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Analytical method development and validation for simultaneous estimation of Voglibose and Mitiglinide calcium hydrate in pharmaceutical dosage form

Sandip P. Dholakia¹, Reepa M. Patel^{1*}, **Jitendra Patel**, **M M Patel** 1. Shankersinh Vaghela Bapu Institute of Pharmacy, Vasan, Gandhinagar, Gujarat, India

ABSTRACT

A simple, rapid, precise and reliable RP-HPLC method was developed for estimation of Voglibose (VOG) and Mitiglinide calcium hydrate (MGN) in pharmaceutical dosage form. The method is based of precolumn derivatization of Voglibose with 9-Fluorenylmethyloxycarbonyl chloride (FMOC - chloride) due to lack of chromophoric group it cannot directly estimated by UV detector in RP-HPLC method. Precolumn derivatization (PCD) conditions were optimized by evaluating the parameters such as concentration of borate buffer, concentration of FMOC-Cl and reaction time of derivatization. The chromatographic separation was achieved on Cosmosil BDS C18 (15 cm \times 0.46 cm id, 5 μ m particle size) column using phosphate buffer (pH 4.0) and methanol (30:70) as mobile phase. Detection was carried out at 233 nm using UV detector. The retention time of Voglibose and Mitiglinide calcium hydrate were found to be 5.233 min and 3.580 min respectively. The developed method was validated for parameters such as accuracy, precision, linearity and solution stability.

Keywords: Voglibose, Mitiglinide calcium hydrate, Fixed dose combination, Precolumn derivatization, RP-HPLC, 9-Fluorenylmethyloxycarbonyl chloride (FMOC - chloride)

*Corresponding Author Email: <u>sandip.chemistry@gmail.com</u> Received 16 February 2016, Accepted 21 February 2016

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INTRODUCTION

Voglibose is chemically 3,4-Dideoxy-4-[2-hydroxy-1-(hydroxyl methyl) ethyl] amino-2-c-(hydroxyl methyl)-D-epiinositol, a new potent α -glucosidase inhibitor used for type- 2 diabetes, has shown strong anti-obesity and anti-diabetic activity. Alpha-glucosidase inhibitors are agents that delay the glucose absorption at the intestinal level and thus, reduce the post-prandial blood glucose levels. Voglibose is the safest and most effective drug of its class. Voglibose obtained from organic synthesis processes is similar to structurally related carbohydrates found naturally and has empirical formula C₁₀H₂₁NO₇. Voglibose molecule lackes any chromophores capable of giving a relaible signal in the UV region this means that a direct HPLC analysis of Voglibose using UV detection is not straightforward. The determination of Voglibose feasible by derivatization with chromoaphoric agents and subsequent analysis by HPLC .The method is based on precolumn derivatization of Voglibose with 9- Fluorenyl methyl oxy carbonyl chloride (FMOC - chloride). The reaction of FMOC-Cl with secondary amine is perform in a mild alkaline medium using borate buffer pH . The buffer is used to keep the drugs in dissociative form in order to retain their nucleophilic character. Hydrolysis of FMOC-Cl is considerably higher at lower pH values. FMOC - chloride reacts with secondary amines to form a polar UV - absorbing products which can be detected by UV absorbance. ¹⁻²³





Mitiglinide calcium hydrate is chemically 4-[2-[(5-chloro-2-methoxybenzoyl)amino] ethyl]benzoic acid and has chemical formula $C_{19}H_{25}NO_3$, a new antidiabetic drug, is thought to stimulate insulin secretion by closing the ATP-sensitive K⁺ (K_{ATP}) channels in pancreatic β -cells. Mitiglinide exerts a hypoglycemic effect with rapid onset and short duration of action, by increasing insulin secretion. This effect results from the inhibitory effect of Mitiglinide on the β -cell K_{ATP} channel.



Voglibose

Mitiglinide calcium hydrate

Figure 2: Chemical structure

A fixed dose combination of Voglibose (0.2mg) and Mitiglinide calcium hydrate (10mg) is used in Type-2 diabetes. Literature review reveals that there are many methods available for single Voglibose and single Mitiglinide calcium hydrate but there are no any RP-HPLC method reported for Voglibose and Mitiglinide calcium hydrate in combined dosage form so it was thought of interest to develop a simple, accurate, precise and rapid RP-HPLC for analysis of Voglibose and Mitiglinide calcium hydrate in pharmaceutical dosage form.

