Stability Indicating RP- UPLC Method for the estimation of Teneligliptin and Remogliflozin

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Abstract:

A simple, Accurate, precise method was developed for the simultaneous estimation of the Teneligliptin and Remogliflozin in dosage form. Chromatogram was run through Acquity UPLC STD HSS C_{18} (100 x2.1mm, 1.8µ). Mobile phase containing KH2PO4: Acetonitrile was taken in the ratio of 45:55 was pumped through column at a flow rate of 0.3 ml/min. Temperature was maintained at 30°C. Optimized wavelength selected was 229 nm. Retention time of Teneligliptin and Remogliflozin were found to be 0.385 min and 0.929 min. %RSD of the Teneligliptin and Remogliflozin were and found to be 1.2 and 0.5 respectively. % Recovery was obtained as 100.29% and 100.29% for Teneligliptin and Remogliflozin respectively. LOD, LOQ values obtained from regression equations of Teneligliptin and Remogliflozin were 0.03ppm, 0.46ppm and 0.09ppm, 1.39ppm respectively. of Teneligliptin is y = 42357x + 962.96, and of Remogliflozin is y = 19600x + 3110,, Retention times were decreased and that run time was decreased, so the method developed was simple and economical that can be adopted in regular Quality control test in Industries.

Key Words: Teneligliptin, Remogliflozin, RP-UPLC

1. 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-hyperglycaemic 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 contro.[8-14]

The literature survey[15-19]reveals that a few analytical methods for the determination of combination of Teneligliptin and Remogliflozin in dosage forms by UPLC.

REMOGLIFLOZIN :

Remogliflozin etabonate has been used in the treatment of Type 2 Diabetes Mellitus

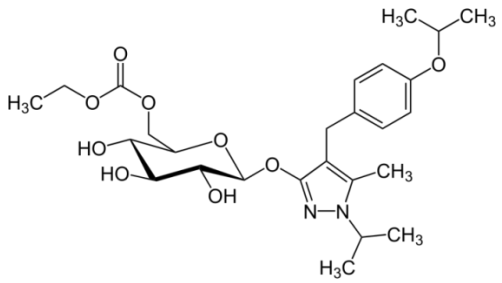

Figure 1 Structure of Remogliflozin

IUPAC : ethyl [(2R,3S,4S,5R,6S)-3,4,5-trihydroxy-6-{[5-methyl-1-(propan-2-yl)-4-{[4-(propan-2-yloxy)phenyl]methyl}-1H-pyrazol-3-yl]oxy}oxan-2-yl]methyl carbonate	
Molecular Weight	: Average: 522.595
Molecular Formula	: $C_{26}H_{38}N_2O_9$
Category	: selective SGLT2 inhibitors

TENELIGLIPTIN:

Teneligliptin used for the treatment of Type 2 Diabetes Mellitus.

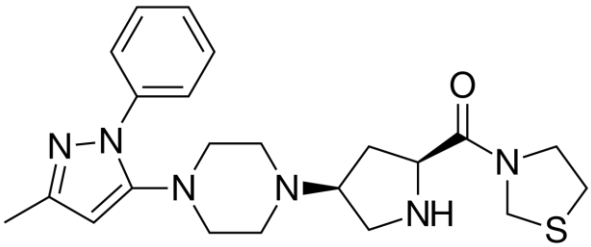

Figure 2 Structure of Teneligliptin

IUPAC : 1-(3-methyl-1-phenyl-1H-pyrazol-5-yl)-4-[(3S, 5S)-5-(1, 3-thiazolidine-3-carbonyl) pyrrolidin-3-yl] piperazine		
Molecular Weight	:	450.91
Molecular Formula	:	C23H27ClO7
Category	:	dipeptidyl peptidase-4 inhibitors

2. Materials and Methods

2.1 Chemicals:

Teneligliptin and Remogliflozin pure drugs (API), Combination Teneligliptin and Remogliflozin tablets (Zita plus R), Distilled water, Acetonitrile, Phosphate buffer, Methanol, Potassium dehydrogenate Ortho phosphate buffer, Ortho-phosphoric acid. All the above chemicals and solvents are from Rankem.

2.2 Instrument:

Electronics Balance-Denver, p^H meter -BVK enterprises, India, Ultrasonicator-BVK enterprises, UPLC instrument used was of WATERS Acquity UPLC SYSTEM with Auto Injector and Acquity TUV detector. Software used is Empower 3,UV-VIS spectrophotometer PG Instruments T60 with special bandwidth of 2mm and 10mm and matched quartz was be used for measuring absorbance of Teneligliptin and Remogliflozin solutions.

3. Preparation:

Diluent: Depends up on the solubility of the drugs, diluent was selected, Acetonitrile &Water taken in the ratio of 50:50.

