IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 1, August 2024

RP-HPLC Method Development and Validation for Analysis of Voglibose and Linagliptinin Tablet Dosage Form

Poonam Suresh Deshpande, Bagnawar Ashabai Maruti, Mr Sandeep Audhude
Dr. Vedprakash Patil Pharmacy College, Chh. Sambhajinagar, Maharashtra, India

Abstract: *The development and validation of a reliable RP-HPLC method for the simultaneous analysis of Voglibose and Linagliptin in tablet dosage form are presented. The method ensures precise quantification of both compounds with optimal resolution and reproducibility. Methanol was identified as a suitable solvent for both Voglibose and Linagliptin due to its high solubility properties. A wavelength of 215 nm was selected based on peak absorption intensities for simultaneous determinations. The mobile phase comprised methanol and a 0.1% ortho-phosphoric acid (OPA) buffer solution in a 75:25 v/v ratio, adjusted to pH 4.5. Chromatographic separation was achieved using a Fortis C18 column (4.6 × 100 mm, 2.5 µm particle size) with a flow rate of 0.8 mL/min at ambient temperature. Validation followed ICH guidelines, assessing parameters such as linearity, accuracy, precision, LOD, LOQ, and robustness. Linearity was established over the range of 66-396 µg/mL for Voglibose and 10-60 µg/mL for Linagliptin, with correlation coefficients (R^2) of 0.9996 and 0.9995, respectively. Recovery studies indicated mean values within ±2% of the actual value, confirming accuracy. The LOD and LOQ were found to be 2.80 µg/mL and 8.485 µg/mL for Voglibose, and 0.55 µg/mL and 1.674 µg/mL for Linagliptin. The method proved robust against small variations in chromatographic conditions. This validated RP-HPLC method offers a reliable approach for routine analysis of Voglibose and Linagliptin in pharmaceutical formulations, ensuring consistency and compliance with regulatory standards.*

Keywords: Simultaneous analysis, RP-HPLC, Voglibose, Linagliptin, tablet dosage form, method validation, pharmaceutical analysis, chromatographic separation

I. INTRODUCTION

The management of type 2 diabetes mellitus (T2DM) remains a significant challenge in modern medicine due to its complex pathophysiology and associated complications.[1,2] T2DM is characterized by insulin resistance and progressive β-cell dysfunction, leading to hyperglycemia. Effective management of T2DM requires a multifaceted approach, often involving combination therapy to achieve optimal glycemic control and reduce the risk of complications.[3]

Voglibose and Linagliptin are two pharmacological agents commonly used in the management of T2DM. Voglibose, an alpha-glucosidase inhibitor, acts by delaying the absorption of carbohydrates in the small intestine, thereby preventing postprandial hyperglycemia. Linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, enhances the incretin effect by increasing the levels of active incretin hormones, which in turn stimulate insulin secretion and suppress glucagon release in a glucose-dependent manner.[4,5]

The combination of Voglibose and Linagliptin offers a synergistic approach to managing T2DM, targeting both postprandial and fasting blood glucose levels. The simultaneous use of these drugs necessitates the development of robust analytical methods for their quality control and dosage form analysis. High-performance liquid chromatography (HPLC) has been widely recognized as a powerful analytical technique due to its high resolution, sensitivity, and specificity.[6]

Despite the availability of individual analytical methods for Voglibose and Linagliptin, there is a paucity of validated methods for their simultaneous determination in combined dosage forms. This study addresses this gap by developing a novel reverse-phase high-performance liquid chromatography (RP-HPLC) method for the simultaneous analysis of

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Voglibose and Linagliptin in tablet dosage forms. The method is designed to be simple, accurate, and precise, ensuring its applicability in routine quality control and regulatory compliance.[7]

The development of a simultaneous analytical method not only streamlines the quality control process but also enhances the efficiency of pharmaceutical analysis, reducing the time and resources required for separate assays. The validation of the method according to International Council for Harmonisation (ICH) guidelines ensures its reliability and robustness, providing a standardized approach for the quantification of Voglibose and Linagliptin in pharmaceutical formulations.[8]

In this study, we describe the optimization of chromatographic conditions, including the selection of the mobile phase, column type, and detection wavelength. We also present the validation results for parameters such as linearity, accuracy, precision, specificity, limit of detection (LOD), and limit of quantitation (LOQ). The successful validation of this RP-HPLC method establishes it as a valuable tool for the pharmaceutical industry, facilitating the quality control and regulatory compliance of combination therapies for T2DM.

