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Spectrophotometric Determination of Sitagliptin in Tablets Formulations

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A simple, rapid and sensitive spectrophotometric method for the determination of sitagliptin was developed. The method is based on the proton transfer reaction with quinalizarin (Quiz) in dimethyl sulphoxide to form a violet product showing maximum absorbance at 580 nm with molar absorptivity of 10561.16 L mol^{-1} cm^{-1}. The method follows Beer's law over the concentration range 15-65 µg/mL. The recovery of the method is between 99.520-101.856 % and the relative standard deviation (RSD) of the method is less than 1. 439 %. The method was successfully applied for the determination of sitagliptin in tablets formulations.

Keywords: Sitagliptin, Spectrophotometric method, Quinalizarin, Tablets formulations.

INTRODUCTION

Sitagliptin is a novel oral hypoglycemic drug of the dipeptidylpeptidase-4 inhibitor class. Dipeptidyl peptidase-4 (DPP-4) inhibitors are a new class of oral anti-hyperglycemic agents that enhance the body's ability to regulate blood glucose by increasing the active levels of incretins, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulin tropic peptide (GIP)[1,2]. There are numerous DPP-4 inhibitors in development with sitagliptin as the first approved agent for the treatment of patients with type 2 diabetes[3]. Sitagliptin is (R)-3-amino-1-[3-(trifluormethyl)-5,6,7,8-tetrahydro[1,2,4]triazol[4,3-*a*]pyrazin-7-yl]-4-(2,4,5trifluorphenyl) butan-1- one[4] Fig. 1.a. The literature reveals several methods for determining sitagliptin in tablets alone or in combination with other hypoglycemic agents. The major reported analytical methods depended on sophisticated instrumental techniques *e.g.* RP-HPLC[5,6], HPTLC[7], UPLC[8] and capillary zone electrophoresis[9].

Spectrophotometric methods were described either direct[10], after chemical derivatization[11-13], ion pair complexation[14] and charge transfer complexation[15]. Some reported spectroscopic methods suffer from one or more disadvantage such as poor sensitivity, rigid pH control, heating or extraction step, complicated experimental setup and meticulous control of experimental variables. Spectrophotometry continues to be very popular, because of its simplicity, versatility, availability in quality control laboratories and low cost. So, we present a new spectrophotometric method for determining sitagliptin in tablets by using quinalizarin reagent. Fig. 1.b.

EXPERIMENTAL

UV-visible double beam spectrophotometer Jasco V-650 (Japan), quartz cells 1 cm, All chemicals were of analytical grade, Quinalizarin produced by The British Drug Houses, BDH (England), Dimethylsulfoxide produced by S D Fine-Chem Limited, SDFCL (India), Sitagliptin phosphate monohydrate 99.7 % contains 3.54 % water content by KFR (%w/w) produced by by Nutra Specialities Private Limited (India).

Drug products: We determined the dosage of sitagliptin 50 or 100 mg/tablet, respectively in some Syrian trade names products: Sitacretin (Ibn Alhaytham), Janu Asia (Asia), Gliptin (Ultra Medica).

Sitagliptin stock solutions: Stock solutions 1×10^{-3} mol/L and 1.22×10^{-3} mol/L were prepared by dissolving a suitable amount of drug powder in DMSO.

Reagent stock solution: Quinalizarin, 1,2,5,8-tetrahydroxyanthra quinone, Stock solutions 1×10^{-3} mol/L and 4×10^{-3} mol/L were prepared by dissolving a suitable amount in DMSO.

Samples preparation: Ten tablets were weighed and ground to fine powder. An accurately weighed powder equivalent to 50 mg of sitagliptin was transferred to 100 mL volumetric flask and the volume was completed to the mark with DMSO.

RESULTS AND DISCUSSION

The study and development of the method for the determination of sitagliptin in bulk powder and tablets, exploring its charge transfer reaction with quinalizarin, was performed

