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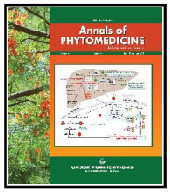

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A novel stability indicating RP-HPLC method for the simultaneous determination of dapagliflozin and vildagliptin in tablet dosage forms

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Abstract

A simple, accurate, precise RP-HPLC method was developed for the simultaneous estimation of dapagliflozin and vildagliptin in pure and tablet dosage forms. Chromatography was performed on a standard Kromosil® C18 (4.6 x 150 mm, 5 µm) column. The mobile phase comprised of acetonitrile and sodium hydrogen phosphate taken in the ratio of 30:70 was pumped through the column at a flow rate of 0.9 ml/min. The buffer used in this method is phosphate buffer and pH was adjusted to 5.4 by adding 0.1% formic acid. Temperature was maintained at 30°C (room temperature). The optimized wavelength selected was 220 nm. The retention time of dapagliflozin and vildagliptin were found to be 2.890 min and 2.349 min, respectively. % RSD of the dapagliflozin and vildagliptin were found to be 0.3 and 1.0, respectively. % Recovery was obtained as 99.95% and 100.07% for dapagliflozin and vildagliptin, respectively. The limit of detection (LOD) and limit of quantification (LOQ) values obtained from regression equations of dapagliflozin and vildagliptin were 0.07 ppm, 0.21 ppm, and 0.46 ppm, 1.39 ppm, respectively. The regression equation of dapagliflozin is y = 8461.7x + 842.05 and y = 4162.9x + 747.14 for vildagliptin. The method developed was simple and economical and can be adopted in regular quality control tests in industries.

1. Introduction

Diabetes mellitus develops when there is persistent hyperglycemia brought on by elevated blood glucose levels in the body (Divya and Sanjeev, 2021). Defects in insulin secretion and increased insulin resistance by body cells cause type 2 diabetes mellitus, which is not insulin-dependent (Amarish *et al*., 2021). The condition cannot be fully cured; instead, diabetic medication, a healthy diet, and regular exercise are typically recommended to control insulin levels.

FDA-approved in 2014, dapagliflozin is an oral hyperglycemic medication that is classified as part of the sodium glucose co-transporter (SGLT-2) inhibitor class of drugs. The chemical formula for dapagliflozin is $C_{21}H_{25}ClO_6$ and IUPAC name is (2S,3R,4R,5S,6R)-2-[4-Chloro-3-(4-ethoxyphenyl)methyl]phenyl]–6(hydroxymethyl) oxane-3,4,5-triol. By preventing glucose reabsorption in the kidney's proximal tubule of nephrons, dapagliflozin enhances glycaemic management. Heart failure is another condition for which it is used (Thiyagaranjan and Magharla, 2018; Grace *et al*., 2019; Sherif and Obaid, 2021).

The European Medicines Agency authorized the antihyperglycemic medication vildagliptin in 2008. It is one of the classes of drugs designated as dipeptidyl peptidase (DDP-4) enzyme inhibitors, which are used to treat type 2 diabetes mellitus, a condition in which the secretion of glucagon-like peptide (GLP-1) and associated insulinotropic effects are compromised. The chemical formula of vildagliptin is $C_{17}H_{25}N_3O_2$ and IUPAC name is (2S)-1-[2-[(3- hydroxy-1-adamantyl)amino]acetyl]pyrrolidine-2-carbonitrile (Safila *et al*., 2014; Pontarolo *et al*., 2014; Chaphekar and Purnima, 2016).