II. MATERIALS AND METHOD

The solubility of Voglibose and Tenegliptin was evaluated in various solvents, with both compounds found to be soluble in methanol, which was thus chosen for further analysis. For the estimation of Voglibose and Linagliptin, the wavelength of 215 nm was selected due to its highest absorption peak intensities, allowing for simultaneous determinations at this wavelength. Buffer preparation involved selecting appropriate components, such as monobasic potassium phosphate (KH_2PO_4) and dibasic sodium phosphate (Na_2HPO_4), to create a 0.1 M phosphate buffer. The required amounts of KH_2PO_4 and Na_2HPO_4 were dissolved in distilled water, adjusted to pH 7.4, and diluted to 1 liter. For the stock standard solution, 66 mg of Voglibose and 10 mg of Linagliptin were separately dissolved in 50 mL of methanol, sonicated for 10 minutes, and diluted to 100 mL, resulting in 660 µg/mL and 100 µg/mL concentrations, respectively. Working standard solutions were prepared by diluting 1.0 mL of the stock solutions to 10 mL, achieving final concentrations of 66 µg/mL for Voglibose and 10 µg/mL for Linagliptin. RP-HPLC with a standard Fortis C18 column (4.6×100 µm, 2.5 µm particle size) was selected to develop a stability-indicating assay method. The mobile phase consisted of methanol and a 0.1% OPA buffer solution in a 75:25 v/v ratio, adjusted to pH 4.5 with ortho phosphoric acid, sonicated for 30 minutes, and filtered through 0.45 µm nylon membrane filters from Phenomenex® Mumbai, India.[9,10]

METHODS:

The various instrumental methods developed and validated in the current study were based on RP-HPLC

RP-HPLC Method:

The RP-HPLC method for one combination was developed based solubility and polarity of sample. Since the combination of drugs selected were soluble in polar solvents a RP-HPLC stationary phase was selected. Based on PKa / PH values of drugs various organic solvents were tried and the system that gave ideal separation and symmetric peaks were selected for the study.[11]

The mobile phase were prepared freshly, filtered and sonicated for 30 minutes prior to use in order to deareate the mobile phase. The column was equiliberated for 30-40 minutes with mobile phase prior to injection of sample. The volume of injection was 20 ul. The system suitability parameter that are critical to the analytical separation and quantification were carefully evaluated throughout the study.The various chromatographic separation were developed by changing parameters included fixing of chromatographic conditions. The optimized method was developed and validated as per ICH recommendations.(Q2R1)[12]

Method Validation: [13-16]

The developed method was validated according to the International Conference on Harmonizastion (ICH) guidelines for validation of analytical procedures.

Linearity

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The ability of the method to obtain test results proportional to the concentration of the analyte within a given range. It was evaluated by linear regression analysis, which was calculated by the least square regression method.
The regression equation for the drugs were determined byplotting peak area (y)versus concentration(x).

Accuracy

Accuracy can be defined as the closeness of agreement between a test result and the accepted reference value. Accuracy of the method was determined by recovery study. Analytical method may be considered validated in terms of accuracy if the mean value is within ± 20% of the actual value.

Limit of detection

The limit of detection (LOD) is the lowest concentration of analyte in a sample that can be detected but not necessary quantified.

$$LOD = 3.3 \times \sigma / S$$

Where, σ = the standard deviation of the response and S= slope of the calibration curve

Limit of quantitation

The limit of quantitation is the lowest concentration or amount of analyte that can be determined quantitatively within an acceptable level of repeatability precision and trueness.
Where, σ = the standard deviation of the response and S= slope of the calibration curve

Precision

The precision of the method was determined repeatability (intra-day) and intermediate (inter-day) Precision and was expressed as RSD of series of measurements. Intra-day precision was evaluated by six replicated reading at three concentration levels within the linearity range. Inter-day precision was studied by comparing the results on 3 different days. [13-16]

