Q-ABSORBANCE RATIO SPECTROPHOTOMETRIC METHOD OF DAPAGLIFLOZIN AND VILDAGLIPTIN IN BULK AND MARKEDED DOSAGE FORM

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ABSTRACT:
Using a UV-visible spectrophotometer, a straight forward, accurate, Q absorbance ratio method has been developed for the instantaneous estimate of Dapagliflozin and Vildagliptin in bulk and combination tablet dose form. The ICHQ2 (R1) recommendations have been followed for all validation parameters. Using a UV-visible spectrophotometer and Methanol: Water in a ratio of (15:85) as the solvent for the preparation of the stock solution (1000 µg/ml), distilled water was used for subsequent dilutions in order to prepare working solutions. The λmax values of Dapagliflozin and Vildagliptin were found to be 195 and 220 nm, respectively. For both the drugs, in the concentration range of 5-30 µg/ml this technique followed Beer's Lamberts law, with a 0.999 correlation coefficient for each. For Dapagliflozin, the limit of detection (LOD) was 0.649 µg/ml, or 1.962 µg/ml, and for Vildagliptin, the limit of quantification (LOQ), or 1.037 µg/ml, or 3.144 µg/ml. The drug's calculated percentage and the commercial dosage form called **Daparyl-V 10/100** agreed well. Three distinct degrees of recovery investigations were carried out, and the results were deemed satisfactory. Furthermore, the outcomes of the techniques designed for precision, robustness and ruggedness are within limits.
Conclusions: The recommended approach is appropriate for regular analysis of Dapagliflozin and Vildagliptin in commercial dosage forms and is inexpensive and simple to use.

Keywords: UV-Visible Spectrophotometer, Dapagliflozin, Vildagliptin, Simultaneous estimation, Q absorbance ratio, Validation.

1. INTRODUCTION

Reduced blood pressure, increased hemoglobin, decreased high-sensitivity cardiac troponin, and decreased body weight are some of the positive effects of Dapagliflozin [1].Vildagliptin increased mean platelet volume but had no effect on hemodynamic characteristics. Vildagliptin [2, 3, 4, 5] is a medication used to treat T2DM that inhibits the enzyme DPP-4(Dipeptidyl Peptidase-4). The mechanism of inhibition of DPP-4 inhibitors is determined by their capacity to increase the incretin hormones levels, glucagon-like peptide-1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP) in the systemic circulation. Dapagliflozin comes in tablet form and is a medication that can be used orally. Patients with T2DM respond very effectively to it both alone and in combination with the other medications of anti-diabetic. According to recent studies, Dapagliflozin reduces fasting plasma glucose levels within a week of starting medication and has a quick beginning of treatment. An appealing strategy is provided by the FDC of sodium-glucose cotransporter type 2 inhibitor [6] (SGT2i) and dipeptidyl peptidase-4 inhibitor (DPP-4i). This study evaluated the bioequivalence of individual tablet-based oral fixed-dose combination (FDC) of Dapagliflozin 10 mg and Vildagliptin SR 100 mg. SGLT2 is preferentially blocked by Dapagliflozin over SGLT1. By preventing the kidneys from reabsorbing glucose, it improves glycemic control in persons with the type-2 diabetes by causing the extra to be expelled in the urine. Pyrrolidine-2-carbonitrile. It is easily soluble in water, methanol, ethanol, DMSO, and dimethylformamide. Vildagliptin is a type 2 diabetes metabolite (T2DM) medication that blocks the DPP-4 enzyme. The ability of DPP-4 inhibitors to raise systemic circulation incretin hormone levels, GIP and GLP-1 determines how well they inhibit DPP-4. Vildagliptin [7] thereby increases insulin secretion and decreases unnecessary glucagon release in T2DM patients. Additionally, it decreases HbA1c without causing weight gain or severe hypoglycemia while utilizing one of the other commonly given classes of oral hypoglycemic drugs, such as sulfonylurea, thiazolidinedione, or insulin. When used orally, Vildagliptin is easily absorbed. Around 70% of Vildagliptin metabolism occurs via hydrolysis, and 23% of the oral dose is excreted in urine unchanged. Renal excretion accounts for 85% of Vildagliptin excretion. The pharmacokinetics of the medication are unaffected by food intake. It neither induces nor inhibits the major P450 enzymes. The Q absorbance ratio method technique of analysis is based on the wavelength maxima of drug absorption for Dapagliflozin and Vildagliptin [8]. 220nm and 195nm are the two wavelengths chosen for the construction of the Q absorbance ratio method. There are numerous analytical techniques available for identifying theses drugs with other combinations in different formulations, such as tablets, capsules, injections, etc. These techniques include UV- Visible Spectrophotometry [9-14], HPLC [15-18] and others [19-20]. There are no proven techniques for estimating Vildagliptin and Dapagliflozin using UV-Visible Spectrophotometry.

