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Validated Method for the Simultaneous Estimation of Remogliflozin and Teniligiptin in Bulk and Table Formulation by RP-HPLC Method

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ABSTRACT:

For the purpose of calculating Remogliflozin and Teneligliptin in pharmaceutical dosage form, a simple, precise, and accurate approach was developed. An Ascentis 150 x 4.6 mm, 5 m column was used to perform the chromatogram. In the mobile phase, 0.01N Kh2:30 is present. A flow rate of 1.0 milliliters per minute was used to force acetonitrile through the column in a 70:30 ratio. Teneligliptin's RSD was found to be 0.5 and Remogliflozin's at 2.706 percent. The retention times of both drugs were found to be 2.271 minutes and 0.6, respectively. %Teneligliptin and remogliflozin showed recovery rates of 99.63% and 99.73%, respectively. Remogliflozin and Teneligliptin regression models yielded LOD and LOQ values of 0.01 and 0.04 and 0.48 and 1.47, respectively. Remogliflozin's regression equation is y = 16468x + 2301, whereas Teneligliptin's is y 40715x + 60.86.

Keywords: Remogliflozin, Teneligliptin, RP-HPLC

INTRODUCTION:

Diabetes mellitus is a family of metabolic disorders characterized by abnormalities in either insulin action or secretion, or both, resulting in abnormally high blood sugar levels over time. Protein, fat, and carbohydrate metabolism abnormalities result from insulin's role as an anabolic hormone. At the level of insulin receptors, the signal transduction system, and/or effector enzymes or genes, these metabolic disorders are brought on by either inadequate insulin to provide an effective response or insulin resistance of target tissues, notably the liver, adipose tissue, and skeletal muscles.[1-6]

The "metabolic syndrome," a collection of illnesses characterized by obesity, insulin resistance, and many cardiovascular risk factors, is often linked to type 2 diabetes. One of the advancements in the treatment of type 2 diabetes is the recognition of the need for aggressive and early management of insulin resistance, dyslipidemia, hypertension, and albuminuria. Its activity is representative of a recently established class of anti-hyperglycemic drugs with a unique method of action.[7]

Type 2 diabetes is treated with a combination of two drugs called teneligliptin and remogliflozin etabonate. It aids in glycemic management for those with diabetes. It is usually administered when other diabetes drugs are not providing enough glycemic control. [8-14]

Chemically speaking, remogliflozin is C26H38N2O9, and it inhibits the type 2 sodium-glucose co-transporter (SGLT2). These drugs lower blood sugar by increasing the quantity of glucose expelled in the urine. Teneligliptin, a DPP-4 inhibitor (chemical formula C22H30N6OS), increases the amounts of active GLP-1 and GIP inhibitor by preventing DPP-4 enzymatic activity. Because of this, these inhibitors cure hyperglycemia in diabetic patients in a glucose-dependent manner by increasing blood insulin levels and decreasing serum glucagon levels.[16]

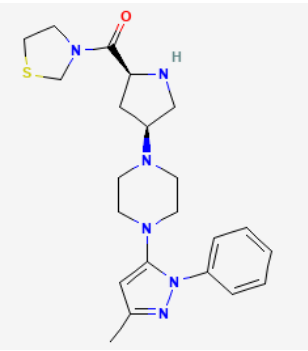


Figure 1: Structure of Teneligliptin

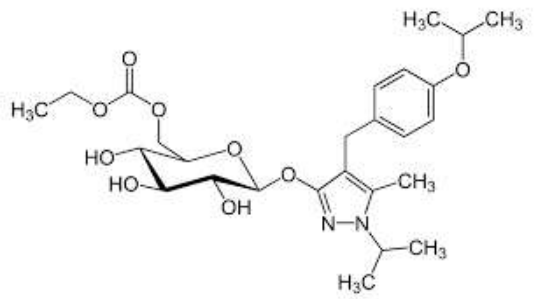


Figure 2: Structure of Remogliflozin

According to a literature review, there are some techniques for the simultaneous estimate of these medicines as well as others for assessment of the drugs alone or in combination with other drugs. Utilizing UV-Spectrophotometry RP-HPLC. There is no established technique for the stability-indicating simultaneous measurement of Remogliflozin and Teneligliptinby RP-HPLC in pharmaceutical dosage form, according to a survey of the literature. The primary goal of this work is to provide an efficient, quick, and accurate RP-HPLC approach for estimating of Remogliflozin and Teneligliptinin medicinal dose and tablet form. According to ICH recommendations, a proven approach was also used to estimate the amounts of Remogliflozin and Teneligliptin. [17-30]

