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RESEARCH ARTICLE

Simultaneous Estimation of Voglibose and Metformin Hydrochloride in Tablet Dosage Form

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ABSTRACT

A simple, rapid, economical, precise and accurate ratio spectra derivative spectrophotometric method for simultaneous determination of Voglibose and Metformin hydrochloride has been developed. The method depends on the use of the first derivative of the ratio-spectra obtained by dividing the absorption spectrum of binary mixtures by a standard spectrum of one of the compounds. For ratio spectra derivative method two λmax 220 (ZCP of Metformin hydrochloride) nm and 242nm (ZCP of Voglibose) were selected for Voglibose and Metformin hydrochloride respectively. Methanol was used as solvent. Above method was validated as per ICH guideline and all validation characteristics were found within the acceptance limits. Hence, the method herein described can be successfully applied in quality control of combined pharmaceutical dosage forms.

KEYWORDS

Voglibose, Metformin Hydrochloride, Ratio Derivative

INTRODUCTION

Voglibose(VGB) is chemically 5-(1,3-dihydroxypropan-2-ylamino) -1-(hydroxy methyl) cyclohexane-1,2,3,4-tetrol.[1] It is an antidiabetic drug.[1] Alpha-glucosidase inhibitors are saccharides that act as competitive inhibitors of enzymes needed to digest carbohydrates: specifically alpha-glucosidase enzymes in the brush border of the small intestines. The membrane-bound intestinal alpha-glucosidases hydrolyze oligo-saccharides, tri-saccharides, and disaccharides to glucose and other monosaccharides in the small intestine. Acarbose also blocks pancreatic alpha-amylase in addition to inhibiting membrane-bound alpha-glucosidases.

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Pancreatic alpha-amylase hydrolyzes complex starches to oligosaccharides in the lumen of the small intestine. Inhibition of these enzyme systems reduces the rate of digestion of carbohydrates. Individual determination of Voglibose is carried out by UV[2,3], HPLC[4,5], HPTLC[6] and LC-MS[7] a representative structure of Voglibose was shown in Figure-1.

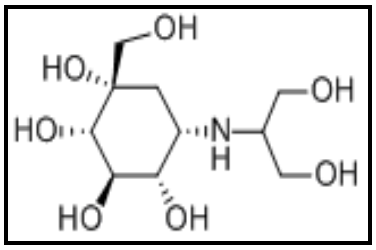

Figure 1: Structure of Voglibose

Metformin HCL (MET) is chemically 1-carbamimidamido-N,N-dimethylmethanimid-amide hydrochloride.[1] Metformin decreases hepatic glucose production, decreases intestinal

absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects (except in special circumstances) and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease..[12] Individual determination of MET is carried out by UV[8,9,10] and HPLC[11]. A representative structure of MET was shown in Figure-2.

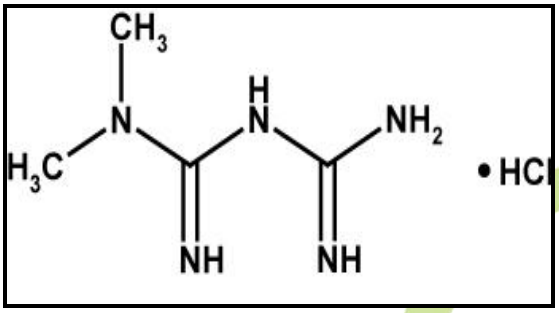

Figure 2: Structure of Metformin hydrochloride

Determination of VGB and MET by RP-HPLC, LC-MS, and UV method.[12,13,14] Till date there have been no published HPTLC methods for simultaneous determination of MET and VOG in bulk or in combined dosage forms. The objective of the work is to develop and validate the simple, economical, precise and accurate UV Spectrophotometric methods for the estimation of Voglibose and Metformin Hydrochloride pharmaceutical formulation.

MATERIAL AND METHODS

Apparatus and Instrument

- UV –visible Spectrophotometry: Shimadzu UV 1800
- Software: UV probe,

Reagent and Material

- Voglibose and Metformin HCl were received as gift sample from Dolffin Pharmaceuticals, Surat, Gujarat.
- 1N Sulphuric acid and Methanol selected as solvent.
- All the chemicals used were of analytical grade.

