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Stability Indicating RP-HPLC Method Development and Validation of Determination of Vildagliptin Tablets

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Abstract:

Vildagliptin (VLD) is a dipeptidyl peptidase-4 (DPP-4) inhibitor used in the management of type 2 diabetes mellitus. A simple, sensitive, rapid, precise and accurate reverse phase high-performance liquid chromatographic (RP-HPLC) method has been developed and validated for the determination of Vildagliptin in tablet dosage form. Chromatographic separation was achieved on a

Hypersil BDS C18 (250 × 4.6 mm, 5 µm) column using a mobile phase consisting of Phosphate buffer (pH 3.0): Methanol: Acetonitrile in the ratio of **70:20:10 v/v**, at a flow rate of 1.0 mL/min. UV detection was performed at 210 nm with an injection volume of 20 µL. The retention time for Vildagliptin was found to be **4.852 min**. The method was validated as per ICH Q2(R1) guidelines for parameters including system suitability, specificity, linearity, precision, accuracy, ruggedness, and robustness. The linearity was established in the concentration range of 25–125 µg/mL for Vildagliptin with a correlation coefficient (r^2) of 0.999. The developed method is simple, economical, and reproducible and can be employed for routine quality control analysis of the tablet formulation.

Keywords: Vildagliptin, RP-HPLC, ICH validation, DPP-4 inhibitor, Pharmaceutical formulation.

Introduction:

Vildagliptin is an orally active inhibitor of dipeptidyl peptidase-4 (DPP-4), an enzyme responsible for the inactivation of incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). By inhibiting DPP-4, Vildagliptin prolongs and enhances the activity of these incretin hormones, resulting in increased insulin secretion and decreased glucagon secretion in a glucose-dependent manner, thereby improving glycaemic control in patients with type 2 diabetes mellitus. Its molecular formula is C17H25N3O2 with a molecular weight of 303.40 g/mol.

Vildagliptin is commercially available as Galvus® tablets (50 mg). A thorough literature survey revealed that limited RP-HPLC methods have been reported for the determination of Vildagliptin in its tablet dosage form. Most of the available methods involve tedious sample preparation, longer run times, or lack complete ICH validation. The present work focuses on developing a

simple, rapid, and cost-effective RP-HPLC method for the determination of Vildagliptin in tablet dosage form and validating it as per ICH Q2(R1) guidelines.

A solution of Vildagliptin was scanned separately over the UV range of 200–400 nm. The compound showed satisfactory absorbance at 210 nm, which was selected as the detection wavelength for RP- HPLC analysis.

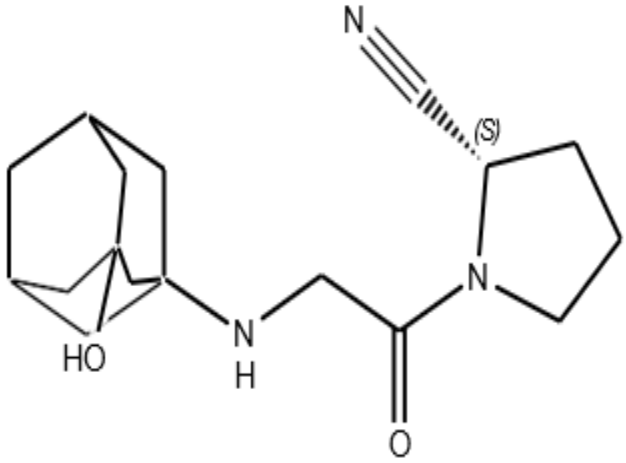


Figure 1: Chemical structure of Vildagliptin

Materials and Methods:

Preparation of Mobile Phase

6.8 g of Potassium dihydrogen phosphate was dissolved in 1000 mL of Milli-Q water and the pH was adjusted to 3.0 ± 0.1 with dilute Orthophosphoric acid. This buffer was mixed with HPLC grade Methanol :Acetonitrile in the ratio of 70:20:10 v/v. The prepared mobile phase was filtered through a 0.45 µm Nylon membrane filter and degassed by sonication for 5 minutes before use.

