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Research Article

Stability Indicating RP-HPLC Method for Simultaneous Estimation Of Remogliflozin And Teneligliptin

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ABSTRACT

A straightforward, accurate, and exact technique for estimating Remogliflozin and Teneligliptin in pharmaceutical dose form was devised. The chromatogram was done via an Ascentis 150 x 4.6 mm, 5m column. 0.01N Kh2:30 is present in the mobile phase. Acetonitrile in the 70:30 ratio was pushed through the column at a flow rate of 1.0ml/min. The retention time of Remogliflozin and Teneligliptin was determined to be 2.271 minutes and 2.706 percent RSD of Remogliflozin and Teneligliptin were found to be 0.6 and 0.5, respectively. %Remogliflozin and Teneligliptin recovered at 99.73% and 99.63%, respectively. The LOD and LOQ values derived from Remogliflozin and Teneligliptin regression models were 0.01, 0.04 and 0.48, 1.47, respectively. Teneligliptin's regression equation is y 40715x + 60.86, whereas Remogliflozin's is y = 16468x + 2301. Retention periods

Keywords: Remogliflozin, Teneligliptin, RP-HPLC

INTRODUCTION

Remogliflozin is a Tenegliptin -class drug that is used to treat nonalcoholic steatohepatitis and type 2 diabetes. Remogliflozin has been shown to increase the amount of glucose that mice and people pee out. Early tests showed that diabetics' blood glucose levels got better[1-2]. Researchers have looked at remogliflozin doses up to 1000 mg[3-4]. Remogliflozin, Tenegliptin, and pioglitazone were all shown to have the same effect on blood sugar (decrease in HbA1c and fasting glucose).The drug remogliflozin is made from remogliflozin . Remogliflozin stops the sodium-glucose transport proteins (SGLT) in the kidney from bringing glucose back into the blood. By blocking this transporter, glucose is taken out of the blood through pee.RE is the newest type of SGLT2 inhibitor that has just been cleared for treatment in India. Remogliflozin etabonate is a strong and specific SGLT2 inhibitor that is given as a prodrug, has active metabolites inside it, and needs to be taken twice a day5. Kissei Pharmaceutical found remogliflozin. Remogliflozin is now being made by BHV Pharma, which is a wholly-owned company of Avolynt and is working with Glenmark Pharmaceuticals[6].
Here we have used Remogliflozin and Teneligliptin.

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Remogliflozin etabonate is a strong and specific SGLT2 inhibitor that is given as a prodrug, has active metabolites inside it, and needs to be taken twice a day [5]. Kissei Pharmaceutical found remogliflozin. Remogliflozin is now being made by BHV Pharma, which is a wholly-owned company of Avolynt and is working with Glenmark Pharmaceuticals6. the drug still sees extensive use worldwide via millions of prescriptions annually and has since become available as a generic and as a brand name product.

Remogliflozin: Remogliflozin is a novel new-generation antihistamine that is highly selective for the H1 histamine receptor, has a rapid onset and prolonged duration of action.

The combination of dipeptidyl peptidase-4 (DPP-4) inhibitors such as (Figure 1A, VLG) and teneligliptin (Figure 1B, TNG) with the sodium-glucose cotrasportase-2 (SGLT-2) inhibitor, remogliflozin etabonate, (Figure 1C, RGE) has just been approved by the Food and Drug Administration for the treatment of diabetes mellitus type 2[6,7]. DPP-4 inhibitors increase the secretion of insulin by inhibiting the enzyme DPP-4 responsible for degradation of incretins in the blood, thereby decreasing the blood glucose level by lowering the blood glucagon level, and improving pancreatic cell function[8,9]. DDP-4 inhibitors also lower HbA1c levels without causing hypoglycemia and weight gain [10,11,12]. Further, teneligliptin can be taken in patients with renal failure without dose adjustment [13,14].