MATERIALS AND REAGENTS

Remogliflozin and Teneligliptin pure drugs were received from Spectrum Pharma research solutions, Hyderabad. The combination tablet Remogliflozin and Teneligliptin (**Zita plus R**) was purchased from a local pharmacy store. Rankem in India provided all of the chemicals and buffers utilised in this method like Acetonitrile, Phosphate buffer, Methanol, Potassium dihydrogen Ortho phosphate buffer, Ortho-phosphoric acid, Distilled water.

Instrumentation and Chromatographic Conditions

For the development and validation method, an automated sample injector was employed with a WATERS HPLC, model: 2695 SYSTEM with Photo diode array detector. For the separation, a Discovery 150 (C18 250 mm x 4.6 mm, 5µm) column was employed. Acetonitrile is employed as mobile phase B, while 0.1% ortho phosphoric acid is used as mobile phase A. (35:65 Ratio). The analysis was done in isocratic mode with an injection volume of 10 mL and a flow rate of 1 mL/min. The duration was six minutes. The measurements were made at 254 nm.

PREPARATION OF SOLUTIONS

Diluent: Based up on the solubility of the drugs, diluent was selected, Acetonitrile and Water taken in the ratio of 50:50

Preparation of buffer:

Buffer: (0.1% OPA)

Accurately 1ml of OPA in a 1000ml of Volumetric flask add about 900ml of milli-Q water added and degas to sonicate and finally make up the volume with water.

Buffer: 0.01N Potassium dihyrogen ortho phosphate

Accurately weighed 1.36gm of Potassium dihyrogen Ortho phosphate in a 1000ml of Volumetric flask add about 900ml of milli-Q water added and degas to sonicate and finally make up the volume with water.

Buffer:0.01N Sodium dihydrogen phosphate

Accurately weighed 1.42gm of Potassium dihyrogen Ortho phosphate in a 1000ml of Volumetric flask add about 900ml of milli-Q water added and degas to sonicate and finally make up the volume with water then PH adjusted to 3.5 with dil. Orthophosphoric acid solution.

Preparation of Standard stock solutions: Accurately weighed 25mg of Remogliflozin, 25mg of Teneligliptin and transferred to 50ml volumetric flask. 3/4th of diluents was added to the flask and sonicated for 10 minutes. Flask was made up with diluents and labeled as Standard stock solution. (500µg/ml of Remogliflozin and 500µg/ml Teneligliptin)

Preparation of Standard working solutions (100% solution): 1ml from each stock solution was pipetted out and taken into a 10ml volumetric flask and made up with diluent. (50µg/ml of Remogliflozin and 50µg/ml of Teneligliptin).

Preparation of Sample stock solutions: weighed 25mg of Remogliflozin, 25mg of Teneligliptin and transferred to 50ml volumetric flask. 3/4th of diluents was added to the flask and sonicated for 10 minutes. Flask was made up with diluents and labeled as Standard stock solution. (500µg/ml of Remogliflozin and 500µg/ml Teneligliptin)

Preparation of Sample working solutions (100% solution): 1ml from each stock solution was pipetted out and taken into a 10ml volumetric flask and made up with diluent. (50µg/ml of Remogliflozin and 50µg/ml of Teneligliptin).

METHOD VALIDATION

To prove that the technique is suggested for routine analysis, the HPLC method's validation was done for the simultaneous estimation of Remogliflozin and Teneligliptin drug material in accordance with the ICH criteria.

Specificity: Checking of the interference in the optimized method. We should not find interfering peaks in blank and placebo at retention times of these drugs in this method. So this method was said to be specific.

Linearity: stock solutions of Remogliflozin and Teneligliptin is taken in to 6 different volumetric flasks and diluted to 10ml with diluents. Linearity solutions are prepared such that 0.25, 0.5, 0.75, 1, 1.25, 1.5ml.

