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Original Research Paper

FIRST DERIVATIVE SPECTROPHOTOMETRIC SIMULTANEOUS DETERMINATION OF VILDAGLIPTIN AND METFORMIN IN TABLET FORMULATIONS

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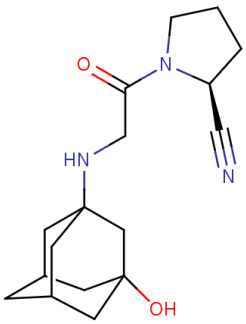
ABSTRACT

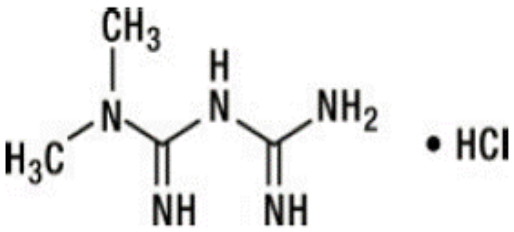
A simple, accurate, precise and reproducible method has been developed for the simultaneous estimation of Vildagliptin and Metformin hydrochloride in combined tablet dosage forms. Vildagliptin has absorbance maxima at 218.25 nm in water and Metformin Hydrochloride has absorbance maxima at 225.5 nm in water. Both these drugs obey Beer's law in concentration range of 60-100 µg/ml (Vildagliptin) and 10-50 µg/ml (Metformin Hydrochloride) with mean recovery 100% for both drugs Vildagliptin and Metformin hydrochloride respectively. The results of the analysis were validated statistically and recovery studies were carried out as per ICH guide lines. Thus the proposed method can be successfully applied for the simultaneous estimation of Vildagliptin and Metformin hydrochloride in routine analysis work.

Keywords: Vildagliptin, Metformin Hydrochloride, Simultaneous estimation, First derivative spectrophotometric, Zero crossing method, Spectrophotometric determination.

INTRODUCTION



Vildagliptin



Metformin Hydrochloride

Vildagliptin is an oral anti-hyperglycemic agent (anti-diabetic drug) of the new dipeptidyl peptidase-4 (DPP-4) inhibitor class of drugs. Its Chemical name is (S)-1-[2-(3-Hydroxyadamantan-1-ylamino) acetyl] pyrrolidine-2(S)-carbonitrile, which is used to reduce hyperglycemia in type 2 diabetes mellitus. Vildagliptin is a reversible, selective, competitive inhibitor of DPP4, an enzyme and binding protein present in many tissues such as the pancreatic duct, liver, kidneys, brush border membranes of the intestine, lymphocytes, and endothelial cells. Vildagliptin binds to and forms a complex with DPP4, resulting in its inhibition. DPP4 is

involved in the inactivation of many chemokines, neuropeptides, cytokines, and gastrointestinal hormones. Two important hormones involved in glucose homeostasis and inactivated by DPP4 are glucose- dependent insulinotropic polypeptide (GIP) and GLP-1. GIP and GLP-1 are incretins, which are hormones discharged from the gut that stimulate insulin secretion in response to food intake. However, GIP does not stimulate insulin secretion in patients with type 2 diabetes mellitus as it does in patients without diabetes. GLP-1, the most potent insulinotropic hormone, improves glucose-dependent secretion of insulin from pancreatic ß-cells and restricts glucagon secretion. Inhibition of DPP4, which results in increased levels of active GLP-1, has been shown to be an effective treatment for type 2 diabetes mellitus. Metformin is a biguanide antihyperglycemic agent which is used for treating non-insulin-dependent diabetes mellitus (NIDDM). By decreasing hepatic glucose production it increase glycemic control, decreasing glucose absorption and increasing insulin-mediated glucose uptake. Metformin is an oral antihyperglycemic agent that increases glucose tolerance in patients with NIDDM, lowering both initial and postprandial plasma glucose. Chemically Metformin is Imidodicarbinimidic, N, N-dimethyl-, monohydrochloride. Metformin mechanism of action is distinct from other classes of oral antihyperglycemic agents. Metformin decreases blood glucose levels by diminishing hepatic glucose production, decreasing intestinal absorption of glucose, and improving insulin sensitivity by accumulating peripheral glucose uptake and utilization.[1]

So far, thirteen methods are reported for the simultaneous determination of these drugs in combination as multicomponent dosage forms. Of these methods, eight methods are by HPLC determination[2-9] three UV- spectrophotometric methods by zero order method[10,11,12] and only one method by second derivative spectrophotometric method.[12] There for; aim of the present study was to develop an accurate, simple, economical first derivative spectrophotometric method for the rapid determination of Vildagliptin and Metformin Hydrochloride in bulk drugs and combined tablet formulations.