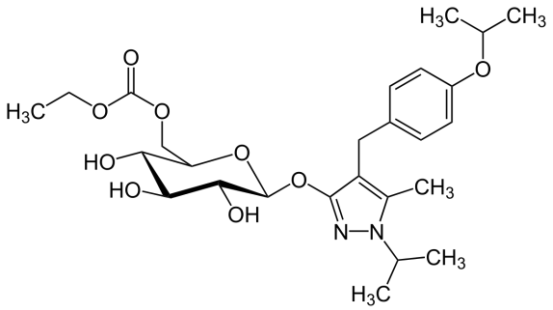

Figure 1: Structure of Remogliflozin

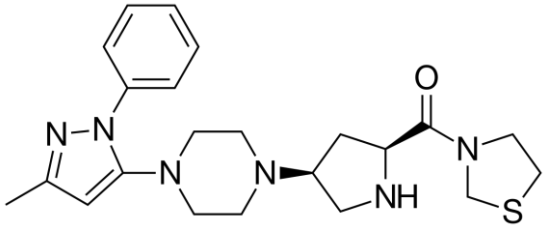

Figure 2: Structure of Teneligliptin

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. [15-28]

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.

Instruments:

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 Teneligliptin and 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 600c. 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 0C. 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 600c. 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/m2 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	Remogliflozin			Teneligliptin			
Inj	**RT (min)**	**USP Plate Count**	**Tailing**	**RT(min)**	**USP Plate Count**	**Tailing**	**RS**
1	2.277	5803	1.01	2.705	13140	1.24	4.0
2	2.277	7014	1.01	2.712	12874	1.16	4.0
3	2.279	6494	1.01	2.713	13512	1.17	4.1
4	2.281	8290	1.00	2.713	13447	1.18	4.1
5	2.281	8623	1.01	2.713	12816	1.12	4.0
6	2.281	8612	1.00	2.716	13841	1.21	4.2

Table 2. Specificity data

Sample name	Retention Time(Mins)	Area
Remogliflozin	2.271	1404014
Teneligliptin	2.706	184644

