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Unique & Novel Spectrophotometric Determination of Linagliptin Drug in Bulk and Pharmaceutical Formulations by using Iron & 1, 10 Phenthroline

Vaishali Parastekar[1], Makhijani Ritika M[2]

[1, 2]Department of Chemistry, V.E.S College of Arts, Science & Commerce, (Autonomous) Maharashtra, India
Email: *ritika.makhijani[at]ves.ac.in*

Abstract: ***For the determination of Linagliptin in pure and dosage forms, a new easy, sensitive, precise and consistent Spectrophotometric method has been developed. This method is based on the principle of developing a orange colour chromogen by oxidation of drug with 1,10-phenanthroline, which is measured at 510nm. The developed method obeyed the Beer's Lambert's Law in the concentration range of 0.0-10 µg/cm^3. For the developed method the molar absorptivity is 1.4176 X 10 ^{4} Lmol^{-1}cm^{-1} and sandell's sensitivity are found to be 0.0333 µg/cm^2. Optimization of different experimental parameters, affecting the colour development and stability of coloured products are carefully studied. This method is victoriously applied to pharmaceutical formulations. Results obtained from the developed method are in good accordance with those of the other proposed method.***

Keywords: Linagliptin, Spectrophotometric method and 1, 10-Phenanthroline

1. Introduction

DDP-4 inhibitors popularly known as Inhibitors of dipeptidyl peptidase 4 are a class of oral hypoglycemic agents (anti-diabetic drugs) are successful in blocking DDP4 enzyme. These oral hypoglycemic agents have been extensively used to tret type 2 diabetes mellitus.Insulin resistance in peripheral tissue and a beta cell deficiency in insulin secretion are two characteristics of type 2 diabetes mellitus, commonly known as noninsulin dependent diabetes mellitus (NIDDM)[1] linagliptin is DPP-4 inhibitors it is potentially used in the management of NIDDM (Mentlein, 1999).

Linagliptin is described chemically as 1H-Purine-2,6-dione, 8-[(3R)-3-amino-1-piperidinyl]-7-(2-butyn-1- yl)-3,7-dihydro-3-methyl-1-[(4-methyl-2-quinazolinyl) methyl]. Linagliptin has empirical formula $C_{25}H_{28}N_8O_2$ and the molecular weight is 472.5. It was approved by the U.S. Food and Drug Administration (FDA) on 2 May 2011 for management of type2 diabetes [3]. Spreitzer, 2008).

White yellowish compound Linagliptin is slightly hygroscopic & slightly soluble in water (0.9 mg/ml), acetone (ca. 1 mg/ml) but soluble in methanol (ca. 60 mg/ml) and sparingly soluble in ethanol (ca. 10 mg/ml) [4]

2. Literature Survey

It reveals some analytical methods for determination of Linagliptin, such as RP HPLC[5-7], HPLC[8] and UV spectrophotometry [9-10] have been reported. These procedures call for costly equipment and highly qualified workers. Our current research aims to develop a straightforward spectrophotometric technique for the quantification of linagliptin in tablet form. The procedure has been optimized.

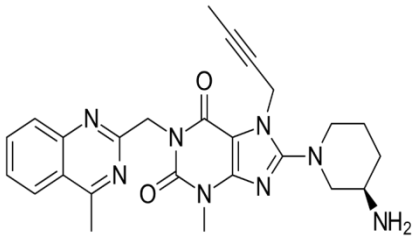


Figure 1: Structure of Linagliptin

3. Materials and Methods Instrumentation

- UV-VIS Spectrophotometer: Model LABMAN in wavelength range 320-1000 nm using quartz cells of 1 cm path length
- Sonicator : PCi Mumbai Model No 3.5 L 100h
- Analytical Balance: Infotech model

A R grade chemical purchased from Loba Chemie.

Preparation of standard drug solution

Ten tablets of Linagliptin drug were accurately weighed, grounded, and powdered. Tablet powder equivalent to 50 mg of Linagliptin was dispersed in 50 ml of methanol, sonicated for an hour and filtered through Whatman filter paper No 42 to remove the insoluble matter. Then the solution was made up to 100ml with methanol. It was used as a stock solution. The working dilution was made by diluting the 50ppm drug solution appropriately.