Drug profile of Dapagliflozin

IUPACName:(2S,3R,4R,5S,6R)-2-[4-Chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol, **(Figure 1)**
Color: White powder
Molecular formula: $C_{21}H_{25}ClO_6$

pH: pH of Dapagliflozin was found to be **7.2.**
Solubility: Dapagliflozin is soluble in organic solvents such as ethanol, DMSO and dimethyl formamide. It is sparingly soluble in aqueous buffer.
Category: Dapagliflozin is a sodium glucose cotransporter 2 inhibitor indicated for managing diabetes mellitus type 2.

State: Solid

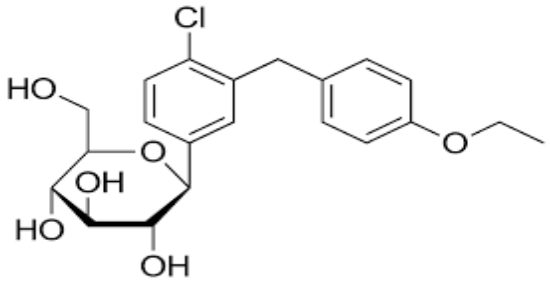


Fig 1: Structure of Dapagliflozin

Drug profile of Vildagliptin

IUPAC Name: (S)-1-[2-(3-Hydroxyadamantan-1-ylamino) acetyl] pyrrolidine-2-carbonitrile.
Color: White crystalline solid, **(Figure 2)**

Molecular formula: $C_{17}H_{25}N_3O_2$
Solubility: Vildagliptin dissolves well in water and is not hygroscopic. Additionally, it dissolves in organic solvents such dimethyl formamide, methanol, ethanol, and DMSO (dimethyl sulfoxide).
Category: Vildagliptin falls under the antidiabetic therapeutic category. It functions by raising the body's levels of two hormones: glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1).
State: Solid

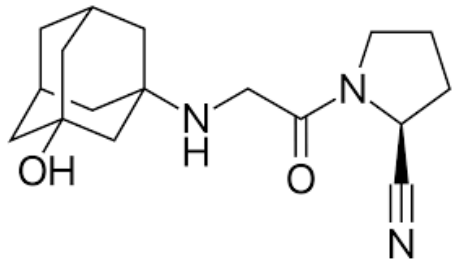


Fig 2: Structure of Vildagliptin

2. MATEIALS AND METHODS

Apparatus and Instrument

Equipment

The UV-1800 and UV-3200 models of SHIMADZU and LAB INDIA UV-Visible spectrophotometers were used for the suggested work. They were equipped with 1cm quartz matched cells, and the electronic balance (Shimadzu-BL220H) was used for weighing. The ultrasonic cleaner, Sonica, and spincotech PVT LTD were used for sonication.

Chemicals and reagents

Dapagliflozin and Vildagliptin standards have been attained as gift samples from Dr.Reddy Laboratories, Hyderabad. Dapagliflozin and Vildagliptin combined formulation **(Daparyl-V 10/100)** label claim containing 10 mg of Dapagliflozin and 100 mg of Vildagliptin manufactured by **Exemed** Pharmaceuticals was bought from the local market and Rankem provided the analytical grade solvent methanol, Maharashtra, India.