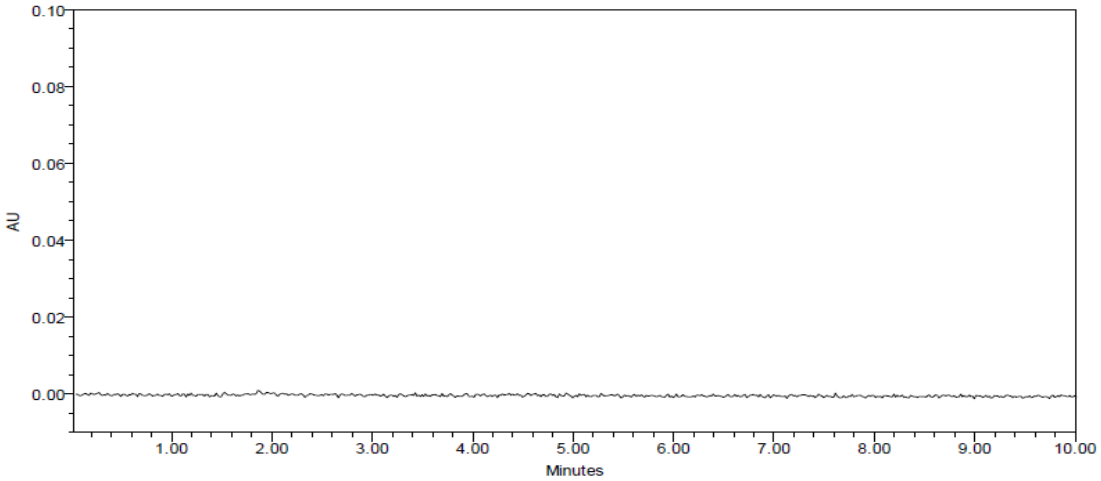

Figure 3. Blank Chromatogram

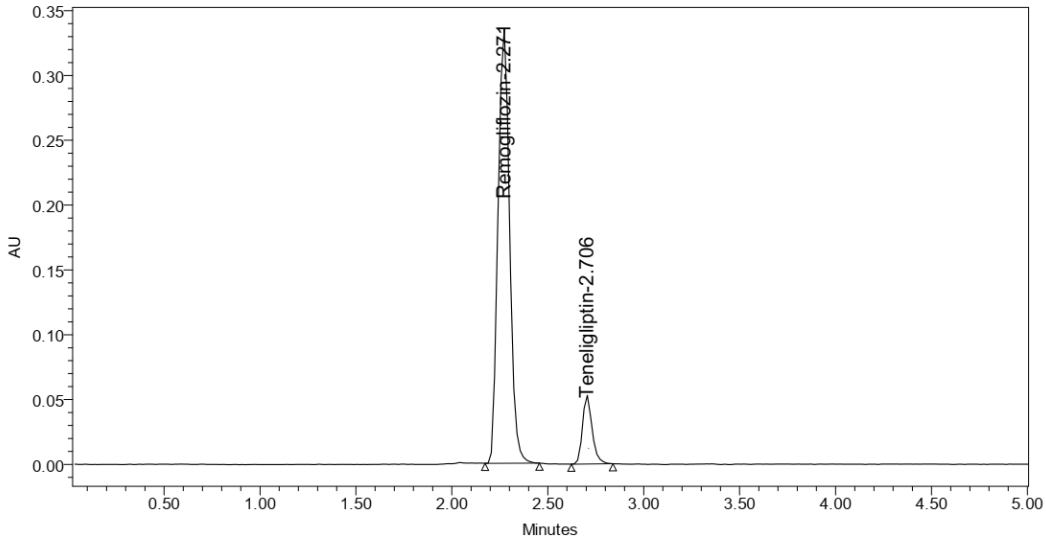

Figure 4. Specificity Chromatograms of Remogliflozin and Teneligliptin

Linearity

Table 3. Linearity table for Remogliflozin and Teneligliptin:

Remogliflozin		Teneligliptin	
Conc (µg/mL)	**Peak area**	**Conc (µg/mL)**	**Peak area**
0	0	**0**	0
25	415144	**1.25**	51631
50	829460	**2.5**	102353
75	1246958	**3.75**	153412
100	1655462	**5**	206616
125	2012413	**6.25**	253045
150	2502336	**7.5**	305983

