inhibits the sodium glucose transport proteins (SGLT), which are in charge of reabsorbing glucose in the kidney. The urine is used to eliminate blood sugar when this transporter is inhibited. Remogliflozin primarily targets SGLT-2. It is Remogliflozin etabonate's mechanism. Its chemical structure is $C_{26}H_{38}N_2O_9$. Remogliflozin etabonate has a molecular weight of 522.595 $g \cdot mol^{-1}$. Remogliflozin etabonate is soluble in Ethanol, DMSO and Dimethyl Formamide **[7-8]**.



ethyl (((2*R*,3*S*,4*S*,5*R*,6*S*)-3,4,5-trihydroxy-6-((4-(4-isopropoxybenzyl)-1-isopropyl-5-methyl-1*H*-pyrazol-3-yl)oxy)tetrahydro-2*H*-pyran-2-yl)methyl) carbonate

Figure 1: Chemical structure of Remogliflozin Etabonate

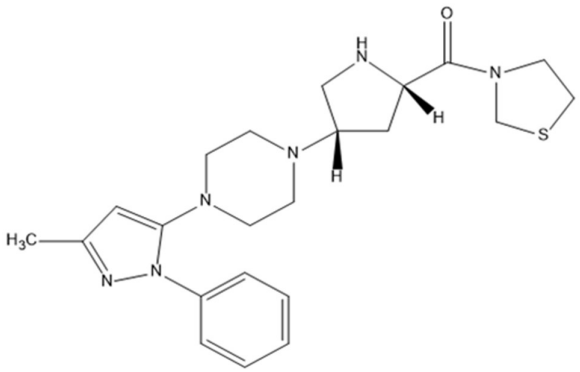


Figure 2: Chemical structure of Teneligliptin

The molecular name for teneligliptin is (2S,4S)-4-[4-(3-Methyl-1-phenyl-1H-pyrazol-5-yl)-1-piperazinyl].-2-pyrrolidinyl}(1,3-thiazolidin-3-yl)methanone. For the treatment of Type 2 Diabetes Mellitus, a DPP-4 inhibitor is employed **[9-14]**. Teneligliptin prevents DPP-4 enzymes from functioning, slowing the incretins' rapid breakdown. Furthermore, it increases the pancreas' synthesis of insulin while decreasing glucagon levels, an insulin counter-hormone, to further lower blood sugar levels. Teneligliptin's mechanism is what it is. Its chemical structure is $C_{22}H_{30}N_6OS$.Teneligliptin has a molecular weight of 426.6 $g{\cdot}mol^{-1}$. Dimethyl Formamide, DMSO, and Ethanol in all Teneligliptin is soluble.

Various methods for determining Remogliflozin and Teneligliptin have been published, according to a literature review. Remogliflozin and Teneligliptin have been determined in some articles, either alone or in combination with Metformin, Ertugliflozin, Rosuvastatin, Pioglitazone, Vildagliptin, and Dapagliflozin. UV, UPLC, LC-MS, LC-MS/MS are also reported in bulk and formulation **[15-17]**.

MATERIALS AND METHOD

Lupin Ltd. in Vadodara and Bajaj Healthcare Pvt. Ltd. in Vadodara, respectively, provided gift samples of the pharmaceutical grade drugs Remogliflozin etabonate and Teneligliptin. We used potassium dihydrogen phosphate, sodium hydroxide, HPLC grade methanol (Rankem (Avantor Performance Material India Ltd.)), and H_2O_2 (Finar Limited). The ZITA PLUS R (produced by Glenmark Pharmaceutical Ltd.) pill, which contains 10 mg of Teneligliptin and 100 mg of Remogliflozin etabonate, was purchased from a neighborhood pharmacy and used for the analysis of the commercial formulation.

Chromatographic conditions:

Shimadzu HPLC i-series LC-2050C with Photo Diode Array (PDA) detector was used. BDS Hypersil C18 column (250 x 4.6 mm, 5µ) was used as stationary phase. Methanol: Potassium Dihydrogen phosphate buffer (75:25, %v/v) was used as a mobile phase. Eluents are monitored at 242 nm, and

the mobile phase flow rate was held constant at 1 mL/min. Injection volume was 10 µL. Run time was kept at 7 minutes. The chromatographic data were recorded using Labsolutions software.

