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Research Article

SIMULTANEOUS METHOD DEVELOPMENT AND VALIDATION OF COMBINED DOSAGE FORM DAPAGLIFLOZIN AND VILDAGLIPTIN IN BULK AND COMBINED TABLET DOSAGE FORM BY UV SPECTROPHOTOMETER

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ABSTRACT

Objectives: In the present work on the determination of dapagliflozin and vildagliptin in tablet dosage form, a simple, rapid, inexpensive, accurate, and precise stability-indicating ultraviolet (UV) method was established.

Methods: A UV-visible spectrophotometric technique was done. Double-distilled water was used as the dapagliflozin's diluent. Vildagliptin's diluent was 0.1 N NaOH. The diluent used in the dosage form that contains both vildagliptin and dapagliflozin was 0.1 N NaOH. This approach was verified for linearity, accuracy, precision, QL, and detection limit (DL).

Results: The Combined Dosage form of Dapagliflozin and vildagliptin Linearity was found to be in the ratio of (0.16:1.6–2.2:22 µg/mL). Vildagliptin and dapagliflozin were found to have QLs of 3.7432 µg/mL and 1.2860 µg/mL, respectively. Vildagliptin and dapagliflozin were found to have DLs of 1.2352 and 0.4244, respectively. The developed method for estimating the dosage of dapagliflozin and vildagliptin in tablet form was proven to be accurate, exact, and quick. Under identical circumstances, the medication was stressed by hydrolysis, oxidation, photolysis, and thermal deterioration. The UV-visible system was used to analyze the stress sample.

Conclusion: The proposed method was found to be simple, precise, accurate, and reproducible and can be used for routine analysis of dapagliflozin and vildagliptin in bulk and tablet dosage forms.

Keywords: Vildagliptin, Dapagliflozin, Validation, Ultraviolet-visible spectroscopy, 0.1 N NaOH, Linearity.

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INTRODUCTION

Two antidiabetic drugs are combined together as dapagliflozin + vildagliptin. Dapagliflozin lowers the blood glucose levels and enhances the urine glucose excretion [1]. By increasing the level of insulin and lowering the level of glucagon (a hormone that raises the blood's glucose levels), vildagliptin lowers the level of glucose generated by the liver [2].

Drug profile of dapagliflozin

[5-chloro-3-(3,5-dimethylhepta-1,3-dienyl)-8a-hydroxy-7-methyl-6,8-dioxo-1H-isochromen-7-yl] Acetate is the IUPAC name for this compound [3].

PH: In a 1:1 ethanol solution, dapagliflozin dissolves at a rate of about 0.5 mg/mL PBS (pH 7.2) [4].

State: White Crystalline powder [5].

Molecular formula: C21H25ClO6

PKa: 12.6

408.9: Molecular weight

Solubility: Water is a free solvent for dapagliflozin, making it soluble. Methanol and ethanol are only slightly soluble [6].

Class: Dapagliflozin belongs to the group of drugs known as sodium glucose cotransporter 2 (SGLT2) inhibitors [7].

USFDA approval date: Submitted on January 8, 2014.

Drug profile of vildagliptin

2S-1-[2-[(3-hydroxy-1-adamantyl) amino] acetyl] pyrrolidine-2-carbonitrile is its IUPAC name.

PH: A pH of 7.2 equals about 10 mg/mL. The aqueous solution should not be kept for longer than a day. 1. White crystalline powder for color [8].

Molecular formula: C17H25N3O2.

PKa: 9.03

303.4: Molecular weight

Solubility: Vildagliptin is completely insoluble in 0.1 N NaOH and 0.1 N HCl, but easily soluble in water, methanol, and other solvents [9].

Class: Dipeptidyl peptidase-4 (DPP-4) inhibitor oral antihyperglycemic medication (antidiabetic medicine) [10].

USFDA approval: January 20, 2010

State: Solid

The USFDA-approved date for the combined dosage form of dapagliflozin and vildagliptin is January 8, 2022.

According to a literature review, only a few techniques, including Fourier-transform infrared spectroscopy, ultraviolet (UV), and reversed-phase high-performance liquid chromatography, are available for this combined dosage form of dapagliflozin and vildagliptin.

