Article

Quality by Design Tool Assessed Ultraperformance Liquid Chromatography Method for the Analysis of Remogliflozin and Teneligliptin in Oral Dosage Form

Jyothsna Menda, Vaishnavi Chintala, Phani Raja Kanuparthy,* Naresh Kumar Katari,*
Leela Prasad Kowtharapu, and Sreekantha Babu Jonnalagadda

Read Online

ACCESS | Metrics & More | Article Recommendations

ABSTRACT: The UPLC methodology was used to establish a method for determining the qualitative and quantitative content of teneligliptin and remogliflozin tablets in oral solid dose form, as no simultaneous method was available. The developed liquid chromatography method consists of an X-Bridge C18 100 mm × 3.5 mm, 2.1 mm column with an economical 0.2 mL/min flow rate. A wavelength of 248 nm was used for detection, and the temperature of the column compartment was 30 °C. The method was evaluated using a static tool quality by design after it was validated as per the regulations. The data from validation result in linearity for both analytes with a correlation coefficient of more than 0.999. The accuracy data were found from a minimum of 98.1 to a maximum of 100.9. All of the validation results met the acceptance criteria. The stability of the analytical solutions proved for 24 h at bench and refrigerator temperatures. Studies of force degradation proved the stability indicating the nature of the method. A factorial design was used to evaluate the method performance.
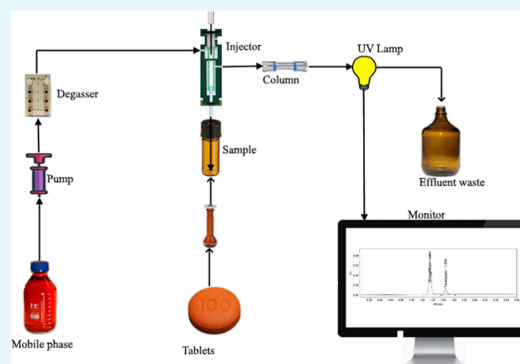
1. INTRODUCTION

Remogliflozin etabonate is a sodium glucose cotransporter 2 inhibitor, a treatment with verbal antidiabetics. Remogliflozin etabonate reduces the amount of excess sugar that you get from your body through the urine. Remogliflozin etabonate lowers the amount of glucose in the blood. Remogliflozin etabonate works by controlling blood sugar levels and helping to lower blood sugar levels. The chemical formula for remogliflozin etabonate is $C_{26}H_{38}N_2O_9$, and the molecular weight is 522.595.

Teneligliptin is an antidiabetic dipeptidyl peptidase-4 (DPP-4) inhibitor. The sum of insults delivered by the pancreas can be expanded by teneligliptin. The hormones that increase blood sugar levels are reduced by teneligliptin. The amount of sugar in the blood is controlled by teneligliptin. Zita plus R tablet can be used to control blood sugar levels. The chemical formula for teneligliptin is $C_{22}H_{30}N_6OSe$, and the molecular weight is 426.58. The structures of both analytes are shown in Figure 1.
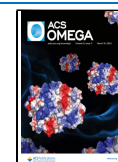
Remogliflozin etabonate and teneligliptin combination phrasings are available in oral solid dosage form. The quantification of both analytes in the formulation is the quality, safety, and efficacy factor of the dosage form. The quantification method is needed to identify the content present in the formulation. The current research targeted the content determination for the targeted formulation. There was

only one article available for the content determination using the UV spectroscopy,[1] but this method is not suitable for shelf life analysis due to the lack of stability indicating nature. Attimarad et al. developed simultaneous quantification of two binary formulations containing remogliflozin and gliptins.[2] Dhara et al. developed a UV spectroscopic method for determination of remogliflozin etabonate in bulk and tablet dosage form.[3] Attimarad et al. developed multicomponent antidiabetic formulation analysis.[4] Shah et al. developed a liquid chromatographic method for the estimation of remogliflozin etabonate.[5] Itigimatha et al. developed remogliflozin etabonate in pure and pharmaceutical formulations analysis.[6] Attimarad et al. developed multicomponent antidiabetic formulation by the HILIC method.[7] Vinodbhai developed the estimation of remogliflozin and vildagliptin in pharmaceutical dosage form method.[8] Ali et al. developed quantification of vildagliptin and remogliflozin etabonate in bulk drug and formulations method.[9] Jaiswal et al. developed
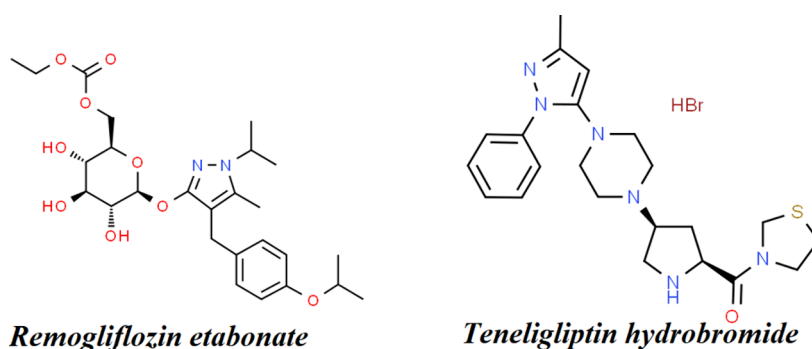
Figure 1. Chemical structure of remogliflozin and teneligliptin.

the estimation of metformin hydrochloride and remogliflozin enabonate in pharmaceutical dosage form method.[10] Kumar et al. developed teneligliptin by the RP-HPLC method.[11] Kant et al. developed metformin, gliclazide, pioglitazone, dapagliflozin, empagliflozin, saxagliptin, linagliptin, and teneligliptin using the central composite design method.[12] Lokhande developed teneligliptin by using the RP-HPLC method.[13] Biswas et al. developed teneligliptin in tablet dosage form by the RP-HPLC method.[14] Bichala et al. developed estimation of metformin and teneligliptin in its bulk and tablet dosage form by using the RP-HPLC method.[15] Musmade et al. developed the impurity profiling method and validation of metformin hydrochloride and teneligliptin hydrobromide hydrate in their combination tablet dosage form by using the RP-HPLC method.[16] Shah et al. developed estimation of antidiabetic drug teneligliptin by the HPTLC method.[17] Kumar et al. developed teneligliptin by the RP-HPLC method.[18] These available research targeted individual determination and combination with some other formulations. The detailed literature revealed that no single determination method was available, and only individual content determination methods are available for both analytes. The present research work aimed to create a simple, sensitive, and environmentally friendly content determination method for the combination dosage form. Quality by design is a stationary tool, which is useful for optimizing the method and assessing the system performance with minimum changes.[19,20] The presently developed method originally optimized conditions and estimated the system performance with the factorial design by studying the critical method parameters with design expert software.[21]

2. MATERIALS AND METHODS

2.1. Chemicals, Reagents and Materials. The standard gift sample of remogliflozin etabonate and teneligliptin tablets and placebo was from a reputed pharma company. Standards are procured from the international supplier. Milli Q water available from the Millipore purification system was used. Analytical grade was used for hydrochloric acid, whereas HPLC grade was used for acetonitrile, triethylamine, orthophosphoric acid, and methanol.