Buffer preparation: -0.01N Kh2Po2Buffer: - Dissolve 0.36gm of di-Potassium hydrogen phosphate in 1000 milli of glass beaker and add A-Grade water to 1000 ml beaker at at level of $3/4^{th}$ and sonicate and degas as required and adjust the volume of each solution to 1000 mL, Check the pH of the solution at room temperature. If necessary, adjust the pH to 4.6 by adding acetic acid.

Preparation of Standard stock solutions: Accurately weighed 2.5 mg of Teneligliptin, 25 mg of Remogliflozin and transferred to individual 50 ml volumetric flasks separately. 3/4 th of diluents was added to both flasks and sonicated for 10 minutes. Flasks were made up with diluents and labeled as Standard stock solution 1and 2. (50µg/ml of Teneligliptin and 500µg/ml of Remogliflozin)

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. (5µg/ml of Teneligliptin and 50µg/ml of Remogliflozin)

Preparation of Sample stock solutions: 5 tablets were weighed and the average weight of each tablet was calculated, then the weight equivalent to 1 tablet was transferred into a 100 ml volumetric flask, 5ml of diluents was added and sonicated for 25 min, further the volume was made up with diluent and filtered by HPLC filters (100µg/ml of Teneligliptin and 1000µg/ml of Remogliflozin)

Preparation of Sample working solutions (100% solution): 0.5ml of filtered sample stock solution was transferred to 10ml volumetric flask and made up with diluent.(5µg/ml of Teneligliptin and 50µg/ml of Remogliflozin).

3.1 Validation:

System suitability parameters:

The system suitability parameters were determined by preparing standard solutions of Teneligliptin (5ppm) and Remogliflozin (50ppm) and the solutions were injected six times and the parameters like peak tailing, resolution and USP plate count were determined.

The % RSD for the area of six standard injections results should not be more than 2%.

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. Therefore, this method was said to be specific.

3.2 Precision:

Preparation of Sample stock solutions: 5 tablets were weighed and the average weight of each tablet was calculated, then the weight equivalent to 1 tablet was transferred into a 100 ml volumetric flask, 5ml of diluents was added and sonicated for 25 min, further the volume was made up with diluent and filtered by UPLC filters (100µg/ml of Teneligliptin and 1000µg/ml of Remogliflozin)

Preparation of Sample working solutions (100% solution): 0.5ml of filtered sample stock solution was transferred to 10ml volumetric flask and made up with diluent. (5µg/ml of Teneligliptin and 50µg/ml of Remogliflozin)

The prepared standard solutions of Teneligliptin (5ppm) and Remogliflozin (50ppm) and the solutions were injected six times and the % RSD for the area of six standard injections results should not be more than 2%.

3.3 Linearity:

Preparation of Standard stock solutions: Accurately weighed 2.5 mg of Teneligliptin, 25 mg of Remogliflozin and transferred to individual 50 ml volumetric flasks separately. 3/4 th of diluents was added to both flasks and sonicated for 10 minutes. Flasks were made up with diluents and labeled as Standard stock solution 1and 2. (50µg/ml of Teneligliptin and 500µg/ml of Remogliflozin)

Table 1

Level	ml
25 %	0.25 ml from Pipette
50 %	0.5 ml from Pipette
75 %	0.75 ml from Pipette
100 %	1.0 ml from Pipette
125 %	1.25 ml from Pipette
150 %	1.5 ml from Pipette

3.4 Accuracy:

Preparation of Sample stock solutions: 5 tablets were weighed and the average weight of each tablet was calculated, then the weight equivalent to 1 tablet was transferred into a 100 ml volumetric flask, 5ml of diluents was added and sonicated for 25 min, further the volume was made up with diluent and filtered by UPLC filters (100µg/ml of Teneligliptin and 1000µg/ml of Remogliflozin)

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. (5µg/ml of Teneligliptin and 50µg/ml of Remogliflozin)

Table 2

Level	ml
50 %	1.5 ml from Pipette
100 %	2.0 ml from Pipette
150 %	2.5 ml from Pipette

3.5 Forced Degradation:

Oxidation:

Add 1 ml of 20 % hydrogen peroxide (H_2O_2) to 1 ml of test stock solution. The solutions were held at 60^0c for 30 min. The resulting solution was diluted to obtain 5µg / ml & 50µg / ml solution for HPLC analysis, and 10 µl was injected into the device, and the chromatograms were reported to determine the sample stability.

Acid Degradation Studies:

At 60^0c, 1ml of 2N hydrochloric acid was applied to 1 ml of stock s solution Remogliflozin and Teneligliptin and refluxed for 30mins. The resulting solution was diluted to obtain 5µg/ml &100µg/ml solution and 10 µl solutions were injected into the system and chromatograms were reported to determine sample stability.