On April 8, 2022, CDSCO authorized dapagliflozin and vildagliptin as a fixed dose combination for type 2 diabetes mellitus (CDSCO, 2022). Compared to metformin alone, the combined effects of dapagliflozin's glucose reabsorption and vildagliptin's GLP-1 inhibitory action offer a more effective and comprehensive treatment for type 2 diabetes mellitus. Prior to this work, no RP-HPLC method development for dapagliflozin and vildagliptin has been described. In quality control labs, RP-HPLC data are essential for examination of any medication combinations. We aimed to create an affordable, accurate, and straightforward RP-HPLC method for estimating the amounts of dapagliflozin and vildagliptin in both pure and commercial formulations. Degradation experiments were conducted on the drug compounds to ascertain the stability of the analyte and the methodology. In accordance with ICH Q2 (R1) recommendations, the method validation parameters were tested (Afroz *et al*., 2023; Dhritimoni and Sumithra, 2023; Gandhimathi *et al*., 2023).

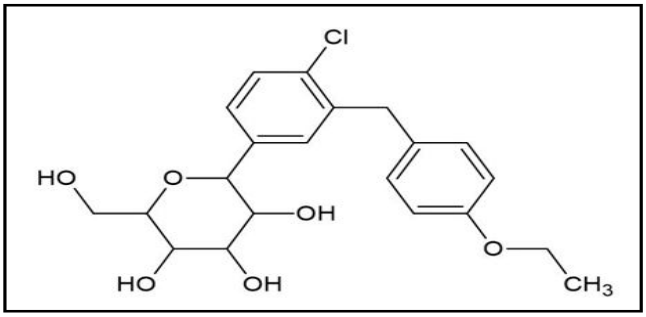

Figure 1: Structure of dapagliflozin.

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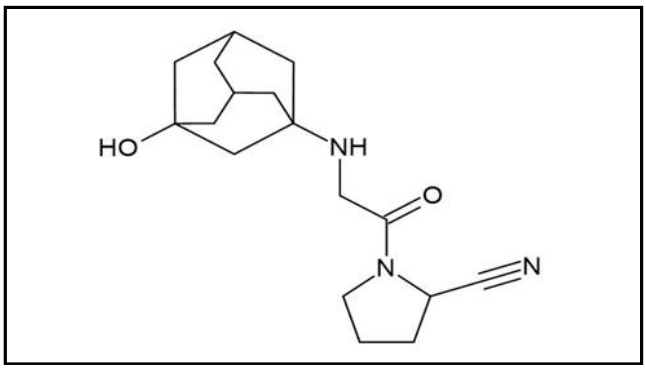

Figure 2: Structure of vildagliptin.

2. Materials and Methods

2.1 Chemical reagents and instrumentation

A combination fixed dose of dapagliflozin and vildagliptin (Jalra DP-USV Ltd.) was obtained from the local pharmacy, and pure gift samples of both drugs were obtained from Spectrum Pharma Labs. Rankem® provided the following HPLC-grade supplies: distilled water, acetonitrile, phosphate buffer, methanol, potassium dehydrogenate, orthophosphate buffer, and orthophosphoric acid.

Electronic weighing balance [Denver®], pH meter [BVK Enterprises], ultrasonicator [BVK Enterprises], UV-vis spectrophotometer [PG Instruments T60] with UV Win 6 Software and HPLC unit [Water® 2695] with Waters® 2996 photodiode array detector, standard Kromosil® C_{18} (4.6 x 150 mm, 5 µm) column was used.

2.2 Chromatographic conditions

The chromatographic conditions were achieved on Waters® 2695 HPLC unit with Waters® 2996 photodiode array detector integrated with Empower 2 software. The column found suitable for this process was standard Kromosil® C_{18} (4.6 x 150 mm, 5 µm). The mobile phase pumped through the system was acetonitrile and sodium hydrogen phosphate [CH_3CN:Na_2HPO_4] at a ratio of 30:70 and the flow rate was set a 0.9 ml/min. Phosphate buffer was used and pH was adjusted to 5.4 by using 0.1% formic acid. The optimized wavelength was selected at 220 nm. Column temperature was adjusted to room temperature for efficient separation.