2.2. Instruments and Software. The ACQUITY TUV UPLC has a photodiode array detector that was used for the entire research. The research was carried out using Empower software. The Skymen Ultrasonicator and HA vacuum pump were used for buffer and mobile phase degassing. Using a Mettler-Toledo Pan Balance (Model ME2002TE/02), a Mettler-Toledo Semi-Micro Balance (Model XPE105DR),

and a Sartorius Microbalance (Model MSXLSGEA1), standards and samples were weighed. The Yesi drug photo stability chamber was subjected to forced degradation investigations. The column from Waters was used for the separation. The DoE trials in the method evaluation were carried out using Stat-ease Inc., Minneapolis, USA's Design Expert software version 13.

2.3. Analytical Solution Preparation. *2.3.1. Standard Solution Preparation.* Fifty mg of remogliflozin and 5 mg of teneligliptin standards were accurately weighed and transferred into 100 mL clean dry volumetric flasks; 10 mL of diluent was added; it was then sonicated for 10 min and made up to the final volume with diluent (500 μg/mL teneligliptin and 50 μg/mL of remogliflozin). One mL of the two stock solutions was taken into a 10 mL volumetric flask and made up to 10 mL with diluent (50 μg/mL remogliflozin and 5 μg/ mL of teneligliptin).

2.3.2. Preparation of Sample Stock Solutions. Ten tablets were weighed and ground into fine powder, and an equivalent to 1 tablet was weighed and transferred to a 100 mL volumetric flask; to this, 50 mL of diluent was added and sonicated. The volume was made up to 50 mL with diluent and filtered through 0.45 μm or finer porosity membrane filter (1000 μg/mL remogliflozin and 100 μg/mL of teneligliptin). A 0.5 mL portion of filtered sample stock solution was transferred to a 10 mL volumetric flask and made up with diluent (50 μg/mL remogliflozin and 5 μg/mL of teneligliptin).

2.4. Forced Degradation Study. The safety and efficacy of drug products are dependent on the chemical stability of the molecule. Stability data is required by the FDA and ICH to understand the quality of the drug product.[22−26] To find the stability of the drug product as well as to see whether the drug product forms any new impurities in the stability that impact the quantitative analysis and efficacy of the drug product, the drug product was subjected to forced degradation studies. A forced degradation study was performed on the drug product and placebo to see whether there was interference with the analyte. Acid, alkali, oxidizer, thermal, neutralization, and photostability studies were performed.

2.4.1. Acid Degradation Studies. Ten tablets were weighed and ground into fine powder, and an equivalent to 1 tablet is weighed and transferred to 100 mL volumetric flask; to this, 50 mL of diluent was added and sonicated. Volume was made up to 50 mL with diluent and filtered through 0.45 μm or finer porosity membrane filter (1000 μg/mL remogliflozin and 100 μg/mL of teneligliptin). To 1 mL of stock solution remogliflozin and teneligliptin, 1 mL of 2 N hydrochloric acid
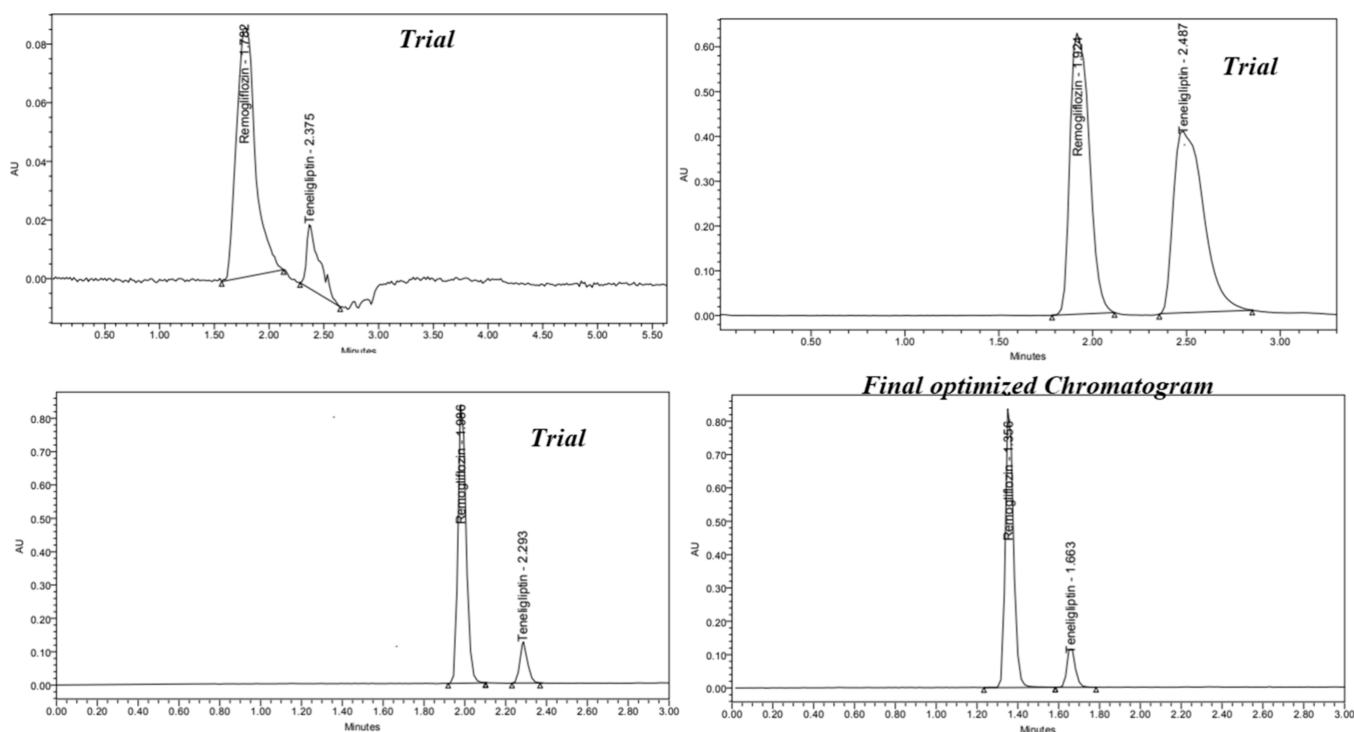
Figure 2. Standard solution chromatogram in the significant trials and in the final optimized condition.

was added and refluxed for 30 min at 60 °C. For UPLC study, the resultant solution was diluted to obtain 50 and 5 ppm solutions, 10 μL was injected into the system, and the chromatograms were recorded to assess the stability of the sample.

2.4.2. Alkali Degradation Studies. Ten tablets were weighed and ground into fine powder, and an equivalent to 1 tablet is weighed and transferred to 100 mL volumetric flask; to this, 50 mL of diluent was added and sonicated. The volume was made up to 50 mL with diluent and filtered through 0.45 μm or finer porosity membrane filter (1000 μg/mL remogliflozin and 100 μg/mL of teneligliptin). To 1 mL of stock solution remogliflozin and teneligliptin, 1 mL of 2 N sodium hydroxide was added and refluxed for 30 min at 60 °C. For UPLC study, the resultant solution was diluted to obtain 50 and 5 ppm solutions, 10 μL was injected into the system, and the chromatograms were recorded to assess the stability of the sample.