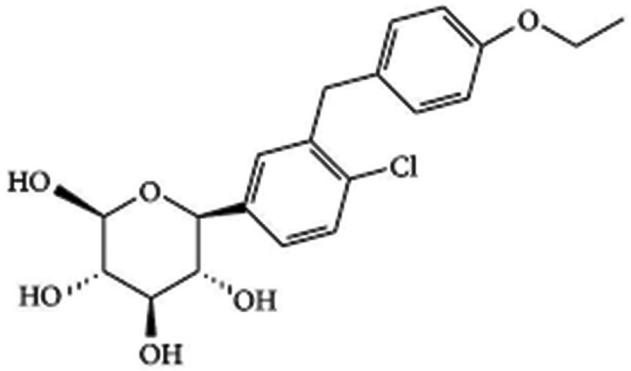

Fig. 1: The Structure of Dapagliflozin is shown in the above figure

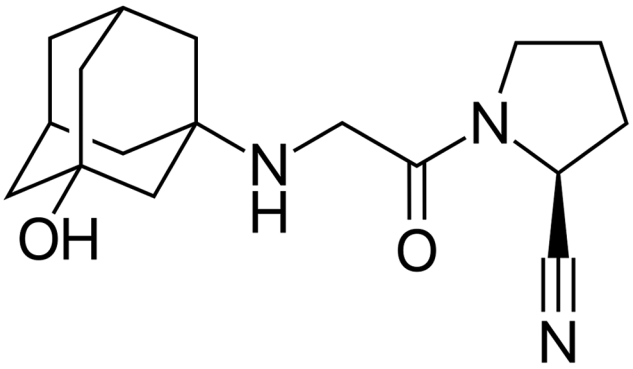

Fig. 2: The Structure of vildagliptin is shown in the above figure

Therefore, there is a need to establish a simple, precise, accurate, and rapid approach for estimating dapagliflozin and vildagliptin, as well as to improve their linearity and sensitivity.

METHODS

Apparatus and instrument

The "Elico SL 210" double-beam UV-visible spectrophotometer, the dissolution test device, the digital analytical balance, and the ultrasonic water bath were all employed. It was done using volumetric flasks, pipettes, measuring cylinders, and beakers.

Chemicals and reagents

The Samples of Dapagliflozin and Vildagliptin were bought from the Pharmaceutical Industry. The Dapagliflozin and Vildagliptin Combined Dosage form in the ratio 10:100 was bought from the nearby store. Throughout the experiment, analytical-grade materials were used.

Method development

Solvent selection

Water was chosen as the dapagliflozin solvent since it is widely soluble in water. Vildagliptin was chosen to be dissolved in 0.1 N NaOH as the solvent.

The standard solution preparation (dapagliflozin)

To generate a standard solution of dapagliflozin, different diluents were used to dilute 10 mg of the medication into 10 mL of a volumetric flask, achieving a 1000 µg/mL concentration. Pipette 1 mL of the 1000 µg/mL solution into a 10 mL volumetric flask and dilute it to the proper level with water to achieve the working standard concentration of 100 µg/mL. Pipette 1 mL of the working standard into a 10 mL volumetric flask and add the diluent to the mark to get 10 µg/mL.

The standard solution preparation (vildagliptin)

To generate a standard solution of dapagliflozin, different diluents were used to dilute 10 mg of the medication into 10 mL of a volumetric flask, achieving a 1000 µg/mL concentration. Pipette 1 mL of the 1000 µg/mL solution into a 10 mL volumetric flask and dilute it to the proper level with water to achieve the working standard concentration of 100 µg/mL. Pipette 1 mL of the working standard into a 10 mL volumetric flask and add the diluent to the mark to get 10 µg/mL.

The determination of wavelength

To determine the wavelength, the standard solution, which contained 10 µg/mL of dapagliflozin and vildagliptin, was scanned between 200 and 400 nm.

Validation parameters

Linearity

The linearity of an analytical procedure is its ability (within a given range) to obtain test results which are directly proportional to the concentration (amount) of analyte in the sample.