2.3 Buffer solution preparation

0.01 N sodium hydrogen phosphate buffer was prepared by accurately weighing 1.41 g of sodium hydrogen phosphate in a 1000 ml volumetric flask and adding 900 ml of Milli-Q water. The buffer solution was degassed; and sonicated and the final volume was adjusted with water. The pH was adjusted to 5.4 using 0.1% formic acid [1 ml conc. formic acid in 1000 ml water].

2.4 Preparation of standard stock and working solution

Based on the solubility of the drugs, the diluents selected were acetonitrile and water at 70:30 ratio. The standard stock solution was prepared by accurately weighing 10 mg of dapagliflozin and 100 mg of vildagliptin and transferring it to 100 ml volumetric flasks, separately. 3/4th of the diluent was added and sonicated. The volume was made up to the mark and labeled as standard stock solution [100 µg/ml of dapagliflozin and 1000 µg/ml of vildagliptin]. The standard working solution was prepared by pipetting 1 ml from each stock solution of dapagliflozin and vildagliptin and taken into a 10 ml volumetric flask and the final volume was adjusted using diluent [10 µg/ml of dapagliflozin and 100 µg/ml of vildagliptin]. They were filtered using 0.45 µ syringe filters.

2.5 Preparation of sample stock and working solution

To prepare a sample stock solution, 10 tablets [Jalra DP] were taken and weighed individually. The average weight was calculated. The weight equivalent of one tablet was taken and transferred to a 100 ml volumetric flask, and 50 ml of diluent was added and sonicated for 25 min. The remaining volume was made up to the mark with diluent and filtered using 0.45 µ syringe filters [100 µg/ml of dapagliflozin and 1000 µg/ml of vildagliptin]. For preparing, the sample working solution, 1 ml of sample stock solution was pipetted and transferred to a 10 ml volumetric flask, and the volume was made up to the mark using diluent [10 µg/ml of dapagliflozin and 100 µg/ml of vildagliptin].

2.6 Method validation

The ICH Q2 (R1) guidelines were followed in the development and validation of the method, and the following parameters were assessed: accuracy, precision, linearity, robustness, specificity, robustness, detection limit, and quantification limit. The runtime for each parameter was 5 min, and the % RSD was reported.

2.6.1 System suitability parameters

Before conducting each day's sample analysis, the operator has to make sure that the equipment and process being used are producing data that is acceptable in quality. System suitability tests are used to confirm this. The parameters were determined by using standard solutions of dapagliflozin (10 ppm) and vildagliptin (100 ppm) the solutions were injected six times and peak areas were calculated. The % RSD for the areas of the six standard injections should not exceed 2%.

Table 1: System suitability parameters and their recommended limits

Parameter	Recommendation
Capacity factor (K')	The peak should be well-resolved from other peaks and the void volume generally K>2.
Repeatability	RSD d™ 2% (N e™ 5 is desirable)
Relative retention	Not essential as the resolution is stated.
Resolution (R_S)	R_S of >2 between the peak of interest and the closest elutingpotential interferon.
Tailing factor (T)	T d™ 2
Theoretical plates (N)	In general should be >2000.

2.6.2 Specificity

According to ICH, The method that generates a response for a particular analyte exclusively is referred to as specificity while the term selectivity refers to a method that responds to many chemical entities that may or may not be distinguished from each other. The approach is considered selective, if the response stands out from all other responses. We should check for interference in the optimized method. The placebo and blank chromatograms should not have any interference peaks. To determine the specificity, the stock solution was injected into the system.

2.6.3 Precision

The term "precision" refers to "the degree of agreement among individual test results when the procedure is applied repeatedly to multiple samplings of a homogeneous sample". For the homogenous sample, system, method and intermediate precision were determined. Six injections of 10 µl of the standard working solution were injected over the course of 5 min. For the system precision, method precision, and intermediate precision, respectively, the % RSD for the area of six duplicate injections was estimated.