Preparation of Standard Stock Solution of VGB

Accurately weighed quantity of VGB(100mg) was transferred into 100ml volumetric flask, dissolve and diluted up to mark with methanol to obtain a stoke solution having strength of 1000µg/ml.

Preparation of Working Standard Stock Solution of VGB

1ml aliquot was taken from standard stoke solution in 100ml volumetric flask and diluted up to mark with methanol to obtain 100µg/mlof VGB.

Preparation of Standard Stock Solution of MET

Accurately weighed quantity of MET(100mg) was transferred into 100ml volumetric flask, dissolve and diluted up to mark with methanol to obtain a stoke solution having strength of 1000µg/ml.

Preparation of Working Standard Stock Solution of MET

1ml aliquot was taken from standard stoke solution in 100ml volumetric flask and diluted up to mark with methanol to obtain 100µg/ml of MET.

Preparation of Calibration Curve for VGB and MET

Aliquots of working standard solution of VGB (100µg/ml) and MET (100µg/ml) were transferred in separate 10 ml volumetric flasks and add 1N sulphuric acid and dilute up to 10 ml with methanol. From each working standard solutions of VGB and MET the amount was pipette out to prepare solution having concentrations of 2, 4, 6, 8,10µg/ml of VGB and 10, 20, 30, 40, 50µg/ml of MET was injected and the spectrum were recorded. The respective calibration curves were plotted of the response factor against the concentration of drug. (Figure 3 and 4)

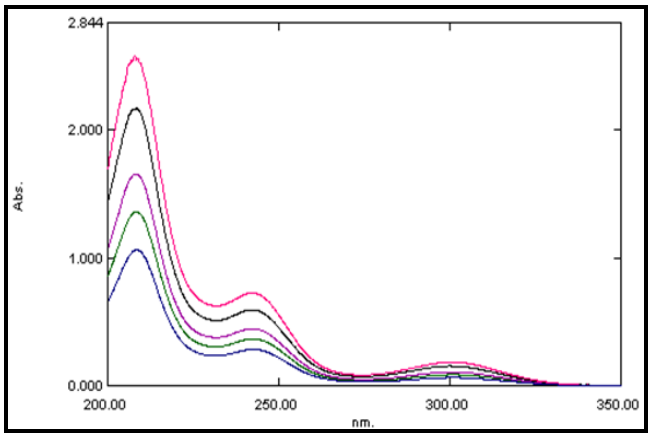

Figure 3: Calibration curve spectra for VGB conc. range (2-10µg/ml) (λ_{max}240nm)

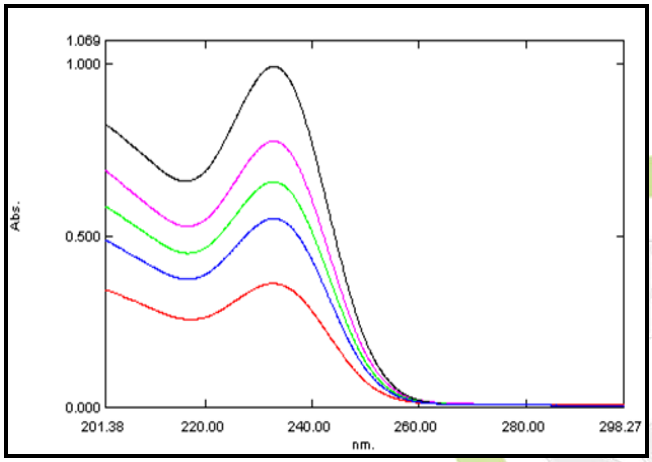

Figure 4: Calibration curve spectra for MET conc. range (10-50µg/ml) (λ_{max}233nm)

Estimation of VGB and MET in Pharmaceutical Tablets

Twenty tablets were weighed and average weight was calculated. An accurately weighed finely powdered quantity of tablets equivalent to about 500 mg of MET (VOG 0.2 mg) was transferred to 100.0ml volumetric flask. The volume was adjusted up to the mark with methanol. (Stock solution) The stock solution was then filtered through Whatman filter paper and accurately measured; then 1.0 ml portion of filtrate was diluted to 10 ml with methanol before that add 1N sulphuric acid in it. Then these sample solutions were measured using first order ratio derivative method at selected wavelength for determination of VGB and MET. The concentration of each drug was calculated using calibration curve.