Selection of wavelength

Both medications are soluble in Methanol, DMSO, and ACN according to solubility tests, although Methanol is more cost-effective than DMSO and Acetonitrile. Methanol is therefore chosen as the solvent for the further procedure. The chosen wavelength is 242 nm **(Figure 3)**.

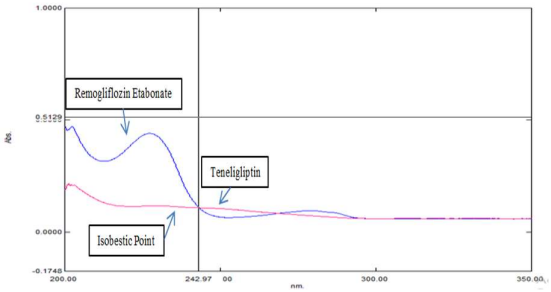


Figure 3: overlay spectra

Preparation of standard stock solution

Preparation for Standard Solution of Remogliflozin Etabonate: 10 mg of Remogliflozin etabonate was dissolved in 10mL of methanol to create standard stock solution of Remogliflozin Etabonate (1000 µg/mL).

Preparation for Standard Solution of Teneligliptin: 10 mg of Teneligliptin was dissolved in 10mL of methanol to create standard stock solution of Teneligliptin (1000 µg/mL).

Preparation for Standard Solution of Remogliflozin Etabonate and Teneligliptin in combination: A standard mixture solution of Remogliflozin Etabonate and Teneligliptin (10:1) was prepared by taking 1 mL from standard solution of Remogliflozin Etabonate (100 µg/mL) and 0.1 mL from standard solution of Teneligliptin (10 µg/mL) in a same 10 mL volumetric flask and diluting up to the mark with Methanol.

METHOD VALIDATION

System suitability: Under ideal chromatographic conditions, system suitability tests were carried out on freshly produced solutions of Teneligliptin and Remogliflozin etabonate.

Linearity: The linearity of the method was obtained by preparation of the calibration standards of 5 different concentrations in 3 replicates. The calibration curve plots for Teneligliptin and Remogliflozin etabonate were obtained by plotting the peak areas on the y-axis and concentrations on the X-axis over the concentration ranges of 10-20 µg/mL for Teneligliptin and 100-200 µg/mL for Remogliflozin etabonate. The correlation coefficient should be greater than 0.99.

Accuracy: Recovery studies were used to test the method's accuracy by adding a known amount of pure standard medication to the sample solution and recovering the same in terms of peak regions. Standard was added to the sample at concentrations that were 80%, 100%, and 120% of the test

concentrations. The resulting spiked sample performed a triple analysis. Each level's recovery percentage should be between 98% and 102%.

Precision

Interday precision: On various days, sample solutions were injected under ideal conditions and their peak regions were noted. %RSD for the peak areas of the standard injection results should not be greater than 2.

Intraday precision: Sample solutions were injected under optimized conditions on same day at different time interval and their peak regions were recorded. %RSD for the peak areas of the standard injection results should not be greater than 2.

Repeatability: On the same day, six identical samples of the sample solutions were injected under optimal conditions, and area of peaks were noted. The peak areas of the six replicate injection results should have %RSD of not more than 2 percent.

Robustness: By intentionally making small modifications to the method, such as the flow rate, mobile phase ratio, and analyst, the robustness of the method was assessed. The collected values, however, should fall within the ICH guidelines' limits and should not show any significant alterations.

Limit of detection and limit of quantitation (LOD and LOQ): LOD stands for lowest detectable concentration, which cannot always be precisely measured. It is measured using the formula **LOD=3.3 x SD/Slope**

The lowest amount of analyte in the solution that can be accurately and precisely quantified is known as the limit of quantification, or LOQ. **LOQ=10 x SD/Slope**

FORCED DEGRADATION STUDIES

Forced degradation studies were carried out for Acid degradation (0.1 N HCl), Alkali degradation (0.1 N NaOH), Oxidative degradation (3% H_2O_2), Photolytic degradation (UV light), Thermal degradation (70°C heating).