MATERIALS AND METHODS

The standard solutions of Vildagliptin (60 µg/ml) and Metformin Hydrochloride (10µg/ml) each in distilled water were scanned separately in the wavelength range of 200 nm to 400 nm at zero order and the first order derivative spectra were taken at N=5 using Shimadzu 1800 Spectronic UV-Visible spectrophotometer (Shimadzu corporation, Japan). Zero crossing point of Vildagliptin was found to be at 222.5 nm. Zero crossing point for Metformin Hydrochloride was found to be at 218.25nm. The following figure shows the overlain first derivative spectra of Vildagliptin and Metformin Hydrochloride. (Figure 1); Vildagliptin has zero crossing point at 235.5 nm and Metformin Hydrochloride can be determined at 222.5 nm. Similarly, Metformin Hydrochloride has zero crossing point at 218.25 nm and Vildagliptin can be determined at 218.25nm. The calibration curve of Vildagliptin was found to be linear at 218.25 nm and the calibration curve of Metformin Hydrochloride was found to be linear at 222.5nm. In order to determine the feasibility of the developed method on the assay of marketed pharmaceutical formulations, the method was first tried on bulk drugs in their synthetic mixture sample and concentrations were estimated. (Figure 2); Then the method was applied to the assay of tablets in marketed formulations and satisfactory results were obtained within the acceptable limits as per the content of the label claim for Vildagliptin and Metformin Hydrochloride respectively.

The method was validated as per ICH guidelines for various parameters including specificity, linearity, accuracy, precision, ruggedness, robustness and the results were found to be satisfactory.

RESULTS

The standard solutions of Vildagliptin and Metformin in distilled water (10 µg/ml each) subjected to a scan 200 nm to 300 nm at first order and the derivative spectra were taken at

N=5 using Shimadzu 1800 spectronic UV-Visible spectrophotometer. Zero crossing point of Vildagliptin was found to be at 222.5 nm. Zero crossing point for Metformin was found to be at 218.25 nm. There for, 222.5 nm was selected as zero crossing point of Vildagliptin and 218.25 nm was selected as zero crossing point of Metformin for the present study. Vildagliptin has zero crossing point at 222.5 nm and Metformin can be determined at 222.5 nm. Similarly, Metformin has zero crossing point at 218.25 nm and Vildagliptin can be determined at 218.25 nm. The calibration curve of Vildagliptin was found to be linear at 218.25 nm (Figure 2, 3, 4 and 5) and the calibration curve of Metformin was found to be linear at 222.5 nm. (Figure 6, 7, 8 and 9) There for, it was clear that Vildagliptin and Metformin can be determined in presence of each other with no intervention of any irrelevant substance in multicomponent combination pharmaceutical products.

The newly developed method was validated as per the international guidelines and parameters. The novel method for the quantitative investigation of Vildagliptin and Metformin was subjected to different validation parameters like selectivity and specificity in presence of formulation additives and excepients, studied for Linearity and range at different levels of concentrations and calibration standards where the determination range was optimized, accuracy was proved by recovery studies at different concentration levels, precision was established through different analyst studies. With the intention of determining the practicability of the developed technique for the assessment of commercially available brands of medicinal formulations, the technique was initially attempted on bulk drugs in their synthetic mixture sample and concentrations were estimated. Then the technique was subjected to the assay of tablets in marketed dosage forms and satisfactory results were attained within the acceptable limits as per the content of the label claim for Vildagliptin and Metformin respectively. (Table 1); The technique was validated by principles of ICH guidelines for various parameters including specificity, linearity, accuracy, precision- repeatability and the results were found to be satisfactory with lower standard deviation and coefficient of variation values within the acceptable limits for Vildagliptin as well as Metformin in their combined synthetic mixtures and combined dosage forms i.e. marketed tablet formulations for their simultaneous First derivatization UV-spectrophotometric estimation. The method showed specificity in presence of formulation additives, because there was no interfering from the tablets formulation additives. The method was linear, with low deviation values and the regression equation was calculated by the method of least squares. The method was also accurate, indicated by satisfactory recovery studies at different level of confidence. Intermediate precision studies were carried out by different analysts and the results were found to be satisfactory demonstrating that, the process was reproducible. The scheme was not susceptible to change in the method parameters, because the data obtained were reproducible in different temperature conditions applied at the time of determination of these drug substances with very negligible deviations under the conditions employed (Tables 2 and 3).