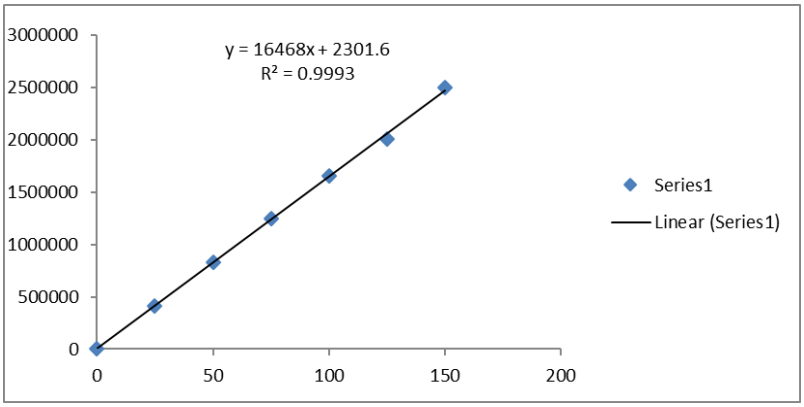

Figure 5. Calibration curve of Remogliflozin

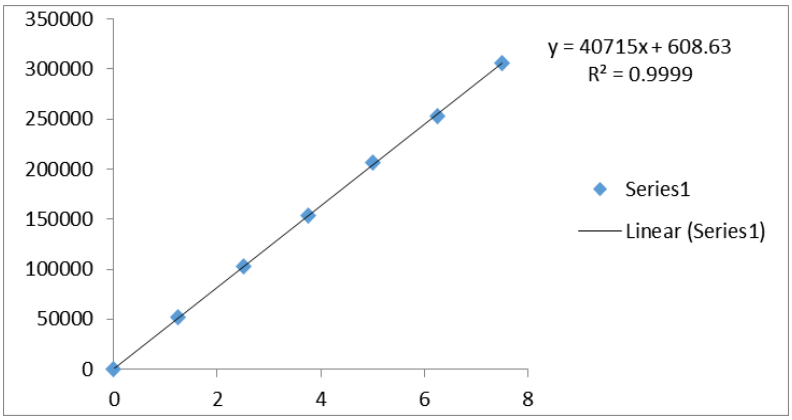

Figure 6. Calibration curve of Teneligliptin

Accuracy:

Table 4. Accuracy table of Remogliflozin

% Level	Amount Spiked (µg/mL)	Amount recovered (µg/mL)	% Recovery	Mean %Recovery
50%	50	50.55	99.88	**99.63%**
	50	50.04	100.08	
	50	49.53	99.06	
100%	100	99.25	99.25	
	100	99.83	99.83	
	100	99.07	99.07	
150%	150	150.37	100.25	
	150	148.89	99.26	
	150	150.02	100.01	

Table 5. Accuracy table of Teneligliptin

% Level	Amount Spiked (µg/mL)	Amount recovered (µg/mL)	% Recovery	Mean %Recovery
50%	2.5	2.49	99.45	**99.73%**
	2.5	2.50	100.15	
	2.5	2.48	99.10	
100%	5	4.98	99.51	
	5	4.96	99.30	
	5	5.03	100.51	
150%	7.5	7.47	99.66	
	7.5	7.52	100.28	
	7.5	7.47	99.64	

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 6. System precision

S. No	Area of Remogliflozin	Area of Teneligliptin
1.	204792	1663330
2.	207942	1658536
3.	208313	1662283
4.	209484	1656697
5.	206749	1676292
6.	203332	1660072
Mean	**206769**	**1662868**
S.D	**2317.5**	**7006.1**
%RSD	**1.1**	**0.4**

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 7. Method precision

S. No	Area of Remogliflozin	Area of Teneligliptin
1.	208315	1677394
2.	206885	1676235
3.	205459	1668217
4.	208024	1690273
5.	206487	1660760
6.	208734	1654445
Mean	**207317**	**1667887**
S.D	**1251.5**	**8914.7**
%RSD	**0.6**	**0.5**

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

Table 8. Robustness

S.No.	Condition	%RSD of Remogliflozin	%RSD of Teneligliptin
1	**Flow rate (-) 0.9ml/min**	0.4	0.6
2	**Flow rate (+) 1.1ml/min**	0.2	0.2
3	**Mobile phase (-) 60B:40A**	0.2	0.3
4	**Mobile phase (+) 70B:30A**	0.6	0.4
5	**Temperature (-) 25°C**	0.2	0.1
6	**Temperature (+) 35°C**	0.5	0.4

Table 9. 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 10. Degradation results of Remogliflozin and Teneligliptin

Type of degradation	Remogliflozin		Teneligliptin	
	%Recovered	% Degraded	%Recovered	% Degraded
Acid	94.23	5.77	94.80	5.20
Base	95.60	4.40	95.60	4.40
Peroxide	93.99	6.01	93.36	6.64
Thermal	96.25	3.75	95.87	4.13
Uv	97.59	2.41	98.07	1.93
Water	99.22	0.78	99.67	0.33