Accuracy:

Preparation of Standard stock solutions: Accurately weighed 25mg of Remogliflozin, 25mg of Teneligliptinand transferred to 50ml volumetric flask. 3/4 th of diluents was added to the flask and sonicated for 10 minutes. Flask was made up with diluents and labeled as Standard stock solution. (500µg/ml of Remogliflozin and 500µg/ml Teneligliptin)

Preparation of 50% Spiked Solution: 0.5ml of sample stock solution was taken into a 10ml volumetric flask, to that 1.0ml from each standard stock solution was pipetted out, and made up to the mark with diluent.

Preparation of 100% Spiked Solution: 1.0ml of sample stock solution was taken into a 10ml volumetric flask, to that 1.0ml from each standard stock solution was pipetted out, and made up to the mark with diluent.

Preparation of 150% Spiked Solution: 1.5ml of sample stock solution was taken into a 10ml volumetric flask, to that 1.0ml from each standard stock solution was pipetted out, and made up to the mark with diluent.

Acceptance Criteria:

The % Recovery for each level should be between 98.0 to 102.

Robustness: Small deliberate changes in method like Flow rate, mobile phase ratio, and temperature are made but there were no recognized change in the result and are within range as per ICH Guide lines.

Robustness conditions like Flow minus (0.9ml/min), Flow plus (1.1ml/min), mobile phase minus, mobile phase plus, temperature minus (25°C) and temperature plus(35°C) was maintained and samples were injected in duplicate manner. System suitability parameters were not much affected and all the parameters were passed. %RSD was within the limit.

LOD sample Preparation: 0.25ml each from two standard stock solutions was pipetted out and transferred to two separate 10ml volumetric flasks and made up with diluents. From the above solutions 0.1ml each of Remogliflozin and Teneligliptin, solutions respectively were transferred to 10ml volumetric flasks and made up with the same diluents

LOQ sample Preparation: 0.25ml each from two standard stock solutions was pipetted out and transferred to two separate 10ml volumetric flask and made up with diluent. From the above solutions 0.3ml each of Remogliflozin and Teneligliptin, solutions respectively were transferred to 10ml volumetric flasks and made up with the same diluent.

System suitability parameters: The system suitability parameters were determined by preparing standard solutions of Remogliflozin (50ppm) and Teneligliptin (50ppm) and the solutions were injected six times and the parameters like peak tailing, resolution and USP plate count were determined.

Degradation studies:

Oxidation:

To 1 ml of stock solution of Remogliflozin and Teneligliptin, 1 ml of 20% hydrogen peroxide (H2O2) was added separately. The solutions were kept for 30 min at 60^0c. For HPLC study, the resultant solution was diluted to obtain 50 µg/ml & 50 µg/ml solution and 10 µl were injected into the system and the chromatograms were recorded to assess the stability of sample.

Acid Degradation Studies:

To 1 ml of stock s solution Remogliflozin and Teneligliptin, 1ml of 2N Hydrochloric acid was added and refluxed for 30mins at 60 ^{0}C. The resultant solution was diluted to obtain 50µg/ml & 50µg/ml solution and 10 µl solutions were injected into the system and the chromatograms were recorded to assess the stability of sample.

Alkali Degradation Studies:

To 1 ml of stock solution Remogliflozin and Teneligliptin, 1 ml of 2N sodium hydroxide was added and refluxed for 30mins at 60^0c. The resultant solution was diluted to obtain 50µg/ml & 50µg/ml solution and 10 µl were injected into the system and the chromatograms were recorded to assess the stability of sample.

Dry Heat Degradation Studies:

The standard drug solution was placed in oven at 105°C for 6 h to study dry heat degradation. For HPLC study, the resultant solution was diluted to 50µg/ml & 50µg/ml solution and 10µl were injected into the system and the chromatograms were recorded to assess the stability of the sample**.**

Photo Stability studies:

The photochemical stability of the drug was also studied by exposing the 200µg/ml& &100µg/ml solution to UV Light by keeping the beaker in UV Chamber for 7days or 200 Watt hours/m^2 in photo stability chamber. For HPLC study, the resultant solution was diluted to obtain 50µg/ml &50µg/ml solutions and 10 µl were injected into the system and the chromatograms were recorded to assess the stability of sample.