2.6.4 Linearity

The degree to which a response versus concentration calibration plot yields a straight line indicates how linear a procedure is. One way to evaluate linearity is to do single measurements at various analyte concentrations. After that, a linear least squares regression technique is applied to the data. The desired linearity information is provided by the plot slope, intercept, and correlation coefficient factor. The linearity of the method was calculated by analyzing six concentrations of both drugs ranging from 2.5-15 µg/ml for dapagliflozin and 25-150 µg/ml for vildagliptin, respectively.

2.6.5 Accuracy

The degree to which the measured value closely approximates the true value is known as accuracy. Accuracy is represented and determined by recovery studies using 50%, 100%, and 150% spiked solutions. Each percentage was injected three times. The accuracy was calculated in the form of percentage recovery of test analyte, recovered by assay. The % Recovery for each level should be within 98.0 to 102.0%.

2.6.6 Robustness

Robustness evaluates the impact of purposeful internal variations on the test data. The system's flow rate, mobile phase composition, and column temperature were all altered. The flow rate was changed from 0.8 to 1.0 ml/min, the temperature was changed from 27-33ºC and mobile phase composition was altered. For every criterion, duplicate samples were injected. The results indicated no significant variations.

2.6.7 Limit of detection and limit of quantification

The lowest analyte concentration in a sample that can be detected but not necessarily quantified under the specified experimental conditions is known as the limit of detection (LOD), whereas the lowest analyte concentration in a sample that can be quantified with reasonable precision and accuracy under the specified experimental conditions is known as the limit of quantification (LOQ). Applying the signal to noise ratio method, the LOD and LOQ values for dapagliflozin and vildagliptin were determined.

2.7 Forced degradation studies

In order to examine the stability of the analyte and the procedure, multiple sets of stock solutions containing 1 ml each of dapagliflozin and vildagliptin were put through acidic, basic, neutral, oxidative, thermal, and photostability testing.

3. Results

The combination of dapagliflozin and vildagliptin can be effectively determined by the RP-HPLC method using phosphate buffer at pH 5.4 (adjusted using 0.1% formic acid) and mobile phase composition of acetonitrile and sodium hydrogen phosphate at a ratio of 30:70 v/v pumped at a flow rate of 0.9 ml/min and detection wavelength set at 220 nm. The optimized temperature was around 30ºC.

Both the peaks had good resolution and the retention time for dapagliflozin and vildagliptin were found out to be 2.890 min and 2.349 min, respectively. The % RSD of dapagliflozin and vildagliptin were 0.3 and 1.0, respectively. The percentage recoveries for dapagliflozin and vildagliptin were 99.95% and 100.07%, respectively. The plate count and tailing factor were very satisfactory.

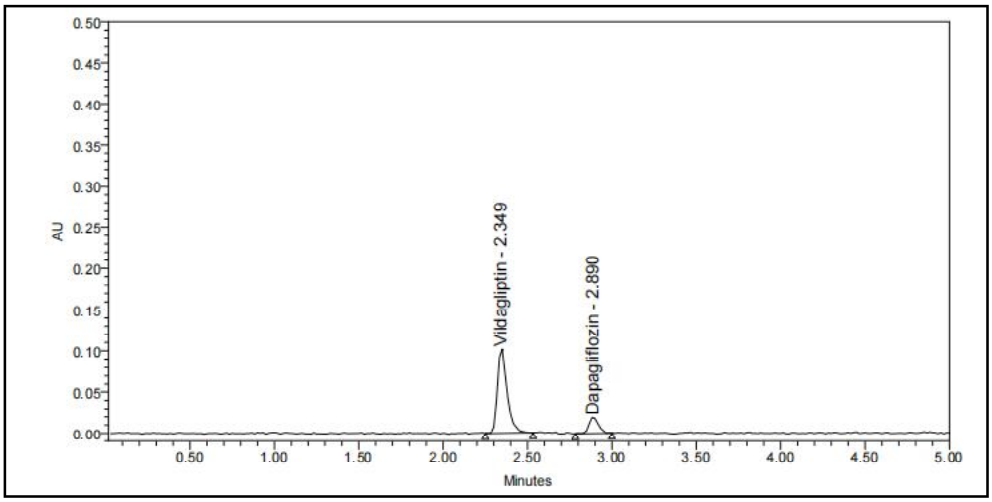

Figure 3: Optimized chromatogram of dapagliflozin and vildagliptin.

