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Eco-Friendly Solvent-Free Infrared (IR) Spectroscopic Method for Voglibose Determination

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ABSTRACT

Background: Voglibose, an α-glucosidase inhibitor used in diabetes management, traditionally requires chromatographic or solvent-based methods for quantification. However, IR spectroscopy offers a rapid, non-destructive, and cost-effective alternative without chemical waste. This method enhances sustainability while maintaining accuracy and sensitivity in pharmaceutical analysis.

Purpose: To validate a method for quantifying voglibose using Fourier-transform infrared (FTIR) spectroscopy, emphasizing its environmental benefits and applicability in academic and industrial settings.

Methods: The FTIR spectroscopy method was developed without the use of organic solvents, requiring only grinding of powders for pellet preparation. Spectra were recorded in absorbance mode within the 868.47–829.40 cm^{-1} region, based on Beer's law, to construct a calibration model. Validation was performed according to International Council for Harmonization (ICH) guidelines.

Results: The method demonstrated linearity with a regression coefficient of 0.996. It was precise, accurate (average recovery of 98.68%), and robust across a concentration range of 0.5 to 5.0 mg. The method minimizes waste generation, offering an eco-friendly alternative to conventional techniques.

Conclusion: The validated FTIR spectroscopy method for voglibose quantification in raw materials is a reliable, accurate, and environmentally sustainable alternative for standard quality control processes in both academic and industrial applications.

1. Introduction

Voglibose is an antidiabetic drug and inhibits α-glucosidase. The drug was first discovered in Japan, isolated from validamyan on culture media in 1981. It began clinical use in 1994 (Saito *et al.*, 1998; Pattanaik *et al.*, 2018). The α-glucosidase enzyme is secreted from the small intestine (Kanoshima *et al.*, 2017). According to the International Diabetes Federation (IDF) guidelines, α-glucosidase inhibitors help manage elevated fasting and postprandial glucose levels, reduce cardiovascular incident risks, enhance glucagon-like peptide-1 (GLP-1), and decrease glucose variability (Talaviya *et al.*, 2016). Voglibose significantly reduces the risk in individuals with impaired glucose tolerance transitioning to type 2 diabetes and greatly improves normoglycemia. It also lowers diurnal insulin secretion by reducing postprandial hyperglycemia, thereby alleviating stress on overburdened β-cells (Riyaz *et al.*, 2015). Side effects include flatulence, diarrhea, abdominal pain, bloating, nausea, and fullness (Pattanaik *et al.*, 2018). The structure of voglibose is presented in Figure 1.

Numerous quantitative and qualitative methods for voglibose analysis are documented in the literature, including UV spectroscopy (Rao *et al.*, 2010a), spectrofluorimetry (Rao *et al.*, 2010b), RP-HPLC (Kadam *et al.*, 2014; Dholakia *et al.*, 2022; Lakshmi & Rajesh, 2010), HPTLC (Shinde *et al.*, 2015), and LC-MS (Raman *et al.*, 2009; Rajput *et al.*, 2011). Fourier-transform infrared (FTIR) spectroscopy has also been effectively applied to the quantitative analysis of antidiabetic drugs like repaglinide, rosiglitazone maleate, pioglitazone hydrochloride, and metformin hydrochloride (Farouk *et al.*, 2016). However, the quantification of voglibose using FTIR spectroscopy has not been previously reported.

In this method, organic solvents are not generally required, which makes this technique more favorable than others for analysis, as it minimizes unwanted waste generation by industries, thereby reducing environmental

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impact (Fanelli *et al.*, 2018; Figueiredo & Salgado, 2017). Other advantages of these methods include nominal sample preparation, the ability to analyze poorly soluble drugs, and faster analysis (Rao *et al.*, 2010a; Ali *et al.*, 2018). Nowadays, governmental consultants and civil society are increasingly focused on environmental matters, and pharmaceutical industries are appreciating the development of harmless or minimal waste-generation techniques for analysis (Riyaz *et al.*, 2015; Raman *et al.*, 2009).