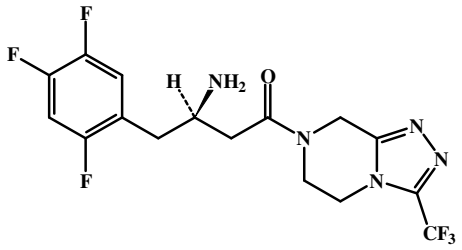


Fig. 1a. Sitagliptin

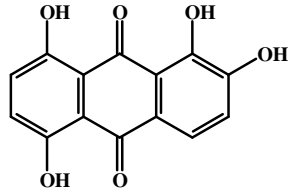


Fig. 1b. Quinalizarin

through three steps: (i) optimization of the experimental conditions in order to achieve both maximum sensitivity and selectivity. This step comprised the evaluation of the effect of the solvent nature, the influence of the concentration of reactant and time required to complete the reaction. (ii) Study and characterization of the reaction, which was carried out by the evaluation of the reaction stoichiometry (Job's continuous variation method and molar ratio method), calculation of the association constant and molar absorptivity of the coloured compound formed. Finally, (iii) the method was applied to the determination of sitagliptin in samples of commercial drugs in order to test its applicability.

Absorption spectra: The reaction of sitagliptin with Quiz results in the formation of a charge transfer complex between sitagliptin as electron-donor when they reacted with selected π-acceptor (Quiz) in dimethyl sulphoxide medium at optimum conditions, the radical anion (absorbing species) was formed in the medium immediately after mixing of the reagent and showed maximum absorption at 580 nm.

Optimization of reaction conditions

Evaluation of the effect of the solvent nature: The solvent plays an important role in the charge transfer reactions, since it must be able to stabilize the radical anion formed upon the charge transfer reaction. Additionally, sitagliptin is soluble in dimethylformamide, dimethylsulfoxide and methanol but it is practically insoluble in acetonitrile and most of organic solvents. Higher sensitivity of the reactions was attained in DMSO. Hence it was used as a solvent (Fig. 2).

Effect of quiz concentration: To study the effect of Quiz concentration and volume on the reaction, Quiz solutions ranged from 2×10^{-3} to 8×10^{-3} M by taken 1 mL from each concentration to 5 mL separation volumetric flask, Sitagliptin constant concentration 0.15×10^{-3} M were used as described in construction of calibration curve and the absorbance were measured. High absorption readings were attained in the range 4×10^{-3}-5×10^{-3} M beyond which the absorbance slightly decreased. Different volumes (0.5-3.0 mL) of Quiz (4×10^{-3} M) were also tested. A Quiz concentration of 4×10^{-3} M (1.5 mL) was used in the subsequent experiments.

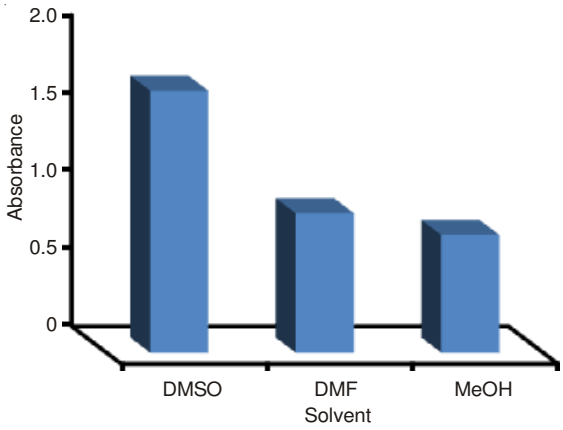


Fig. 2. Effect of different solvents on the charge transfer complex of sitagliptin-Quiz. Solution obtained against (1.2×10^{-3} M) Quiz

Effect of the reaction time: The optimum reaction time was determined by continuous monitoring of the absorbance at 580 nm of a solution containing sitagliptin 0.15×10^{-3} M plus Quiz 1.2×10^{-3} M at laboratory ambient temperature (25 ± 2 °C). Stable absorbance values were observed from the beginning of the experiment up to 90 min. of studied time. In view of this result, all measurements were carried out after 5 min of mixing with the reagent.

Stoichiometric ratio by molar ratio: The stoichiometric ratio of the reactants was determined by molar ratio method. Molar ratio graph for the reaction between sitagliptin 1×10^{-3} M and Quiz reagent 1×10^{-3} M shows that the interaction occurs between a constant moles solution of the drug and varied moles solution of the reagent. The result indicated that the complex was formed in the ratio of 1:1 and 1:2 (Drug: Quiz reagent) (Fig. 3).