Alkali Degradation Studies:

1 ml of 2N sodium hydroxide was applied to 1 ml of stock solution Remogliflozin and Teneligliptin and refluxed at 600c for 30mins. The resulting solution was diluted to achieve a solution of 5µg / ml & 50µg / ml, and 10 µl was injected into the device, and the chromatograms were reported to determine the sample stability.

Dry Heat Degradation Studies:

For test dry heat degradation the typical drug solution was put in the oven at 105 ° C for 1 h. The resulting solution was diluted to 5µg / ml & 50µg / ml solution for UPLC analysis, and

10µl was injected into the device, and the chromatograms were reported to determine the sample stability.

Photo Stability studies:
The drug's photochemical stability was also tested by exposing the 5µg / ml & 50µg / ml solution to UV light by holding the beaker in a photo stability chamber for 1days or 200 Watt hours / m2. The resulting solution was diluted to obtain 5µg / ml & 50µg / ml solutions for UPLC analysis, and 10 µl was injected into the device, and the chromatograms were reported to determine the sample stability.

Neutral Degradation Studies:
Under neutral conditions stress monitoring was performed by refluxing the medication into water at a temperature of 60o for 1hrs. The resulting solution was diluted to 5µg / ml & 50µg / ml solution for HPLC analysis, and 10 µl was injected into the device, and the chromatograms were reported to determine the sample stability**.**

4. Results

4.1 Optimized Chromatogram:

Teneligliptin and Remogliflozinwere eluted at 0.787 min and 1.058 min respectively with good resolution. Plate count and tailing factor was very satisfactory, so this method was optimized and to be validated.

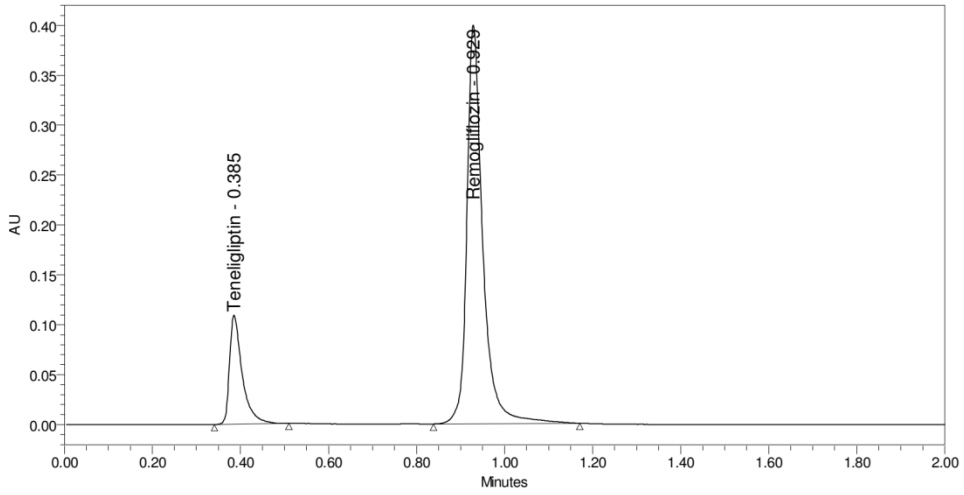

Figure 3: Optimized Chromotogram

4.2 Linearity:

The detector respond was found to be linear in the concentration range of Teneligliptin and Remogliflozin peak areas are measured.

The calibration curves of Teneligliptin and Remogliflozin are shown in figures 4 - 5 respectively and calibration data is Table 3

Table 3 Calibration data of Teneligliptin and Remogliflozin

% level of concentration	Teneligliptin		Remogliflozin	
	conc (µg/ml)	Response	Conc (µg/ml)	Response
0	0	0	0	0
25	1.25	53967	12.5	247200
50	2.5	107659	25	503082
75	3.75	158646	37.5	733454
100	5	213524	50	981082
125	6.25	269902	62.5	1229496
150	7.5	314924	75	1472480
(y=mx+b)	y = 42357x + 962.96		y = 19600x + 3110	
Slope(m)	42357		19600	
Intercept(b)	962.96		3110	
R2	0.999		0.999	