Voglibose is a non-chromophoric compound (Lakshmi & Rajesh, 2010) with very low UV absorbance; therefore, detectors like refractive index or spectrofluorometers are required, which are costly, time-consuming, and demand large amounts of organic solvents. Consequently, there is a need to develop an alternative solvent-free and rapid analytical method. Bearing this concept in mind and considering the significance of drug quality control, we aimed to develop and validate an analytical procedure for the determination of voglibose in raw materials via FTIR spectroscopy. FTIR spectroscopy offers several advantages in quantification, including rapid, non-destructive analysis with minimal sample preparation. It allows for the direct measurement of functional groups, enabling high specificity and accuracy. Additionally, FTIR is solvent-free, eco-friendly, and suitable for both qualitative and quantitative analysis.

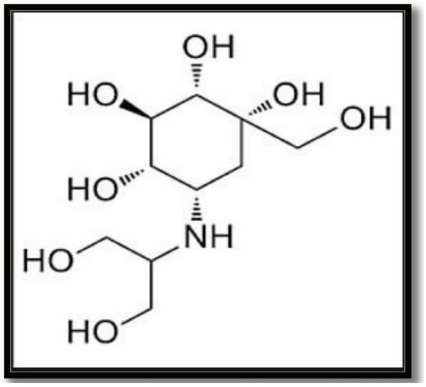

Figure 1: Voglibose Structure

2. Experimental

2.1. Chemicals

The materials and methods utilized in this study included Voglibose reference standard (VOG RS), which was generously donated by Pure & Cure Health Care Pvt. Ltd. (Uttarakhand, India). Voglibose raw material, with a net weight of 1000 mg, was also kindly provided by the same company. Potassium bromide, of spectroscopic grade and dried at 110°C prior to use in pellet preparation, was sourced from Mumbai, India. Metformin and various excipients (lactose monohydrate and microcrystalline cellulose) were obtained from ISFAL at ISF College of Pharmacy, Moga, Punjab.

The FTIR spectroscopy was performed using a Cary 630 model from Agilent Technologies, USA, in conjunction with Agilent MicroLab Version B.05.5 software for data analysis. The spectrometer was equipped with a thermoelectrically-cooled deuterated triglycine sulfate (dTGS) detector and a wire-wound element as the infrared source. The KBr pellet spectra were recorded in the mid-infrared (IR) region, spanning 4000 to 650 cm^{-1}, with 32 scans at a resolution of 4 cm^{-1}.

2.2. Interference Study of VOG Spectra with Metformin and Excipients

Spectra of standard metformin and excipients were taken to observe if there was interference in the region when compared with standard VOG spectra. Pellets were prepared for metformin and excipients, and interference was checked by overlapping spectra of VOG-Metformin-Excipients.

From the overlay spectra of voglibose-metformin-excipients shown in Figure 2, it was concluded that were no interference at the wavenumber region from 868.47-829.40 cm^{-1}.

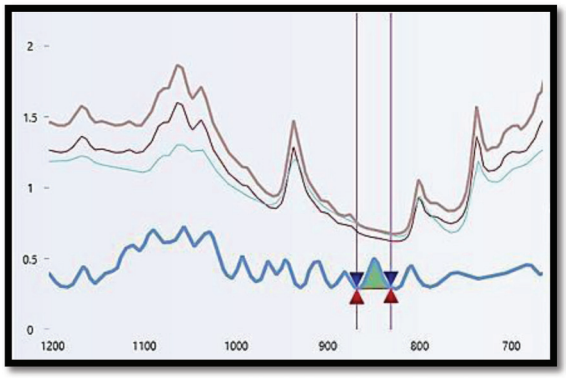

Figure 2: Overlay Spectra of Voglibose-Metformin-Excipients
Index: Blue: Voglibose STD; Green: Metformin STD; Break Red: Excipients; and Light Pink: Excipients

2.3. Obtaining the Analytical Curve

Weight equivalent amounts of 0.5, 1.0, 2.0, 3.0, 4.0, and 5.0 mg VOG RS, diluted previously with potassium bromide in 1: 10 w/w, then mixed with adequate quantity of KBr to achieve a 150 mg of pellet weight. A mixer of powders was homogenized and compressed with mechanical die compress for 10 minutes to shape them into a translucent pellet so that a spectroscopic beam of light could pass. To acquire a calibration curve, absorbance at spectral range

from 868.47-829.40 cm^{-1} was obtained using simple Beer's law, an average of three different measurements was utilized. A good calibration was produced with great regression with the help of Agilent MicroLab Version B.05.5 software (Agilent Technologies, USA). Figure 3, shows the overlay spectra of VOG RS (0.5-5.0 mg/pellet) at wavenumber range 868.47-829.40 cm^{-1} by FTIR spectroscopy.