Solvent selection

Methanol: Water (15:85) was selected as the solvent after considering the solubility and stability factor of Dapagliflozin and Vildagliptin. Dapagliflozin and Vildagliptin were freely soluble in methanol, so methanol was used for the solubilization of the drugs and further dilutions were done with distilled water.

Standard Solution Preparation: Dapagliflozin

As the drugs were found to be soluble in methanol, to create the standard stock solution, 10 mg of Dapagliflozin was dissolved in 1.5ml of methanol, and the volume has been then increased to 10 ml with distilled water to achieve a 1000 µg/ml concentration. Distilled water was used to appropriately dilute the standard stock solution to create the working standard solution, which contained 10 µg/ml.

Standard Solution Preparation: Vildagliptin:

As the drugs were found to be soluble in methanol, to create the standard stock solution, to reach a 1000 µg/ml concentration, 10 mg of Vildagliptin was dissolved in 1.5 ml of methanol, and the amount was then raised to 10 ml using distilled water.

The working standard solution, which included 10 µg/ml, has been made by standard stock solution suitable dilution using distilled water.

Determination of maximum Absorption wavelength

A UV-Visible Spectrophotometer was used to scan 10 µg/ml of Standard Dapagliflozin between 190 and 400 nm. The drug's λmax was discovered to be 220 nm, as shown in **(Figure 3),** similarly 10 µg/ml of Vildagliptin was scanned between 190 and 400 nm and the λmax of Vildagliptin were found to be 195 nm as in **(Figure 4)** and their overlain spectra **(Figure 5)**