2.4.3. Oxidation Degradation Studies. Ten tablets were weighed and ground into fine powder, and an equivalent to 1 tablet is weighed and transferred to 100 mL volumetric flask; to this, 50 mL of diluent was added and sonicated. The volume was made up to 50 mL with diluent and filtered through 0.45 μm or finer porosity membrane filter (1000 μg/mL remogliflozin and 100 μg/mL of teneligliptin). To 1 mL of stock solution of remogliflozin and teneligliptin was added 1 mL of 20% hydrogen peroxide (H_2O_2) separately. The solutions were kept for 30 min at 60 °C. For the UPLC study, the resultant solution was diluted to obtain 50 and 5 ppm solutions, 10 μL was injected into the system, and the chromatograms were recorded to assess the stability of the sample.

2.4.4. Thermal Degradation Studies. The standard drug solution was placed in an oven at 105 °C for 6h to study dry heat degradation. For the UPLC study, the resultant solution

was diluted to obtain 50 and 5 ppm solutions, 10 μL was injected into the system, and the chromatograms were recorded to assess the stability of the samples.

2.4.5. Photostability studies. The photochemical stability of the drug was also studied by exposing the 500 and 50 ppm solutions to UV Light by keeping the beaker in a UV chamber for 7 days or a 200 W h/min photostability chamber. For the UPLC study, the resultant solution was diluted to obtain 50 and 5 ppm solutions, 10 μL was injected into the system, and the chromatograms were recorded to assess the stability of the sample.

2.4.6. Neutral Degradation Studies. Stress testing under neutral conditions was studied by refluxing the drug in water for 6 h at a temperature of 60 °C. For UPLC study, the resultant solution was diluted to obtain 20 and 80 ppm solutions, 10 μL was injected into the system, and the chromatograms were recorded to assess the stability of the sample.

2.5. Chromatography Conditions. The qualitative and quantitative methods were developed by using the Waters X-Bridge C18 100 mm × 3.5 mm, 2.1 μm column. The mobile phase consists of 35:65 v/v buffer (0.1% Orthophosphoric acid buffer): Methanol. The flow rate for the separation was 0.2 mL/min, and the volume of the injection was 10 μL. The temperature of the column chamber was 30 °C, and the detection took place at 248 nm. The overall run time was only 3.0 min. Based on the solubility of the drugs, diluent was selected which was methanol and water taken in the ratio of 65:35 and sonicated for 15 min and Filter with 0.45 μm nylon filter.

3. RESULTS AND DISCUSSION

3.1. Optimization of chromatography method. The purpose of this research is to develop and validate a precise, accurate, linear, robust, and stability-indicating chromato-

graphic method to determine both analytes remogliflozin etabonate and teneligliptin in solid oral dosage formulation in UPLC. UPLC techniques were used for development in light of green chemistry and economy due to the fast elution. Predicated on the physicochemical properties of both analytes, a reverse-phase Waters X-Bridge C18 100 mm × 3.5 mm, 2.1 mm column was selected for initial optimization. Water, acetonitrile, and methanol were used for cumulation mobile phases selected for initial chromatography conditions with a 0.3 mL/min flow rate; the column compartment temperature was chosen at 30 °C to maintain the stable condition. Both standard solutions were injected in the initial chromatography conditions, and the UV spectra were recorded to identify the wavelength for quantification. 248 nm was selected for further studies; both peaks were eluted at void volumes; and the peak was eluted with fronting and tailings. Elution denotes that water as a buffer does not work for the elution of both analytes; buffer strength was needed for better chromatography. To increment the buffer strength, 0.1% OPA (Ortho phosphoric acid) and 0.1% TFA (trifluoroacetic acid) buffers are chosen, and the trials were performed with different ratios of mobile phase with methanol. Methanol was selected because it was economically cheaper than the acetonitrile. 0.1% OPA buffer providing symmetrical peak shapes compared with the 0.1% TFA and 0.1% OPA is selected as the buffer of final optimization. Different ratios of mobile phase were endeavored with 0.1% buffer and methanol with a flow rate of 0.2 mL/min for slow elution. Conclusively, the combination of buffer and methanol in the ratio 35:65 v/v with a Waters X-Bridge C18 100 mm × 3.5 mm, 2.1 mm column was found suitable for the current research. The obtained chromatogram showed that the remogliflozin etabonate was eluted at a retention time of about 1.3 min, and teneligliptin was eluted at a retention time of about 1.6 min. The final chromatogram shown in Figure 2.

3.2. Method Validation Study. *3.2.1. Specificity.* To determine the specificity of the method, injections of standard solution, diluent, placebo, and sample were used. The resulting sample solutions were tested for the retention time and maximum purity. The elution times of the placebo peaks and degradants were recorded. The placebo or diluent did not interfere with the analytes. Results are mentioned in Table 1.

3.2.2. Forced Degradation Study. The combination of rRemogliflozin etabonate and teneligliptin was found to be sensitive to aAcid hydrolysis, alkali hydrolysis, peroxide conditions, and thermal conditions. No degradation was caused by light or neutral conditions. No interference or coelution of the peak with the analyte occurred. The method was specific, and the peak purity of the analyte peaks was passed through. Table 2 demonstrates the obtained result.

All chromatograms of forced degradation are displayed in Figures 3 and 4.

3.2.3. Precision. Precision was carried out by preparing six test samples and analyzed as per the method. After analyzing the samples, the amount of analytes was calculated. Precision % RSD results for remogliflozin etabonate was 0.7%, and for teneligliptin, 0.5% was found. The obtained findings indicate the method's confidence% RSD of less than 2.0%. Table 1 summarizes the findings.

Intermediate precision was accomplished by using different UPLCs with different columns and another analyst. The method was followed for the rest of the study. Samples with a precision and intermediate precision were computed.

Table 1. System Suitability, Linearity, Accuracy, and Precision Results for Remogliflozin and Teneligliptin

parameters	remogliflozin	teneligliptin
system suitability		
USP tailing factor	1.13	1.07
USP plate count (N)	5924	8430
resolution	1.55	4.20
Rt (min)	1.352	1.649
linearity		
range (μg/mL)	12.5−75.0	1.25−7.50
slope	48660	68462
intercept	12540	767.8
correlation coefficient	0.9997	0.9999
precision[a]		
method precision (% RSD)	0.7	0.5
intermediate precision(%RSD)	0.6	0.9
accuracy (% recovery)[b]		
50% mean ± SD	99.8 ± 0.3	99.2 ± 1.0
100% mean ± SD	100.4 ± 0.4	99.6 ± 0.2
150% mean ± SD	100.5 ± 0.3	99.9 ± 0.8
solution stability		
24 h % assay difference with initial @ bench top	0.5	0.3
24 h % assay difference with initial @ 2− 8 °C	0.9	0.8

[a]Mean of six preparations. [b]Mean of triplicate preparations.

Table 2. Forced Degradation Summary Data[a]

nature of stress	condition	%assay of stressed samples		peak purity
		A	B	
unstressed	NA	99.92	99.50	purity angle less than purity threshold and no purity flag
acid	2 N HCl@ 60 °C, for 30 min	93.99	93.54	
base	2 N NaOH@ 60 °C, for 30 min	95.18	95.01	
peroxide	20% H$_2$O$_2$@ 60 °C, for 30 min	94.07	93.22	
thermal	105 °C for 6 h	97.15	97.72	
photostability	7 days or 200 W h/min	98.53	98.30	
neutral	60 °C for 6 h	99.92	99.29	

[a]A = remogliflozin. B= teneligliptin.