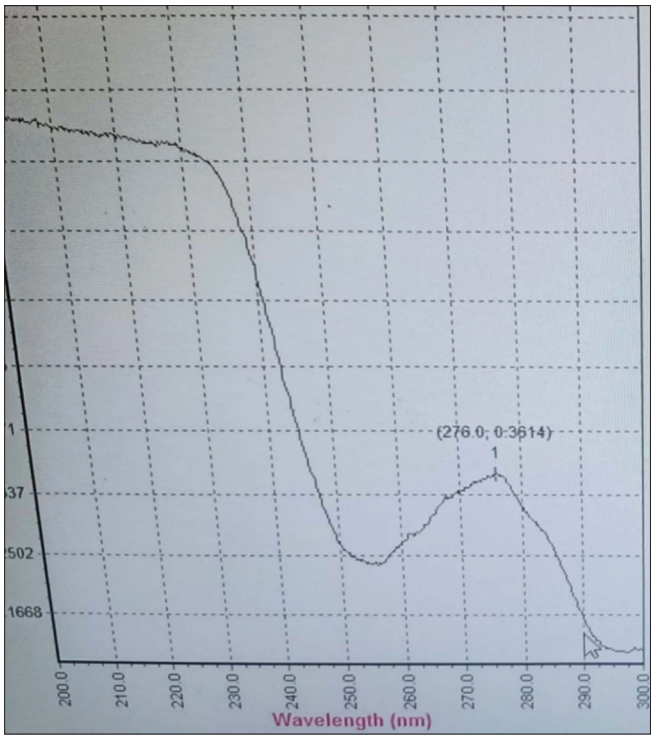

Fig. 3: The Lambda max of Dapagliflozin is shown in the above figure was found to be at lambda max of 276nm

Table 1: Linearity data of Dapagliflozin

Concentration	Absorbance
20 ppm	0.4006
25 ppm	0.5915
30 ppm	0.8221
35 ppm	0.9985
40 ppm	1.1982
45 ppm	1.4491
50 ppm	1.6768
55 ppm	1.8715
60 ppm	2.1276
65 ppm	2.3416
70 ppm	2.5455
75 ppm	2.8051

Precision

To provide statistically valid values of SD or %RSD, a homogeneous sample with a sufficient number of aliquots was analyzed. Equation 1 illustrates the formula for computing the percentage RSD. Equation 2 displays the standard deviation calculation formula.

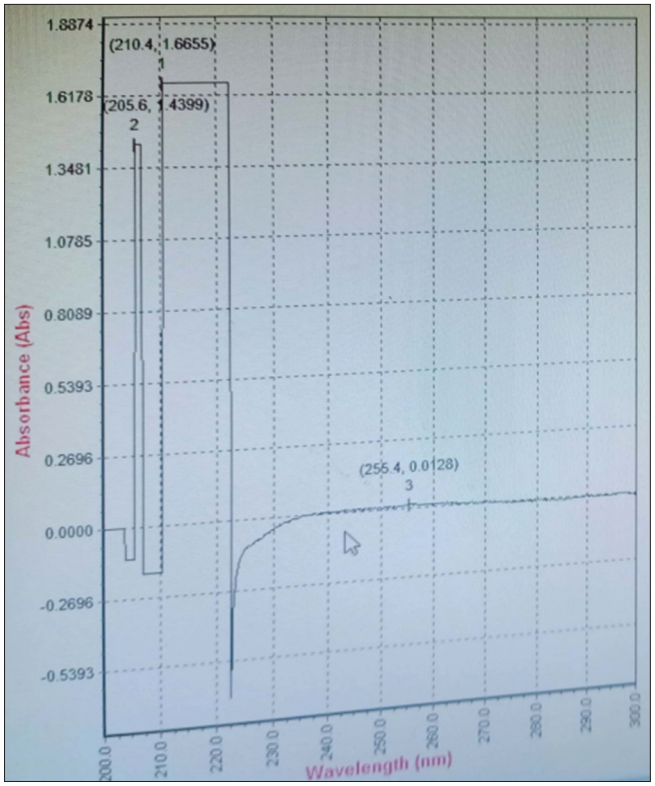

Fig. 4: Lambda max of vildagliptin is shown in the above figure was found to be at lambda max of 255nm

$$\%RSD = \frac{\text{SD measurement}}{\text{mean of measurement}} \times 100 \quad (1)$$

$$s\sqrt{\frac{\sum(X-\bar{X})^2}{n-1}} \quad (2)$$

s = standard deviation

Each value in the dataset is denoted by x, and its mean is denoted by x. The total number of values in the dataset is denoted by n.

Limit: %RSD needs to be lower than 2%. Outcomes of precision.

Accuracy

The accuracy was assessed by adding three different concentrations of standard solution to the sample solution (50, 100, and 150).