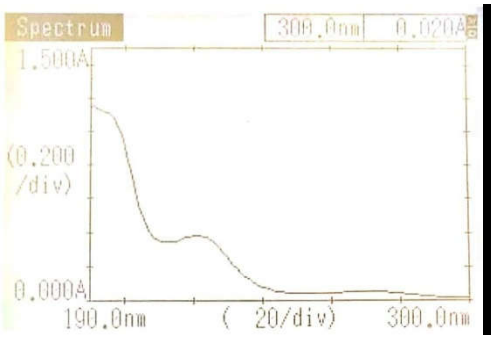


Fig 3: UV Visible spectrum of Dapagliflozin

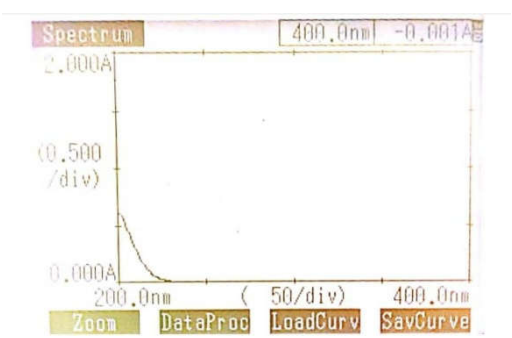


Fig 4: UV Visible spectrum of Vildagliptin

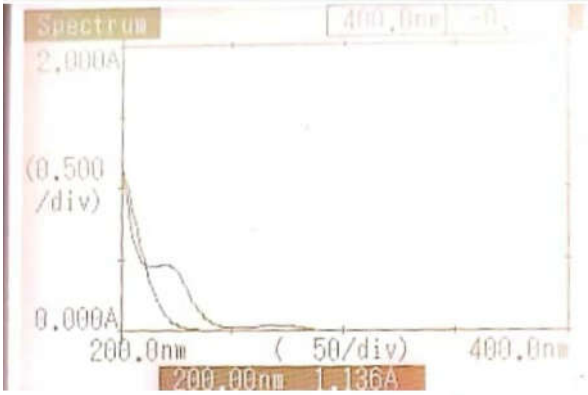


Fig 5: Overlain spectra of DAPA and VILDA

Method –Assay by Q-Absorption Ratio approach: This approach is a variation of simultaneous equation approach. This approach states that a substance's ratio of absorbance at any 2 wavelengths, that is governed by Beer's law, is a constant that is unaffected by concentration or path length. The phrase "Hufner's Quotient," or Q-value, refers to this constant. Using this technique, absorbance is measured at two wavelengths: the iso-absorptive point (λ_1), which is the wavelength at which the two components have equal absorptivity, and the λ_{max} of one of the components (λ_2).
λ_1 and λ_2= 205nm & 220nm.
C_x and C_y= concentration of X & Y correspondingly
a_1 and a_2 = Absorptivity of x & y at the wavelength of Iso-absorptive.
A=sample absorbance at Iso-absorptive point.
Qx= ("Absorptivity of X at λ_{max} of one of the components (λ2)) / (Absorptivity of X at Iso-absorptive wavelength") (λ1)
Qm= (Absorbance of sample solution at λ max of one of the components (λ2)) / (Absorbance of sample solution at iso-absorptive wavelength) (λ1)
Qy= ("Absorptivity of Y at λ_{max} of one of the components (λ2)) / (Absorptivity of Y at Iso-absorptive wavelength") (λ1).
The each component concentration could be computed as:
$Cx= (Qm-Qy) \times A_1 / (Qx-Qy) \times ax_1$,
$Cy= (Qm-Qx) \times A_1 / (Qy-Qx)\, ay_1$

Method Validation

Linearity: The capability of a technique to yield test findings that are proportionate to the analyte concentration in sample is known as linearity.

Precision: The degree of agreement between multiple measurements taken from multiple samplings of the same sample under specific conditions is the definition of precision in an analytical method.

- **Repeatability/Intraday or Assay Precision:** Accuracy within similar operational parameters for a brief period of time. Six distinct samples with the same concentration were measured at various time intervals to complete the experiment.
- **Intermediate Precision:** It conveys accuracy within the context of laboratory variances, such as various days, analysts, equipment, etc. It has been completed by many analysts.

Accuracy: It is degree to which test outcomes produced by the procedure resemble the actual value. The percentage recovery of standard API to blank was used to calculate it. It was determined what the analyte average recovery was for 50 percent, 100 percent, and 150 percent solution. Make three sets of 5, 10, and 15µg/ml Vildagliptin and Dapagliflozin solutions using the standard stock solution. Add standard concentrations of Dapagliflozin and Vildagliptin to the sample at 50 percent, 100 percent, and 150 percent. The preparation of the tablet formulation (sample) complies with the label claim.

Ruggedness: It is the extent to which test results may be repeated when the same samples are analyzed in other settings, like various labs or analysts. It was completed by two distinct analysts.

Robustness: It is the technique's ability to continue working even when minor but intentional changes are made to its parameters. 10µg/ml was extracted from the standard stock solution. The analysis was carried out by varying and Dapagliflozin and Vildagliptin wavelengths (220 and 22 nm) (195 and 201 nm). Finding the Isosbestic point was at (205 nm).

3. RESULTS AND DISCUSSION

The Q absorbance ratio approach, which was established in this work, offers a practical, accurate, and exact means of simultaneously analyzing Dapagliflozin and Vildagliptin. The absorption maxima of Dapagliflozin and Vildagliptin have been observed to be 220 nm &195 nm correspondingly. The Iso-absorptive point has been observed to be 205nm. The assay of Vildagliptin and Dapagliflozin has been observed to be 97 & 102% respectively by this method. The findings have been displayed in **Tables 1, 2..**

LINEARITY

In order to investigate linearity, standard stock solutions of Vildagliptin and Dapagliflozin were diluted to concentrations of 5 to 30µg/ml and 5 to 30µg/ml, respectively. Plotting of calibration curves showing concentration against absorbance was done at the appropriate wavelengths, which are 205 and 220 nm. **Table 3** presents the findings, and Figure 6 displays the linear standard curves for Vildagliptin and Dapagliflozin, respectively, with strong correlation coefficients (R^2 = 0.999 & 0.999). **Table 4** displays the results of the calculation of the % RSD at both intraday and Interday precision, which came out to be < 2. For method I, accuracy was computed and is displayed in **Table 5**. **Table 6** displays the findings of the Ruggedness % RSD, which were found to be < 2.The findings of the analysis of robustness are displayed in Table 7.