III. RESULTS AND DISCUSSION

Optimization of a solvent system

Chromatographic conditions (optimized chromatographic condition with table, graph, figures and charts)

The chromatographic separation was performed on standard fortis C18 (4.6×100µm with 2.5µm particle size) at an ambient temperature. The samples were eluted using Methanol : Buffer solution (75:25v/v) as a mobile phase at a flow rate 0.8ml/minute. The common wavelength of absorption of Voglibose and Linagliptin was found to be 215.0nm. The chromatograms of the prepared standard stock solutions of Voglibose and Linagliptin were recorded under optimized chromatographic conditions.

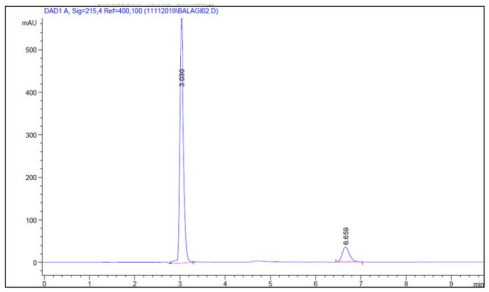

Fig 1: Optimized chromatogram of Voglibose and Linagliptin

The chromatographic analysis was conducted using an Agilent Tech Gradient HPLC system equipped with an auto injector and a UV-DAD detector. The separation was achieved on a Fortis C18 column (Cosmosil) with dimensions of 4.6 × 100 µm and a particle size of 2.5 µm. The mobile phase consisted of a mixture of methanol and a buffer solution (0.1% OPA) in a 75:25 v/v ratio. The detection wavelength was set at 215 nm, with a flow rate of 0.8 mL/min. The

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temperature was maintained at ambient conditions, and the injection volume was 20 µL. Data analysis was performed using Chemstation 10.1 software.

System suitability test/parameters

System suitability test

The homogenous mixture of freshly prepared stock solution of equal concentration of Voglibose(66ppm) and Linagliptin (10 ppm) were injected 6 times to determine the closeness of results achieved for relative standard deviation (RSD) in percentage; The calculated values should always less than 2%. Moreover, other system suitability parameters including, retention or capacity factor (k'), resolution (Rs) and theoretical plates (N), tailing factor/peak asymmetry (As) and separation factor were tested and evaluated.

Table 1: System suitability test

Parameters	Estimates for Voglibose	Estimates for Linagliptin
Retention time (Rt) (min)	3.02 ± 0.022	6.50 ± 0.01
Theoretical Plates	8203 ± 0.56	9746 ± 0.11
Tailing factor	1.00 ± 0.02	1.11 ± 0.03
Resolution	2.34	

Validation

Calibration curve (Linearity table, graph, figures)

The linearity was evaluated by determining six standard working solution drug, over range 66-396ug/ml and 10-60ug/ml and found to be linear with linear regression value 0.9996 and 0.9995 respectively

Table 2: Linearity data of Voglibose

Name of Drug Voglibose		
Sr. No.	**Concentration in (µg.mL^{-1})**	**Peak Area {n=6}**
1	66	3327.02
2	132	5871.61
3	198	8731.47
4	264	11139.20
5	330	13634.20
6	396	16359.46
Regression Equation		y = 39.33x + 758.0
Correlation coefficient (R^2)		R^2 = 0.999
Std. error of intercept		
Std. Dev. Of intercept		
LOQ		8.485µg/ml
LOD		2.80µg/ml

Table 3: Linearity data of Linagliptin

Name of Drug Linagliptin		
Sr. No.	**Concentration in (µg.mL^{-1})**	**Peak Area {n=6}**
1	10	398.76
2	20	794.80
3	30	1134.33
4	40	1481.06
5	50	1873.87
6	60	2240.38
Regression Equation		y = 36.54x + 41.32
Correlation coefficient (R^2)		R^2 = 0.999

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Std. error of intercept	
Std. Dev. Of intercept	
LOQ	1.674µg/ml
LOD	0.55µg/ml