Procedure:

Acid degradation studies: Pipette out mixture's stock solution (10 g/mL Teneligliptin and 100 g/mL Remogliflozin etabonate), and put it to a 10 mL volumetric flask, then add freshly made 0.1 N HCl and the mixture should be stored for 3 hours. Add 0.1 N NaOH solution to neutralize it and fill the remaining space with methanol. Inject the prepared sample, under optimal conditions, verify the peak area.

Alkali degradation studies: Pipette out mixture's stock solution (10 g/mL Teneligliptin and 100 g/mL Remogliflozin etabonate), and put it to a 10 mL volumetric flask, then add freshly made 0.1 N NaOH and the mixture should be stored for 3 hours. Use a solution of 0.1 N HCl to neutralize the sample and fill the remaining space with

methanol. Inject the prepared sample, under ideal conditions, verify the peak area.

Oxidative degradation studies: Pipette out mixture's stock solution (10 g/mL Teneligliptin and 100 g/mL Remogliflozin etabonate), add it to a 10 mL volumetric flask, then add prepared 3% hydrogen peroxide. After that, leave the mixture for two hours and make up the volume with methanol. Inject the prepared sample, under optimum conditions, verify the peak area.

Photolytic degradation studies: Take stock solution of mixture (10 µg/mL Teneligliptin and 100 µg/mL Remogliflozin etabonate), and add into a 10 mL flask and make up the volume with methanol. Keep the mixture in UV Chamber for 5 hours. Inject the sample and check the peak area at optimized conditions.

Thermal degradation studies: Take stock solution of mixture (10 µg/mL Teneligliptin and 100 µg/mL Remogliflozin etabonate), and add into a 10 mL flask and make up the volume with methanol. Keep the mixture in hot air oven at 70°C for 3 hours. Inject the sample and check the peak area at optimized conditions

Formulation analysis The solution that is prepared from tablet formulation ZITA PLUS R of Remogliflozin etabonate and Teneligliptin was analyzed in developed method. The results which are observed during analysis were verified for the confirmation of the applicability of the developed method for the analysis of Teneligliptin and Remogliflozin etabonate in pharmaceutical formulations.

RESULTS AND DISCUSSION

System suitability: Appropriate tests were performed to check chromatographic reproductiveness and system suitability for their effectiveness in drug analysis. Results are shown in **Table 1** and **Figure 4**.

Table 1: System suitability test

Parameters	Observed Value	
	Remogliflozin Etabonate	Teneligliptin
Retention time	5.712	3.200
Peak area	251341	151122
Theoretical Plate	6411	4061
Tailing factor	0.949	0.912

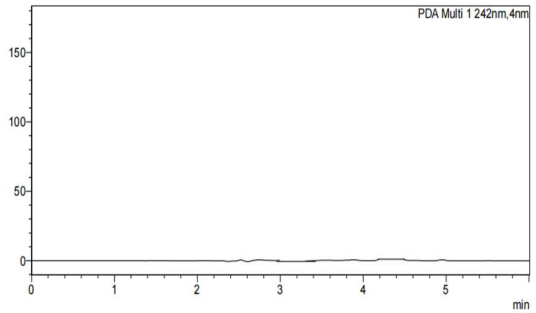


Figure 4: Blank

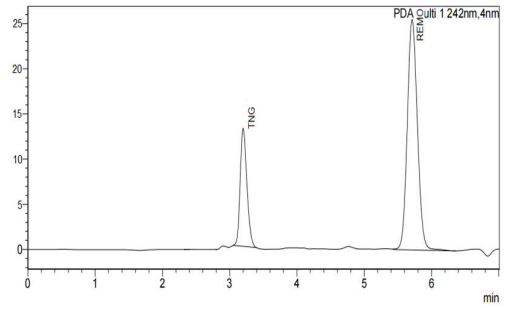


Figure 5: HPLC Chromatogram of standard Teneligliptin and Remogliflozin etabonate