Ratio Spectra Derivative Method[10]

The spectra of the prepared standard solutions were recorded from 200 to 400 nm and stored in the computer. For the determination of VGB, the stored spectra of VGB were divided (amplitude at each wavelength) by the spectrum of 10µg/ml standard MET, and then the first derivatives of the ratio spectra were obtained. The amplitude of the first derivative peak at 220 nm was used to calculate the content of VGB. For the determination of MET, the stored spectra of MET were divided (amplitude at each wavelength) by the spectrum of 6µg/ml standard VGB, then the first derivative of the ratio spectra were obtained with the amplitude of the first derivative peak at 242 nm was used to calculate the content of MET.

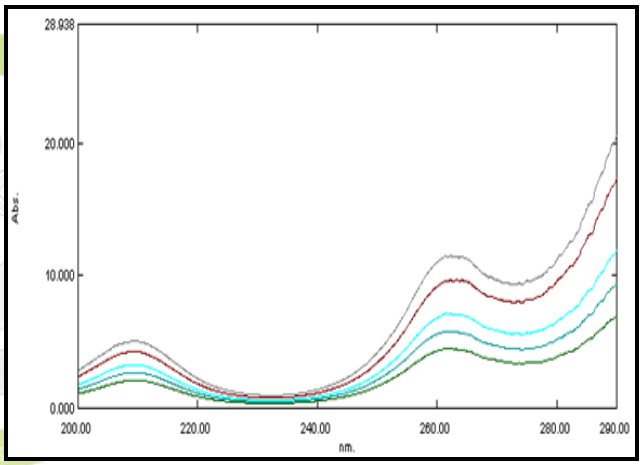

Figure 5: ratio derivative spectra of VGB (2, 4, 6, 8, 10µg/ml); Divisor: MET-10µg/ml

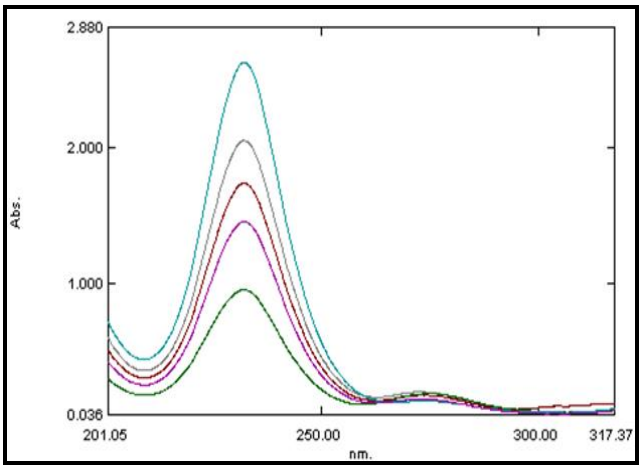

Figure 6: Ratio derivative spectra o MET (10, 1, 20, 30, 40, 50µg/ml); Divisor: VGB-6µg/ml

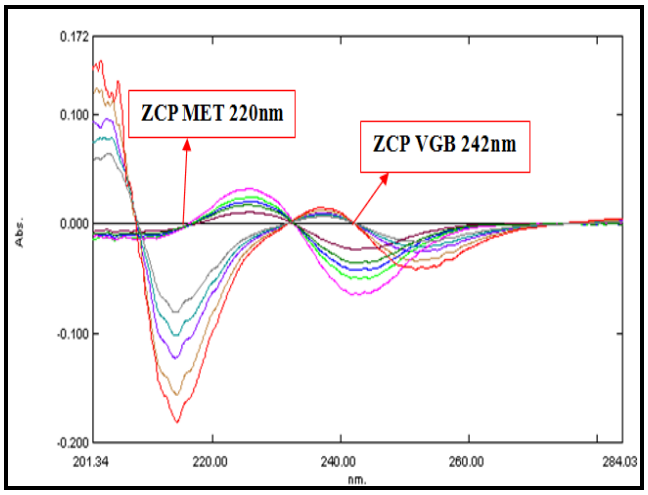

Figure 7: Overlay first order derivative spectra of VGB and MET showing λ_{max} at 220nm and 242nm

Determination of Wavelength for Measurement

Aliquot portions equivalent to 100 µg/ml VGB and MET were transferred separately into two 10 ml volumetric flasks and add 1ml 1N sulphuric acid in it and then volume was completed with methanol. The zero order absorption spectra of both solutions were recorded.