Neutral Degradation Studies:

Stress testing under neutral conditions was studied by refluxing the drug in water for 6hrs at a temperature of 60º. For HPLC study, the resultant solution was diluted to 50µg/ml&50µg/ml solution and 10 µl were injected into the system and the chromatograms were recorded to assess the stability of the sample**.**

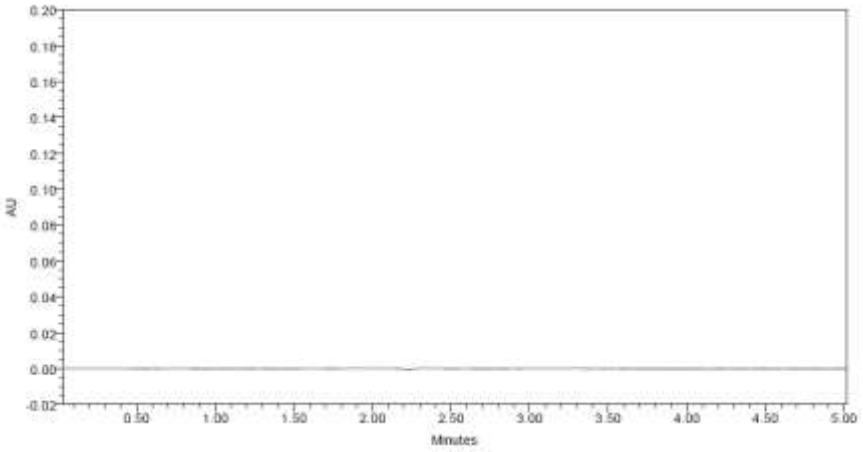
RESULTS AND DISCUSSIONS:

Table 1: System suitability table

S no	**Teneligliptin**			**Remogliflozin**			
Inj	RT(min)	USP Plate Count	Tailing	RT(min)	USP Plate Count	Tailing	Resolution
1	2.150	7484	1.19	2.665	9570	1.20	5.1
2	2.151	7635	1.21	2.666	9668	1.21	5.0
3	2.152	7729	1.24	2.669	9574	1.21	5.0
4	2.152	7801	1.25	2.669	9539	1.21	5.0
5	2.153	7554	1.31	2.669	9890	1.21	4.8
6	2.163	7263	1.19	2.684	9418	1.21	5.0

Table 2: Specificity data

Sample name	**retention time(Mins)**	**Area**
Remogliflozin	2.271	1404014
Teneligliptin	2.706	184644