Table 1: Absorption ratio method values

Drug	Absorbance maxima (λ_1-220 nm)	Absorbance maxima (λ_2- 205 nm)
Formulation (Daparyl-V)	0.079 (A_1)	0.244 (A_2)
Absorbance of Dapagliflozin	0.454	0.647
Absorbance of Vildagliptin	0.032	0.174
Absorptivity of Dapagliflozin	0.0454(a_{x1})	0.0647(a_{x2})
Absorptivity of Vildagliptin	0..0032(a_{y1})	0.0174(a_{y2})

$Qm = (0.244) / (0.079) = 3.08$

$Qx = (0.0647) / (0.0454) = 1.42$

$Qy = (0.0174) / (0.0032) = 5.43$

$Cx = (3.08-5.43) / (1.42-5.43) \times (0.079) / (0.0454) = 1.019$µg/ml

$$Cy = (3.08-1.42) / (5.43-1.42) \times (0.079) / (0.032) = 10.242 \mu g/ml$$

Assay

Table 2: Assay for method

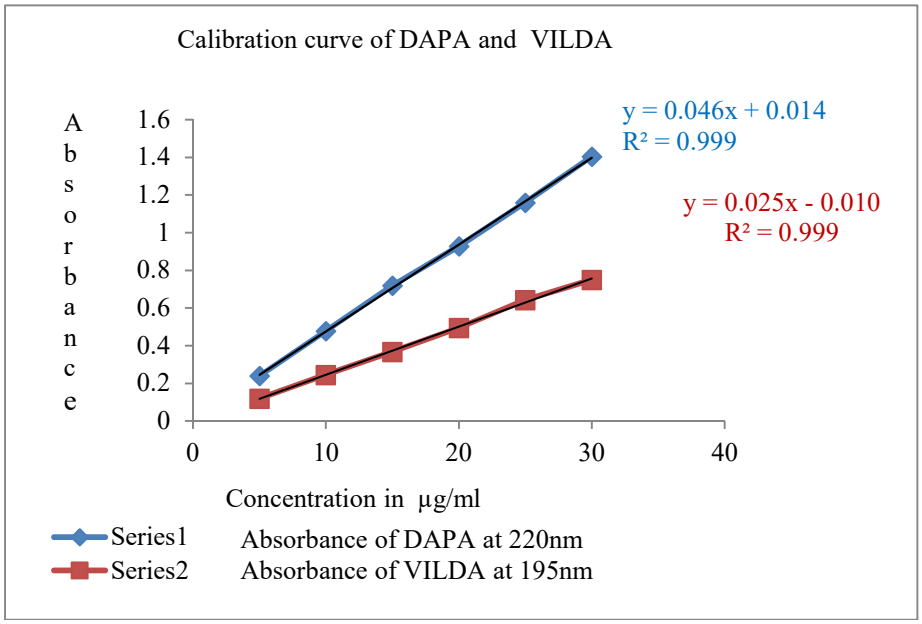
Formulation	Label claim (mg/ Tablet)		Assay (content in mg)		% Assay	
	DAPA	VILDA	DAPA	VILDA	DAPA	VILDA
Daparyl-V	10 mg	100 mg	9.7 mg	102 mg	97 %	102.4 %

Linearity

Table 3: Calibration Curve Data of Dapagliflozin and Vildagliptin

S.NO	Concentration (µg/ml)	Absorbance of DAPA	Absorbance of VILDA
1	5	0.24	0.119
2	10	0.479	0.245
3	15	0.719	0.368
4	20	0.928	0.496
5	25	1.16	0.643
6	30	1.405	0.750