The %RSD is given in the equation 3, the % recovery formula is displayed.

$$\%Recovery = \frac{\text{Absorbance of sample}}{\text{Absorbance of Standard}} \times 100 \quad (3)$$

Robustness

Robustness is performed by checking the absorbance at ±1nm of the fixed wavelength.

Limit: %RSD was discovered to be below the threshold or 2%.

Ruggedness

A number of analyzers and devices were used to examine the absorbance in different ways. In this procedure, two different analysts checked the absorbance of the same solution, and %RSD was computed.

Limit: %RSD was found to be <2% and within the limits.

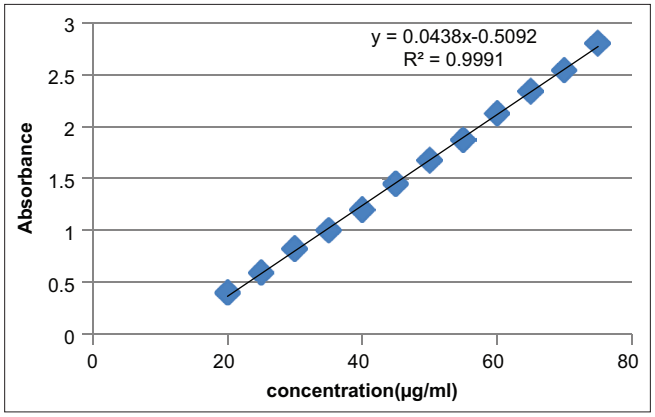

Fig. 5: The Calibration plot of Dapagliflozin was Shown in the above figure where the r2 value was found to be 0.999

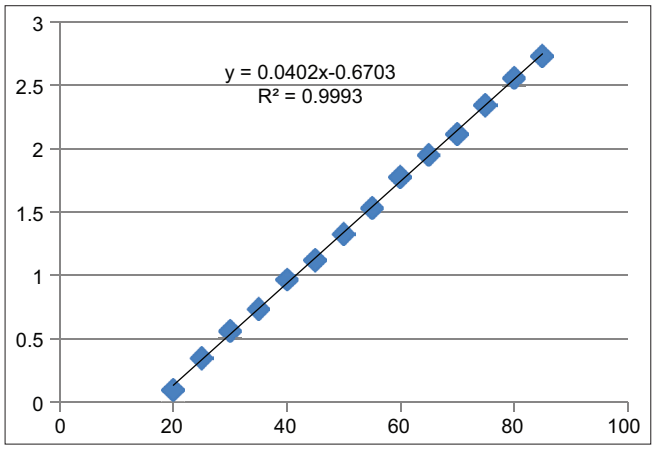

Fig. 6: The Calibration plot of vildagliptin was Shown in the above figure where the r2 value was found to be 0.999

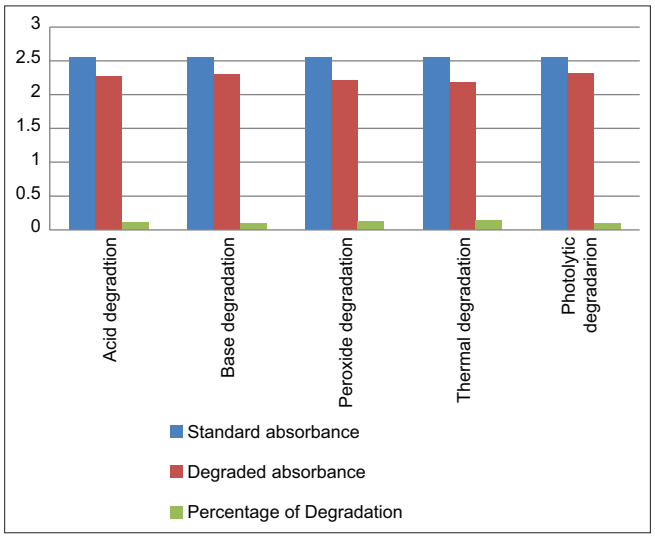

Fig. 7: The Forced degradation data of Dapagliflozin is shown in the above figure

Detection limit (DL)

The DL of an analytical method is defined as the lowest concentration of analyte in a sample that can be detected but not necessarily quantitated in the given experimental environment. Equation 4 gives the formula for computing DL.

$$DL=\frac{3.3XSD}{Slope} \quad (4)$$

QL

It is the smallest quantity of analyte in the sample that can be quantitatively measured under the designated experimental conditions with acceptable precision and accuracy. Equation 5 gives the formula for computing QL.