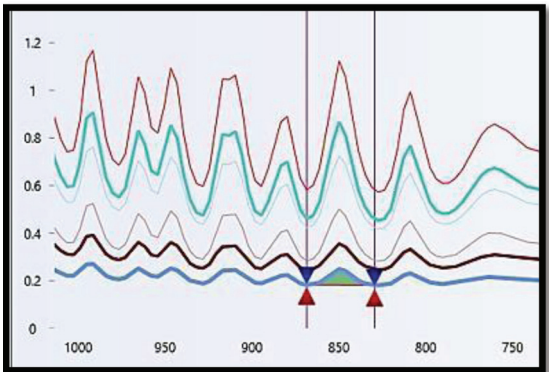

Figure 3: Overlay Spectra of VOG RS (0.5-5.0 mg/pellet) at Wavenumber Range 868.47-829.40 cm^{-1} by FTIR Spectroscopy

2.4. Method Validation

To validate the method, the parameters linearity, precision, accuracy, robustness, specificity, LOD, and LOQ were performed following ICH guidelines.

2.4.1. Linearity

Six concentrations of VOG RS (0.5, 1.0, 2.0, 3.0, 4.0, and 5.0 mg/pellet) were studied on three different days, and linear regression was calculated by the least-squares method and ANOVA.

2.4.2. Precision

Repeatability and intermediate precision are the two criteria for evaluating precision. Analysis of repeatability was done on the same day by preparing 6 different pellets of VOG RS of concentration 3.0 mg/pellet, and then %RSD was calculated between determinations. Intermediate precision was studied by analyzing the absorbance of 3.0 mg/pellet of VOG RS on 3 consecutive days and also by the different analysts.

2.4.3. Accuracy

Accuracy for the method was evaluated by a recovery test by adding a sample of a known amount. Recovery was achieved at three different levels—R1 (50%), R2 (100%), and R3 (150%)—and preparation of pellets was done as per Table 1, in triplicate.

Table 1: Pellets Preparation for the Recovery Test for Voglibose Quantification by FTIR Method

Level	Voglibose Sample (mga)	VOG RS (mga)	KBr (mga)	Final Concentration (mg/pellet)
Sample	20.0	-	130.0	2.0
R1	20.0	5.0	125.0	2.5
R2	20.0	10.0	130.0	3.0
R3	20.0	15.0	115.0	3.5
RS	-	10.0	140.0	1.0

Note: Diluted previously with 1+10 (w/w) in KBr; suitable amount of KBr was added to prepare a total of 150 mg pellet.

2.4.4. Robustness

Robustness was performed by variation as follows: 2.0 mg above and below the total mass of the pellet, 2 min above and below the time of compression, and the brand of KBr.

2.4.5. LODs and LOQs

Calculation of LODs and LOQs were done by using Equations 1 and 2, respectively, based on calibration curves acquired in the linearity study.

$$LOD = 3.3 \times \delta / S \quad (1)$$

$$LOQ = 10 \times \delta / S \quad (2)$$

Where δ refers to the standard deviation of intercepts of calibration curves and S refers to the slope of a calibration curve.

2.4.6. Assay Determination (Percentage Purity w/w) of VOG

For raw material, an assay was performed at a concentration of 3 mg/pellet to check the percentage purity of the VOG. Spectra of three different pellets were obtained.

3. Results and Discussion

The spectra that show the best linear data between a series of concentrations and their area was a choice and used to be a test of its validity parameters, such as LOD, LOQ, accuracy, robustness, and precision. Based on the linearity test displayed in Table 2, the wavenumber range from 868.47 to 829.40 cm^{-1} was selected for validation and quantification

of voglibose, as it signified the best linearity compared to other wavenumbers. Figure 2 shows the overlapping of the absorption spectra of VOG RS and raw material, with the spectral region for quantitatively analyzed established.

Table 2: Linearity Test Data at Five Different Wavenumber Regions

Sl. No.	Wavenumber (cm^{-1})	Correlation Coefficient (R^2)
1	1281.52-1245.08	0.988
2	1184.29-1150.58	0.990
3	1004.72-979.57	0.990
4	975.73-956.02	0.991
5	927.03-896.69	0.991
6	893.80-864.90	0.993
7	868.47-829.40	0.996

3.1. Linearity

The analytical curve is acquired by calculating the average value of an area and its corresponding concentration in the range of 0.5 to 5.0 mg/pellet. Figure 4 signified suitable linearity, verified through its correlation coefficient (R^2 = 0.996). Linear regression data were summarized in Table 3.