RESULTS AND DISCUSSION

The spectra of the prepared standard solutions were recorded from 200 to 400 nm and stored in the computer. For the determination of VGB, the stored spectra of VGB were divided (amplitude at each wavelength) by the spectrum of 10µg/ml standard MET, and then the first derivatives of the ratio spectra were obtained. The amplitude of the first derivative peak at 220 nm was used to calculate the content of VGB. For the determination of MET, the stored spectra of MET were divided (amplitude at each wavelength) by the spectrum of 6µg/ml standard VGB, then the first derivative of the ratio spectra were obtained with. The amplitude of the first derivative peak at 233 nm was used to calculate the content of MET.

Method Validation

The developed method was validated according to the International Conference on Harmonization (ICH) guidelines.[18]

Linearity

The linearity of the method was evaluated by analyzing different concentration of the drugs. According to ICH recommendations, in this study five concentrations were chosen, in the ranges 2-10µg/ ml and 10-50µg/ ml for VGB and MET, respectively.

Table 1: Straight line equation

No	Drug	Straight line equation	Slope	Intercept
1	VGB	Y_{VGB} = 0.0581x + 0.1349 R^2 = 0.9983	0.0581	0.1349
2	MET	Y_{MET} = 0.0161x + 0.1756 R^2 =0.9976	0.061	0.1756

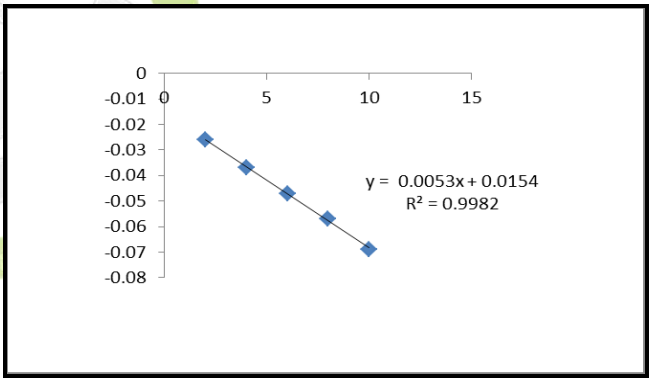

Figure 8: Calibration curve of VGB at 220nm (ZCP of MET)

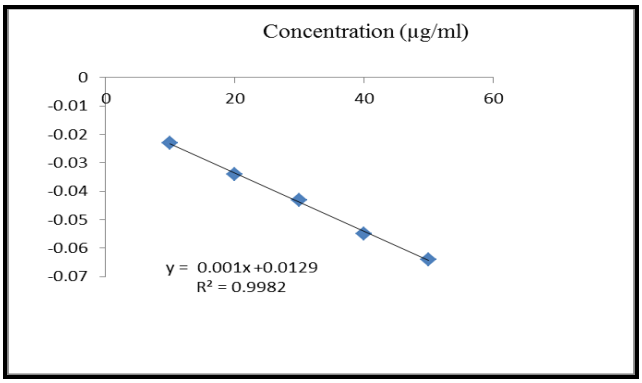

Figure 9: Calibration curve of MET at 242nm (ZCP of VGB)

Table 2: Intraday precision

Conc. taken (µg/ml) VGB	Conc. taken (µg/ml) MET	%Estimated VGB	%Estimated MET	%RSD	
				VGB	MET
4	20	98.12	98.28		
4	20	98.4	98.12		
4	20	100.12	98.17		
	Mean ± SD	99.11±1.53	99.11±1.71	1.54	1.72
6	30	98.28	98.18		
6	30	98.39	98.37		
6	30	100.2	101.3		
	Mean ± SD	98.25±0.25	99.2±0.87	0.27	0.88
8	40	100.3	98.17		
8	40	98.13	100.2		
8	40	98.27	98.43		
	Mean ± SD	98.25±1.85	99.71±1.49	1.87	1.49