$$QL=\frac{10XSD}{Slope} \quad (5)$$

Simultaneous equation method

It would be possible to identify both medications using the simultaneous equation approach if a sample contains two absorbing substances (X and Y), each of which absorbs at the λmax of the other (λ1 and λ2). 10 tablets of Glyduo brand (Dapagliflozin and Vildagliptin 10:100 ratio) were weighed and taken in a mortar then crushed to get a fine powder. The weight of 10 mg was then placed in a 100-mL volumetric flask, and the powder was then dissolved using modest volumes of diluent. For 15 min, sonicate in an ultrasonic water bath. Then, add the diluent to make up the volume. The solution was then filtered. This filtrate had a 100 µg/mL concentration. To obtain a sample of 10 µg/mL solution, 1 mL from the 100 µg/mL concentration was pipetted into a 10 mL volumetric flask. This solution was taken for the simultaneous equation method.

$$CX=\frac{Alay2\text{-}A2ayl}{AXlay2\text{-}aX2ayl} \quad (6)$$

$$Cy=\frac{AlaX2\text{-}A2aXl}{AXlay2\text{-}aX2aXl} \quad (7)$$

Where,

A1 and A2 are absorbances of λ1 and λ2, respectively

ax1 and ax2 are absorptivities of X at λ1 and λ2, respectively

ay1 and ay2 are absorptivities of Y at λ1 and λ2, respectively,

Cx and Cy are concentrations of X and Y, respectively

RESULTS AND DISCUSSION

Linearity

Dapagliflozin standard preparation

Pipette out 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, and 6 mL from 100 ppm stock solution and transfer to separate 10 mL volumetric flasks and make up to the mark with the diluent to yield 20, 25, 30, 35, 40, 45, 50, 55, and 60 ppm solution, respectively.

Vildagliptin standard preparation

From the 100ppm standard Stock Solution of Dapagliflozin and Vildagliptin Pipette out 2,3,4,5,6,7,8,9 ml 100 ppm stock solution and transfer to separate 10 mL volumetric flasks and make up to the mark with diluent to yield 20, 30, 40, 50, 60, 70, 80, and 90 ppm solution, respectively.

Precision

Dapagliflozin and vildagliptin 100 g/mL stock was used to make 10 µg/mL of dapagliflozin and 10 µg/mL of vildagliptin. These solutions' absorbances were measured and confirmed 6 times. The %RSD was Calculated. Tables 3 and 4 provide the precise outcomes for the drugs dapagliflozin and vildagliptin, respectively.

Accuracy

By adding sample solutions to the standard solutions at concentrations of 50%, 100%, and 150%, the recovery was estimated. To obtain 50%, 2 mL of the 50 ppm standard solution was mixed with 2 mL of the 4 ppm sample. To obtain 100%, 2 mL of the 4 ppm standard solution was mixed with 2 mL of the 4 ppm sample. To obtain 150%, 2 mL of the 6 ppm standard solution was mixed with 2 mL of the 4 ppm sample. These solutions' absorbance was examined, and the recovery was computed. In Tables 5 and 6, respectively, the Dapagliflozin and Vildagliptin accuracy results are presented

Robustness

10 µg/mL of dapagliflozin and 10 µg/mL of vildagliptin were synthesized from the stock of a 100 µg/mL solution of dapagliflozin and vildagliptin.

Table 2: Linearity data of vildagliptin

Concentration	Absorbance
20 ppm	0.0953
25 ppm	0.3443
30 ppm	0.5617
35 ppm	0.7356
40 ppm	0.9683
45 ppm	1.1179
50 ppm	1.3314
55 ppm	1.5321
60 ppm	1.7774
65 ppm	1.9524
70 ppm	2.1156
75 ppm	2.3451
80 ppm	2.5617
85 ppm	2.7321

Table 3: Precision data of dapagliflozin

Concentration	Absorbance
50 ppm	1.3325
50 ppm	1.3356
50 ppm	1.3226
50 ppm	1.3243
50 ppm	1.3328
50 ppm	1.3304
Mean	1.3297
Standard deviation	0.00514432
RSD	0.38687804

Table 4: Precision data of vildagliptin

Concentration	Absorbance
45 ppm	1.4629
45 ppm	1.4151
45 ppm	1.4307
45 ppm	1.4251
45 ppm	1.4612
45 ppm	1.4213
Mean	1.43041667
Standard deviation	0.01609601
RSD	1.12526751