Remogliflozin etabonate's method precision and intermediate precision were determined to be extremely low at 0.9 and 1.1%, respectively, for the % RSD of 12 spiking impurity samples. The results were consistent with the requirements. This demonstrates the method's robustness. Table 1 summarizes the findings.

3.2.4. Stability of Analytical Solution. The stability of the standard and sample solutions was tested over time at room temperature and refrigerated temperatures. For the experiments, standard solutions and test sample solutions were made. The solutions were injected immediately after preparation. The solution was split in half, put into two volumetric flasks, and kept there for 24 h at both room temperature and a 2−8 °C refrigerator. After 24 h, the standard and sample solutions were both injected against
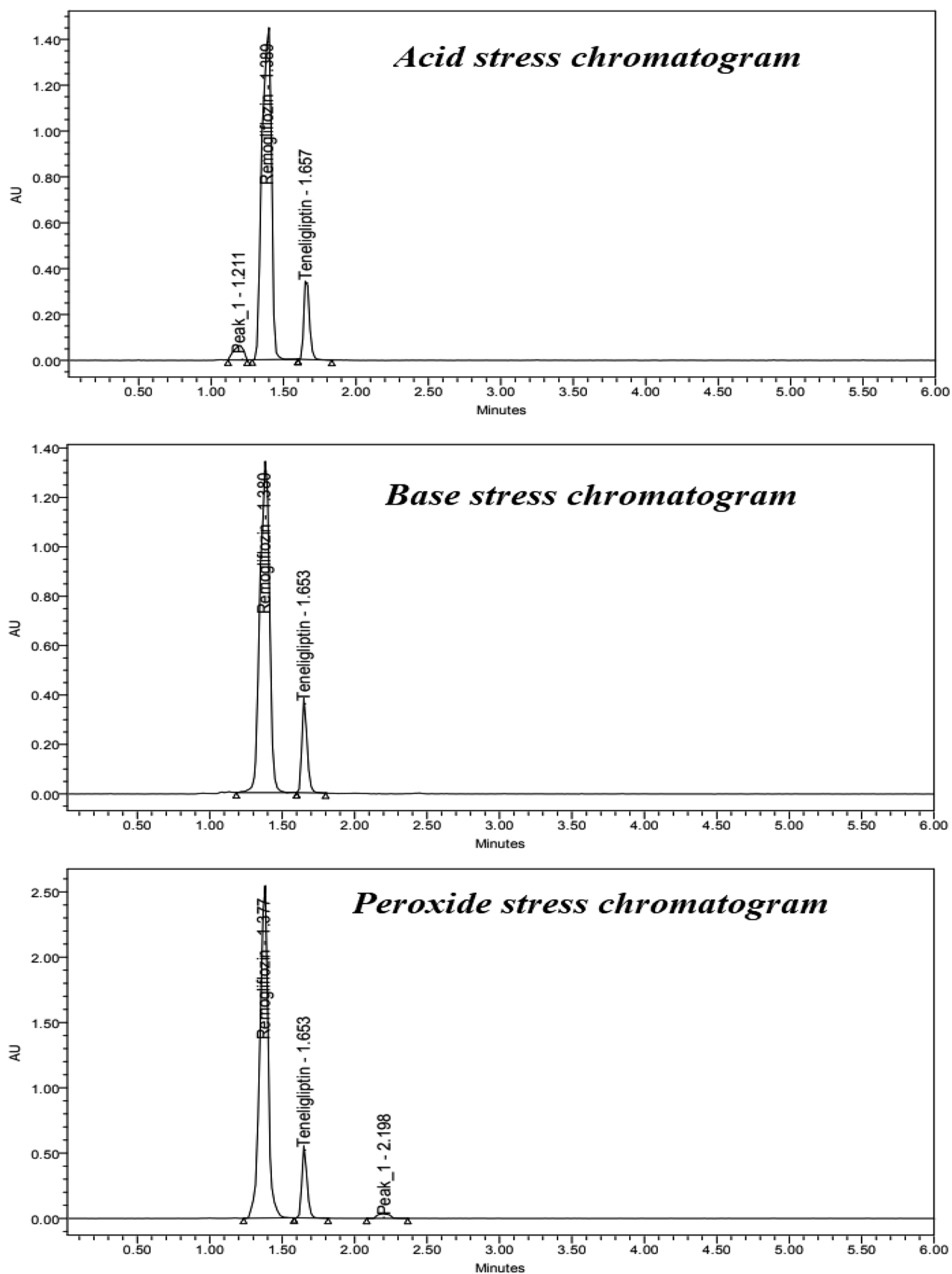
Figure 3. Forced degradation study. Acid, base, and peroxide stress chromatograms.
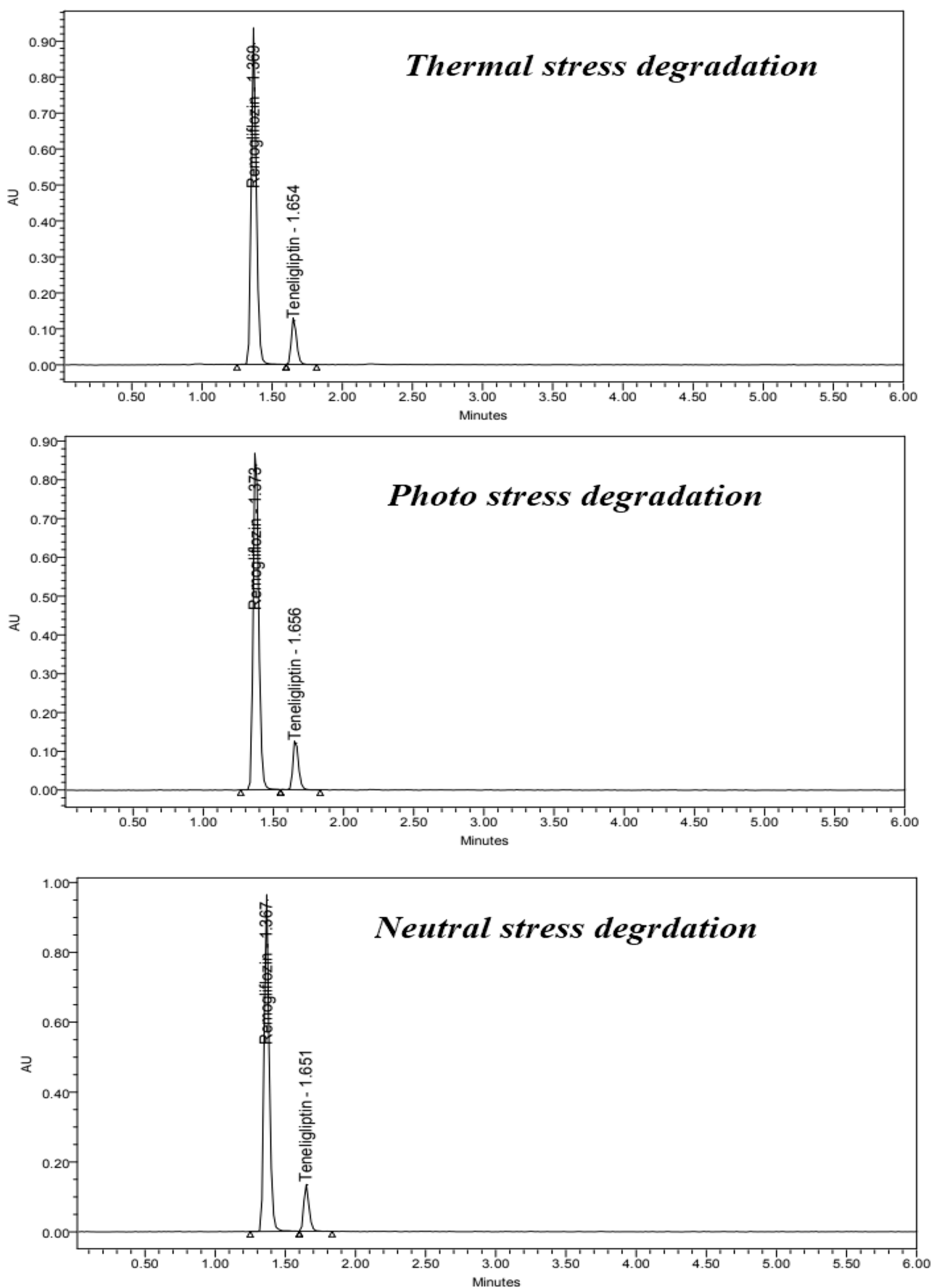
Figure 4. Forced degradation study. Thermal, photo, and neutral stress chromatograms.