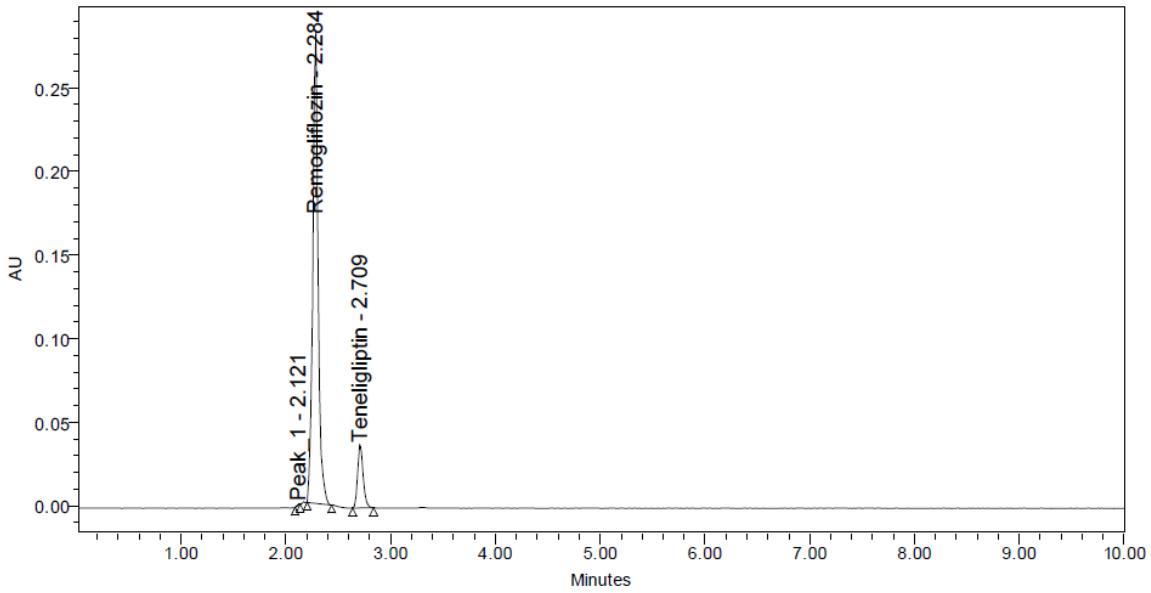

Figure 7. Acid chromatogram of Remogliflozin and Teneligliptin

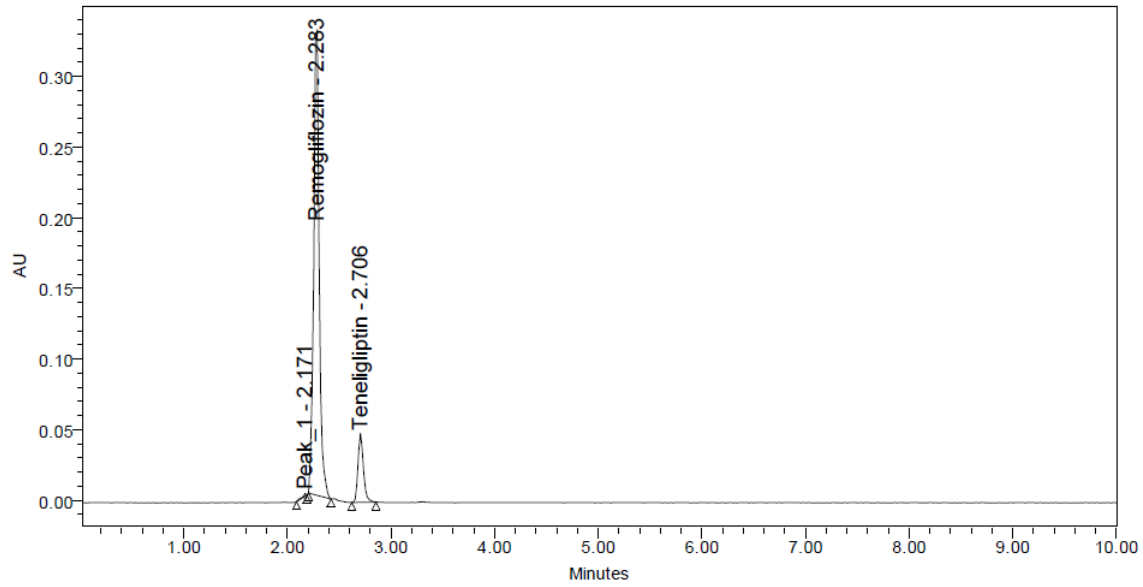

Figure 8. Base chromatogram of Remogliflozin and Teneligliptin

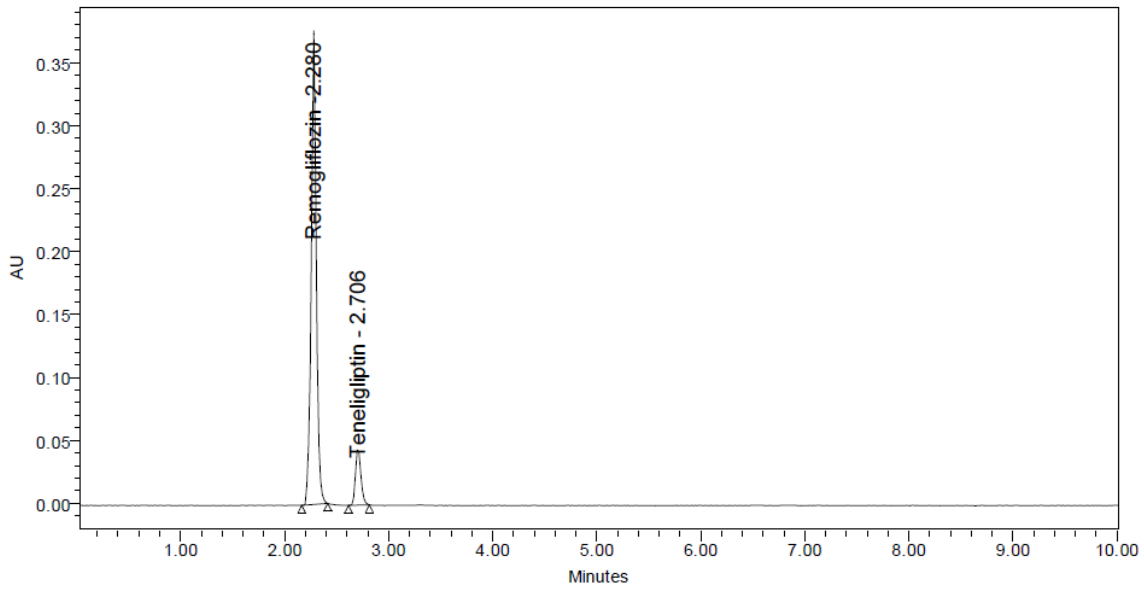

Figure 9. Peroxide chromatogram of Remogliflozin and Teneligliptin

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, **Teneligliptin 5mg, Remogliflozin 10mg**, assay was carried out by injecting sample into HPLC System.

Table 11. Assay Data of Remogliflozin:

S.no	Standard Area	Sample area	% Assay
1	1663330	1677394	100.47
2	1658536	1676235	100.40
3	1662283	1668217	99.92
4	1656697	1690273	101.24
5	1676292	1660760	99.47
6	1660072	1654445	99.10
Avg	**1662868**	**1667887**	**99.90**
Stdev	**7006.1**	**8914.7**	**0.5**
%RSD	**0.4**	**0.5**	**0.5**

Table 12. Assay Data of Teneligliptin

S.no	Standard Area	Sample area	% Assay
1	204792	208315	100.34
2	207942	206885	99.66
3	208313	205459	98.97
4	209484	208024	100.20
5	206749	206487	99.46
6	203332	208734	100.55
Avg	**206769**	**207317**	**99.86**
Stdev	**2317.5**	**1251.5**	**0.60**
%RSD	**1.1**	**0.6**	**0.6**

Table 13. 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.

ACKNOWLEDGEMENT

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