Blank Chromatogram

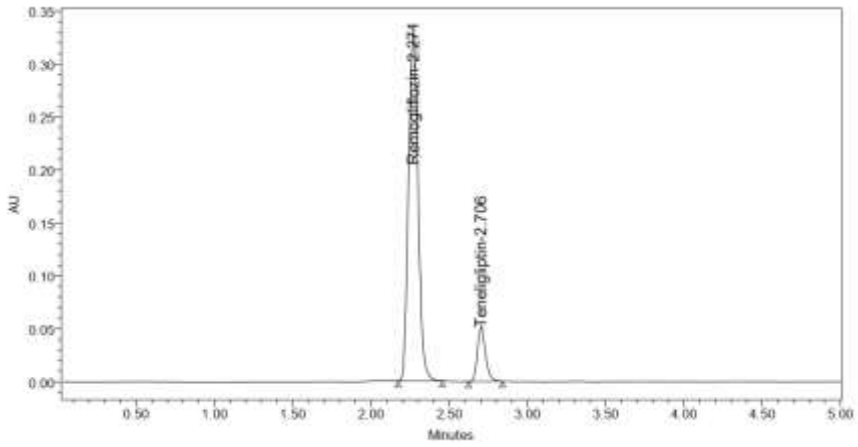
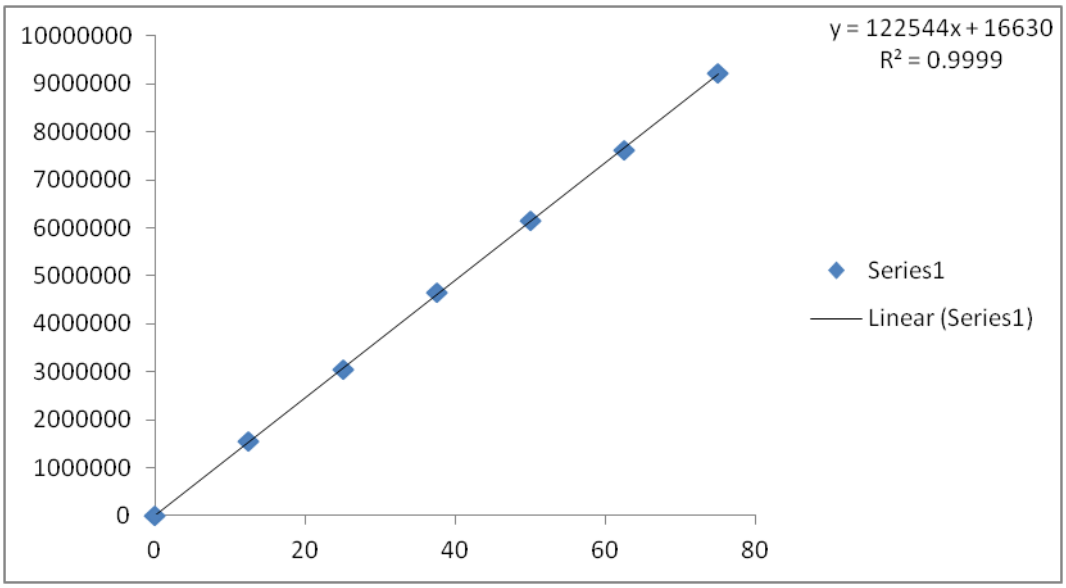


Figure 3: Specificity Chromatograms of Remogliflozin and Teneligliptin

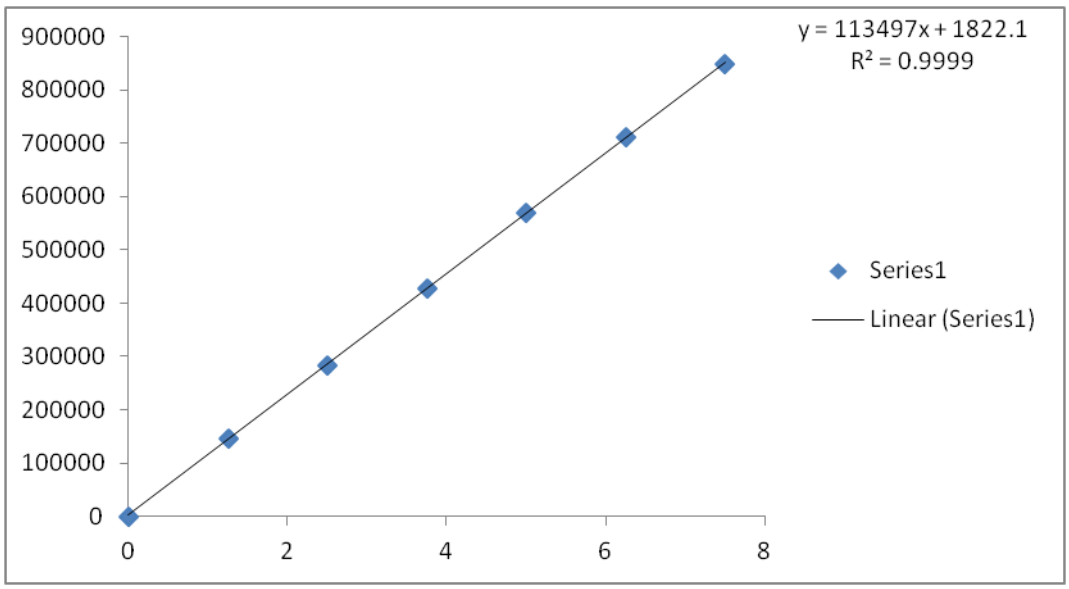
Linearity

Table 2: Linearity table for Remogliflozin and Teneligliptin:

Remogliflozin		**Teneligliptin**	
Conc (µg/mL)	**Peak area**	**Conc (µg/mL)**	**Peak area**
0	0	0	0
12.5	1563938	1.25	146761
25	3057007	2.5	283205
37.5	4657174	3.75	428246
50	6155979	5	569506
62.5	7631079	6.25	713403
75	9219062	7.5	850942



Calibration curve of Remogliflozin



Calibration curve of Teneligliptin

Accuracy:

Table 3: Accuracy table of Remogliflozin

% Level	**Amount Spiked (µg/mL)**	**Amount recovered (µg/mL)**	**% Recovery**	Mean %Recovery
50%	25	25.12	100.49	100.21%
	25	25.23	100.93	
	25	25.06	100.23	
100%	50	50.10	100.19	
	50	50.25	100.51	
	50	50.25	100.50	
150%	75	75.23	100.30	
	75	74.78	99.71	
	75	74.29	99.05	

Table 4: Accuracy table of Teneligliptin

% Level	**Amount Spiked (µg/mL)**	**Amount recovered (µg/mL)**	**% Recovery**	Mean %Recovery
50%	2.5	2.50	99.86	100.08%
	2.5	2.52	100.70	
	2.5	2.49	99.71	
100%	5	5.00	99.97	
	5	5.04	100.77	
	5	4.99	99.80	
150%	7.5	7.45	99.29	
	7.5	7.57	100.89	
	7.5	7.48	99.72	

System Precision: With regard to the working strength of Remogliflozin and Teneligliptin, six duplicate injections of the standard solution at 100% of the prescribed limit were analysed to determine the system accuracy. In Table 5, the results of the peak area are compiled.

Table 5: System precision

S. No	**Area of Remogliflozin**	**Area of Teneligliptin**
1.	6131938	317034
2.	6120578	318013
3.	6124564	317578
4.	6197459	313966
5.	6154973	318183
6.	6168890	314126
Mean	6149734	316483
S.D	29907.8	1930.0
%RSD	0.5	0.6

The % RSD for the peak areas of Remogliflozin and Teneligliptin obtained from six replicate injections of standard solution was within the limit of (<2%).

Method precision: Analyzing a sample of Remogliflozin and Teneligliptin allowed researchers to gauge the method's accuracy (Six individual sample preparations). Table 6 provides a summary of the data.

Table 6: Method precision

S. No	Area of Remogliflozin	Area of Teneligliptin
1.	6199386	315688
2.	6194152	315432
3.	6187372	314586
4.	6151005	318411
5.	6193195	319598
6.	6113489	317370
Mean	6173100	316848
S.D	34009.7	1936.2
%RSD	0.6	0.6

Results shows, the % RSD of Repeatability study was within the range for Remogliflozin and Teneligliptin is (<2%)

Table 7: Robustness

S.no	Condition	%RSD of Remogliflozin	%RSD of Teneligliptin
1	Flow rate (-) 0.8ml/min	0.4	0.3
2	Flow rate (+) 1.0ml/min	0.5	0.5
3	Mobile phase (-) 65B:35A	0.3	0.6
4	Mobile phase (+) 75B:25A	0.5	0.3
5	Temperature (-) 27°C	0.4	0.5
6	Temperature (+) 33°C	0.6	0.5

Table 8: Forced degradation for Remogliflozin and Teneligliptin

Stress condition	Solvent	Temp (^{0}C)	Exposed time
Acid	2N HCL	60^0c	30 mins
Base	2N NAOH	60^0c	30 mins
Oxidation	20% H_2O_2	60^0c	30 mins
Thermal	Diluent	105^0c	6 hours
Photolytic	Diluent	-	-
Hydrolytic	Water	60^0c	

DEGRADATION

Degradation Studies: Degradation studies were performed with the formulation and the degraded samples were injected. Assay of the injected samples was calculated and all the samples passed the limits of degradation

Table 9: Degradation results of Remogliflozin and Teneligliptin

Type of degradation	Remogliflozin			Teneligliptin		
	AREA	%RECOVERED	% DEGRADED	AREA	%RECOVERED	% DEGRADED
Acid	5894872	95.66	4.34	304132	95.91	4.09
Base	5901401	95.77	4.23	302092	95.26	4.74
Peroxide	5748911	93.30	6.70	298042	93.98	6.02
Thermal	6005350	97.46	2.54	308785	97.37	2.63
Uv	6059135	98.33	1.67	311982	98.38	1.62
Water	6110030	99.16	0.84	314346	99.13	0.87