DISCUSSION

The described method offer precise and accurate results for the quantitization of Vildagliptin and Metformin simultaneously in their synthetic mixture of bulk drugs and commercial multicomponent tablets formulations exclusive of separation and applied without any difficulty for the regular determinations. The method is also simple, rapid and economical method which gives reproducible results on the instrument used. The reported method is an economical method in which only distilled water is used as the solvent and does not require the use of costly reagents. This proposed method is competent of being used for the quantitization of Vildagliptin and Metformin drugs in bulk and tablet dose forms devoid of the interfering of additives with a significant and comparative correctness and exactness with the reported methods. This newly developed method has the advantages over the

previously reported methods because, present methods is economical. The percentage standard deviation values show that the proposed method provides acceptable variation of Vildagliptin and Metformin. The standard deviation percentages of proposed technique is within the acceptable limits for Vildagliptin and Metformin shows the competence of the technique to stay unchanged by minute and purposeful changes in the system restraints and assures its consistency in regular routine application.

CONCLUSION

It can be concluded that the proposed newly developed method is a rapid, economical, reproducible, accurate and precise method for the routine determination of Vildagliptin and Metformin Hydrochloride in their combined multicomponent synthetic bulk drug mixture as well as commercial tablet formulations; economically alternative to HPLC and better than UV-spectrophotometric simultaneous equation methods.