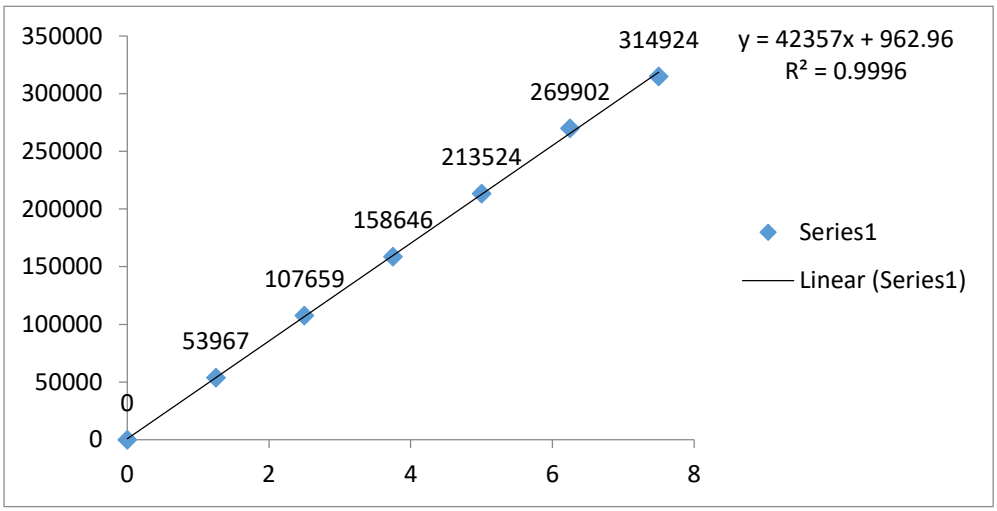

Figure 4 Calibration data of Teneligliptin

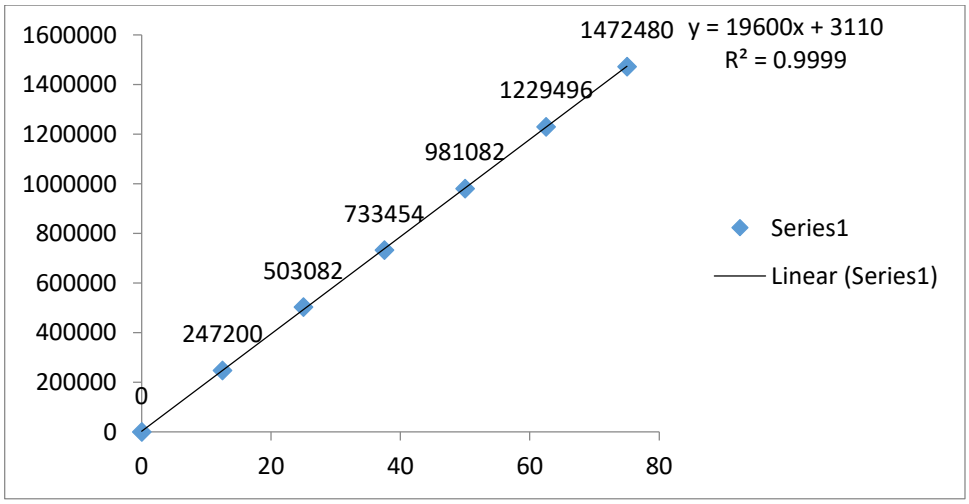

Figure 5 Calibration data of Remogliflozin

4.3 Precision:

From a single volumetric flask of working standard solution six injections were given and the obtained areas were mentioned above. Average area, standard deviation and % RSD were calculated for two drugs. % RSD obtained as 1.2% and 0.5% respectively for Teneligliptin and Remogliflozin. As the limit of Precision was less than "2" the system precision was passed in this method.

Table 4 System Precision of Teneligliptin and Remogliflozin

	Teneligliptin	Remogliflozin
1	212465	985991
2	214120	983327
3	214632	988037
4	215150	985470
5	213851	988427
6	208239	974734
Mean	213076	984331
Std. Dev	2537.0	5053.2
%RSD	1.2	0.5

Table 5: Intraday precision and inter day Precision

Intraday Precision		Inter day Precision	
Teneligliptin	Remogliflozin	Teneligliptin	Remogliflozin
213099	989402	206748	985069
214666	980339	207091	984738
213054	985946	206882	988398
214431	985494	207157	979681
215904	988147	205298	987302
215150	978470	210308	986483
214384	984633	207247	985279
1131.3	4335.4	1648.2	3064.1
0.5	0.4	0.8	0.3

4.4 Accuracy:

Three concentrations 50%, 100%, 150%, were injected in a triplicate manner and amount Recovered and % Recovery were displayed in Table 6

Table 6: Accuracy of Teneligliptin and Remogliflozin

	Teneligliptin				Remogliflozin			
% Level	Peak Area	Amount Spiked (µg/mL)	Amount recovered (µg/mL)	% Recovery	Peak Area	Amount Spiked (µg/mL)	Amount recovered (µg/mL)	% Recovery
50%	318989	25	25.1	100.4	1475217	2.5	2.51	100.33
	319013	25	25.1	100.5	1475498	2.5	2.51	100.35
	319270	25	25.2	100.7	1476524	2.5	2.51	100.59
100%	426303	50	50.3	100.6	1968502	5	5.04	100.84
	425919	50	49.8	99.5	1958226	5	5.03	100.65
	424142	50	50.3	100.6	1969182	5	4.99	99.82
150%	530549	75	75.2	100.2	2456565	7.5	7.50	100.04
	532566	75	75.3	100.4	2459456	7.5	7.55	100.67
	528177	75	74.7	99.6	2447656	7.5	7.45	99.29
Mean %Recovery	100.29%				100.29%			

4.5 Limit of Detection and Limit of Quantification:

LOD value for Teneligliptin was found to be 0.03 and Remogliflozin was 0.46 respectively. LOQ value for Teneligliptin and Remogliflozin were found to be 0.09 and 1.39 respectively. These low LOD and LOQ values indicate that the proposed RP-UPLC method is sensitive.