Preparation of Standard Stock and Working Solutions

Vildagliptin: 50.5 mg was accurately weighed, transferred into a 100 mL volumetric flask, dissolved, and diluted to volume with the diluent (mobile phase). This stock solution was further diluted appropriately to prepare working standard solutions at concentrations of 25, 50, 75, 100, and 125 µg/mL for linearity studies. A working concentration of approximately 50 µg/mL was used as the test concentration for assay purposes.

Method Development and Optimization

The optimized chromatographic conditions were finalized after systematic evaluation of column type, mobile phase composition, pH, flow rate, and detection wavelength to achieve adequate resolution (≥ 2.0), good peak symmetry, and a short run time. The optimized conditions are presented in Table 1a.

Table 1a: Optimized Chromatographic Conditions for the Proposed RP-HPLC Method

Parameter	Chromatographic Conditions
Column	Hypersil BDS C18 (250 × 4.6 mm, 5 µm)
Mobile Phase	Phosphate buffer (pH 3.0): Acetonitrile: Methanol (70:10: 20 v/v)
Flow Rate	1.0 mL/min
Detection Wavelength	210 nm
Injection Volume	20 µL
Column Temperature	25°C (Ambient)
Run Time	10 minutes
Detector	UV Detector
Diluent	Mobile phase

Method Validation

The method was validated as per ICH Q2(R1) guidelines for the following parameters: system suitability, specificity, linearity, system precision, method precision, accuracy, ruggedness, and robustness.

System Suitability

System suitability was assessed by injecting six replicate injections of the standard solution into the HPLC system. Parameters including retention time, peak area response, and %RSD were calculated. The results are presented in Table 1b.

Table 1b: System Suitability Parameters

System Suitability Parameter	Limits	Vildagliptin	Result
Retention Time (min)	—	4.852	—
Tailing Factor (T)	≤ 2.0	1.12	Complies
Theoretical Plates	NLT 2000	5187	Complies
% RSD (6 injections)	NMT 2.0	0.6543	Complies

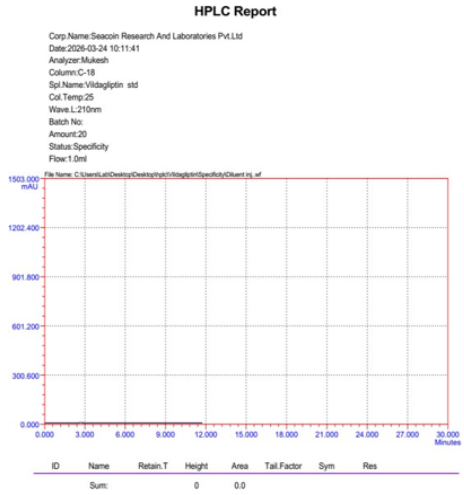
* Average of six determinations. SD = Standard deviation. RSD = Relative standard deviation.

Specificity

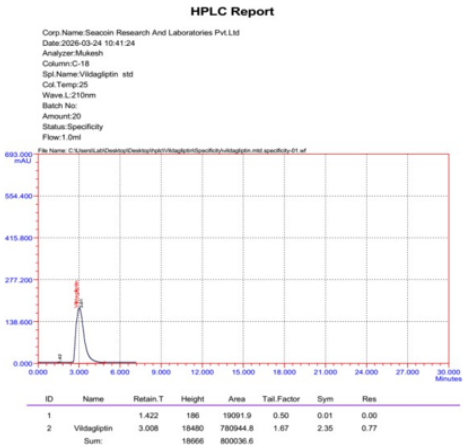
Blank (diluent) and mobile phase injections showed no peaks at the retention time of Vildagliptin (4.852 min), confirming that the solvents and excipients used in the formulation do not interfere with the estimation. The results are presented in Table 2.