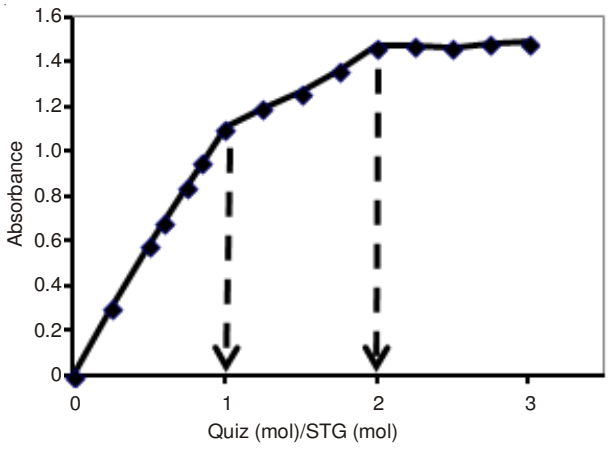


Fig. 3. Molar ratio method graph for the reaction of sitagliptin complex with Quiz

Stoichiometric ratio by continuous variation: The stoichiometric ratio of the reactants was determined by Job's method of continuous variation and modified by Vosburgh and Coober. Job's continuous variation graph for the reaction between sitagliptin 1×10^{-3} M and Quiz reagent 1×10^{-3} M shows that the interaction occurs between an equimolar solution of the drug and the reagent. The result indicated that the complex was formed in the ratio of 1:1 and 1:2 (Drug: Quiz reagent) Fig. 4. These finding by molar ratio method and

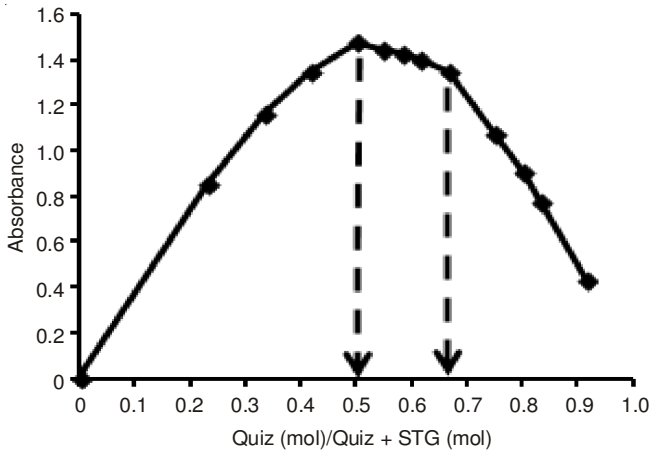
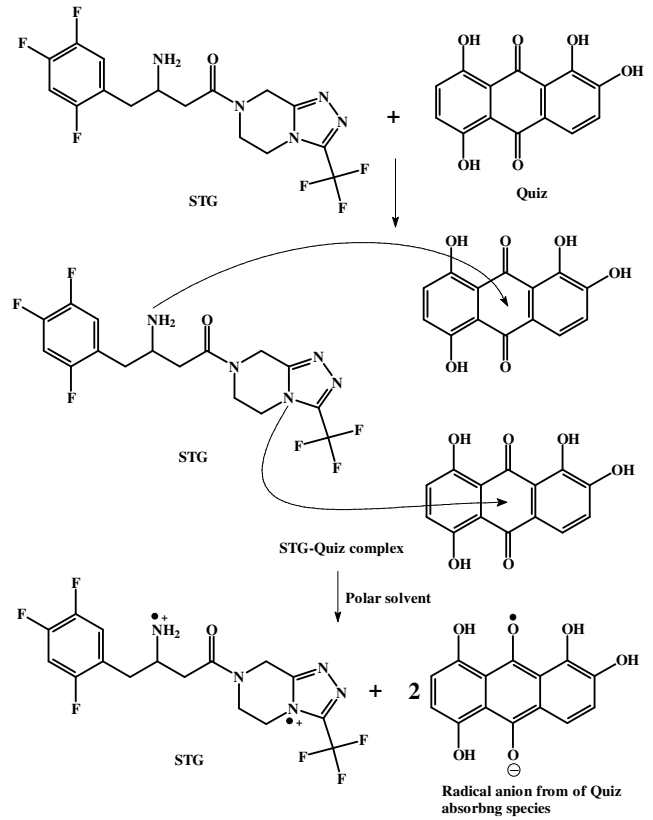