Preparation of Reagents

1) 0.005M Fe (III) - Dissolve 0.241g of anhydrous ferric ammonium sulphate in 100cm^3 of double distilled water,
2) 0.05M o-phenanthroline - Dissolve 0.991g of the reagent in 100 cm^3 of alcohol,
3) 0.02M Ortho phosphoric acid - Dilute 0.15cm^3 of laboratory reagent (AR Grade) of o-phosphoric acid to 100 cm^3 with distilled water.

4. Experimental Procedure

Varied volumes (0.0- 5.0mL, 50µg/cm^3) of standard Linagliptin solution is taken in to serially arranged 25cm^3 calibrated standard measuring flask and then 2.0cm^3 of 0.005M of Fe (III) solution, 4.0 cm^3 of 0.05M 1,10-Phenanthroline are added in sequential order. After adding some distilled water, the standard measuring flasks are heated by placing it on a boiling water bath for about 60 minutes. The flasks are then removed from the boiling water bath and then cooled to room temperature. 4.0 cm^3 of 0.02M of Orthophosphoric acid is added to and for the final dilution is done with distilled water. After 5 minutes the absorbance value of the colored complex solution is measured at 510nm with the help of a reagent blank prepared under similar condition without drug solution. The calibration curve was computed.

Analysis of Pharmaceutical Sample

Powdered tablets that are equivalent to 50 g of the drug is weighed exactly and taken into 100 ml beaker and 50cm^3 methanol is added and shaken. This standard solution is filtered into 100cm^3 standard flask and volume is adjusted with 50% methanol. For the determination of Linagliptin suitable aliquots of this solution is used as per the procedure describe earlier.

5. Result and discussion

From 400 to 700 nm, the absorbance of the coloured complex solution was taken against reagent blank generated under the same circumstances. The absorption spectra have a strong peak at 510 nm. (Fig-2) Beer's Law is obeyed within the range of 1 to 11 µg/ml of Linagliptin, Molar absorptivity is found to be 1.4176 X 10 ^{4} Lmol^{-1} cm^{-1} and Sandell sensitivity is found to be 0.0333 µg/cm^2. The graph depicts infinitesimal intercept and is described by regression equation given as y = 0.0363X - 0.0134 (where Y stands for the absorbance of 1 cm layer, b gives the slope, a gives the intercept and C is the concentration of the measured solution in µg/mL) (Fig-3).