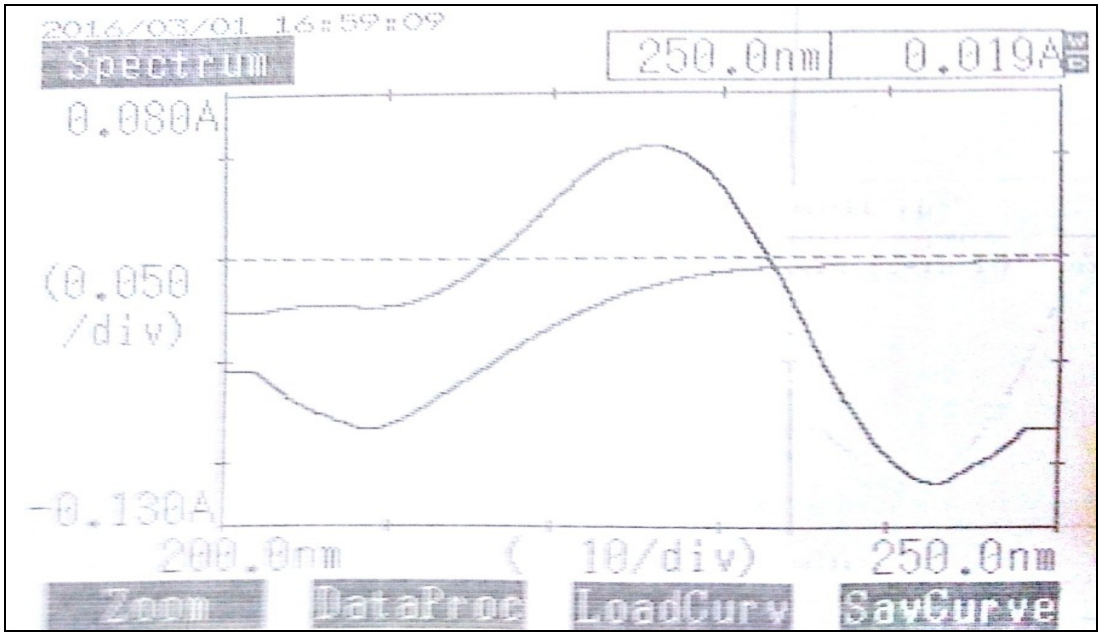


Figure 1: Overlain first derivative spectra of Vildagliptin and Metformin

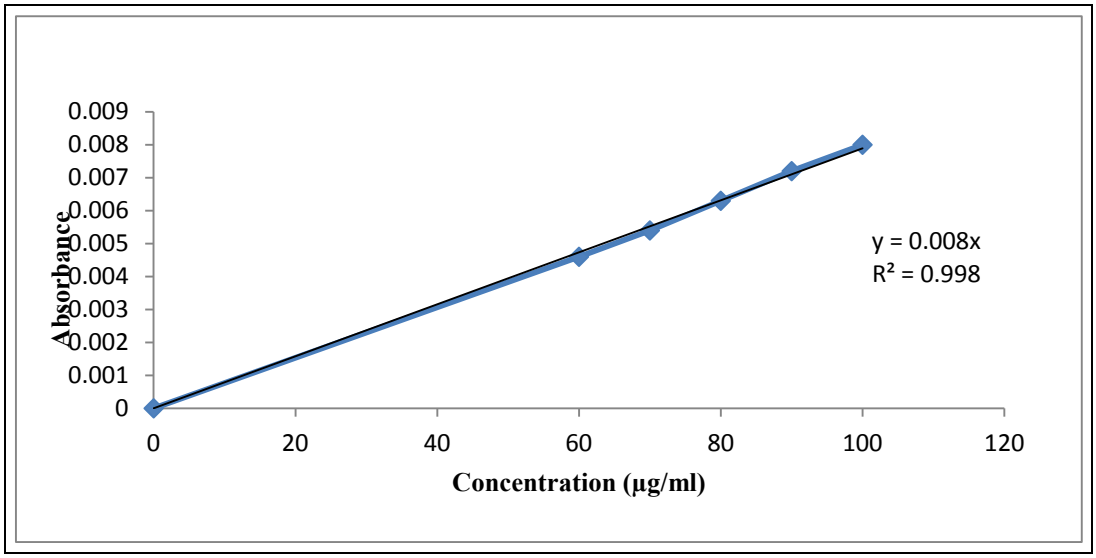


Figure 2: Calibration curve of Vildagliptin at 218.25 nm.

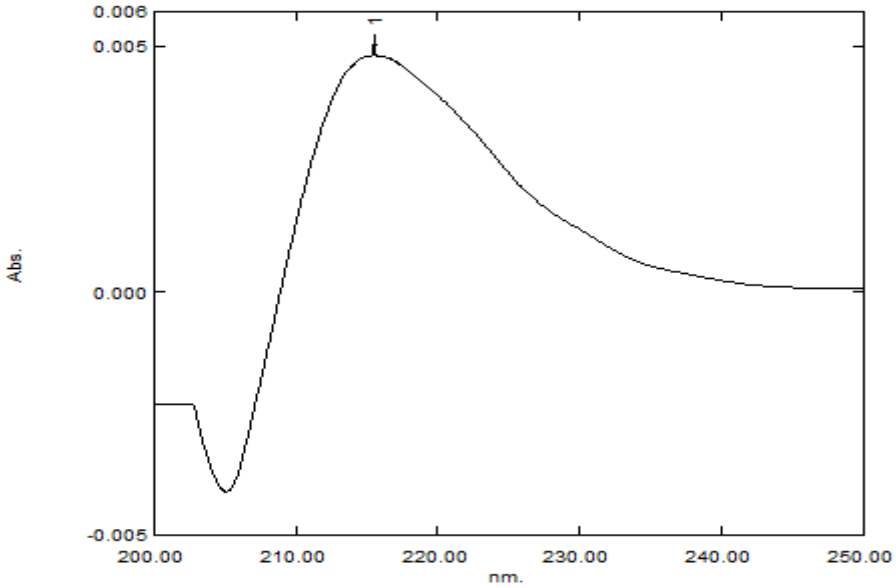


Figure 3: First derivative spectrum of Vildagliptin conc. 60 µg/ml.