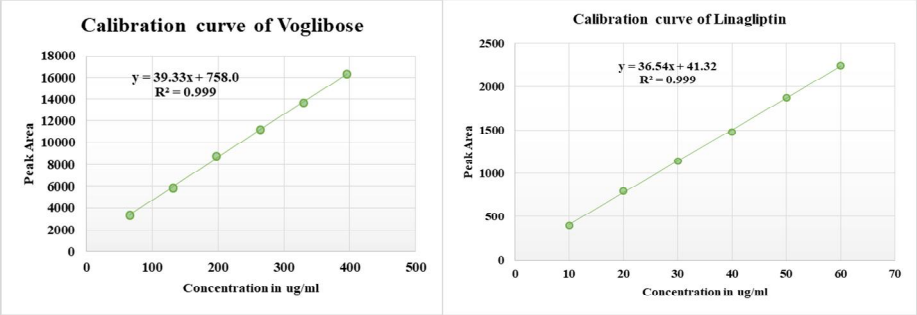

Fig 2: Calibration curve of Voglibose and Linagliptin

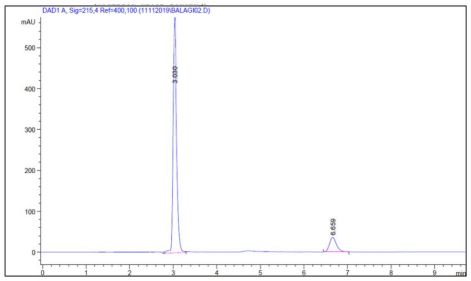

Fig 3: Chromatogram of Voglibose and Linagliptin

Analysis of bulk samples

Voglibose and Linagliptin (66 mg and 10 mg), were accurately weighed and transferred in 100 mL of the calibrated volumetric flask; solubilized in methanol, and the volume was diluted to the mark of a calibrated volumetric flask with same to have 660µg/ml and 100µg/ml concentrations of Voglibose and Linagliptin. The suitable volumes (1.0ml dilute to 10ml)of this were diluted with a solvent system to get the final concentrations of 66 µg/ml and 10 µg/ml of Voglibose and Linagliptin that was analysed according to the procedure of chromatographic conditions; the peak areas of both analytes were estimated, and the findings are presented in table 8.5.

Table 4: Analysis (Assay) of Voglibose and Linagliptin in bulk material

Drugs	Amount taken [µg/mL]	Amount found [µg/mL] ± SD	% Amount found	% RSD {n=6}
Voglibose	66	65.97 ± 0.05	99.97 ± 0.57	0.33
Linagliptin	10	10.26 ± 0.32	100.86 ± 0.16	0.23

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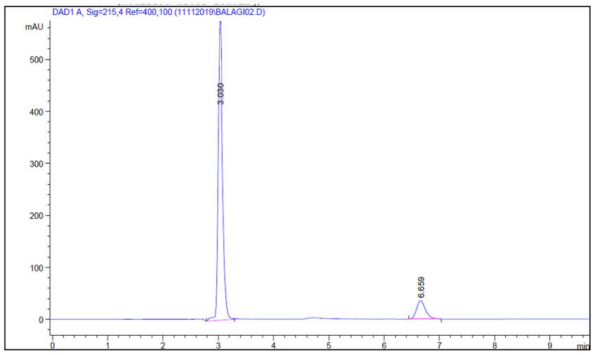

Fig 4: Chromatogram of Assay of Voglibose and Linagliptin 66ug/ml and 10ug/ml

Analysis of marketed formulation

Voglibose and Linagliptin came in the ratio of 100mg and 15mg tablet in the market as **Steglujan** brand

Table 5: Analysis of Voglibose in tablet formulation

Drug name	Conc. 50 ppm; Peak Area	Amount found[µg/mL]	% Amount found
Voglibose	4153577	48.80	97.61
	4182566	49.14	98.29
	4238045	49.80	99.60
	4288000	50.38	100.77
	4308597	50.62	101.25
	4312570	50.67	101.35
	Mean ± STD. DEV.	**49.90± 0.12**	**99.81± 0.56**
	RSD (%)	**1.64**	**1.64**