Table 3. Design of Experiments of Three Factors and Responses[a]

		factor 1	factor 2	factor 3	response 1	response 2	response 3
std	run	A: flow	B: organic ratio	C: column temp	R1	R2	R3
2	1	0.1	315	25	1.4	1.71	3.4
6	2	0.1	385	25	1.415	1.716	5.2
11	3	0.3	315	35	1.295	1.562	3.3
8	4	0.3	385	25	1.396	1.785	4.7
16	5	0.3	385	35	1.4	1.8	4.8
17	6	0.2	350	30	1.351	1.662	4.3
15	7	0.3	385	35	1.41	1.71	4.8
18	8	0.2	350	30	1.356	1.663	4.3
14	9	0.1	385	35	1.411	1.77	5.1
1	10	0.1	315	25	1.299	1.51	4.1
3	11	0.3	315	25	1.251	1.551	3.8
4	12	0.3	315	25	1.241	1.518	3.7
10	13	0.1	315	35	1.31	1.576	3.6
12	14	0.3	315	35	1.291	1.509	3.3
7	15	0.3	385	25	1.359	1.71	5.1
13	16	0.1	385	35	1.408	1.785	4.8
19	17	0.2	350	30	1.361	1.659	4.3
5	18	0.1	385	25	1.419	1.81	4.2
9	19	0.1	315	35	1.295	1.481	3.5

[a]R1= retention time of remogliflozin. R2= retention time of teneligliptin. R3= resolution between remogliflozin and teneligliptin.

Table 4. ANOVA Table[a]

response	source	sum of squares	df	mean square	F-value	p-value	
R1	model	0.0541	4	0.0135	21.37	<0.0001	significant
	A-flow	0.0062	1	0.0062	9.74	0.0081	
	B-organic ratio	0.0437	1	0.0437	69.01	<0.0001	
	C-column temp	0.0001	1	0.0001	0.158	0.6975	
	AC	0.0042	1	0.0042	6.57	0.0236	
	curvature	0.0001	1	0.0001	0.1437	0.7108	
	residual	0.0082	13	0.0006			
	lack of fit	0.0022	3	0.0007	1.19	0.3635	not significant
	pure error	0.0061	10	0.0006			
	cor total	0.0624	18				
R2	model	0.1741	1	0.1741	58.23	<0.0001	significant
	B-organic ratio	0.1741	1	0.1741	58.23	<0.0001	
	curvature	0.0001	1	0.0001	0.0203	0.8886	
	residual	0.0478	16	0.003			
	lack of fit	0.01	6	0.0017	0.4392	0.8369	not significant
	pure error	0.0379	10	0.0038			
	cor total	0.222	18				
R3	model	6.25	1	6.25	81.47	<0.0001	significant
	B-organic ratio	6.25	1	6.25	81.47	<0.0001	
	curvature	0.0193	1	0.0193	0.2521	0.6224	
	residual	1.23	16	0.0767			
	lack of fit	0.3475	6	0.0579	0.6581	0.6851	not significant
	pure error	0.88	10	0.088			
	cor total	7.5	18				

[a]R1= retention time of remogliflozin. R2= retention time of teneligliptin. R3= resolution between remogliflozin and teneligliptin.

freshly made standard solutions. We compared the differences between the initial and 24 h samples' results. The results were acceptable, with a difference of less than 2.0% between the initial and 24 h results. The findings demonstrated that the standard and sample solutions remained stable for 24 h in both refrigerator and lab environments. In Table 1, results are displayed.