MATERIALS AND METHOD

Chemicals and reagents

Voglibose pure sample was kindly provided by Torrent Pharmaceutical Pvt Ltd., Ahmadabad, India and Mitiglinide calcium hydrate pure sample was kindly provided by Molecule lab., Ahmadabad, India. 9-flourenylmethylchloroformate (FMOC-Cl) and Glycine were purchased from Sigma-Aldrich, Ahmadabad. All chemicals were at least of analytical grade were used. Boric acid, Potassium chloride, Potassium hydroxide, HPLC grade triethyl amine, ortho phosphoric acid , Potassium dihydrogen phosphate (KH₂PO₄) were purchased from Seva Fine Chemicals, Ahmadabad. HPLC grade Water was purchased from Astron Chemicals, Ahmadabad, India and HPLC grade Methanol was purchased from Rankem Ltd, Ahmadabad, India.

Instruments

HPLC was performed with a Prominent, Shimadzu Japan, using LC -20 AT pump and Rheodven injector valve with 20.0 μ L loop. Chromatographic separation was achieved using a Cosmosil BDS C18 (15 cm × 0.46 cm id, 5 μ m particle size) column with Spinchrom Software. Detection was carried out by UV detector (Shimadzu UV spectrophotometer 1800. Software UV Prob.)

METHOD DEVELOPMENT

Preparation of standard drug solutions

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The derivatization reagent was prepared by dissolving 500mg FMOC-Cl in 100mL of acetonitrile. Borate buffer solution (0.2M) was firstly prepared by dissolving 1.25 gm boric acid and 1.50gm potassium chloride in 100ml water and adjusted pH with 0.2 M potassium hydroxide, pH should be around 8.2. Voglibose and Mitiglinide calcium hydrate were dissolved in methanol as stock solution (1 μ g/mL) and (50 μ g/mL), respectively.

Procedure of Voglibose derivatization

100 μ L of 1 μ g/ml Voglibose in 200mM borate buffer solution and 100 μ L of 50 μ g/ml Mitiglinide calcium hydrate solution were pipetted into a 10 ml volumetric flask. Add 500 μ L of FMOC-Cl solution and mix for 20 sec. Incubate this solution at 50°C for 15 min. In order to terminate the reaction, 100 μ L glycine solution was added to the solution. After derivatization 20 μ L of the solution was injected directly into HPLC system. The reaction was conducted in different concentration of borate buffer (2mM ,20mM, 200mM and 300mM) by adding different volume of FMOC-Cl (200 μ L,500 μ L,750 μ L) for 15 min and 25 min for optimization of derivatization.

Preparation of Mobile phase

Phosphate buffer (0.05M) was prepared by dissolving 6.80 gm Potassium Dihydrogen Phosphate (KH_2PO_4) in 1000 ml volumetric flask, dissolved in 500 ml HPLC grade water and sonicated for about 10 min and diluted up to the mark with HPLC grade water. Buffer pH was adjusted to 4 using ortho-Phosphoric acid. The mobile phase was prepared by taking HPLC grade Methanol (700ml) and 0.05M Potassium dihydrogen phosphate buffer-pH 4 (300ml) and sonicated for 30 min. It was filtered through 0.45 µm membrane filter.

Selection of wavelength

The 1 μ g/mL standard solution of Voglibose (derivatized) was scanned between 200-400nm and found that the peak at 233.32nm showed maximum absorption and 50 μ g/mL standard solution of Mitiglinide calcium hydrate showed maximum absorption at 212.48 nm. Both drugs give good peak height and shape at 233 nm. So, 233 nm was selected for simultaneous estimation of Voglibose and Mitiglinide calcium hydrate.



Figure 4: UV spectra of Mitiglinide calcium hydrate

Mobile phase selection

Chromatographic separation was achieved by using phosphate buffer (pH 4.0) and methanol (30:70) as mobile phase in RP-HPLC method showed both peaks was separated and matches with system suitability parameters.