Table 6: Analysis of Linagliptin in tablet formulation

Drug name	Conc. 100 ppm; Peak Area	Amount found[µg/mL]	% Amount found
Voglibose	11791974	98.61	98.61
	11817679	99.29	99.29
	11836991	99.60	99.60
	11918728	100.17	100.17
	11940675	100.55	100.55
	11962649	100.75	100.75
	Mean ± STD. DEV.	**99.82± 0.28**	**99.82± 0.28**
	RSD (%)	**1.82**	**1.82**

Validation:-

The design HPLC method for Voglibose and Linagliptin was explored for accuracy, precision (intra- and inter-day, and repeatability), sensitivity (LOD and LOQ), robustness, specificity, and selectivity ICH reference.

Accuracy

Percentage drug accuracy of three different concentrations; 80%, 100% and 120% (injected thrice) to estimate the Voglibose and Linagliptin from marketed formulation and results obtained have been reported. Accuracy can be studied by applying the calibration curve; the Y-intercept and the slope of the graph were used to determine the % drug

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recovery, attributed to the developed method for the simultaneous quantification of selected drugs or by comparing with similar concentration of reference standard.

As resulted, the achieved drug recovery of both Voglibose and Linagliptin were in the range of 99.41-100.81 and 99.59-100.61, respectively. As recommended by International conferences of Harmonization (ICH) guidelines the drug recovery should be within the range and the RSD in percentage should be less than 2%. Hence, the calculated drug recoveries for simultaneous estimation of Voglibose and Linagliptin represents the drug recovery were in the acceptance limit given by ICH guidelines.

Table 7: Accuracy data of Voglibose and Linagliptin

Voglibose					
Sr.No.	**Accuracy level**	**Initial Conc.**	**Amount spiked**	**Amount recover % Recovery**	**Statistical Analysis**
1	**80%**	66	52.8	99.78	Mean=99.46
2		66	52.8	99.16	SD=0.31
3		66	52.8	99.43	%RSD=0.31
1	**100%**	66	66	101.07	Mean=100.81
2		66	66	100.43	SD=0.34
3		66	66	100.93	%RSD=0.33
1	**120%**	66	79.2	100.63	Mean=100.64
2		66	79.2	100.81	SD=0.17
3		66	79.2	100.47	%RSD=0.17
Linagliptin					
Sr.No.	**Accuracy level**	**Initial Conc.**	**Amount spiked**	**Amount recover % Recovery**	**Statistical Analysis**
1	**80%**	10	8	99.33	Mean= 99.59
2		10	8	99.77	SD= 0.23
3		10	8	99.66	%RSD=0.23
1	**100%**	10	10	100.70	Mean=100.46
2		10	10	100.57	SD=0.32
3		10	10	100.10	%RSD=0.31
1	**120%**	10	12	99.51	Mean=99.91
2		10	12	99.98	SD=0.37
3		10	12	100.25	%RSD=0.37

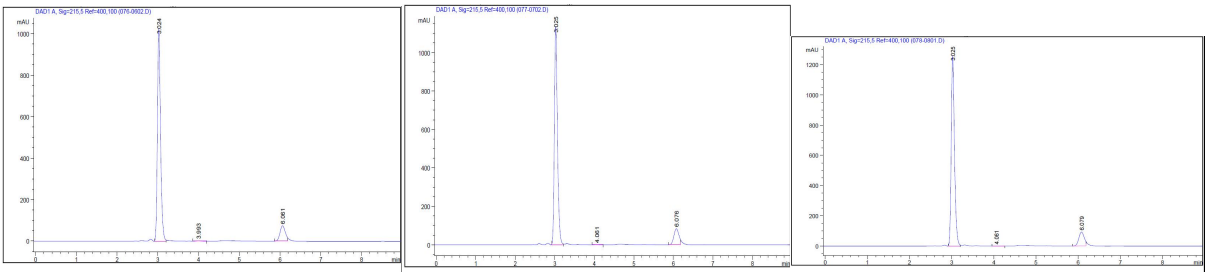

Fig 5: HPLC analysis of marketed formulation of tablet (Concentration 80,100,120 %)

Precision (Intraday & Interday), Repeatability study

The precision of RP-HPLC method reflects its closeness to the agreement among the series of repetitive results, derived after multiple sampling of the same homogenous mixture of selected drugs under the given conditions. As displayed in Table 2; for intermediate variability for precision studies, this method is significantly precise over selected tested range of Voglibose and Linagliptin. Moreover, the peak area of the studied samples was also correlated with selected

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concentration; where the % RSDs were <2%. The RSDs were observed well below 2% that reflects an acceptable precision with minimum variations of the proposed method.