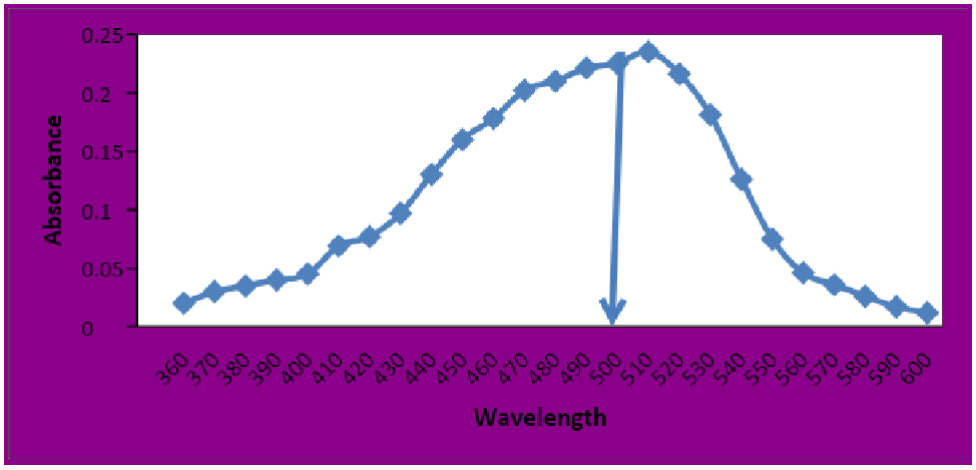


Figure 2: Absorption spectra of Linagliptin with Fe (III)/1,10-Phenanthroline

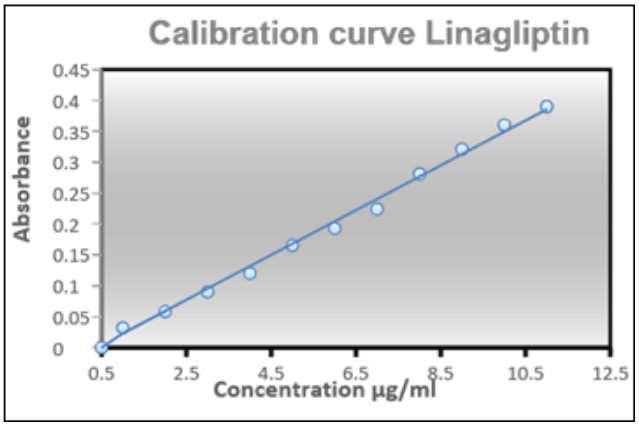
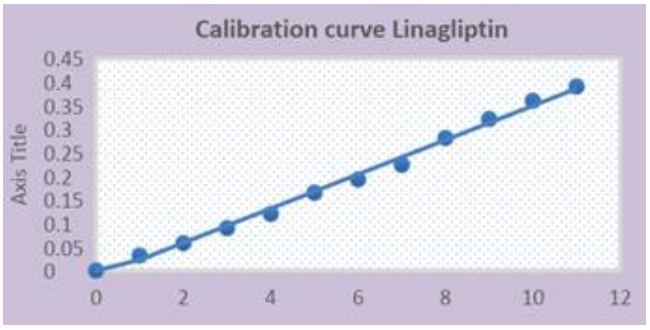


Figure 3: Calibration curve of Linagliptin with Fe (III)/O-PHEN



Optimization of parameters:

Effect of Concentration of H_3PO_4 on Color Development: Absorbance remains constant after 0.015M concentration of H_3PO_4.Hence 0.02M H_3PO_4 is selected for the colour development and further experimental studies. (Fig-4)

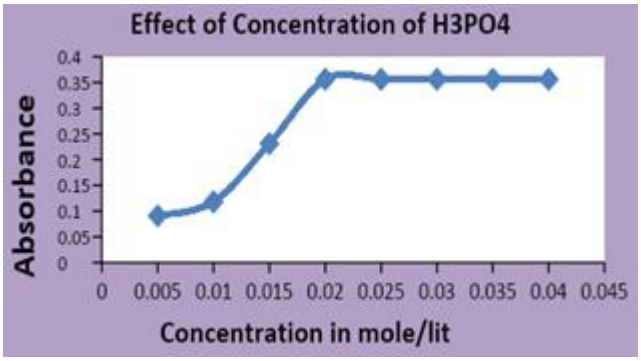


Figure 4: Effect of concentration of H_3PO_4 on colour development Effect of Concentration of 1,10-Phenanthroline:

Various concentration of 1,10 Phenthroline were used however 0.05 M Concentration of 1,10 Phenanthroline is sufficient for full colour development. Hence it was selected for further experimental studies. (Fig-5)

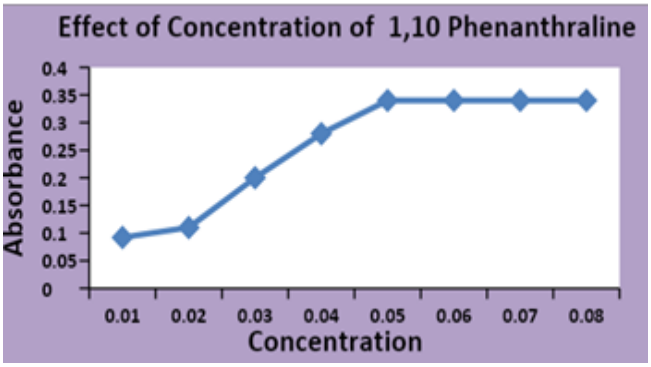


Figure 5: Effect of concentration of 1,10-Phenanthroline on absorbance of developed system Effect of Heating Time on Absorbance:

For colour development 60 minutes are sufficient and hence 60 minutes time is selected for further experimental studies. (Fig-6)

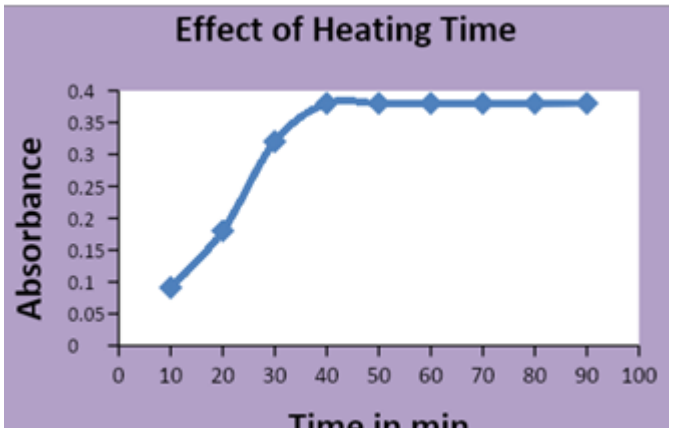


Figure 6: Effect of heating time on absorbance

Principle of developed method

As an oxidant, ferric salts are widely used in the spectrophotometric analysis of numerous medicinal medication compounds. [11&12] The end product $[Fe(phen)3]^{2+}$ being a strongly coloured & easily extractable chelate the Fe+3/O-phenanthroline (Fe+3/Phen) system is useful reagent for any analytes having reducing characteristics

In weak acidic medium drug Linagliptin is oxidized by FPL reagent, forming an orange red colored complex with absorption maximum at 510 nm. Several exploratory experiments were conducted to determine the optimum reaction parameters. Drug Linagliptin oxidizes ferric salts to ferrous salts which reacts with reagent O-Phenanthroline to form triscomplex of Fe (III) (ferroin). Intense colored compound (equation shown in fig 7)

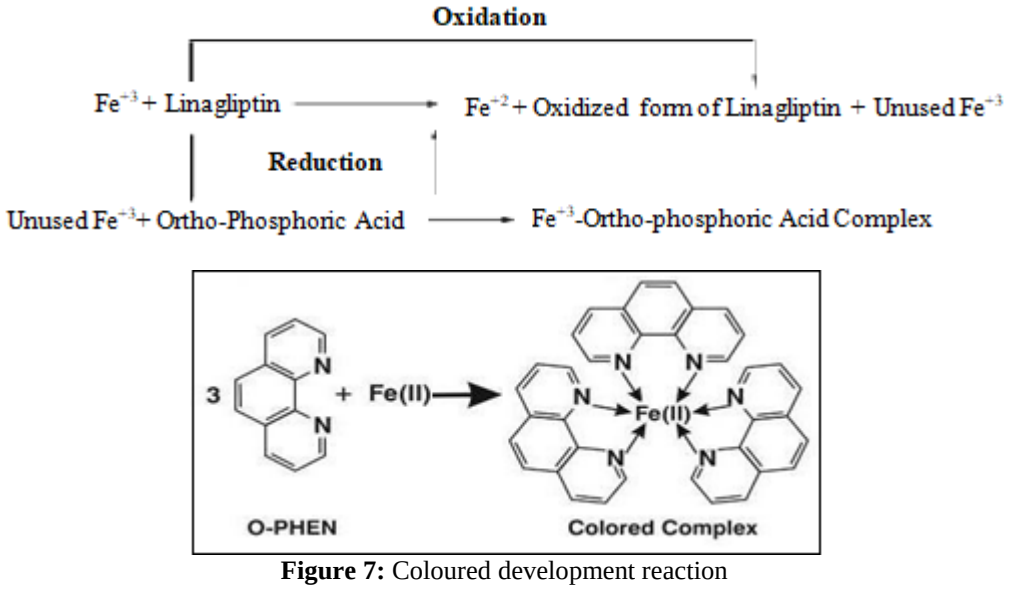


Figure 7: Coloured development reaction

Method of Validation

The method developed for quantification of drugs has been validated in terms of linearity, selectivity, precision, accuracy, limit of detection, limit of quantification and ruggedness.