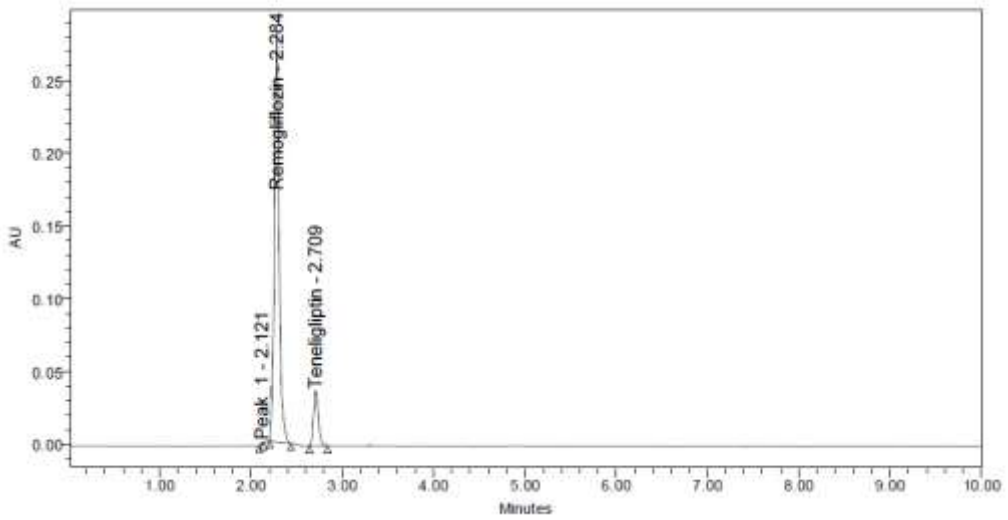


Figure 6: Acid chromatogram of Remogliflozin and Teneligliptin

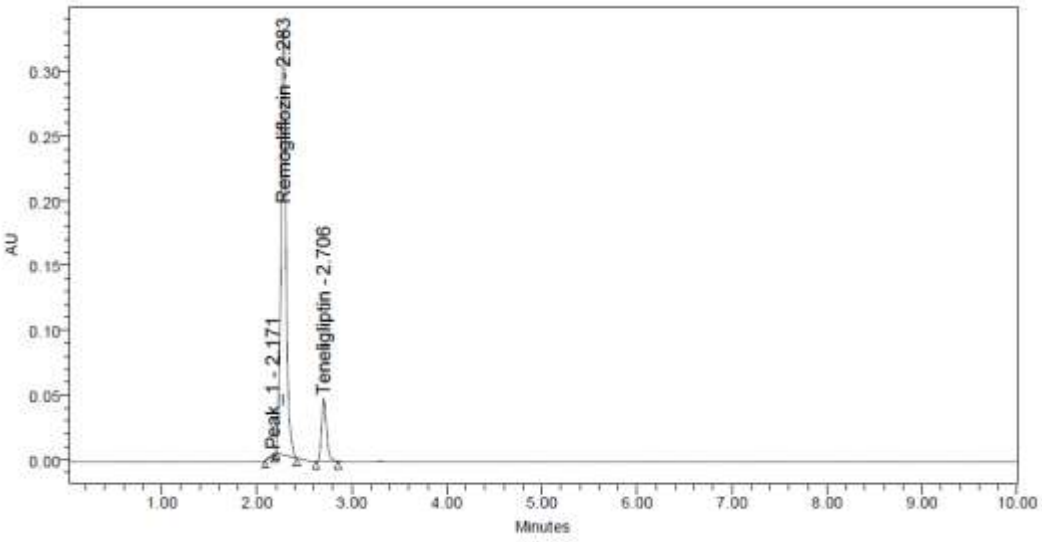


Figure 7: Base chromatogram of Remogliflozin and Teneligliptin

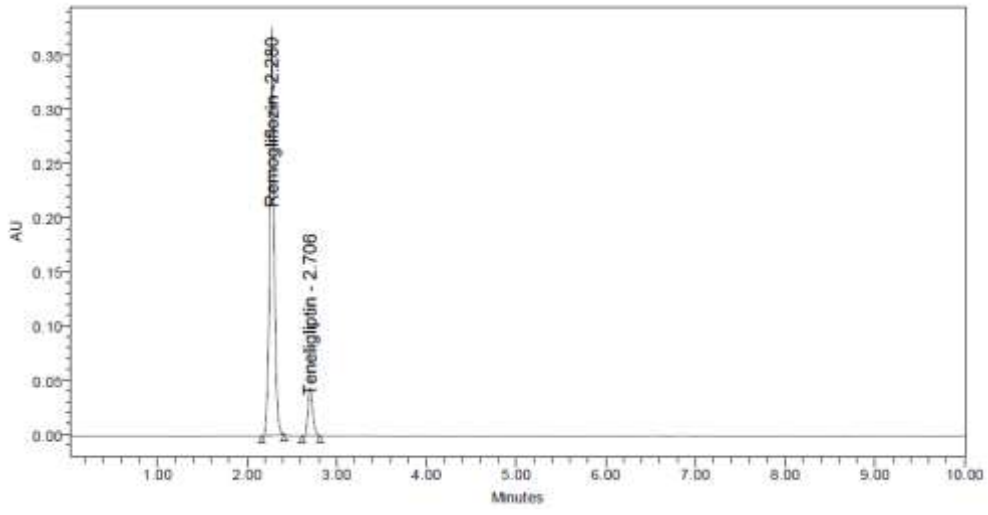


Figure 8: Peroxide chromatogram of Remogliflozin and Teneligliptin

According to the results, samples were degraded when they were subjected to an acid, base, and oxidation interaction. Hydrolysis reaction, heat reaction, and light reaction all showed no deterioration. According to the stress research, none of the degradants co-eluted with the maxima of the active medication.

Assay: (Zita plus R) bearing label claim,100 Teneligliptin 5mg, Remogliflozin 10mg, assay was carried out by injecting sample into HPLC System.

Table 10: Assay Data of Remogliflozin

S.no	Standard Area	Sample area	% Assay
1	6131938	6199386	100.61
2	6120578	6194152	100.52
3	6124564	6187372	100.41
4	6197459	6151005	99.82
5	6154973	6193195	100.51
6	6168890	6113489	99.21
Avg	6149734	6173100	100.18
Stdev	29907.8	34009.7	0.552
%RSD	0.5	0.6	0.6

Table 11: **Assay Data of Teneligliptin**

S. no	Standard Area	Sample area	% Assay
1	317034	315688	99.55
2	318013	315432	99.47
3	317578	314586	99.20
4	313966	318411	100.41
5	318183	319598	100.78
6	314126	317370	100.08
Avg	316483	316848	99.91