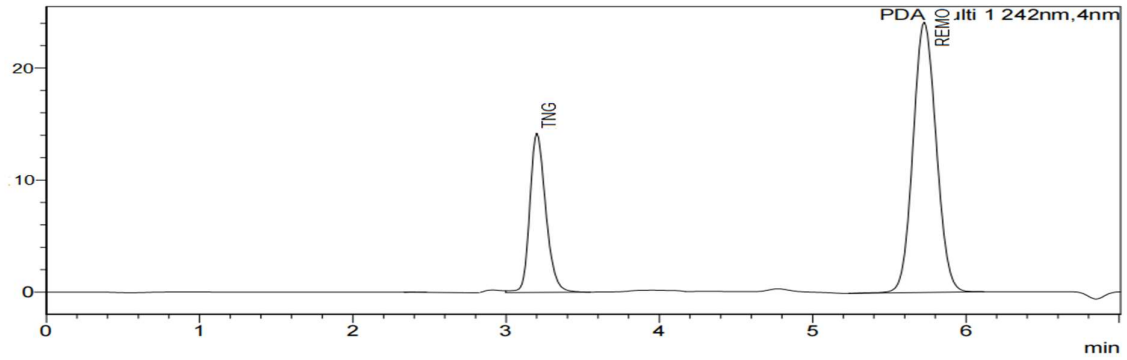


Figure 6: HPLC Chromatogram of sample solution (Tablet formulation)

Linearity: The linearity for Teneligliptin and Remogliflozin etabonate were carried out by analysis of mixture standard solution in range of 10-20 µg/mL and 100-200 µg/mL respectively. 1, 1.25, 1.5, 1.75, 2 mL solutions were pipette out from the stock solution of Remogliflozin etabonate (1000 µg/mL) and Teneligliptin (100 µg/mL) and transfer to 10 mL volumetric flask and make up the volume with methanol to get 100, 125, 150, 175, 200 µg/mL and 10, 12.5, 15, 17.5, 20 µg/mL for REMO and TNG respectively. Results are shown in **Table 2**. Calibration curve for Remogliflozin etabonate and Teneligliptin were shown in **Figure 7, Figure 8** and **Figure 9**.

Table 2: Linearity data for Remogliflozin Etabonate and Teneligliptin

Sr. No	Remogliflozin Etabonate			Teneligliptin		
	Conc. (µg/ml)	Peak Area ±SD	%RSD	Conc. (µg/ml)	Peak Area ±SD	%RSD
1	100	196328.6± 1839.3	0.93687202	10	96237.6± 1053.4	1.094680835
2	125	318595.3± 811.9	0.254843705	12.5	123156± 1067.4	0.866777997
3	150	417803± 2191.6	0.5245551	15	155313.3± 1393.9	0.897522981
4	175	533782.6± 4839.2	0.906598545	17.5	181054.3± 924.6	0.510679965
5	200	633502± 1046.3	0.165164847	20	217892± 1174.8	0.539177123