4.6 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

Table 7 Robustness data of Teneligliptin

Parameter	Optimized condition	Used condition	Peak area	Retention Time	Plate Count	Tailing factor
Flow rate (±0.1ml/min)	1ml/min	0.27ml/min	241379	0.432	1093	1.85
		0.3ml/min	212465	0.385	9589	1.77
		0.33ml/min	186706	0.341	8350	1.63
Column temp. (±5^{0}c)	30^{0}c	27^{0}c	186452	0.342	8312	1.63
		30^{0}c	214120	0.385	9588	1.77
		33^{0}c	186140	0.340	8314	1.63
Mobile phase Composition (5%v/v)	40:60	60:40	186405	0.342	8370	1.64
		55:45	214632	0.385	9589	1.76
		50:50	187254	0342	8312	1.63

Table 8 Robustness data of Remogliflozin

Parameter	Optimized condition	Used condition	Peak area	Retention Time	Plate Count	Tailing factor
Flow rate (±0.1ml/min)	1ml/min	0.27ml/min	1167810	1.021	4153	1.44
		0.3ml/min	985991	0.928	3842	1.35
		0.33ml/min	897074	0.798	3430	1.30
Column temp. (±5^{0}c)	30^{0}c	27^{0}c	897041	0.799	3419	1.31
		30^{0}c	983327	0.929	3839	1.35
		33^{0}c	897070	0.797	3455	1.30
Mobile phase Composition (5%v/v)	40:60	60:40	895672	0.798	3438	1.30
		55:45	988037	0.929	3849	1.35
		50:50	896774	0.800	3437	1.30

4.7 Forced Degradation Studies:

Degradation of both Teneligliptin and Remogliflozin shown in table 9 and Chromatogram in Figure 6 - 11

Table 9 Degradation data of Teneligliptin and Remogliflozin

	Teneligliptin			Remogliflozin		
FD condition	Area	% Recovered	% Degradation	Area	% Recovered	% Degradation
Acid	209440	98.20	1.80	977113	99.17	0.83
Alkali	204156	95.72	4.28	950157	96.43	3.57
Oxidation	201923	94.67	5.33	949182	96.33	3.67
Thermal	210085	98.50	1.50	972575	98.71	1.29
Photolytic	210347	98.62	1.38	983539	99.82	0.18
Neutral	209185	98.08	1.92	976828	99.14	0.86