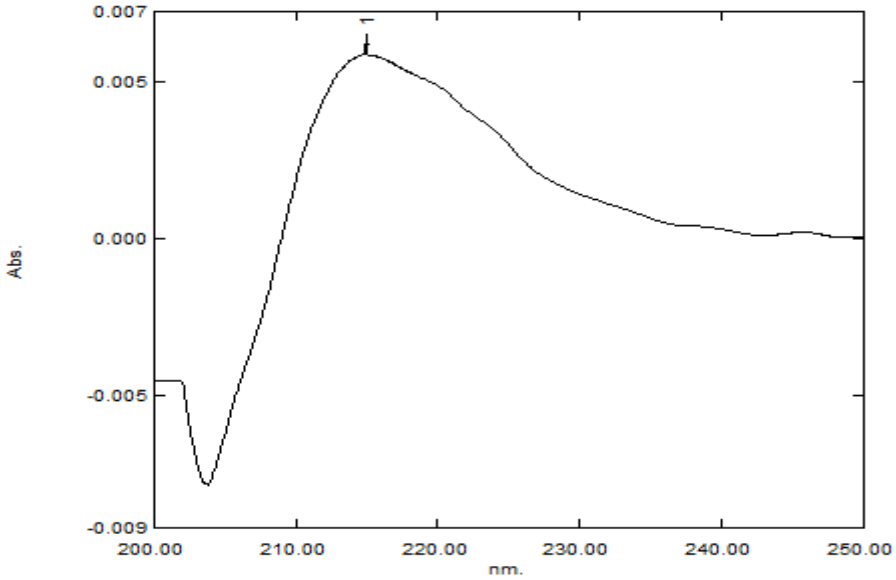


Figure 4: First derivative spectrum of Vildagliptin conc. 80 µg/ml.

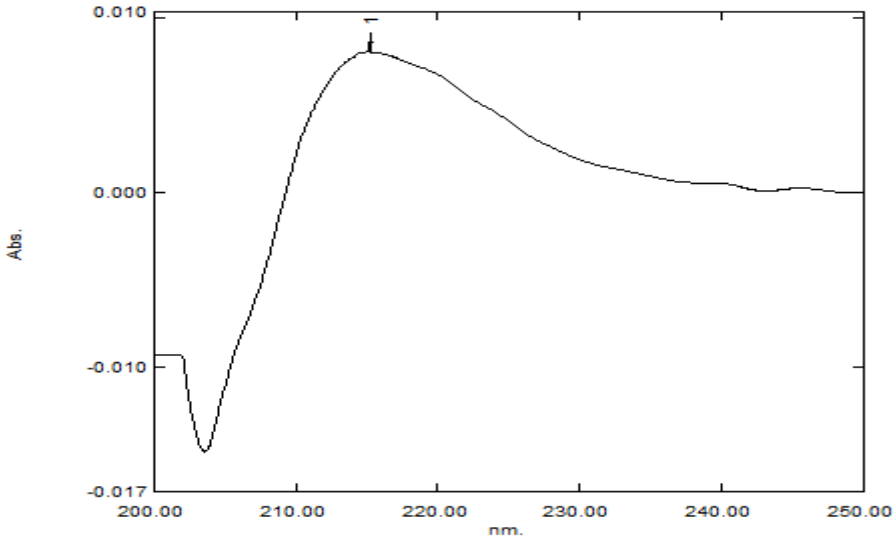


Figure 5: First derivative spectrum of Vildagliptin conc. 100 µg/ml.