Table 3. Linear Regression Data for Voglibose

Parameter	Voglibose
Wave Number (cm^{-1})	868.47-829.40
Linearity Range (% w/w)	0.5-5.0 mg/pellet
y = mx+c	y = 1.6435x + 0.1009
Slope	1.6435
Intercept	0.1009
Regression Coefficient R^2	0.996

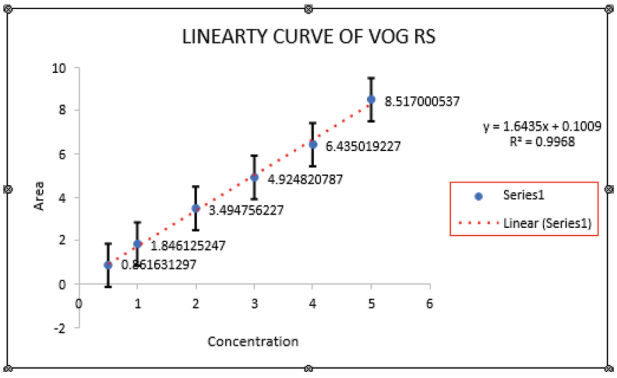

Figure 4: Graphical Depiction of the Voglibose Analytical Curve by FTIR Spectroscopy

3.2. Precision

The two parameters for evaluating the precision of the method are repeatability and intermediate. The repeatability provided the % RSD value of 1.96. The RSD achieved from intra-day precision was 1.98%, whereas the precision between analysts, the RSD obtained, was 1.94%. The data represents the precision of the method, since the % RSD values are less than 5% as mentioned in the literature.

3.3. Accuracy

The method's accuracy was verified by finding out the average recovery from the samples by utilizing the standard addition method. As presented in Table 4, the average recoveries were 98.68%.

Table 4: Determination of the Accuracy for the Analysis of Voglibose by FTIR Spectroscopy

Recovery Level	VOG RS mg	Recovery %	Avg. Recovery %
R1	5.0	98.14	-
R2	10.0	99.06	98.68
R3	15.0	98.83	-

3.4. Robustness

The robustness was assessed by a few alterations, individually, in the method parameters: total pellet weight, the brand of potassium bromide, and time of compression. The results are signified in Table 5. The % RSD values revealed are less than 2%. Hence, the proposed method shows the robustness for the analysis of the VOG by FTIR spectroscopy.

Table 5: Parameters of the Robustness of the Method for the Analysis of VOG by FTIR Spectroscopy

Variable	Range	% RSD
Total Pellet Weight	148 mg	2.02
	152 mg	1.96
Brand of KBr	Loba Chemie	2.02
	Mark Index	1.95
Time of Compression	8 mins	1.97
	12 mins	2.03

3.5. LODs and LOQs

The resulting values for LOD and LOQ were 0.43 and 1.30 mg/pellet, respectively. Results signify the lowest concentration for the method to be detected and quantify voglibose in the raw material.

3.6. Raw Material Assay

When the evaluation of validation parameters has been completed, an assay was carried out at a concentration of 3 mg/pellet of both VOG RS and raw material in triplicates to compare the area obtained after analyzing both the standard and raw material pellet, and the mean was obtained to be 98.94%.

4. Conclusion

An analytical method for the quantification of voglibose in raw material via FTIR spectroscopy was successfully developed and validated. The results indicate that the FTIR method for the voglibose quantification displayed agreeable linearity, precision, accuracy, and robustness in the concentration range of 0.5 to 5.0 mg/pellet and satisfied all conditions mentioned in the literature for the analytical method validation. Hence, the proposed method can be substituted for quantification of voglibose in raw material in regular Quality Control analysis and also help to minimize the industrial waste and eliminate solvent consumption which leads to a decline in hazardous impact on the environment caused by pharmaceutical industries.

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Author Contribution

Kritika Verma has written the manuscript; Shibam Das has validated the manuscript; Amit Sharma has corrected the manuscript; and Rohit Bhatia has conceptualized the manuscript.

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Declaration

This is an original article and has not been submitted anywhere else.

Conflict of Interest

The authors declare no conflicts of interest, financial or otherwise.

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