Table 3: Interday precision

Conc. taken (µg/ml) VGB	Conc. taken (µg/ml) MET	%Estimated VGB	%Estimated MET	%RSD	
				VGB	MET
4	20	98.12	98.28		
4	20	98.4	98.12		
4	20	100.12	98.17		
	Mean ± SD	98.87±1.07	99.66±1.54	1.08	1.55
6	30	98.28	98.18		
6	30	98.39	98.37		
6	30	100.2	101.3		
	Mean ± SD	98.27±1.12	98.89±1.07	1.12	1.09
8	40	100.3	98.17		
8	40	98.13	100.2		
8	40	98.27	98.43		
	Mean ± SD	98.9±1.21	99.59±1.22	1.22	1.23

Precision

The precision of the method was assessed by studying intra-day and inter-day variation. In the intra-day studies, standard and sample solutions were analyzed in triplicate on the same day and percentage RSD was calculated. In the inter-day studies, standard and sample solutions were analyzed in triplicate on three consecutive days and percentage RSD were calculated.

Accuracy

For carrying out the accuracy of the proposed method recovery studies were employed by the standard addition method. This was carried out by adding known amounts of standard combination of VGB and MET at three different levels of 80%, 100%, and 120% to the sample.

Limit of Detection and Limit of Quantitation

In accordance with ICH recommendations, the approach based on the standard deviation of the response and the slope of the calibration plots was used to determine detection and quantification limits. LOD and LOQ values were estimated as [(standard deviation of repeatability)/ (Slope of the regression equation)] by multiplying with 3.3 and 10 respectively.

LOD= 3.3× (SD/Slope)

LOQ= 10× (SD/Slope)

Where, SD = Standard deviation of Y intercepts of the 5 calibration curve.

Slope = Mean slope of 5 calibration curve

Table 4: Recovery data of VGB and Met from Tablet dosage form

Assay Level	Tablet content taken eq. to (mg)		Standard added (mg)		Total drugs recovered (mg)		%Recovery of standard added	
	VGB	MET	VGB	MET	VGB	MET	VGB	MET
Blank	0.6	100	0	0	0.51	99.5	0	0
	0.6	100	0	0	0.46	100	0	0
	0.6	100	0	0	0.9	99.8	0	0
80%	0.6	100	0.08	80	0.47	80.1	99.08	98.25
	0.6	100	0.48	80	0.48	79.9	100	98.15
	0.6	100	0.48	80	0.49	80.2	99.7	102.5
100%	0.6	100	0.6	100	0.59	100.1	98.33	101
	0.6	100	0.6	100	0.61	99.8	101.66	98.13
	0.6	100	0.6	100	0.57	99.9	99.64	99.01
120%	0.6	100	0.72	120	0.71	120.1	98.61	100.13
	0.6	100	0.72	120	0.70	119.9	98.89	99.16
	0.6	100	0.72	120	0.69	120.2	101.38	101.06

Table 5: LOD and LOQ of VGB and MET

Method	**Ratio derivative Method**	
Drug	**VGB**	**MET**
LOD(µg/ml)	0.62	0.86
LOQ(µg/ml)	1.87	2.60

Assay

Application of proposed method was tested by assay of commercially available tablet formulation Obimet*V 0.2

Table 6: Analysis of marketed formulation (n=6)

	Mg/tablet		**Assay (% of tablet claim*)**	
Tablet	VGB	MET	VGB	MET
Obimet*V	0.2	500	98.2±1.24	98.46±1.26

Summary

Table 7: Summary of Validation Parameter

Sr. No.	**Parameters**	**Result for VGB**	**Result for MET**
1	**Linearity range(µg/ml)**	2-10µg/ml	10-50µg/ml
2	**Corrrelation coefficient**	0.9982	0.9976
3	**Precision (%RSD) Intraday Interday**	1.06 0.87	1.25 1.55
4	**Accuracy (%recovery)**	99.08-101.38	98.25-101.06
5	**LOD(µg/ml)**	0.62	0.86
6	**LOQ(µg/ml)**	2.25	5.11

CONCLUSION

The method was found to be linear between the range of 2-10 µg/ml for VGB and 10-50µg/ml for MET. The mean percentage recovery was found 99.08-101.38for VGB and 98.25-101.06 for MET at three different levels of standard additions. The precision (intra-day, inter-day) of methods were found within limits (RSD <2%). It could be concluded from the results obtained in the present investigation that the above developed and validated method for the simultaneous estimation of VGB and MET in tablet dosage form was rapid, simple, accurate and precise and can be used, successfully in other routine laboratory analysis.

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