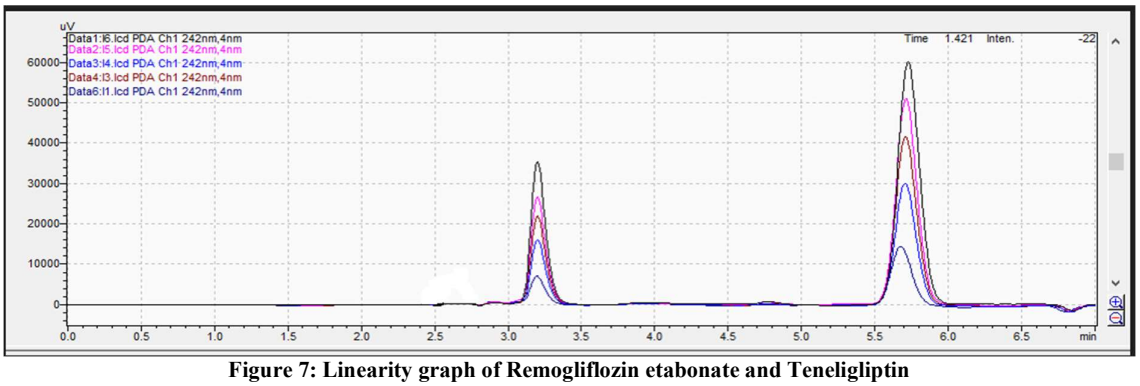


Figure 7: Linearity graph of Remogliflozin etabonate and Teneligliptin

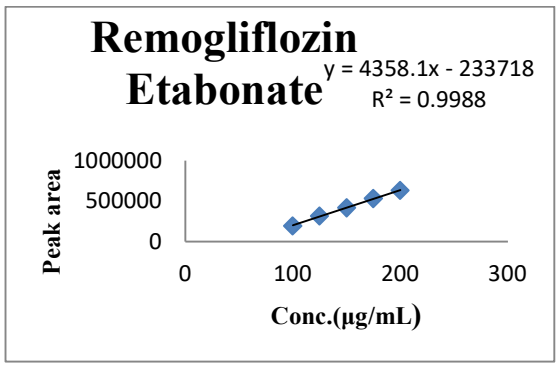


Figure 8: Calibration curve of Remogliflozin etabonate

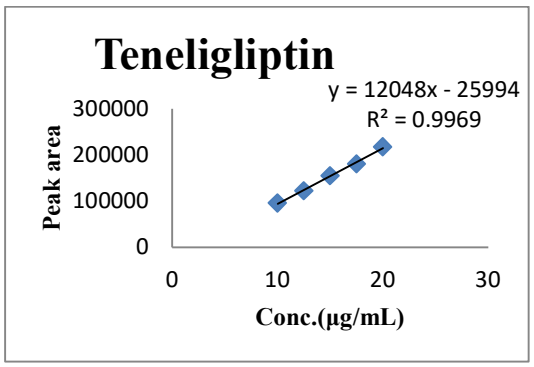


Figure 9: Calibration curve of Teneligliptin

Precision

Interday Precision: Standard solutions containing 100, 150, 200 µg/mL of Remogliflozin etabonate and 10, 15, 20 µg/mL of Teneligliptin were analyzed three times on different days and %RSD was calculated. **Table 3**.

Table 3: Interday precision for Remogliflozin etabonate and Teneligliptin

Conc.(µg/ml) REMO	Peak area± SD	%RSD	Conc.(µg/ml) TNG	Peak area± SD	%RSD
100	196948.3± 1038.2	0.527188099	10	96441± 788.1	0.817142374
150	417769.6± 1149.7	0.275216589	15	155646.6± 873.1	0.560897297
200	634035.3± 1338.1	0.21104577	20	217825.3± 1072.261318	0.492257398

Intraday precision: Standard solutions containing 100, 150, 200 µg/mL of Remogliflozin etabonate and 10, 15, 20 µg/mL of Teneligliptin were analyzed three times on same day at different time intervals and % RSD was calculated **Table 4**.

Table 4: Intraday precision for Remogliflozin etabonate and Teneligliptin

Conc.(µg/ml) REMO	Peak area± SD	%RSD	Conc.(µg/ml) TNG	Peak area± SD	%RSD
100	196948.3± 1402.1	0.711868766	10	96343± 914.5	0.949268748
150	417369.6± 1158.8	0.277659779	15	155147.3± 1475.5	0.951065146
200	634235.3± 1499.5	0.236438218	20	217566.3± 1497	0.688068369

Repeatability: Six replicates of sample solutions 125 µg/mL of Remogliflozin etabonate and 12.5 µg/mL of Teneligliptin were injected under optimized conditions and their peak regions were recorded. %RSD for the peak areas of the 6 replicates was calculated. **Table 5**.

Table 5: Repeatability data for Remogliflozin etabonate and Teneligliptin

DRUG	Concentration (µg/ml)	No. of Replicates		Peak area± SD	%RSD
Teneligliptin	10 (µg/ml)	1 2 3 4 5 6	123469 122521 124455 125143 122768 125436	123965.3 ± 1229.2	0.99162805
Remogliflozin etabonate	100 (µg/ml)	1 2 3 4 5 6	318713 317045 318055 319526 319998 318060	318566 ± 1079.3	0.33879898

Accuracy

For Remogliflozin etabonate: 100 µg/ml drug solution was taken in three different flask and label them as 80%, 100% and 120% , then spike the solution with standard drug according to labeled flasks and make up the volume with methanol. The peak area of Remogliflozin etabonate was calculated at each level and %recoveries were computed. Results are shown in **Table 6**.