Table 2: Results of Specificity Study for Vildagliptin

Solution	Retention Time (min)	Peak Purity	Inference
Diluent	—	—	No interference at RT of analyte peak
Mobile Phase (Blank)	—	—	No interference at RT of analyte peak
Vildagliptin Standard	4.852	—	No interference
Vildagliptin Sample	4.852	Pass	No interference



Chromatogram 1 – Mobile Phase



Chromatogram 2 – Standard Vildagliptin

Precision

System Precision: Six replicate injections of the standard solution were injected into the HPLC system. The values of %RSD for peak area responses are given in Table 2a.

Table 2a: System Precision Data

Inj. No.	Vildagliptin RT (min)	Vildagliptin Area
1	4.85	658432
2	4.85	663218
3	4.85	660471
4	4.85	657389
5	4.85	661504
6	4.85	659872
Mean		660148
SD		2142.5
% RSD		0.6543

Acceptance Criteria: % RSD should be NMT 2.0%.

Linearity

The linearity of Vildagliptin was determined over the concentration range of 25–125 µg/mL. Five concentrations were prepared from the stock solution and injected into the HPLC system. The peak area responses were recorded and a calibration curve was plotted. The linearity data are presented in Table 2b.

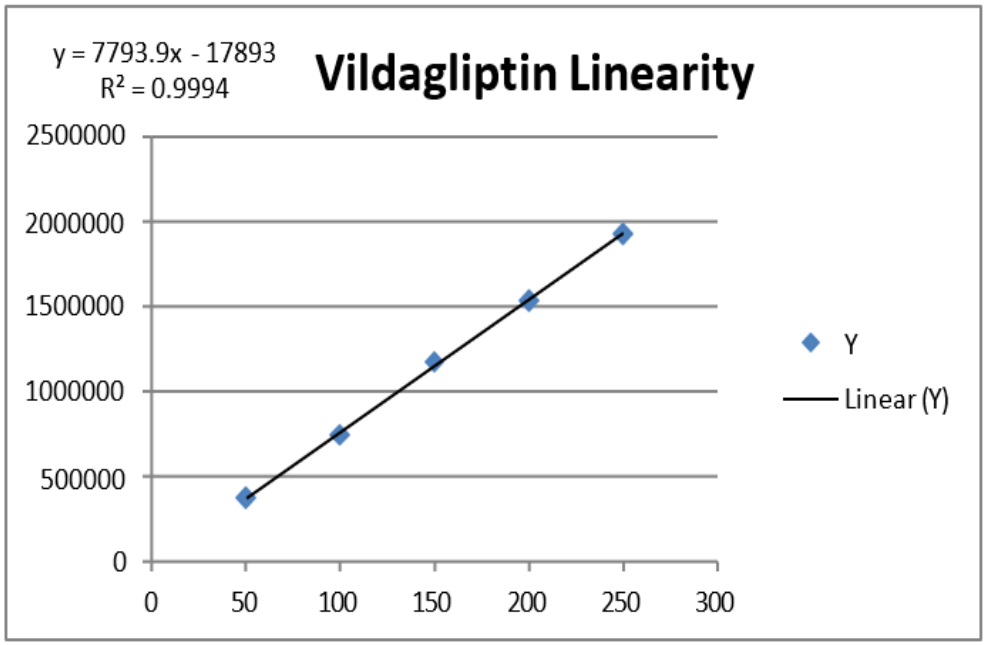
Table 2b: Linearity Data of Vildagliptin

Conc. (µg/mL)	Area Response	Avg. Area Response
25	163524, 163748, 163612	163628
50	328941, 329205, 329074	329073
75	492816, 493040, 492958	492938
100	657389, 658112, 657800	657767
125	820174, 821003, 820598	820592
Regression Equation	**y = 6566x + 1204**	
Correlation Coefficient (r^2)	**0.999**	

Acceptance Criteria: Correlation coefficient (r^2) should be NLT 0.999.