RESULTS AND DISCUSSION

Optimization of derivatization condition

When derivatization reaction was performed in different concentration of borate buffer (2mM, 20mM, 200mM, 300mM), it was shown (**Figure 5a**) that at lower concentration of borate buffer (2mM) derivatization reaction did not occur, as increasing the concentration of borate buffer it will promotes the reactivity of amine functional group of Voglibose and stabilizes the solubility of derivatizing reagent by favoring the process of derivatization. When derivatization reaction was performed at different volume of FMOC-Cl (200 μ L, 500 μ L, 750 μ L) it was shown (**Figure 5b**) that at lower concentration of FMOC-Cl analyte detection becomes more difficult since the lowest concentration of molecule decrease the probability of reaction, the concentration of FMOC-Cl 500 μ L was found to be more efficient in derivatization. When derivatization reaction was performed at different time interval 15 min and 25 min. it was shown (**Figure 5c**) that the reaction was completed within 15 min.



Figure 5 (b)



Figure 5

Figure 5: Effect of borate buffer concentration, reagent concentration and reaction time on derivatization.

Optimized chromatographic conditions

Stationary phase : Cosmosil BDS C18 (15 cm \times 0.46 cm id, 5 μ m particle size)

Mobile phase : Phosphate Buffer(pH4.0) : Methanol (30:70)

Flow rate: 1.0 mL/min.

Detection wavelength: 233 nm

Operating temperature: Room temperature

Total run time: 8 min.

Injection volume: 20 μ L





VALIDATION

The method was validated with respect to linearity, limit of detection, limit of quantification, precision, accuracy, recovery and robustness.

System suitability

The suitability of the system was studied by performing the experiment and looking for changes in separation, retention times and asymmetry of the peaks. The resolution, areas, retention time, theoretical plates values and peak asymmetry were calculated. Results obtained are given in table 1.

Drug	Retention Time(min)	Area	Theoretical plates	Tailing factor	Resolution
Mitiglinide calcium hydrate	3.580	2211.658	5217	1.875	-
Voglibose	5.233	365.967	7385	1.353	7.484

Table 1: Result from system suitability study

Linearity

Linearity was calculated by taking working standard, solution of Voglibose (0.5, 0.75, 1, 1.25, 1.50 μ g/mL) and Mitiglinide calcium hydrate (25, 37.5, 50, 62.5, 75 μ g/mL). An aliquot of 20 μ l of each solution was injected under operating chromatographic condition. Calibration curve of Area versus respective concentration was plotted and found out correlation coefficient and regression line equation for Voglibose and Mitiglinide calcium hydrate. Each response was an average of five determinations.

Table 2: Linearity results

Drug	Linearity range	Correlation coefficient
Voglibose	0.5-1.50 μg/mL	0.998
Mitiglinide calcium hydrate	25-75 μg/mL	0.999



Figure 7: Calibration curve of Voglibose



Figure 8: Calibration curve of Mitiglinide calcium hydrate

Limit of Detection (LOD)

The LOD was estimated from the set of 5 calibration curves.

$LOD = 3.3 \times (S.D./Slope)$

Where,

S.D. = Standard deviation of the Y- intercepts of the 5 calibration curves

Slope = Mean slope of the 5 calibration curves

Limit of Quantification (LOQ)

The LOQ was estimated from the set of 5 calibration curves.

$LOQ = 10 \times (S.D./Slope)$

Where,

S.D. = Standard deviation of the Y- intercepts of the 5 calibration curves.

Slope = the mean slope of the 5 calibration curves.

Parameter	Voglibose	Mitiglinide calcium hydrate
LOD	0.053 μg/mL	2.002 μg/mL
LOQ	0.163 μg/mL	6.069 μg/mL

 Table 3: Results for LOD and LOQ

Precision

A. Repeatability

Repeatability was determined by analyzing Voglibose and Mitiglinide calcium hydrate test solution having the concentration 1 μ g/ml of Voglibose and 50 μ g/ml Mitiglinide calcium hydrate. The solution was measured six times in a day.

%RSD of Voglibose and Mitiglinide calcium hydrate were found to be 1.592 and 0.871 respectively.

B. Intraday precision

Intraday precision was determined by analyzing test solutions of Voglibose in range of 0.5, 1 and 1.50 μ g/ml and Mitiglinide calcium hydrate in range of 25 , 50 and 150 μ g/ml in triplicate on same day.