Table 6: Accuracy data of Remogliflozin etabonate

Conc. of Formul-ation(µg/ml)	Level	Conc. of API spiking (µg/ml)	Total Conc. (µg/ml)	Peak area	Amount Found (µg/ml)	Amount Recovered (µg/ml)	Mean recovery ±SD	% RSD
100(µg/ml)	80%	80	180	553122	180.54	100.3	100.09 ±0.18	0.188592
		80	180	551145	180.09	100.05		
		80	180	550289	179.89	99.93		
	100%	100	200	635471	199.44	99.72	99.92 ±0.17	0.173632
		100	200	637999	200.02	100.01		
		100	200	638215	200.07	100.03		
	120%	120	220	723421	219.62	99.82	99.93 ±0.10	0.101224
		120	220	725123	220.01	100		
		120	220	724987	219.98	99.99		

For Teneligliptin: 10 µg/ml drug solution was taken in three different flask and label them as 80%, 100% and 120% , then spike the solution with standard drug according to labeled flasks and make up the volume with methanol. The peak area of Teneligliptin was calculated at each level and %recoveries were computed. Results are shown in **Table 7**.

Table 7: Accuracy data of Teneligliptin

Conc. of Formul-ation (µg/ml)	Level	Conc. of API spiking (µg/ml)	Total Conc. (µg/ml)	Peak area	Amount Found (µg/ml)	Amount Recovered (µg/ml)	Mean recovery ±SD	% RSD
10(µg/ml)	80%	8	18	191038	18.01	100.05	100.03 ±0.08622	0.086188
		8	18	190765	17.99	99.94		
		8	18	191181	18.02	100.11		
	100%	10	20	217898	20.24	101.2	100.61 ± 0.69	0.689172
		10	20	216981	20.16	100.8		
		10	20	214696	19.97	99.85		
	120%	12	22	238512	21.95	99.77	100.07 ± 0.27	0.274762
		12	22	239434	22.03	100.13		
		12	22	239943	22.07	100.31		

LOD and LOQ (Table 8): The LOD was found out from the set of 3 calibration curves used to determine linearity. The LOD can be calculated as, **LOD = 3.3** x **SD/Slope**

The LOQ was calculated from the set of 3 calibration curves used to determine linearity. The LOQ may be calculated as, **LOQ = 10** x **SD/Slope**

Where, SD= standard deviation of Y-intercepts of three calibration curves, slope= mean slope of the three calibration curves.

Table 8: LOD and LOQ data of Teneligliptin and Remogliflozin etabonate

PARAMETERS	REMOGLIFLOZIN	TENELIGLIPTIN
Slope	4358.1	12048
Standard deviation (SD)	1839.348	1053.495
LOD (µg/ml)	1.392	0.288
LOQ (µg/ml)	4.22	0.874

Robustness (Table 9 and 10): Following parameters were changed one by one and their effect was observed.

Table 9: Robustness data for Remogliflozin etabonate

Sr. No	Factor	Level	Peak Area ± SD	%RSD
1	Change in Wavelength (242±2 nm)	240 nm	160873.3±102.48	0.063703
		244 nm	161594.7±520.93	0.32237
2	Change in Volume of Buffer (25±2mL)	23	159436.7±873.12	0.547631
		27	154501.3±1230.55	0.796465
3	Change in Flow rate (1±0.2 mL/min)	0.8	150576.7±240.56	0.159761
		1.2	123417±884.56	0.716731

Table 10: Robustness data for Teneligliptin

Sr. No	Factor	Level	Peak Area ± SD	%RSD
1	Change in Wavelength (242±2 nm)	240 nm	376460±2437.90	0.647586
		244 nm	375742±2102.11	0.559456
2	Change in Volume of Buffer (25±2 mL)	23	314705.3±2779.61	0.883245
		27	318483.7±1601.68	0.502907
3	Change in Flow rate (1±0.2 mL/min)	0.8	343387.3±2206.47	0.642561
		1.2	298213.7±2082.62	0.698366

Assay:

The average weight of twenty pills was determined. They were then ground using a mortar and pestle, and the amount of powder that was placed into a 100 mL volumetric flask was precisely weighed to equal 10 mg of Teneligliptin and 100 mg of Remogliflozin etabonate. The mixture was then given a 20-minute sonication after receiving 50 mL of methanol. To obtain a concentration of 100 µg/mL for Teneligliptin and 1000 g/mL for Remogliflozin etabonate, the volume was further made up with methanol. The remedy was then filtered. To obtain a concentration of 10 µg/mL for Teneligliptin and 100 g/mL for Remogliflozin etabonate, 1 mL of the filtered aliquot was withdrawn and transferred into a 10 mL volumetric flask, and diluted up to the mark with methanol. The results are shown in **Table 11**.