3.1 System suitability parameters

Both the plate count and tailing factor were good. Each system suitability parameter was met and within acceptable limits.

3.2 Specificity

Since neither the mobile phase nor the blank/placebo interfered with the analyte peaks, the technique was determined to be specific.

3.3 Linearity

Six linear concentrations of dapagliflozin (2.5-15 µg/ml) and vildagliptin (25-150 µg/ml) were injected in a duplicate manner. Linearity equation obtained for dapagliflozin was y = 8461.7x + 842.05 and for vildagliptin was y = 4162.9x + 747.14. Correlation coefficient obtained was 0.999 for the two drugs.

Table 2: Linearity table for dapagliflozin and vildagliptin

Dapagliflozin		Vildagliptin	
Conc. (µg/ml)	Peak area	Conc. (µg/ml)	Peak area
2.5	21625	25	105881
5	43735	50	209019
7.5	65149	75	314876
10	86006	100	411857
12.5	107556	125	524386
15	126061	150	624721

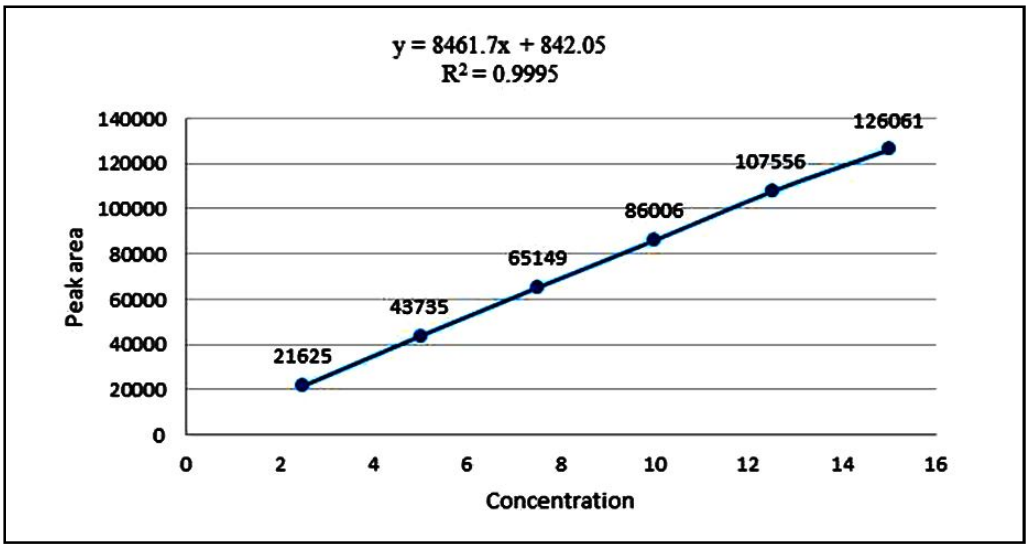

Figure 4: Calibration curve of dapagliflozin.