Interday/intermediate precision:

Implementing the procedure mentioned under experimental section (5.3), the homologous mixture of Voglibose and Linagliptin of three replicates of selected similar concentrations; were tested and evaluated in three successive days (interday/intermediate precision). The%RSD was calculated and it is found less than 2%; for all analytes)

Table 8: Precision data of Voglibose

Voglibose				
Sr. No.	**Conc.**	**Peak area**	**Amount found % Assay**	**Statastical analysis**
Interday				
1	132	5997.93	100.88	SD= 4.21
2	198	8764.80	102.89	%RSD= 0.33
3	264	11195.75	100.65	
Intraday				
1	132	5976.94	100.48	SD= 8.24
2	198	8570.80	100.39	%RSD= 0.38
3	264	11128.45	100.00	

Table 9: Precision data of Linagliptin

Linagliptin				
Sr. No.	**Conc.**	**Peak area**	**Amount found % Assay**	**Statastical analysis**
Interday				
1	20	791.18	102.24	SD= 5.64
2	30	1136.26	99.98	%RSD= 0.51
3	40	1486.05	99.03	
Intraday				
1	20	785.04	101.68	SD= 7.45
2	30	1129.44	99.36	%RSD= 0.70
3	40	1487.75	99.15	

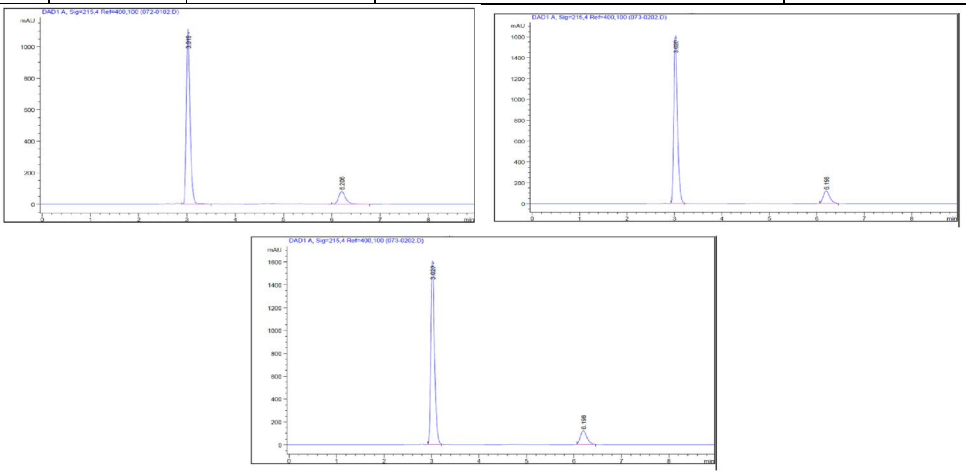

Fig 6: Interday Precision of Voglibose and Linagliptin

DOI: 10.48175/IJARSCT-19326

IJARSCT
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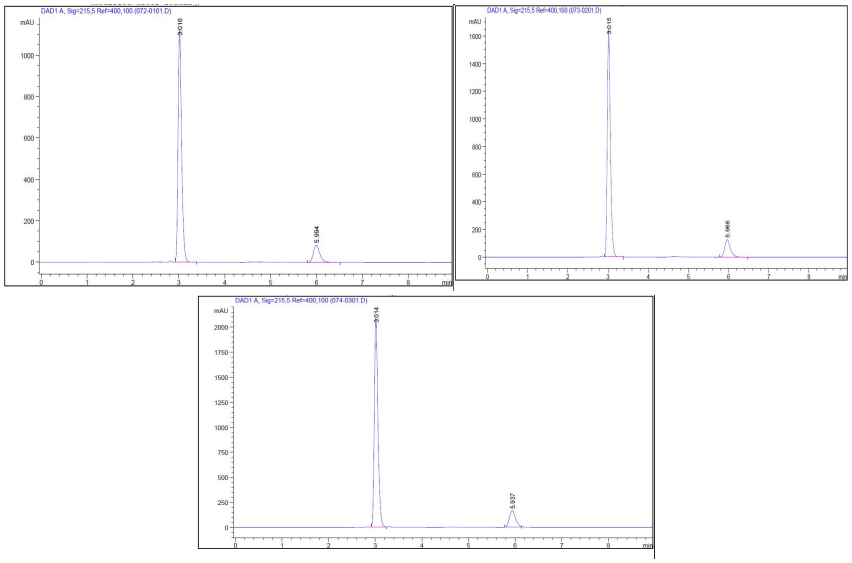

Fig 7: Interday Precision of Voglibose and Linagliptin

Sensitivity

Furthermore, the limit of detection (LOD) and limit of quantification (LOQ) were calculated based on the standard deviation of the response and the slope of the regression equation. The LOD and LOQ were estimated 0.55µg/ml & 1.674µg/ml for Linagliptin and 2.80µg/ml and 8.485µg/ml for Voglibose. The limit of detection and quantitation limits performed based on the slope and standard deviation. These results signify that the selected wavelength 215 nm is more sensitive for Voglibose and Linagliptin. Thus, the proposed method can be used for the routine RP-HPLC analysis of either individual or simultaneous analysis of selected drugs from pharmaceutical drugs or biological fluids.