3.2.5. Linearity Study. The linearity of both analytes was tested between 50 and 150% (50, 80, 100, 120, and 150%)

concentrations. To determine the slope, *y*-intercept, and correlation coefficient, triplicate injections of linear solutions were injected. Beer's law demonstrated that the analytes' response was directly proportionate to concentration. Lambert's correlation coefficient for both analytes was greater than 0.999. The slope and intercept were computed. The preceding results demonstrate that the method is linear. Table 1 summarizes the findings.
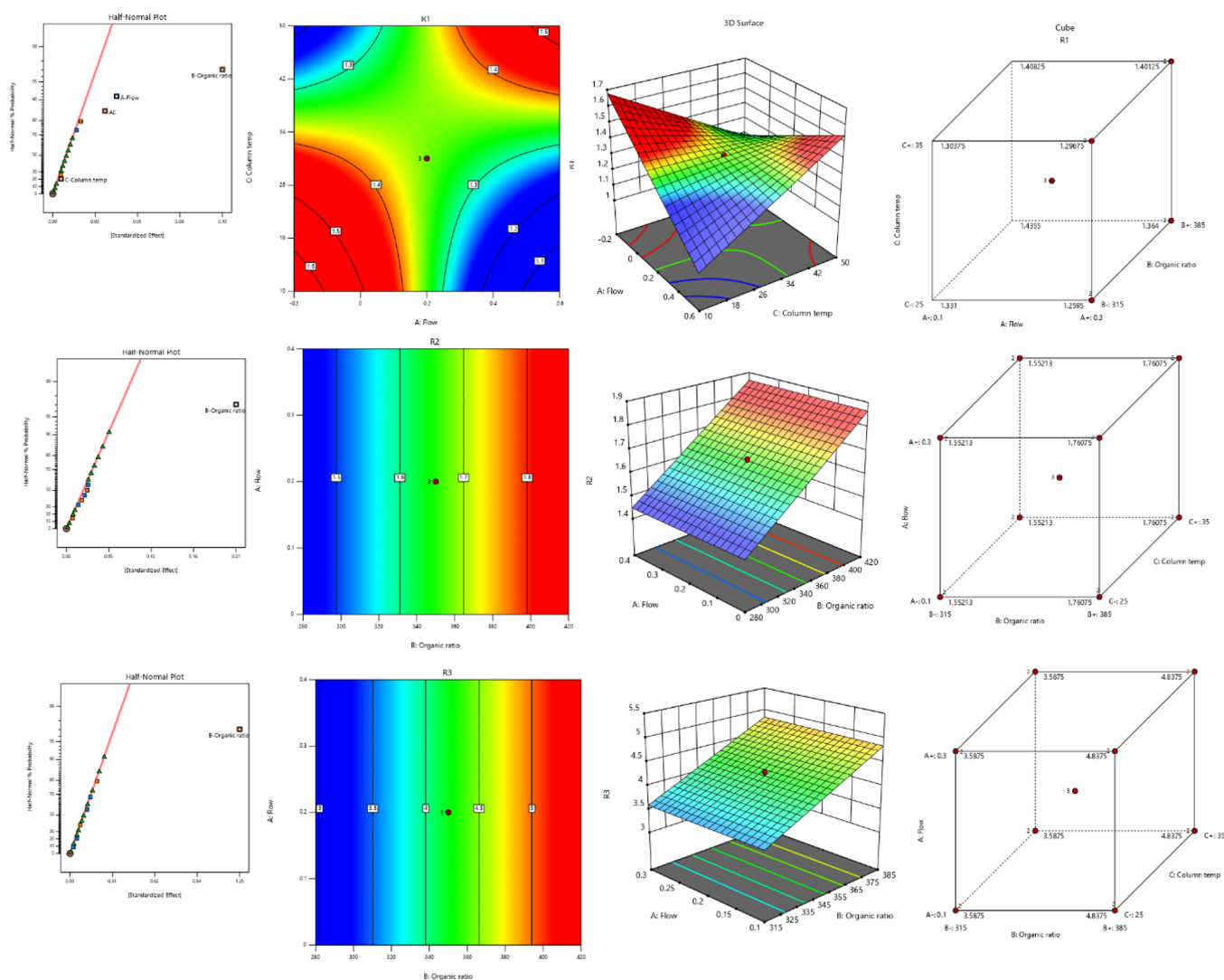
Figure 5. Half normal plots, 2D contour plot, 3D plots, and 3D cube diagrams and for responses R1, R2, and R3.

3.2.6. Accuracy. Recovery of analytes at levels between 50 and 150% was used to gauge the analytical method's accuracy. Prepared sample solutions were at 50, 100, and 150% of the standard value. The samples were injected in triplicate in accordance with the method. Accuracy was demonstrated by the results of the method being similar to the actual values. The accuracy analysis ranged from 50 to 150%. Individual-level triplicate results ranged from a minimum of 98.1 to a maximum of 100.9%. These outcomes allow us to verify the method's accuracy. Table 1 summarizes the findings.

3.2.7. Robustness. Using a QbD-based experimental tool design, the robustness parameters were determined. A two-stage, three-way interaction with three central points, consisting of two replicates and 19 experiments, was chosen. The factors A−C of the input technique were determined to be the flow rate (mL/min), mobile phase ratio (mL), and column oven temperature (°C), respectively. The resolution between both analytes was R1; the retention of remogliflozin etabonate was R2; and the retention time of teneligliptin was R3. Based on the real process conditions, the following changes are made to the input parameters. The flow rate was changed to 10% of what it was before (0.2 mL/min); the organic fraction was changed to 10% of what it was before

(35:65 v/v); and the temperature of the column compartment was changed by 5 °C from what it was before (30 °C). Table 3 shows a summary of the DoE, with input values and output responses.

Seminormal plots were used to find significant effects in the DoE data through statistical analysis. The model is significant for all responses, but the lack of fit is not, as shown by the ANOVA data, suggesting that the design used is suitable for the current investigation. Table 4 provides a summary of the data from the DoE and the ANOVA.

Figure 5 depicts several different types of 3D plots, including a 3D cube plot, a 3D response surface plot, and a 2D half normal plot.

Desirability plot and predicted plots for responses are shown in Figure 6. Figure 7 depicts overlay plots. The tailing factor, resolution, and number of plates used in each experiment were all within acceptable ranges.

3.2.8. Drug Product Analysis. In the final condition, the assay for three batches was determined once completing the validation activity to check the feasibility with the drug product, the results are found satisfactory, and the results are shown in Table 5.
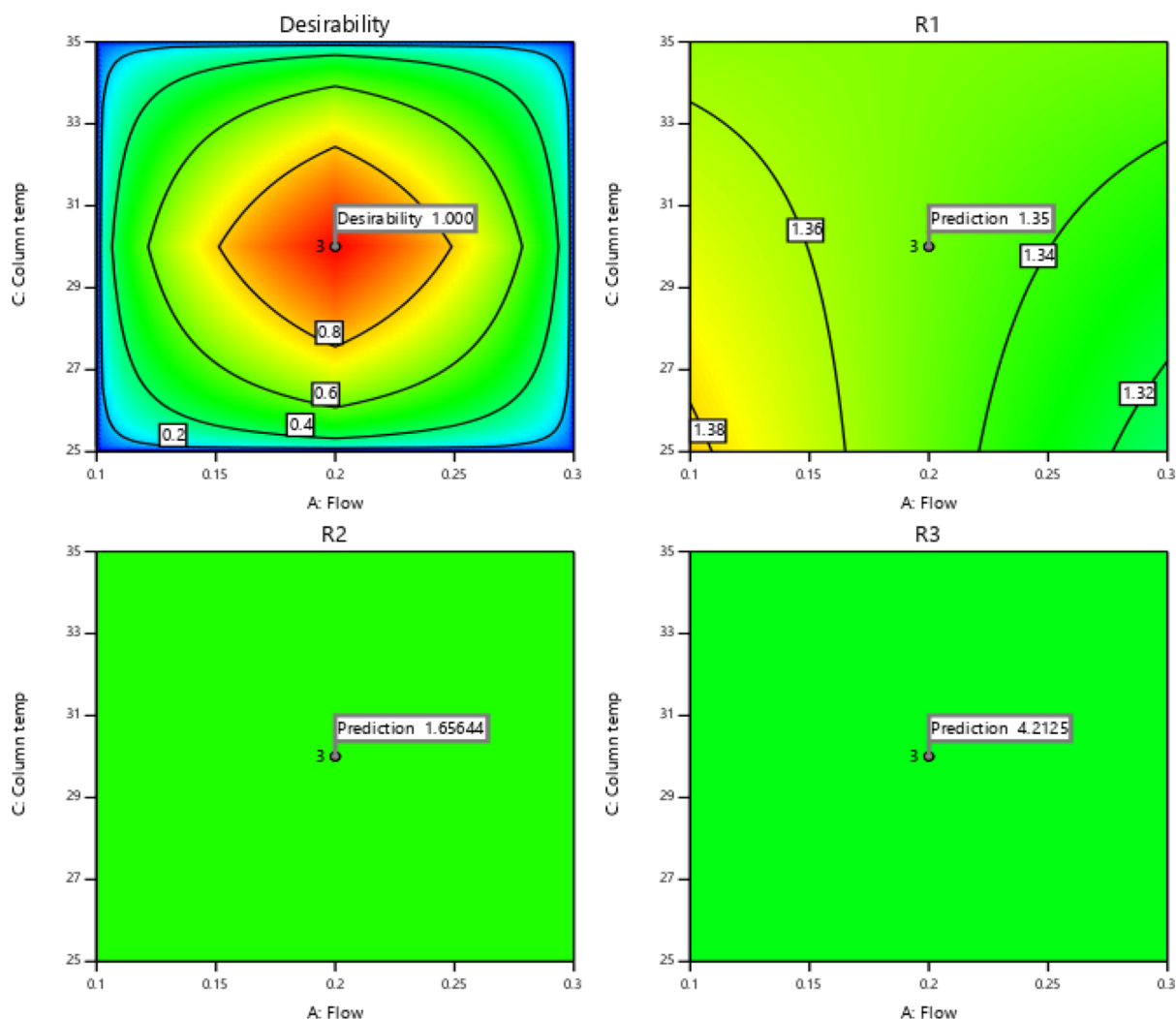
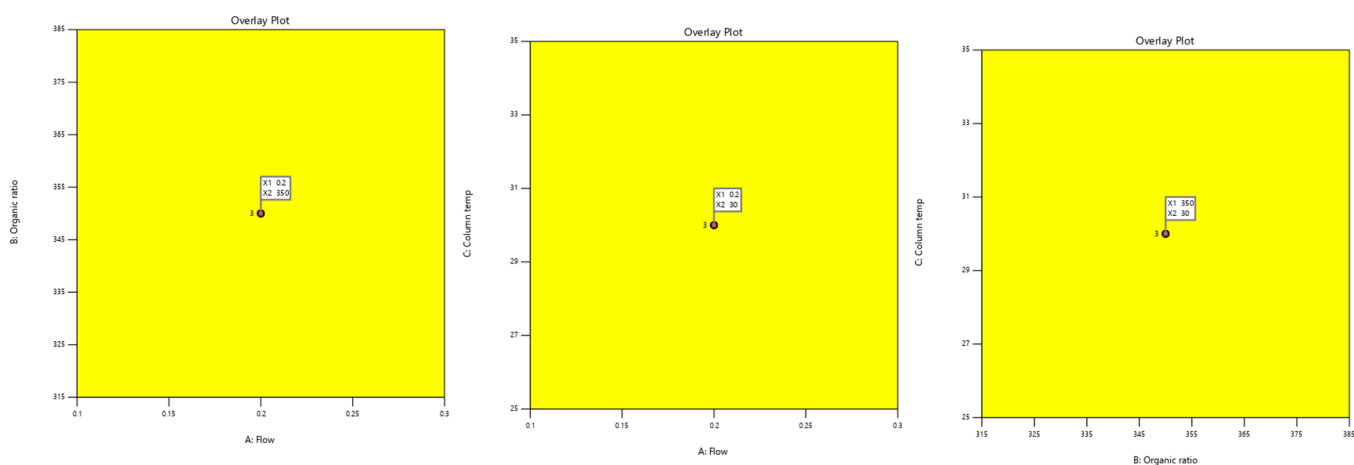**Figure 6.** Desirability Plots and Predicted Plots for Responses R1, R2, and R3.