Table 11: Assay of Formulation (ZITA PLUS R)

Sr. No	Marketed Formulation		%Assay REMO±SD	%RSD	%ASSAY TNG±SD	%RSD
	REMO	TNG				
1	100(µg/ml)	10(µg/ml)	100.09±0.18	0.188592	100.03±0.08622	0.086188

Forced degradation studies

Acid degradation: The degradation that occurs due to addition of acid in peak area of REMO and TNG are shown in **Figure 10** and the %degradation was calculated and shown in **Table 12**.

Figure 10: Acid degradation of Mixture

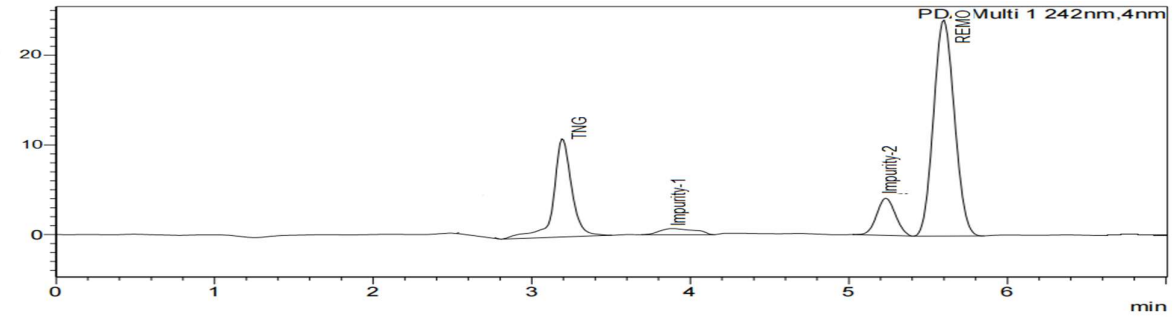


Figure 11: Base degradation of Mixture

Base degradation: The degradation that occurs due to addition of base in peak region of REMO and TNG are shown in **Figure 11** and the %degradation was calculated and shown in **Table 12**.

Oxidative degradation: The degradation that occurs due to addition of 3% H_2O_2 in peak area of REMO and TNG are shown in **Figure 12** and the %degradation was calculated and shown in **Table 12**.

Photolytic degradation: The degradation that occurs due to UV light in peak area of REMO and TNG are shown in **Figure 13** and the %degradation was calculated and shown in **Table 12**.

Thermal degradation: The degradation that occurs due to 70°C temperature in peak area of REMO and TNG are shown in **Figure 14** and the %degradation was calculated and shown in **Table 12**.