Stdev	1930.0	1936.2	0.61
%RSD	0.6	0.6	0.6

Table 12: Assay outcome for Remogliflozin and Teneligliptin

Drug Name	Label claim dose	%Assay	Brand Name
Remogliflozin	5mg	99.47	**Zita plus R**
Teneligliptin	100mg	100.29	

CONCLUSION

The proposed HPLC method was validated as per ICH guidelines and applied for the determination of Remogliflozin and Teneligliptinin tablet dosage form. A method for simultaneously estimating the pharmacological forms of remogliflozin and teneligliptin was devised that is straightforward, accurate, and exact. Remogliflozin and Teneligliptin were found to have retention times of 2.271 minutes and 2.706 seconds, respectively. The percentage RSD of Remogliflozin and Teneligliptin was determined to be 0.5 and 0.6. %Remogliflozin and Teneligliptin showed recovery rates of 99.73% and 99.63%, respectively. Remogliflozin and Teneligliptin's regression equations yielded LOD and LOQ values of 0.01; 0.04; and 0.48; 1.47, respectively. Teneligliptin's regression equation is y 40715x + 608.6, while Remogliflozin's is y = 16468x + 2301. The method that was created was easy to use and cost-effective, making it suitable for routine quality control testing in industries. Both the retention times and the run time were reduced.

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