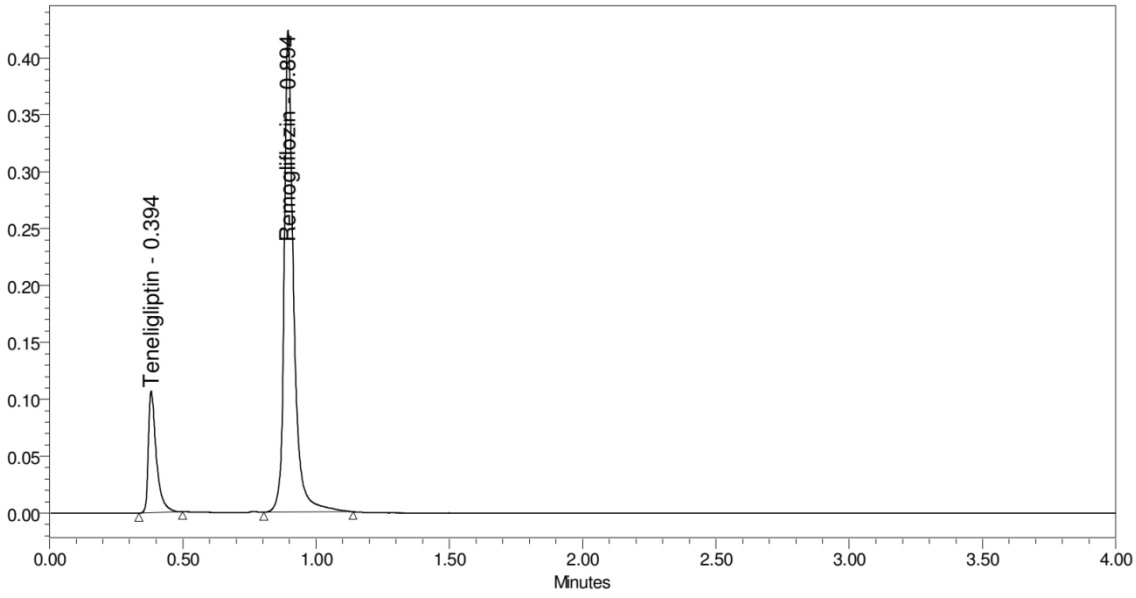

Figure 6 Acid degradation chromatogram

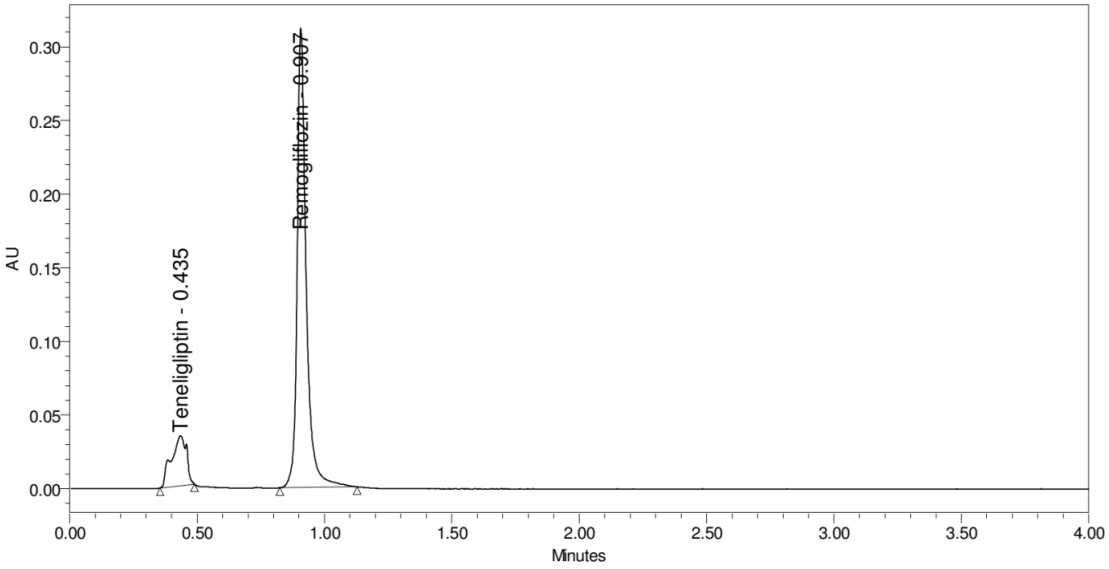

Figure 7 Base degradation chromatogram

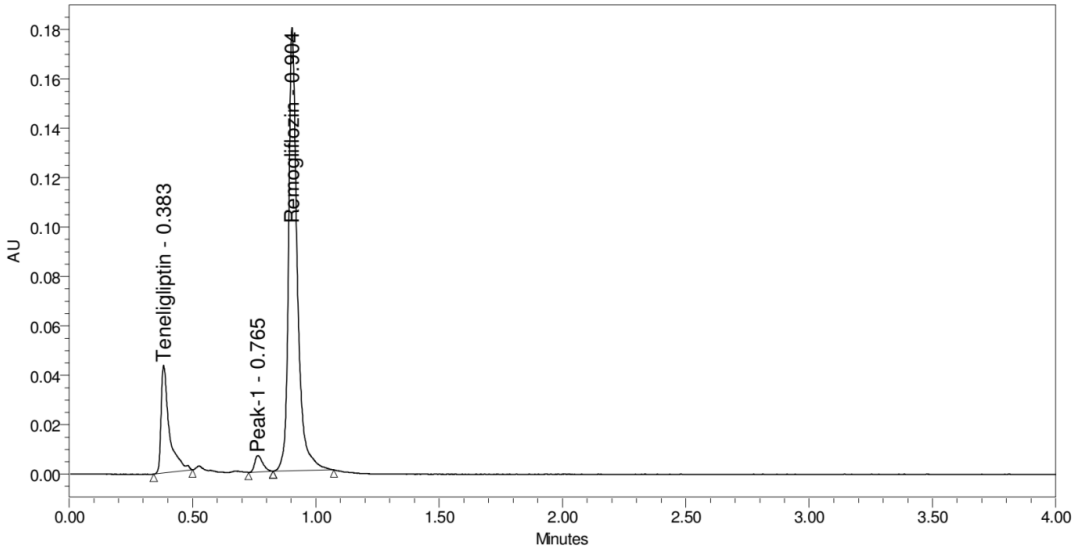

Figure 8 Peroxide degradation chromatogram

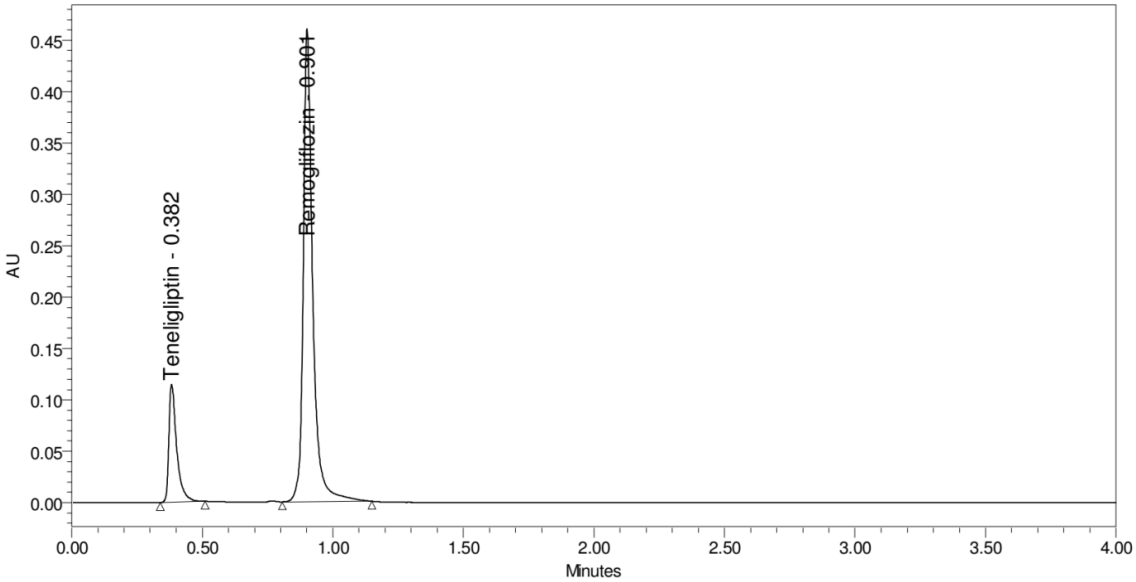

Figure 9 Thermal degradation chromatogram

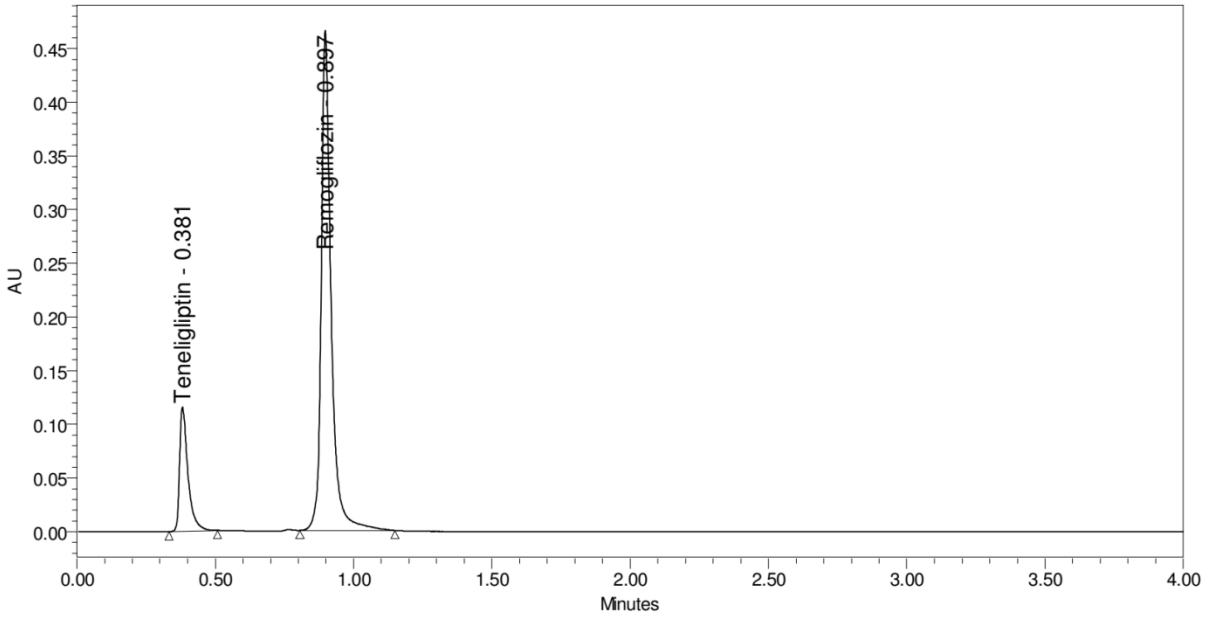

Figure 10 UV degradation chromatogram

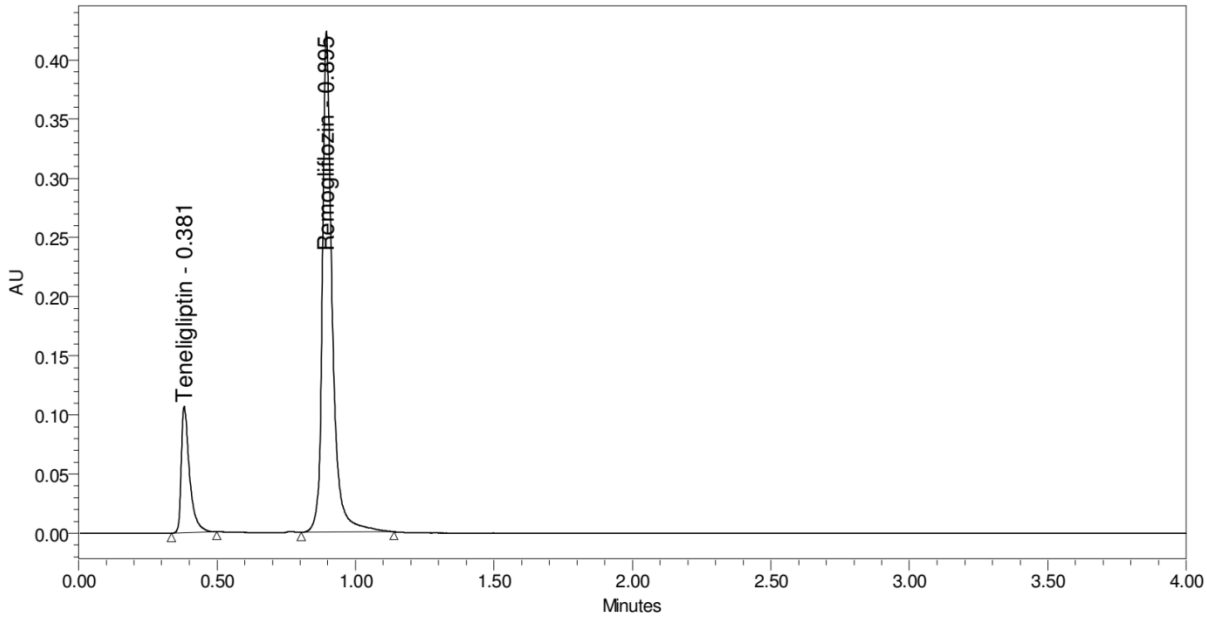

Figure 11 Water degradation chromatogram

5. Discussion:

The working standard solution of concentration 5 µg/mL of teneligliptin and 50 µg/mL of remogliflozin were injected into 10 µg/mL loop, and the chromatogram was recorded. A typical chromatogram was presented in Figure 3. The system suitable parameters such as tailing factor (1.77) and number of theoretical plates (9592) of teneligliptin and tailing factor (1.35) and number of theoretical plates (3848) of remogliflozin and Rs (9.6) are found to be within the limits. The retention time of the component was found to be 0.929 min of Remogliflozin and 0.835 of Teneligliptin. The intraday precision or interday precision of a method was expressed in terms of statistical parameters such as standard deviation and % RSD.