Table 5: Accuracy data of dapagliflozin

%level	Absorbance	%recovery	Mean (%)
50% (40 ppm)	1.1760	98	97
	1.1843	98	
	1.1673	97	
100% (45 ppm)	1.3932	96	97
	1.4123	97	
	1.4234	98	
150% (50 ppm)	1.6289	97	97
	1.6389	98	
	1.6492	98	

Table 6: Accuracy data of vildagliptin

%level	Absorbance	%recovery	Mean (%)
50% (45 ppm)	1.0926	97	97
	1.0869	97	
	1.1073	99	
100% (50 ppm)	1.2986	97	98
	1.3108	98	
	1.3269	99	
150% (55 ppm)	1.4989	97	98
	1.5183	99	
	1.5073	98	

Table 7: Robustness data of dapagliflozin

Concentration	Absorbance at 275 nm	Absorbance at 276 nm	Absorbance at 277 nm
45 ppm	1.3362	1.4629	1.5932
45 ppm	1.3312	1.4151	1.5901
45 ppm	1.3331	1.4307	1.5632
45 ppm	1.3398	1.4251	1.5903
45 ppm	1.3482	1.4612	1.5923
45 ppm	1.3346	1.4613	1.5121
Mean	1.337183333	1.442716667	1.573533333
Standard deviation	0.613723608	0.204816991	1.438801353
RSD	1.142484455	0.267647163	1.647105266

Table 8: Robustness data of Vildagliptin

Concentration	Absorbance at 254 nm	Absorbance at 255 nm	Absorbance at 256 nm
50 ppm	1.2262	1.3325	1.4932
50 ppm	1.2312	1.3356	1.4901
50 ppm	1.2331	1.3226	1.4632
50 ppm	1.2398	1.3243	1.4903
50 ppm	1.2482	1.3328	1.4923
50 ppm	1.2346	1.3304	1.4121
Mean	1.235516667	1.3297	1.473533333
Standard deviation	0.613723608	0.204816991	1.438801353
RSD	1.142484455	0.267647163	1.647105266

These solutions' absorbances were measured and confirmed at least 6 times. At 275, 276, and 277 nm, the absorbance of dapagliflozin was measured. At 254, 255, and 256 nm, the absorbance of vildagliptin was evaluated. It calculated %RSD. In Tables 7 and 8, respectively, dapagliflozin and vildagliptin robustness results are displayed.

Ruggedness

Ruggedness was tested using 45 ppm and 50 ppm doses of the drugs Dapagliflozin and Vildagliptin, respectively. The capacity of these solutions for absorbance was examined by two analysts to determine the method's ruggedness. It calculated %RSD. Tables 9 and 10 illustrate, respectively, how dapagliflozin and vildagliptin fared in terms of ruggedness.

DL of dapagliflozin and vildagliptin

According to the ICH guidelines, the detection limit was determined using the above formula DL= 3.3xσ /S Where s=slope sigma=Y intercept. The findings were tabulated.

DL of dapagliflozin:

=3.3× 0.01609601/0.043

=1.2352 µg/mL

DL of vildagliptin

=3.3 × 0.00514432/0.040

=0.4244 µg/mL

Table 9: Ruggedness data of dapagliflozin

Concentration	Analyst-1	Analyst-2
45 ppm	1.4629	1.5932
45 ppm	1.4151	1.5901
45 ppm	1.4307	1.5632
45 ppm	1.4251	1.5903
45 ppm	1.4612	1.5923
45 ppm	1.4213	1.5121
Mean	1.43605	1.235516667
%RSD	0.602509102	0.617814009

Table 10: Ruggedness data of vildagliptin

Ruggedness	Intra-day	
Concentration	Analyst-1	Analyst-2
50 ppm	1.3325	1.4312
50 ppm	1.3356	1.4343
50 ppm	1.3326	1.4324
50 ppm	1.3243	1.4317
50 ppm	1.3328	1.4361
50 ppm	1.3304	1.4324
Mean	1.331366667	1.433016667
%RSD	0.267563945	0.128477553