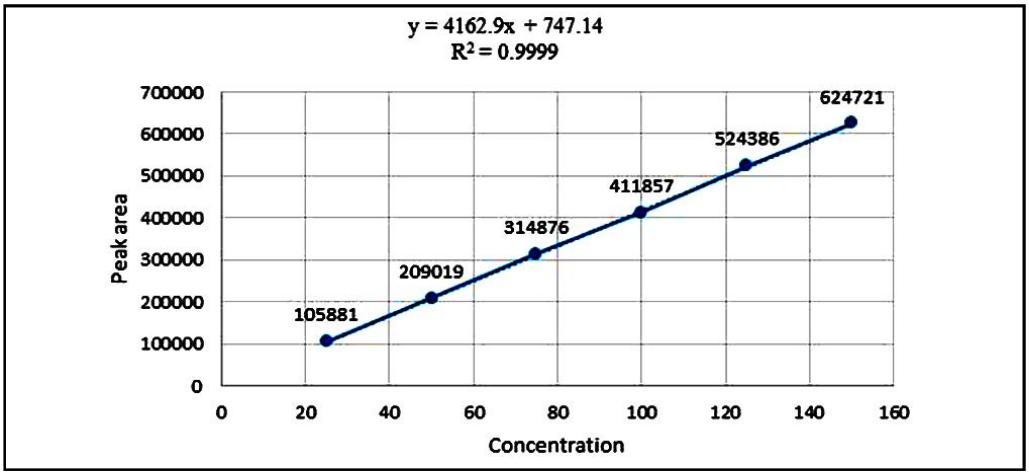

Figure 5: Calibration curve of vildagliptin.

3.4 Precision

Six working sample solutions with the same concentrations were prepared by multiple sampling from the sample stock solution. Peak areas for system, method, and intermediate precision were obtained after a single injection from each working sample solution. The % RSD was all within acceptable limits, and the precision limit should be less than 2. Therefore, the method used was precise.

Table 3: Precision values for dapagliflozin and vildagliptin

Injection No.	System precision		Method precision		Intermediate precision	
	Area of dapagliflozin	Area of vildagliptin	Area of dapagliflozin	Area of vildagliptin	Area of dapagliflozin	Area of vildagliptin
Injection 1	86817	410360	87355	414521	87450	410547
Injection 2	87387	419921	87079	419480	86909	418129
Injection 3	87015	416488	87355	415163	87111	413870
Injection 4	87650	411516	87768	417535	87722	410387
Injection 5	87067	419680	87974	417219	87212	411336
Injection 6	87159	418223	87647	417724	87582	414734
Mean	87183	416031	87530	416940	87331	413167
SD	295.3	4147.4	326.2	1817.0	306.8	3017.2
%RSD	0.3	1.0	0.4	0.4	0.4	0.7

3.5 Accuracy

Samples with three levels of accuracy were created using the standard addition method. For every accuracy level, three injections were administered, and the mean percentage recovery for dapagliflozin and vildagliptin was found to be 99.95% and 100.07%, respectively. They were within the 98 to 102% acceptable range.

Table 4: Accuracy values for dapagliflozin and vildagliptin

Dapagliflozin				
% Level	Amount spiked (µg/ml)	Amount recovered (µg/ml)	% Recovery	Mean % recovery
50%	5	5.01	100.11	99.95
	5	4.95	99.00	
	5	5.04	100.73	
100%	10	10.00	99.98	
	10	9.96	99.61	
	10	9.99	99.86	
150%	15	14.91	99.42	
	15	15.11	100.75	
	15	15.01	100.07	
Vildagliptin				
% Level	Amount spiked (µg/ml)	Amount recovered (µg/ml)	% Recovery	Mean % recovery
50%	50	49.93	99.86	100.07%
	50	49.97	99.93	
	50	50.19	100.38	
100%	100	100.82	100.82	
	100	100.38	100.38	
	100	99.23	99.23	
150%	150	150.59	100.40	
	150	149.27	99.52	
	150	150.26	100.17	

3.6 Limit of detection and limit of quantification

Dapagliflozin had LOD and LOQ values of 0.07 ppm and 0.21 ppm whereas vildagliptin had LOD and LOQ values of 0.46 ppm and 1.39 ppm, respectively.