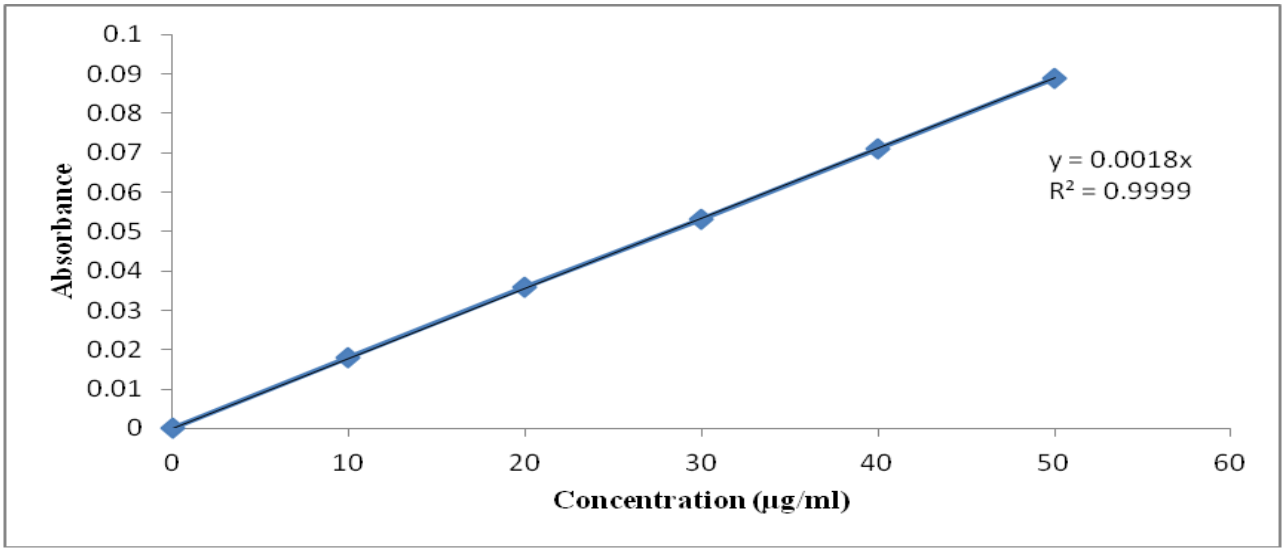


Figure 6: Calibration curve of Metformin at 222.5 nm

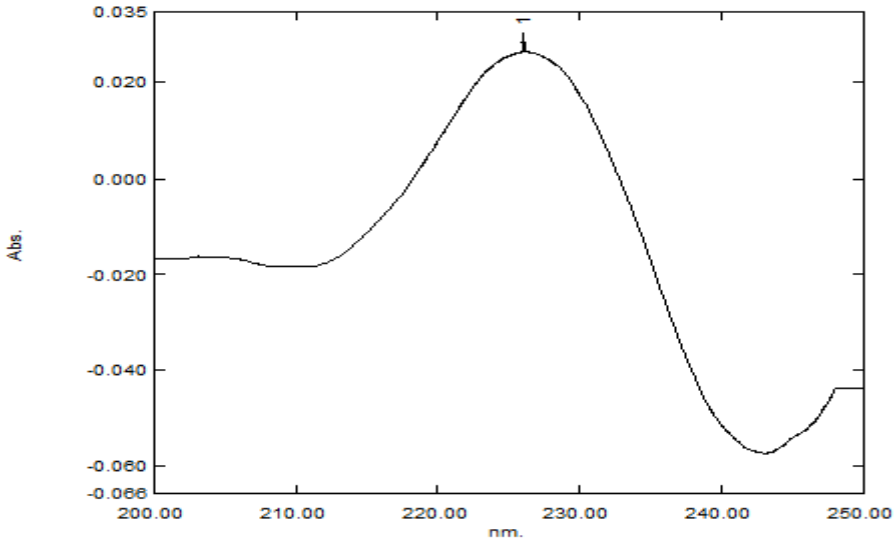


Figure 7: First derivative spectrum of Metformin conc. 10 µg/ml

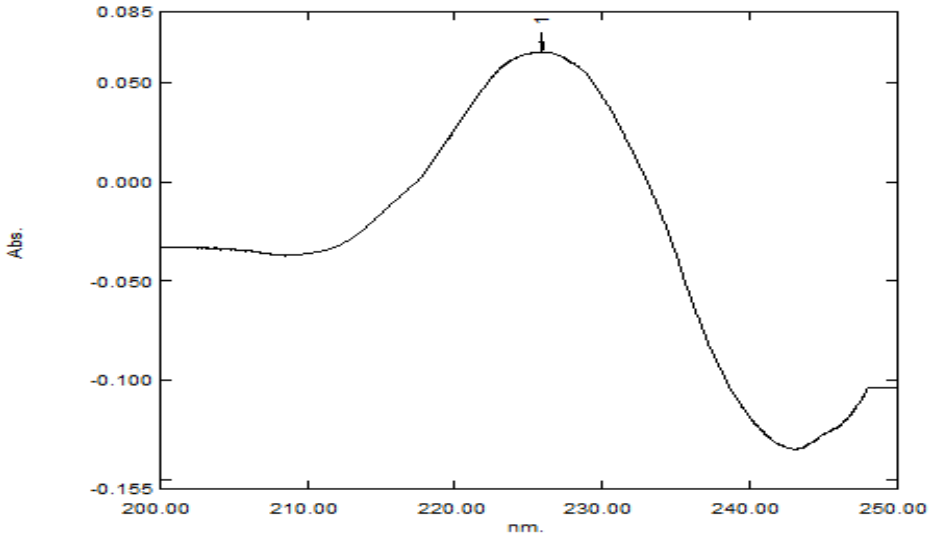


Figure 8: First derivative spectrum of Metformin conc. 30 µg/ml.