Robustness

Robustness studies was determined by small variation in separation parameters like effect of temperature, flow rate, eluent composition, temperature, pH, wavelength, injection volume on selected separation variables including capacity factor (k'), resolution (Rs), tailing factor (*Tf*), separation factor, theoretical plates (N)and peak area. Therefore, increased the flow rate by +0.1 ml/minutes, marginally reduced the t_R values of all selected drugs and impurities whereas reducing it, extended slightly the t_R values of same drugs. Like this each factor selected to examine were changed at two levels (-1, +1) shown in table no 5. Robustness of proposed work was carried out by attempting to make significant changes in % proportion of methanol in solvent system (mobile phase), temperature of column oven compartment, flow rate and wavelength. The influence of each of the independent variables was determined for the peak areas of Voglibose and Linagliptin. The % RSD for robustness studies were found to be less than 2 indicates robustness of method. As resulted, the robustness studies for all drugs and impurities were almost unchanged by small variations which clearly signified that the proposed HPLC method obliged all minimum requirements led by the ICH guidelines.

Table 10; Robustness data of Voglibose and Linagliptin

Sr. No.	Condition/Parameters	Mean Peak Area ± SD %RSD for Voglibose	Mean Peak Area ± SD %RSD for Linagliptin
1	Flow rate(-) 0.7ml/min	0.29	0.71
2	Flow rate(+) 0.9ml/min	0.05	0.16
3	Mobile Phase (-) 74+26 v/v	0.16	0.52
4	Mobile Phase (+) 76+24 v/v	0.12	0.07

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5	Wavelength (-) 214nm	0.38	0.71
6	Wavelength (+) 216nm	0.20	0.70
7	Temperature 30˚C	0.28	0.19
8	Temperature 40˚C	0.37	0.23