Figure 7. Overlay plots for responses R1, R2, and R3.

4. CONCLUSIONS

The health care system places a premium on the reliability, consistency, and effectiveness of pharmaceutical formulations. In an oral solid formulation of remogliflozin etabonate and teneligliptin, quantity determination by the UPLC method was developed. It was found that the method is specific, exact, reproducible, rugged, accurate, linear, and robust after being validated in accordance with ICH Q2 (R1) and the USP general chapter. The stability sample analysis in shelf life studies benefited from the method's stability-indicating nature, as shown by the forced degradation study. The proposed approach requires only limited validation studies before it can

Table 5. Analysis Results of the Three-Batch Assay for Both the Analytes

S. no.	batch	remogliflozin	teneligliptin
1	A	99.8	100.1
2	B	99.6	99.8
3	C	99.7	99.8

be employed in routine pharmaceutical quality control laboratories.

■ AUTHOR INFORMATION

Corresponding Authors

Phani Raja Kanuparthy − *Department of Chemistry, GITAM School of Science, GITAM Deemed to be University, Hyderabad, Telangana 502329, India*; Email: pkanupar@gitam.edu

Naresh Kumar Katari − *Department of Chemistry, GITAM School of Science, GITAM Deemed to be University, Hyderabad, Telangana 502329, India; School of Chemistry & Physics, College of Agriculture, Engineering & Science, Westville Campus, University of KwaZulu-Natal, Durban 4000, South Africa;* orcid.org/0000-0002-5737-8528; Email: nkatari@gitam.edu

Authors

Jyothsna Menda − *Department of Chemistry, GITAM School of Science, GITAM Deemed to be University, Hyderabad, Telangana 502329, India; Department of Chemistry, Gokaraju Lailavathi Womens Engineering College, Hyderabad 500090, India*

Vaishnavi Chintala − *Analytical Research and Development, Cambrex High Point, High Point, North Carolina 27265, United States*

Leela Prasad Kowtharapu − *Department of Chemistry, GITAM School of Science, GITAM Deemed to be University, Hyderabad, Telangana 502329, India*

Sreekantha Babu Jonnalagadda − *School of Chemistry & Physics, College of Agriculture, Engineering & Science, Westville Campus, University of KwaZulu-Natal, Durban 4000, South Africa;* orcid.org/0000-0001-6501-8875

Complete contact information is available at:
https://pubs.acs.org/10.1021/acsomega.3c04589

Notes

■ ACKNOWLEDGMENTS

■ REFERENCES

(1) Attimarad, M.; Venugopala, K. N.; Nair, A. B.; Sreeharsha, N.; Molina, E. I. P.; Kotnal, R. B.; Deb, P. K. Environmental sustainable mathematically processed UV spectroscopic methods for quality control analysis of remogliflozin and teneligliptin: Evaluation of greenness and whiteness. *Spectrochim. Acta A Mol. Biomol.* **2022**, *278*, No. 121303.

(2) Attimarad, M.; Venugopala, K. N.; Nair, A. B.; Sreeharsha, N.; Deb, P. K. Experimental design approach for quantitative expressions of simultaneous quantification of two binary formulations containing remogliflozin and gliptins by RP-HPLC. *Separations.* **2022**, *9* (2), 23.

(3) Dhara, V.; Saad, P. M.; Sohel, P.; Dinesh, P.; Jignesh, P.; Tulsi, P.; Hardik, P. Development and Validation of UV Spectroscopic Method for Determination of Remogliflozin Etabonate in Bulk and Tablet Dosage Form. *Ijprajournal.* **2022**, *7*, 404−411.

(4) Attimarad, M.; Venugopala, K. N.; Chohan, M. S.; David, M.; Molina, E. I. P.; Sreeharsha, N.; Balgoname, A. A. An Experimental Design Approach to Quantitative Expression for Quality Control of a Multicomponent Antidiabetic Formulation by the HILIC Method. *Molecules.* **2022**, *27* (10), 3135.

(5) Shah, D. A.; Gondalia, I. I.; Patel, V. B.; Mahajan, A.; Chhalotiya, U. K. Stability indicating liquid chromatographic method for the estimation of remogliflozin etabonate. *J. Chem. Metrol.* **2020**, *14*, 125−132.