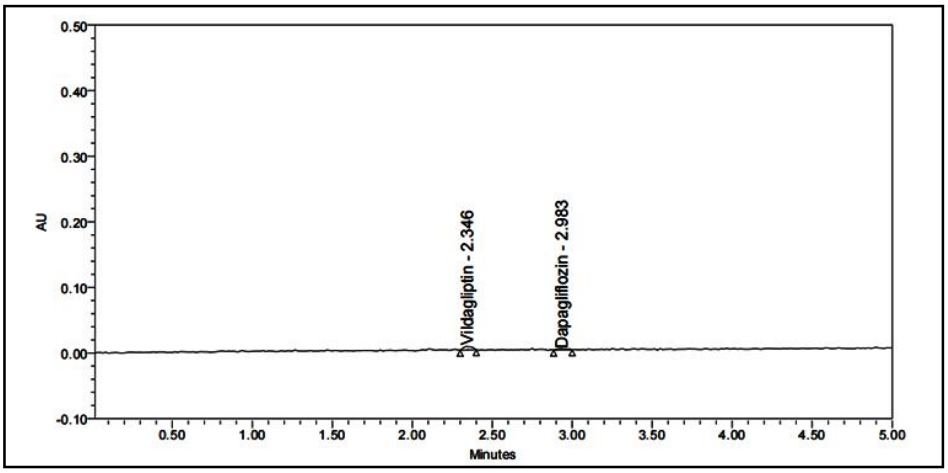

Figure 6: LOD chromatogram for dapagliflozin and vildagliptin.

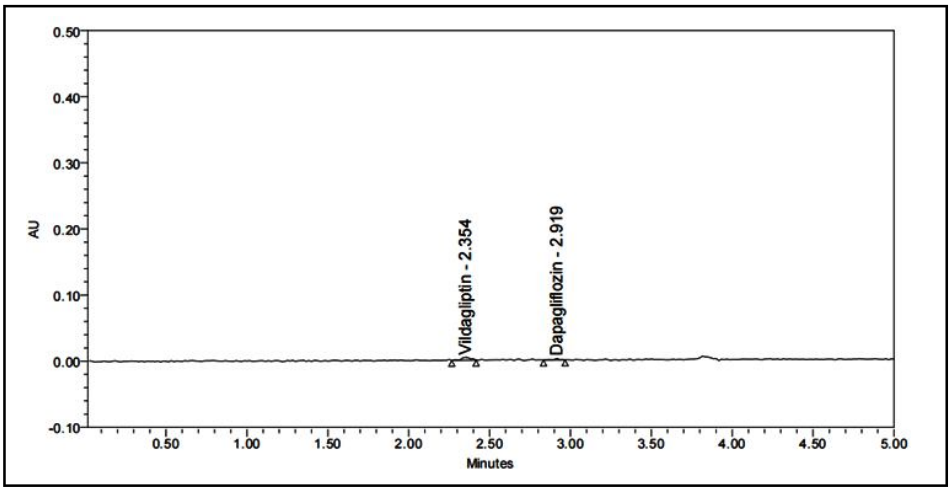

Figure 7: LOQ chromatogram for dapagliflozin and vildagliptin.

3.7 Robustness

Robustness conditions like flow minus (0.8 ml/min), flow plus (1.0 ml/min), mobile phase minus (65B:35A), mobile phase plus (75B:25A), temperature minus (27°C) and temperature plus (33°C) was maintained and samples were injected in duplicate manner. Each of the system suitability parameters passed with minimal to no effect. % RSD was within acceptable limits.

Table 5: Robustness data for dapagliflozin and vildagliptin

Sl. No.	Conditions	% RSD of dapagliflozin	% RSD of vildagliptin
1.	Flow rate (-) 0.8 ml/min	0.3	0.8
2.	Flow rate (+) 1.0 ml/min	0.4	0.5
3.	Mobile phase (-) 65B:35A	0.4	0.6
4.	Mobile phase (+) 75B:25A	0.3	0.4
5.	Temperature (-) 27°C	0.4	0.5
6.	Temperature (+) 33°C	0.4	0.6

3.8 Assay

Jalra-DP (USV Ltd.), bearing the label claim dapagliflozin 100 mg and vildagliptin 10 mg was purchased and assay was performed. Average % assay for dapagliflozin and vildagliptin obtained was 100.00% and 100.02%, respectively.