*Y axis – Peak Area

*X axis – Concentration in ppm



Accuracy (Recovery Studies)

Accuracy was determined by spiking known amounts of Vildagliptin into placebo at three concentration levels (80%, 100%, 120% of the test concentration) in triplicate. The % recovery was calculated and the results are presented in Tables 3a and 3b.

Table 3a: Results of Accuracy Study

Level	Drug	Amount Added (mg)	Amount Recovered (mg)	% Recovery	% RSD
80%	Vildagliptin	40.0	39.81	99.53	0.31
100%	Vildagliptin	50.0	50.09	100.18	0.21
120%	Vildagliptin	60.0	59.87	99.78	0.27

Acceptance Criteria: % Recovery should be within 98.0%–102.0%.

Robustness

The robustness of the method was evaluated by deliberately varying method parameters such as flow rate (±0.1 mL/min), detection wavelength (±5 nm), pH of mobile phase (±0.2 units), organic phase ratio (±2%), and column temperature (±5°C). The system suitability parameters remained within acceptable limits under all tested conditions, demonstrating the robustness of the method. Results are summarized in Table 3b.

Table 3b: Results of Robustness Study

Parameter	Optimized	Variation Used	% RSD (Area)	Remarks
Flow rate (mL/min)	1.0	0.9	1.08	*Robust
Flow rate (mL/min)	1.0	1.0	0.65	Robust
Flow rate (mL/min)	1.0	1.1	1.14	*Robust
Wavelength (nm)	210	205	1.19	Robust
Wavelength (nm)	210	210	0.65	Robust
Wavelength (nm)	210	215	1.37	Robust
pH of Mobile Phase	3.0	2.8	1.24	*Robust
pH of Mobile Phase	3.0	3.0	0.65	Robust
pH of Mobile Phase	3.0	3.2	1.35	*Robust

Acceptance criteria: % RSD NMT 2.0%. * Significant change in Retention time.

Ruggedness

Ruggedness was assessed by performing the assay on two different HPLC instruments (LC-CYBER- LAB and SHIMADZU System-1) using two different columns (Hypersil BDS C18 and Agilent C18) by different analysts on different days. The % RSD for assay values in all cases was found to be within 2.0%, confirming the ruggedness of the developed method.

Stability

Stability tests ensure that the analytes and the method remain stable under storage and experimental conditions. This includes the evaluation of forced degradation (stress testing) under acidic, alkaline, oxidative, thermal, and photolytic conditions to demonstrate the stability-indicating capability of the method.

Stability Data

Stabillity study was carried out for Vildagliptin tablets at different temperatures and RH 75.0±5%:-

S. No.	Test Parameter	STDs	At Temp 10°C	At Temp 20°C	Initial (At Temp 30°C	At Temp 40°C
1	Description	White Concave shaped film coated tablet	White Concave shaped film coated tablet	White Concave shaped film coated tablet	White Concave shaped film coated tablet	White Concave shaped film coated tablet
2	Assay	98.97%	99.01%	100.02%	100.71%	101.02

Acceptance Criteria:

Assay should be within limits 98% to 102%. Tablet passes the test when tested at different temperatures.

Results and Discussion

A simple and sensitive RP-HPLC method was developed and validated for the estimation of Vildagliptin in tablet dosage form. Multiple mobile phase compositions were evaluated before finalizing Phosphate buffer (pH 3.0):Methanol:Acetonitrile (70:20:10 v/v) as the optimal mobile phase. This composition provided a well-resolved, symmetrical chromatographic peak for the analyte within a run time of 10 minutes.

The retention time of Vildagliptin was found to be 4.852 min. The number of theoretical plates (5187) indicated efficient column performance. The UV detection wavelength of 210 nm was selected as the drug showed adequate absorbance at this wavelength.