The % RSD was calculated for six replicate measurements and found to be less than 2.0. Interday precision of the method was determined by carrying out the experiment on different days using same instrument and same column under similar chromatographic conditions. The results are presented in Table 5. The linearity of the method was studied by injecting 10 µl of working standard solutions of concentration ranging from 12.5 to 75 µg/mL of remogliflozin and 1.25 to 7.5 µg/ml into the column and linearity report was obtained.

A calibration curve was constructed by plotting concentration against peak area (Figure 4, 5). The correlation coefficient, slope, and intercept were presented in Table **3**.The accuracy of the method was determined from recovery experiments. The recovery studies were carried out at three different concentration levels (50%, 100%, and 150% of target concentration). The percentage recovery of the drug at three different concentration levels is presented in Table 8. Robustness of the proposed method is checked by making slight deliberate change in the experimental procedures. In the present method, a deliberate change in the flow rate and mobile phase composition is made to evaluate the impact on the method. The results are summarized in Table 9. The developed method is found to be accurate and precise as indicated by recovery studies and % RSD not more than 2.0. Recovery studies are performed at 50%, 100%, and 150% concentration levels, and the results are found to be within the limits mentioned as per ICH Guidelines and values of respective parameters are mentioned in abstract and conclusion.

6. Conclusion:

A straightforward, precise, and accurate approach was created for the simultaneous estimate of Teneligliptin and Remogliflozin in tablet form. Teneligliptin and Remogliflozin were shown to have retention times of 0.385 and 0.929 minutes, respectively. Teneligliptin's and Remogliflozin's percent RSD were discovered to be 1.2 and 0.5, respectively. %For teneligliptin and remogliflozin, recovery was obtained at 100.29% and 100.29%, respectively. Teneligliptin's and Remogliflozin's regression models yielded LOD and LOQ values of 0.46 ppm, 0.03 ppm, and 1.39 ppm, 0.09 ppm, respectively. Teneligliptin's regression equation is y = 19600x + 3110, and Remogliflozin's regression equation is y = 42357x + 962.96).

7. Acknowledgement:

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8. References:

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