Table 6: Assay data of dapagliflozin and vildagliptin

S. No.	Dapagliflozin			Vildagliptin		
	Standard area	Sample area	% Assay	Standard area	Sample area	% Assay
1	86817	87355	99.80	410360	414521	99.44
2	87387	87079	99.48	419921	419480	100.63
3	87015	87355	99.80	416488	415163	99.59
4	87650	87768	100.27	411516	417535	100.16
5	87067	87974	100.50	419680	417219	100.08
6	87159	87647	100.13	418223	417724	100.21
Average	87183	87530	100.00	416031	416940	100.02
SD	295.3	326.2	0.37	4147.4	1817.0	0.436
% RSD	0.3	0.4	0.4	1.0	0.4	0.4

Table 7: Degradation data of dapagliflozin and vildagliptin

Type of degradation	Dapagliflozin			Vildagliptin		
	Area	% Recovered	% Degraded	Area	% Recovered	% Degraded
Acid	82532	94.29	5.71	395386	94.85	5.15
Base	82834	94.63	5.37	397700	95.40	4.60
Peroxide	83201	95.05	4.95	398862	95.68	4.32
Thermal	85052	97.17	2.83	408108	97.90	2.10
UV	86583	98.92	1.08	410833	98.55	1.45
Water	87319	99.76	0.24	414097	99.34	0.66

3.9 Forced degradation studies

The stock solutions of both drugs were used for the degradation tests, and suitable and satisfactory results were achieved.

4. Discussion

In summary, the parameters assessed for the proposed technique were found to be reasonably within acceptable limits, which is a prerequisite for claiming the method to be stable and validated.

The linearity range of dapagliflozin was found to be within 2.5-15 µg/ml and 25-150 µg/ml for vildagliptin, respectively. The regression coefficient for dapagliflozin and vildagliptin was 0.999. The regression equation for dapagliflozin is y = 8461.7x + 842.05 and for vildagliptin is y = 4162.9x + 747.14, respectively. The % assay studies gave us 100% drug compound recovery, precisely within the acceptable limits. The method was found to be very specific with no interference from other peaks and could effectively determine the analyte from the mixture. The system precision and method precision values were within the acceptable limit of NMT 2.0% describing the method as precise. The LOD and LOQ values for dapagliflozin were 0.07 ppm and 0.46 ppm whereas 0.21 ppm and 1.39 ppm for vildagliptin, respectively. The robustness evaluation of the method showed it remains both robust and ineffective when subjected to various changes, like variations in temperature, flow rate, and mobile phase composition. The robustness data fulfilled estimates and fell within acceptable limits. Therefore, the method can be considered stable and is capable of accurately estimating the combination stated above.

5. Conclusion

To simultaneously estimate dapagliflozin and vildagliptin in pure and tablet dose forms, a simple, inexpensive, and accurate method has been developed. Chromatography was performed on a standard Kromosil® C_{18} (4.6 × 150 mm, 5 µ) column. The mobile phase comprised of acetonitrile and sodium hydrogen phosphate taken in a ratio of 30:70 v/v was pumped through the column at a flow rate of 0.9 ml/min. The buffer used in this method is phosphate buffer and the pH was adjusted to 5.4 by adding 0.1% formic acid. The temperature was kept at 30ºC (room temperature). The optimized wavelength selected was 220 nm. The retention time of dapagliflozin and vildagliptin were found to be 2.890 min and 2.349 min. % RSD of the dapagliflozin and vildagliptin were found to be 0.3 and 1.0, respectively. % Recovery was obtained as 99.95% and 100.07% for dapagliflozin and vildagliptin, respectively. LOD and LOQ values obtained from regression equations of dapagliflozin were 0.07 ppm and 0.21 ppm whereas for vildagliptin is 0.46 ppm and 1.39 ppm, respectively. The regression equation of dapagliflozin is y = 8461.7x + 842.05 and for vildagliptin is y = 4162.9x + 747.14, respectively.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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