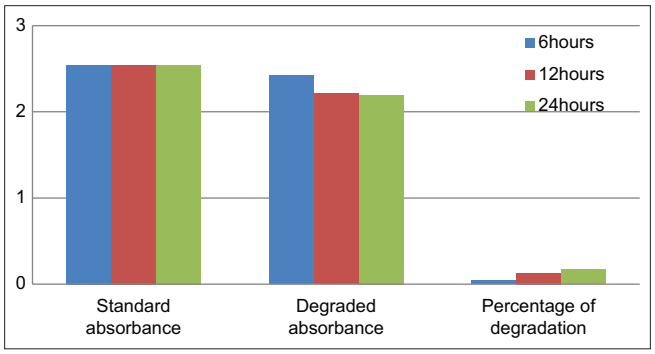

Fig. 8: The Bench top stability data of Dapagliflozin is shown in the above figure

Quantification limit of dapagliflozin and vildagliptin

According to the ICH guidelines, the quantification limit was determined using the formula DL= 10xσ ×/S Where s=slope sigma=Y intercept. The findings were tabulated.

The QL of dapagliflozin

10 × 0.01609601/0.043

=3.7432 µg/mL

The QL of vildagliptin

10 × 0.00514432/0.040

=1.2860 µg/mL

Forced degradation studies

Acid degradation

Dapagliflozin

Prepare the dapagliflozin 100 ppm standard solution. Take 1 mL of the 100 ppm solution, pour it into a 10 mL volumetric flask, add 1 mL of HCL, and let it sit at room temperature for 2 h. Then, neutralize it once more with 1 mL of 1 N NaOH at room temperature and make it up with water.

Vildagliptin

Prepare the 100 ppm stock solution of vildagliptin. From this, take 1 mL of vildagliptin stock solution, add 1N HCL, keep it at room temperature,

Table 11: Forced degradation data of Dapagliflozin

Degradation studies	Standard absorbance	Degraded absorbance	% of Degradation
Acid degradation	2.5451	2.2671	11%
Base degradation	2.5451	2.2913	10%
peroxide degradation	2.5451	2.2143	12%
Thermal degradation	2.5451	2.1843	14%
Photolytic degradation	2.5451	2.3125	10%

Table 12: Bench top stability data of Dapagliflozin

Benchtop stability	Standard absorbance	Degraded absorbance	% of degradation
6 h	2.5451	2.4231	4
12 h	2.5451	2.2121	13
24 h	2.5451	2.1963	17

Table 13: The Forced degradation data of vildagliptin

Degradation studies	Standard absorbance	Degraded absorbance	%recovered
Acid degradation	2.3912	2.1432	11
Base degradation	2.3912	2.0734	10
Peroxide degradation	2.3912	2.0653	13
Thermal degradation	2.3912	2.1564	6
Photolytic degradation	2.3912	2.2132	8

neutralize it with 1 N NaOH, and then make up with water.

Base degradation

Dapagliflozin

Prepare the dapagliflozin 100 ppm standard solution. Take 1 mL of the 100 ppm solution, pour it into a 10 mL volumetric flask, add 1 mL of NaOH, and let it sit at room temperature for 2 h. Then, neutralize it once more with 1 mL of 1 N HCL at room temperature and make it up with water.

Vildagliptin

Prepare the 100 ppm stock solution of vildagliptin. From this, take 1 mL of vildagliptin stock solution, add 1 mL of 1N NaOH, keep it at room temperature, neutralize it with 1N HCL, and then make up with water.

Peroxide degradation

Dapagliflozin

Prepare the dapagliflozin 100 ppm standard solution. Take 1 mL of the 100 ppm solution, pour it into a 10 mL volumetric flask, add 1 mL of 30% water, and let it sit at room temperature for 2 h, and then make it up with water.

Vildagliptin

Prepare the 100 ppm stock solution of vildagliptin. From this, take 1 mL of vildagliptin stock solution, add 1 mL of 30% water, then keep it at room temperature for 2 h, and then make up with water.

Photolytic degradation

Dapagliflozin

By inserting 10 mg of dapagliflozin in a closed Petri dish, the bulk sample containing dapagliflozin had been exposed to UV radiation in a UV chamber for over 2 h. The collected samples were then diluted to a final concentration of ten parts per million in the solutions ranging from 400 to 200 nm using blanks.

Vildagliptin

By inserting 10 mg of vildagliptin in a closed Petri dish, the bulk sample containing dapagliflozin had been exposed to UV radiation in a UV chamber for over 2 h. The collected samples were then diluted to a final concentration of ten parts per million in the solutions ranging from 400 to 200 nm using blanks.