Figure 6: Linearity curve of DAPA and VILDA



Precision

Table 4: Precision study data for Q absorbance ratio method

	Interday				Intraday			
	DAPA		VILDA		DAPA		VILDA	
S.N0	**220 nm**	**205 nm**	**195 nm**	**205 nm**	**220 nm**	**205 nm**	**195 nm**	**205 nm**
1	**0.452**	0.141	0.032	0.155	0.441	0.633	0.031	0.155
2	0.449	0.147	0.032	0.152	0.439	0.630	0.03	0.156
3	0.44	0.142	0.032	0.150	0.444	0.640	0.031	0.158
4	0.449	0.141	0.032	0.147	0.445	0.629	0.031	0.155
5	0.444	0.143	0.033	0.152	0.441	0.637	0.03	0.159
6	0.442	0.145	0.031	0.153	0.446	0.634	0.031	0.153
Mean	0.446	0.143167	0.032	0.1515	0.442667	0.633833	0.0306	0.156
SD	0.00469	0.002401	0.000632	0.002739	0.002733	0.004167	0.0005	0.00219
%RSD	1.051663	1.677338	1.976424	1.807665	0.617286	0.657481	1.6839	1.40441

Accuracy

Table 5: Results of recovery studies of DAPA and VILDA

Drug	% Level of Recovery	Amount taken (μg/mL)	Amount added (μg/mL	Amount found (μg/mL)	% Recovery ±SD (n = 3)
DAPA	50	1	10	11	101.6±0.99
	100	1	20	21	101.4±0.87
	150	1	30	31	102.3±0.98

Drug	% Level of Recovery	Amount taken (μg/mL)	Amount added (μg/mL)	Amount found (μg/mL)	% Recovery ±SD (n=3)
VILDA	50	10	10	20	101.9 ±0.78
	100	10	20	30	101.7±0.54
	150	10	30	40	102.9±1.23

Ruggedness

Table 6: Ruggedness study data for Q absorbance ratio method

Dapagliflozin	Vildagliptin

S.N0	Analyst 1	Analyst 1	Analyst 2	Analyst 2	Analyst 1	Analyst 1	Analyst 2	Analyst 2
	220 nm	205 nm	220 nm	205 nm	195 nm	205 nm	195 nm	205 nm
1	0.447	0.604	0.436	0.596	0.032	0.155	0.032	0.141
2	0.439	0.602	0.447	0.592	0.031	0.152	0.031	0.142
3	0.444	0.604	0.439	0.59	0.032	0.156	0.032	0.139
4	0.445	0.601	0.445	0.589	0.033	0.154	0.031	0.136
5	0.441	0.604	0.439	0.586	0.032	0.153	0.032	0.142
6	0.446	0.603	0.446	0.594	0.032	0.156	0.031	0.142
%RSD	0.693492	0.2097696	1.03183	0.6091219	1.9764235	1.05809	1.73880177	1.72598

Robustness:

Table 7: Robustness Data at various wavelength

Dapagliflozin	220 nm	223 nm	Vildagliptin	195 nm	201 nm
1	0.441	0.399	**1**	0.213	1.153
2	0.439	0.397	**2**	0.215	1.15
3	0.444	0.4	**3**	0.217	1.151
4	0.445	0.398	**4**	0.213	1.152
5	0.441	0.41	**5**	0.214	1.153
6	0.446	0.399	**6**	0.223	1.152
SD	**0.00273**	**0.00476**	**SD**	**0.00382**	**0.00117**
%RSD	**0.61729**	**1.18963**	**%RSD**	**1.76832**	**0.10149**

The Limit of detection and quantification

Table 8: LOD and LOQ

Drug	LOD (µg/ml)	LOQ (µg/ml)
Dapagliflozin	0.649	1.967
Vildagliptin	1.037	3.144

4. CONCLUSION

A new, straightforward, quick, and accurate UV-Visible Spectrophotometric approach has been developed for the simultaneous measurement of Dapagliflozin and Vildagliptin and based on the results obtained this technique can be used in drug testing facilities and the pharmaceutical industry for simultaneous estimation of Dapagliflozin and Vildagliptin by Q absorbance ratio method.

5. ACKNOWLEDGMENT

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6. CONFLICT OF INTEREST

There are no conflicts of interest, according to the authors.

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