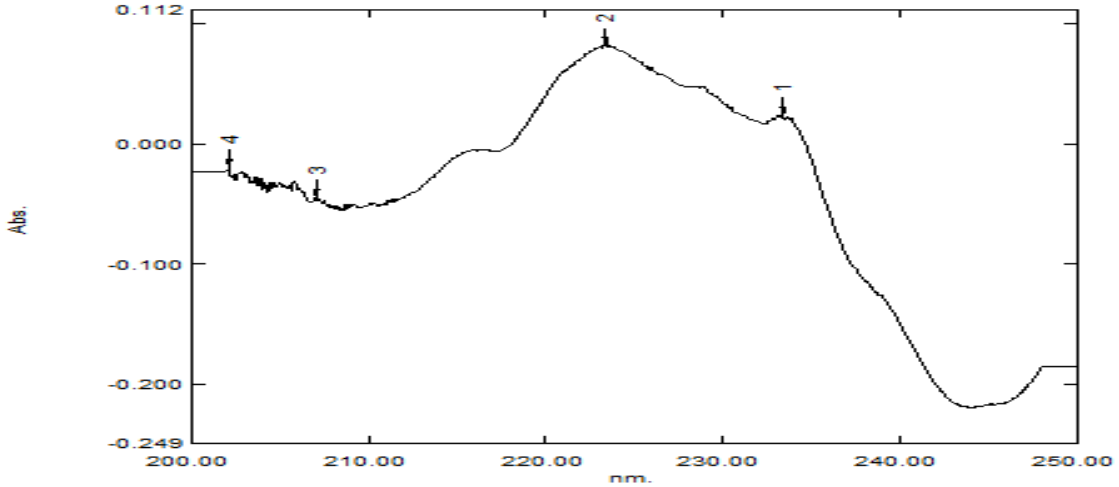


Figure 9: First derivative spectrum of Metformin conc. 50 µg/ml

Table 1: Assay of Vildagliptin and Metformin in Tablet formulation for first derivative method (Galvus Met)

Drug	Label Claim (mg/ml)	Amount Found (mg/tab)	% Of Label Claim	Mean	SD	CV
Vildagliptin	50.00	50.5	101.00	100.06	0.512 5	0.2626
	50.00	49.95	99.90			
	50.00	50.15	100.30			
	50.00	49.9	99.80			
	50.00	49.8	99.60			
	50.00	49.9	99.80			
Metformin	500	498.5	99.70	100.09	0.556 2	0.3094
	500	506	101.20			
	500	499	99.80			
	500	499.25	99.85			
	500	500.25	100.05			
	500	499.75	99.95			

Table 2: Results of accuracy parameter of Vildagliptin (Brand- Zomelis Met)

Level of % Recovery	Amount present (µg/ml)	Amount of standard added (µg/ml)	Total amount recovered (µg/ml)	% Recovery	% mean Recovery	SD	CV
80	50	40	89.41	99.350	99.890	0.6025	0.3631
80	50	40	90.48	100.540			
80	50	40	89.80	99.780			
100	50	50	99.68	99.680	99.676	0.4550	0.2070
100	50	50	99.22	99.220			
100	50	50	100.13	100.130			
120	50	60	109.65	99.690	99.786	0.3842	0.1476
120	50	60	110.23	100.210			
120	50	60	109.40	99.460			

Table 3: Results of accuracy parameter of Metformin (Brand-Zomelis Met)

Level of % Recovery	Amount present (µg/ml)	Amount of standard added (µg/ml)	Total amount recovered (µg/ml)	% Recovery	% mean Recovery	SD	CV
80	500	400	903.06	100.340	99.911	0.4015	0.1612
80	500	400	898.65	99.850			
80	500	400	895.89	99.544			
100	500	500	993.33	99.333	99.710	0.4838	0.2340
100	500	500	1002.56	100.256			
100	500	500	995.43	99.543			
120	500	600	1097.27	99.752	99.940	0.8252	0.6809
120	500	600	1109.27	100.843			
120	500	600	1091.49	99.227			

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