(6) Itigimatha, N.; Chadchan, K. S.; Yallur, B. C.; Hadagali, M. D. Simple and Sensitive RP-HPLC and UV Spectroscopic Methods for the Determination of Remogliflozin Etabonate in Pure and Pharmaceutical Formulations. *Turk. J. Pharm. Sci.* **2022**, *19* (2), 213.

(7) Attimarad, M.; Venugopala, K. N.; Chohan, M. S.; David, M.; Molina, E. I. P.; Sreeharsha, N.; Balgoname, A. A. An Experimental Design Approach to Quantitative Expression for Quality Control of a Multicomponent Antidiabetic Formulation by the HILIC Method. *Molecules.* **2022**, *27* (10), 3135.

(8) Vinodbhai, P. R. Development and Validation of Stability Indicating RP-HPLC Method For Simultaneous Estimation Of Remogliflozin And Vildagliptin In Pharmaceutical Dosage Form. *IJNRD* **2022**, *7* (4), 930−964.

(9) Ali, S. M.; Bharath, P.; Sharif, S. K.; Ramachandran, D. Simple and Fast Stability Indicating UPLC Method for the Simultaneous Quantification of Vildagliptin and Remogliflozin Etabonate in Bulk Drug and Formulations. *Curr. Trends Biotechnol. Pharm.* **2021**, *15* (4), 401−407.

(10) Jaiswal, R.; Kohad, M.; Michael, P. E.; Raval, H. (2022). *Development and Validation of Stability Indicating HPTLC Method for Simultaneous Estimation of Metformin Hydrochloride and Remogliflozin Enabonate in Pharmaceutical Dosage Form.*

(11) Kumar, T. G.; Vidyadhara, S.; Narkhede, N. A.; Silpa, Y. S.; Lakshmi, M. R. Method development, validation, and stability studies of teneligliptin by RP-HPLC and identification of degradation products by UPLC tandem mass spectroscopy. *J. Anal. Sci. Technol.* **2016**, *7*, 1−12.

(12) Kant, R.; Bodla, R. B.; Kapoor, G.; Bhutani, R. Optimization of a single HPLC-PDA method for quantifying metformin, gliclazide, pioglitazone, dapagliflozin, empagliflozin, saxagliptin, linagliptin and teneligliptin using central composite design. *Bioorg. Med. Chem.* **2019**, *91*, No. 103111.

(13) Lokhande, D. P. Analytical method development and validation of teneligliptin by using RP-HPLC with ICH guidelines. *Int. J. Trend Sci. Res. Dev.* **2019**, *3*, 259−263.

(14) Biswas, B.; Kumar, M.; Sharma, J. B.; Saini, V.; Bhatt, S. Method Development and Validation for Estimation of Teneligliptin in Tablet Dosage Form by RP-HPLC. *Res. J. Pharm. Technol.* **2020**, *13*, 1774−1778.

(15) Bichala, P. K.; Kumar, K. J.; Suthakaran, R.; Shankar, C. H. Development and Validation of an Analytical Method for the Estimation of Metformin and Teneligliptin in its Bulk and Tablet Dosage Form by using RP-HPLC. *Asian J. Pharm.* **2020**, *10* (1), 11−14.

(16) Musmade, B. D.; Baraskar, M. L.; Ghodke, V. N.; Bhope, S. G.; Padmanabhan, S.; Lohar, K. S. Impurity profiling method development and validation of metformin hydrochloride and teneligliptin hydrobromide hydrate in their combination tablet dosage form by using RP-HPLC with UV/PDA detector. *Future J. Pharm. Sci.* **2021**, *7* (1), 1−10.

(17) Shah, D. A.; Agarwal, K.; Mehta, F. A.; Patel, V. B. Stability indicating HPTLC method for the estimation of anti-diabetic drug Teneligliptin. *Curr. Pharma. Ana.* **2018**, *14* (6), 547−554.

(18) Kumar, T. N. V.; Vidyadhara, S.; Narkhede, N. A.; Silpa, Y. S.; Lakshmi, M. R. Retraction Note: Method development, validation, and stability studies of teneligliptin by RP-HPLC and identification of

of degradation products by UPLC tandem mass spectroscopy. *J. Ana. Sci. Technol.* **2020**, *11* (1), 1 DOI: 10.1186/s40543-016-0107-4.

(19) Nathi, R.; Kowtharapu, L. P.; Muchakayala, S. K.; Konduru, N. QbD-based stability-indicating liquid chromatography (RP-HPLC) method for the determination of flurbiprofen in cataplasm. *Biomed. Chromatogr.* **2023**, *37* (4), No. e5580.

(20) Kowtharapu, L. P.; Katari, N. K.; Sandoval, C. A.; Muchakayala, S. K.; Rekulapally, V. K. Unique green chromatography method for the determination of serotonin receptor antagonist (Ondansetron hydrochloride) related substances in a liquid formulation, robustness by quality by design-based design of experiments approach. *J. Sep. Sci.* **2022**, *45*, 1711−1726.

(21) Kowtharapu, L. P.; Katari, N. K.; Ch, S.; Sandoval, C. A.; Muchakayala, S. K.; Konduru, N. A Quality by Design and green LC technique for the determination of mast cell stabilizer and histamine receptor antagonist (Olopatadine HCl) in multiple formulations. *Biomed. Chromatogr.* **2022**, *36*, No. e5359.

(22) Deshpande, G. K.; Akshinthala, P.; Katari, N. K.; Deshmukh, B.; Kowtharapu, L. P.; Battula, S. R.; Gundla, R. Anti-microbial lead compound Sulfonamide-Anthranilate derivative Methyl-Ester-Toluene-Sulfonamide and its purity by Liquid Chromatography to develop the New Drug Application. *Biomed. Chromatogr.* **2023**, No. e5646.

(23) Reddy Saddala, M. P.; Konduru, N.; Gundla, R.; Kowtharapu, L. P. Development and validation of novel RP-HPLC method for midostaurin determination using analytical quality by design approach from regulatory perspective and determination of major degradation compounds of midostaurin using LC−MS. *Biomed. Chromatogr.* **2022**, *36* (12), No. e5486.

(24) Kowtharapu, L. P.; Katari, N. K.; Sandoval, C. A.; Muchakayala, S. K.; Rekulapally, V. K. Green liquid chromatography method for the determination of related substances present in Olopatadine HCl nasal spray formulation, robustness by design expert. *J. AOAC Int.* **2022**, *105*, 1247−1257.

(25) Kowtharapu, L. P.; Katari, N. K.; Sandoval, C. A.; Rekulapally, V. K.; Jonnalagadda, S. B. Green Chromatographic Method for Determination of Active Pharmaceutical Ingredient, Preservative, and Antioxidant in an Injectable Formulation: Robustness by Design Expert. *ACS Omega.* **2022**, *7* (38), 34098−34108.

(26) Muchakayala, S. K.; Katari, N. K.; Saripella, K. K.; Schaaf, H.; Marisetti, V. M.; Kowtharapu, L. P.; Jonnalagadda, S. B. AQbD based green UPLC method to determine mycophenolate mofetil impurities and Identification of degradation products by QToF LCMS. *Sci. Rep.* **2022**, *12* (1), 19138.