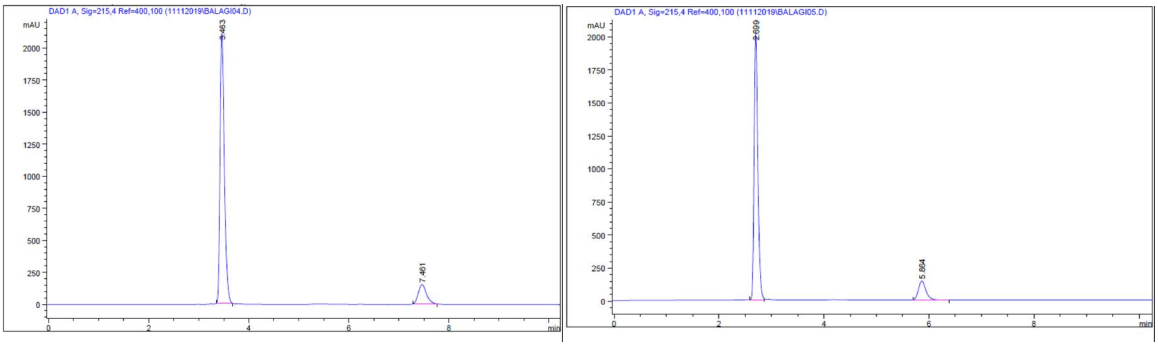

Figure 8: effect of flow rate on Voglibose and Linagliptin

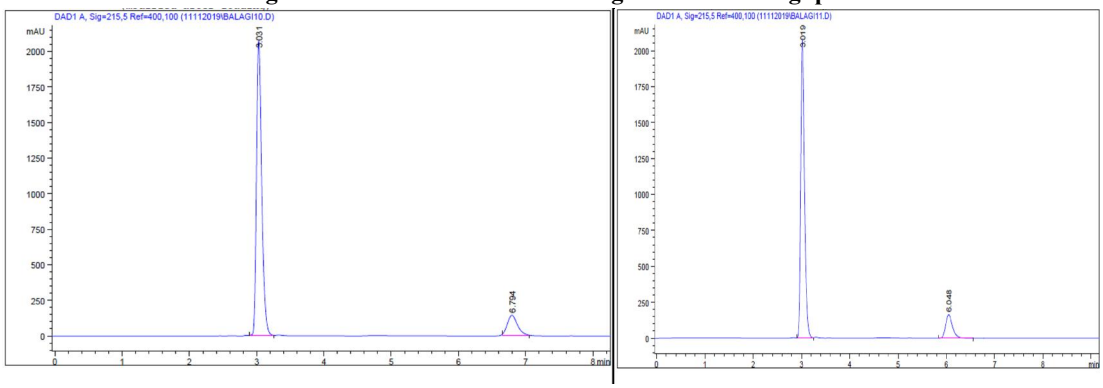

Fig 9: effect of solvent on Voglibose and Linagliptin

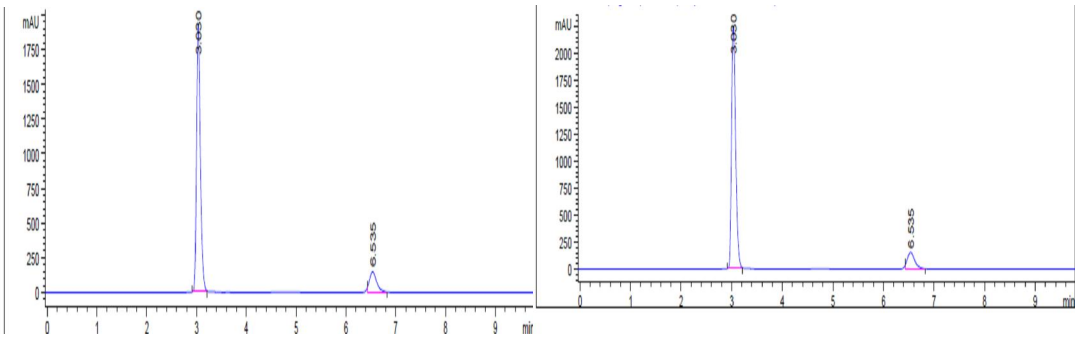

Fig 10: effect of wavelength on Voglibose and Linagliptin

IV. CONCLUSION

A novel, precise, and efficient RP-HPLC method was successfully developed and validated for the simultaneous analysis of Voglibose and Linagliptin in tablet dosage forms. The method demonstrated excellent linearity, accuracy, precision, and specificity, ensuring its suitability for routine quality control and analysis in pharmaceutical environments. The validated parameters met all regulatory requirements, confirming the method's reliability and

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Impact Factor: 7.53
Volume 4, Issue 1, August 2024

robustness for the quantitative determination of these drugs. This study provides a valuable tool for ensuring the quality and efficacy of Voglibose and Linagliptin-containing pharmaceutical products.

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