The linearity of Vildagliptin was demonstrated over the concentration range of 25–125 µg/mL, with a correlation coefficient (r^2) of 0.999, confirming excellent linearity. The %RSD for system precision was 0.6543%, well within the NMT 2.0% limit. The % recovery in accuracy studies ranged from 99.53% to 100.18%, within the acceptable range of 98.0%–102.0%. The ruggedness and robustness studies confirmed that the method is reliable under variable analytical conditions. Assay under stability conditions found to be within limits which is 98-102%.

Application of the Developed Method for Marketed Formulation (Assay)

For the assay, 20 tablets of Galvus® (Vildagliptin 50 mg) were weighed and the average weight was calculated. A quantity of powder equivalent to 50.5 mg of Vildagliptin was accurately weighed, transferred into a 100 mL volumetric flask, sonicated for 30 minutes, filtered through 0.45 µm nylon membrane filters, and diluted appropriately before HPLC injection. The assay results are presented in Table 4a.

Table 4a: Assay Results of Marketed Formulation (Galvus®)

Drug	Label Claim (mg/tab)	Amount Found (mg/tab)	% Labeled Amount	% Recovery ± SD
Vildagliptin	50	50.09	100.18%	100.18 ± 0.7

* Average of two determinations. SD denotes standard deviation. RSD denotes % relative standard deviation.

Summary

The methods employed and results obtained in the study are summarized below in Table 4b.

Table 4b: Summary of RP-HPLC Method Validation for Vildagliptin

S.No.	Validation Parameter	Acceptance Criteria	Results
1	System Suitability	1. %RSD of six replicate injections should be NMT 2.0%. 2. Theoretical plates NLT 2000. 3. Tailing factor ≤ 2.0.	Vildagliptin %RSD: 0.6543 Plates: 5187 – Complies
2	Specificity	No interference from blank, 10iluents, mobile phase, or excipients at retention time of analyte.	No interference observed at RT of Vildagliptin (4.852 min). Complies.
3	Precision (System)	% RSD for six replicate	Vildagliptin: % RSD – 0.6543
		injections should be NMT 2.0%.	
4	Linearity	Correlation coefficient (r^2) should be NLT 0.999.	Vildagliptin: $r^2 = 0.999$
5	Accuracy Study	Mean % recovery should be between 98.0% to 102.0%.	Vildagliptin: 99.53%–100.18% Complies
6	Ruggedness	% RSD for assay across different instruments/analysts should be NMT 2.0%.	Within limits. Complies.
7	Robustness	% RSD NMT 2.0% upon deliberate variation of method parameters (flow rate, wavelength, pH).	Within limits under all tested conditions. Complies.
8	Stability	Assay % should be between 98.0% to 102.0%.	Within limits. Complies under different conditions.

Conclusion

A simple, rapid, precise, accurate, and reproducible RP-HPLC method has been developed and validated for the determination of Vildagliptin in tablet dosage form as per ICH Q2(R1) guidelines. The method employs a Hypersil BDS C18 (250 × 4.6 mm, 5 µm) column with a mobile phase of Phosphate buffer (pH 3.0): Methanol: Acetonitrile (70:20:10 v/v) at a flow rate of 1.0 mL/min, with UV detection at 210 nm.

The chromatographic peak of Vildagliptin (RT: 4.852 min) was well resolved within a run time of 10 minutes. The method was found to be linear ($r^2 = 0.999$), precise (%RSD < 1%), accurate (% recovery 99.53%–100.18%), and robust. The assay of marketed Galvus® tablets gave a % labeled amount of 100.18% for Vildagliptin, confirming the applicability of the method for routine quality control analysis.

The RP-HPLC method offers advantages of low solvent consumption, short run time, good peak symmetry, and single drug estimation in a single chromatographic run. Hence, it can be recommended for routine pharmaceutical quality control analysis of Vildagliptin tablet formulations.

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