Table 14: Benchtop stability studies of vildagliptin

Degradation hours	Standard absorbance	Degraded absorbance	%degraded
6 h	2.3912	2.2142	7%
12 h	2.3912	2.0654	13%
24 h	2.3912	1.9243	17%

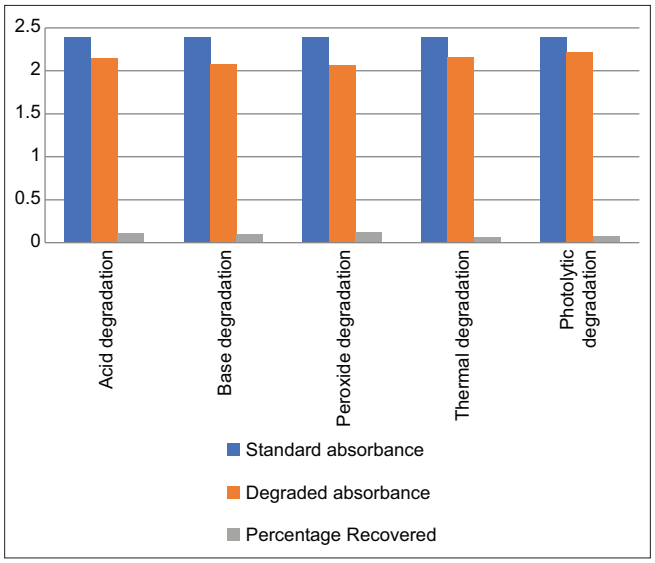

Fig. 9: The Forced degradation data of vildagliptin is shown in the above figure

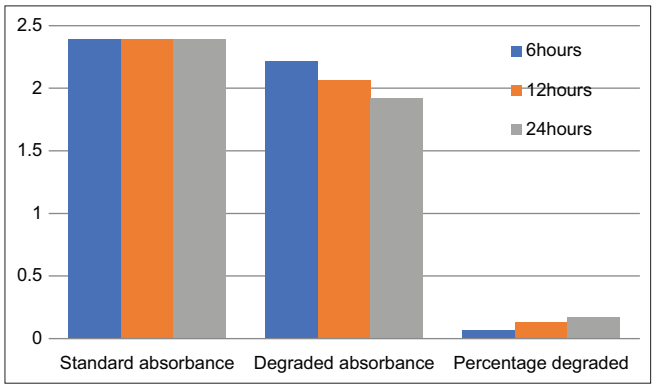

Fig. 10: Bench top stability data of vildagliptin is shown in the above figure

Thermal degradation

Dapagliflozin

Using 10 mg of dapagliflozin, the bulk sample had been heated at 80°C in an oven for 2 h before being scanned at 200–400 nm.

Vildagliptin

Using 10 mg of dapagliflozin, the bulk sample had been heated at 80°C in an oven for 2 h before being scanned at 200–400 nm.

Benchtop stability studies

Prepare the standard solutions of dapagliflozin and vildagliptin using 10 mg of both drugs and check them at 6 h, 12 h, and 24 h.

CONCLUSION

Vildagliptin slows down the incretins' quick breakdown by inhibiting the activity of DPP-4 enzymes and raise incretin concentrations (GLP-1 and GIP), which block the release of glucagon, which then boosts the production of insulin, slows down the gastric emptying, and lowers the blood glucose levels. Because dapagliflozin inhibits SGLT2, it prevents the kidneys from reabsorbing filtered glucose, which raises urine glucose excretion and lowers blood glucose levels. For the simultaneous measurement of vildagliptin and dapagliflozin, the UV method was devised. Good resolution and separation of two medicines were accomplished using the method. The double-distilled water and 0.1 N NaOH were used as diluents for dapagliflozin and vildagliptin, respectively. The suggested approach was exact and accurate. As a result, the suggested method may be applied to routine analyses of tablets containing dapagliflozin and vildagliptin.

Dapagliflozin and vildagliptin were subjected to a forced degradation research using the UV method, which involves thermal, acidic, basic, and oxidative degradation. The results of degradation were found to be within limits.

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AUTHORS CONTRIBUTION

All authors contributed to the research work done in this manuscript. Bhavyasri planned the work, and Nandhini executed it with the help of Bhavyasri. Sumakanth played a key role in giving the facility, instruments, and chemicals for the research work. All authors wrote and revised the manuscript.

CONFLICT OF INTEREST

Conflict of interest declares none.

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