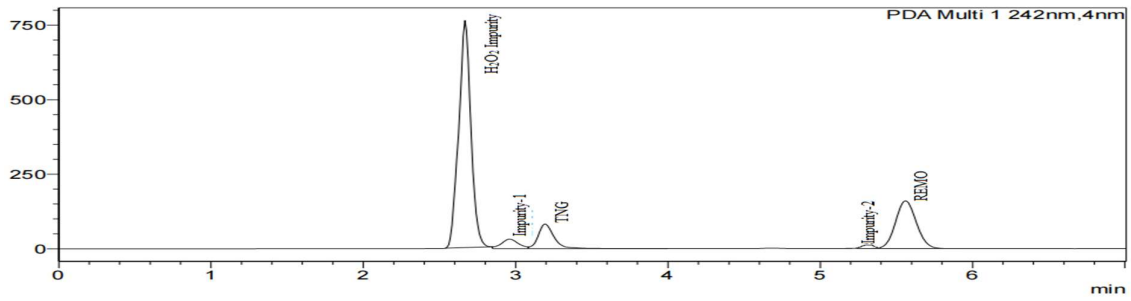


Figure 12: Oxidative degradation of mixture

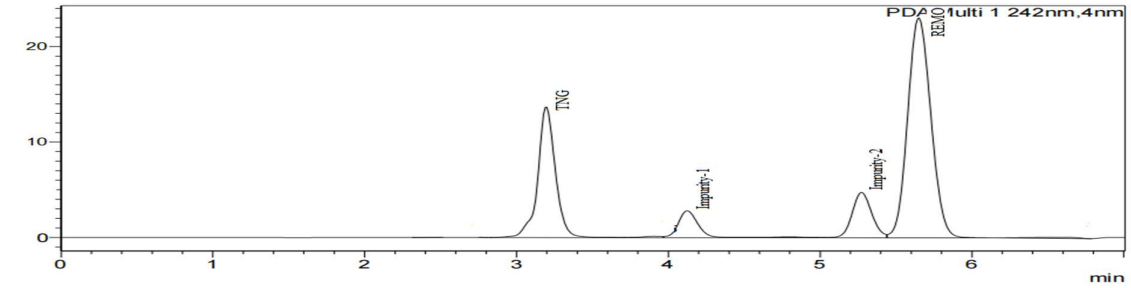


Figure 13: Photolytic degradation of Mixture

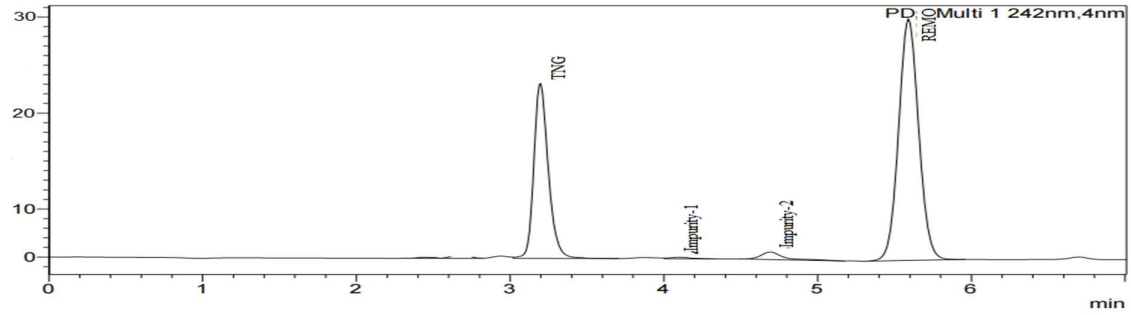


Figure 14: Thermal degradation of Mixture

Table 12: Forced degradation summery

Type of Degradation	Degradation Condition	Peak area		%Degradation	
		REMO	TNG	REMO	TNG
As such	-	251341	151122	-	-
Acid Degradation	0.1 N HCl at RT for 3 Hours	232145	137564	7.63%	8.97%
Alkali Degradation	0.1 N NaOH at RT for 3 Hours	213689	139125	14.98%	7.93%
Oxidative Degradation	3% H_2O_2 at RT for 2 Hours	210749	121578	16.15%	19.5%
Thermal Degradation	70°C for 3 Hours	225930	141979	10.11%	6.05%
Photolytic Degradation	UV light for 5 Hours	230027	139727	8.48%	7.54%

CONCLUSION

In the current work, a straightforward, quick, accurate, and dependable RP-HPLC technique for the simultaneous measurement of remogliflozin etabonate and teneligliptin in pharmaceutical formulations in accordance with ICH criteria was developed and validated. The procedure complies with all system suitability and additional validation requirements. We may infer from the forced degradation that the peaks of the degraded product were clearly distinguished from the peak of the pure drug and had substantial

differences in their retention times. In both medications, greatest degradation was seen with hydrogen peroxide during the stress assay with acid, base, hydrogen peroxide, and temperature, suggesting the susceptibility of the molecule towards oxidative stress. Remogliflozin etabonate and Teneligliptin in tablet formulation can be evaluated and stability samples can be analyzed using the established approach.

ACKNOWLEDGEMENT

I would like to thank Parul Institute of Pharmacy and Research, Parul University, Limda to allow me to complete my project and providing all the necessary facilities.

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