C. Inter day precision

D. Inter day precision was determined by analyzing test solutions of Voglibose in range of 0.5 , 1 and 1.50 μ g/ml and Mitiglinide calcium hydrate in range of 25 , 50 and 75 μ g/ml in triplicate on different day.

Drug	Intra day precision (%RSD)	Inter day precision (%RSD)
Voglibose	0.408-0.697 %	0.760-1.724 %
Mitiglinide calcium hydrate	0.268-1.077 %	0.913-1.692 %

Table 4: Results of Intra-day and Inter-day precision

Accuracy

The accuracy was determined by standard addition method. To a fixed amount of preanalyzed sample mixture containing 1 μ g/mL Voglibose and 50 μ g/mL Mitiglinide calcium hydrate , 80%, 100% and 120% of standard solutions containing 0.5 μ g/mL of Voglibose and 25 μ g/mL Mitiglinide calcium hydrate were spiked. The mean % recovery from of peak areas was calculated. Each solution was injected in triplicate and recovery was calculated from regression equation of calibration curve by measuring peak areas.

Drug	Amt of drug (µg/mL)	Amt of drug added (µg/mL)	Amt recovered Mean (µg/mL)	Mean %Recovery ± S.D(n=3)	Mean %RSD
Voglibose	0.5	0.4	0.403	$100.94\% \pm 0.860$	0.852
	0.5	0.5	0.500	$100.17\% \pm 1.105$	1.103
	0.5	0.6	0.598	99.79%±1.273	1.276
Mitiglinide	25	20	20.177	$100.88\% \pm 0.541$	0.536
calcium	25	25	25.207	$100.83\% \pm 0.454$	0.450
hydrate	25	30	30.209	$100.69\% \pm 0.629$	0.625

Table 5: Results of Accuracy

Robustness

The robustness study was performed to evaluate the influence of small but deliberate variation in the chromatographic condition. The robustness was checked by changing small variation in parameters.

- 1) Flow rate $(\pm 0.1 \text{ ml/min})$
- 2) pH (±0.1 units)
- 3) Mobile phase (1 units)

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After each changes sample solution was injected and % assay with system suitability parameters were checked.

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Drug	Change i	n Flow rate	Chang	ge in pH	Chang	ge in Mobile phase
	0.9 mL	1.1 mL	3.9	4.1	28.71	31.69
Voglibose (RSD%)	0.619	0.696	0.748	0.459	0.636	0.559
Mitiglinide calcium hydrate	0.561	0.796	1.795	0.461	0.525	0.529
(RSD%)						

Table 6: Results of Robustness (%RSD)

Assay of Tablet formulation

Twenty tablets were finely powdered and sample powder equivalent to 0.2 mg of Voglibose or 10 mg of Mitiglinide calcium hydrate was weighed and transferred into a 200 mL of volumetric flask, dissolved with 100 mL methanol and diluted up to mark with 200mM borate buffer (pH 8.2). The solution was filtered using membrane filter 0.22 μ . Take 0.1mL of this solution and further proceeded for derivatization (Voglibose 1 μ g/mL and Mitiglinide calcium hydrate 50 μ g/mL).

Table 7:	Analysis	of tablet	formulation
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Sr. No.Label claim (mg/tablet)		%Assay± S.D.(n=3)		
	Voglibose	Mitiglinide calcium hydrate	Voglibose	Mitiglinide calcium hydrate
1.	0.2mg	10 mg	99.57±0.637	99.77±1.222

CONCLUSION

A simple, specific and precise RP-HPLC method based on precolumn derivatization has been developed and validated for the estimation of Voglibose and Mitiglinide calcium hydrate in pharmaceutical dosage form. There is a significant advantage in using FMOC-Cl reagent, as the whole derivatization procedure is completed in a few minutes and easy to handle. In addition, Voglibose FMOC-Cl derivative was stable under reaction solution. In this study, a derivatization technique was successfully optimized for analysis of Voglibose by RP-HPLC method. All method validation parameters lie within its acceptance criteria as per ICH Q2 (R1) guideline so we can conclude that method is specific, linear and precise. Hence, it can be successfully used for the routine analysis of Voglibose and Mitiglinide calcium hydrate in pharmaceutical dosage forms.

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