Linearity: of calibration curves are expressed with help of Beer's law limit. The high values of the correlation coefficient (r) and the small values of the y-intercepts of the regression equation confirms the linearity of the calibration curve.

Selectivity: is tested by adding known excipients and additives such as starch, magnesium sulphate talc, glucose to the pure Linagliptin sample and many times recovery experiments were performed. Excipients did not interfere indicating a high selectivity for determining the studied Linagliptin in its dosage forms. Low values of LOD and LOQ and high value of (ε) confirm the sensitivity of the method for the determination of Linagliptin in bulk drugs.

The limit of quantification: (LOQ) is the least concentration that can be measured, below which the calibration range is non- linear. The limit of detection (LOD) is the lowest concentration of the analytes that can be readily detected. The LOQ and LOD were calculated according to the following equations (ICH 2005) [13]

LOQ = 10Sa/b LOD = 3.3 Sa/b Where (Sa) is the standard deviation of the intercept of the regression line and (b) is the slope of the calibration curve. LOD is 1.715 and LOQ is 5.208.

Robustness and Ruggedness: Ruggedness is resistance of method for a small change in variables like instrument, and analyst or both. For the evaluation of method robustness, some parameters were interchanged, phosphoric acid concentration, 1,10concentration, wavelength range, and heating time. The result remained unaffected by small deliberate variations. Method ruggedness was evaluated by using the same procedure applied by two analysts and three different instruments on different days. The results showed no significant changes between different analysts and instruments hence it can be concluded that the developed methods were robust and rugged.

Regression parameters, Optical characteristics Precision and Accuracy of the proposed method are shown in Table -1

Table 1: Regression parameters, Optical characteristics Precision and Accuracy of the proposed method

Parameter	Method
λ_{max} Maximum Wavelength	510 nanometer
Beer's Law Limits µg/cm^3	1-11
Sandell's Sensitivity (µg/cm^2 /0.0001 Absorbance)	0.0333
Molar Absorptivity Lt.mole^{-1}.cm^{-1}	1.4176 X 10^4
Slope (b)[a]	0.0363
Intercept (a) [a]	0.0134
S.D on intercept(S_a)	0.0062431
S.D on slope (S_b)	0.000878
Correlation Coefficient (r)	0.99448
Variation from mean at 95% level confidence limit	±0.0359
Limit of Detection (LOD)µg/cm^3	1.715
Limit of Quantification (LOQ)µg/cm^3	5.208

[a]Regression equation is given as Y= a+bC , Where Y is the absorbance and C is the concentration in µg/cm^3 and b is % Relative standard deviation which is calculated for ten determinations

Application of the method:

Linagliptin was analyzed from pharmaceutical sample available in the market by the proposed method & the result obtained are comparable with standard method [7] (Table- 2).

Determination of Pharmaceutical Formulations of Linagliptin by our proposed method and reference method is shown in Table -2

Table 2: Determination of Pharmaceutical Formulations of Linagliptin

Drug	Manufacturing company	Labelled amount(mg)	*Amount found by Proposed Method	*Amount found by Reference Method
(Trajenta) Linagliptin 5 mg	Boehringer Ingelheim	5.00	4.89	4.99
Ondero 5mg Tablet	LUPIN	5.00	4.90	4.98

6. Conclusions

The proposed method is easy, accurate, subtle and consistent. For the analysis of pharmaceutical formulations in any laboratory this method can be successfully applied.

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Author Profile

Dr. Ritika Makhijani, Professor of Chemistry, Department of Chemistry, V.E.S College of Arts, Science & (Autonomous) Maharashtra, India

Vaishali Parastekar, PhD Scholar, Department of Chemistry, V.E.S College of Arts, Science & (Autonomous) Maharashtra, India