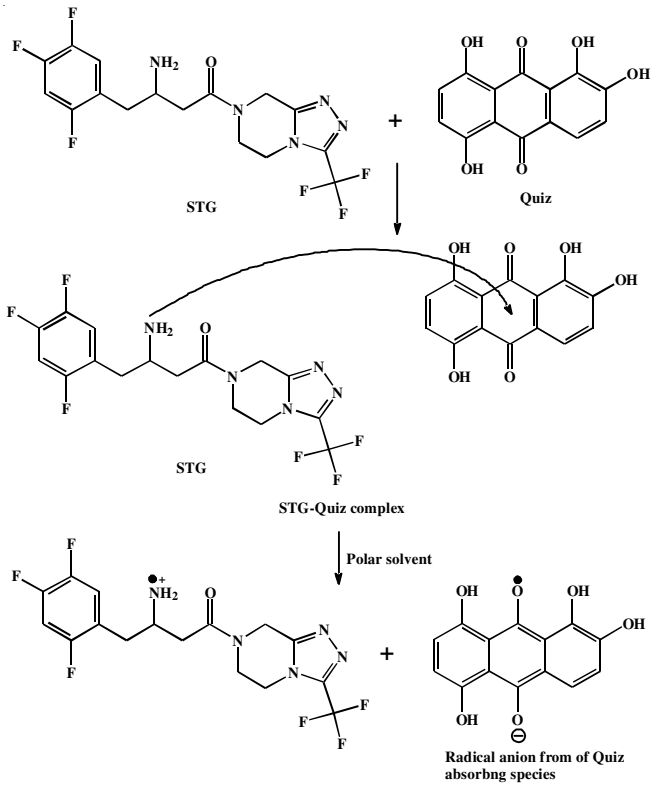
Fig. 4. Job's method of continuous variation graph for the reaction of sitagliptin complex with Quiz

continuous variation method support that the interaction of sitagliptin and Quiz reagent takes place at one and two sites, which were the more sterically free terminal basic amino groups.

In view of this result a reaction mechanism was proposed considering the transfer of free electron of the two nitrogen atom present in one molecule of drug to the charge-deficient center of reagent molecule from the total transfer of charge, the ratio of 1:2 (Drug: Quiz reagent) **Scheme-I:** or, the transfer of free electron of the one nitrogen atom present in one molecule of drug to the charge-deficient center of reagent molecule from the total transfer of charge, the ratio of 1:1 (Drug:Quiz reagent) **Scheme-II**.



Scheme-I: Proposed mechanism of radical anion formation between sitagliptin and Quiz reaction (1:2) drug: reagent



Scheme-II: Propsed mechanism of radical anion formation between sitagliptin and Quiz reaction (1:1) drug: reagent

Range and linearity of sitagliptin: We studied the linearity sitagliptin concentration at the optimal conditions where we made a series of 5 mL separated volumetric flasks each one contains 1.5 mL of Quiz 4×10^{-3} M and variable concentration of sitagliptin stock solution 1.22×10^{-3} M and then completed to 5 mL by DMSO, finally measured the absorbance at 580 nm for each concentration against the blank. Fig. 5 presents the sitagliptin-Quiz complex spectra.

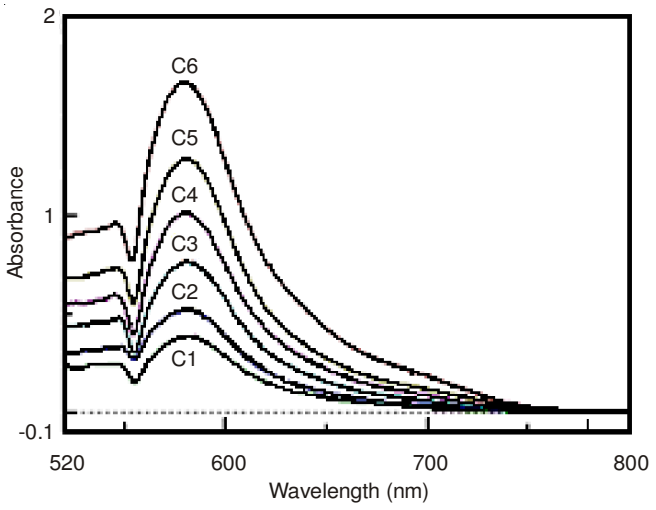


Fig. 5. Complex spectra of variable concentrations of sitagliptin: C_1 = 15 µg/mL, C_2 = 20 µg/mL, C_3 = 30 µg/mL, C_4 = 40 µg/mL, C_5 = 50 µg/mL, C_6 = 65 µg/mL

The range of sitagliptin linearity was obeyed to Beers law in concentration 15-65 µg/mL and the linearity is presented in Fig. 6.

TABLE-2
DETERMINATION OF SITAGLIPTIN IN SOME SYRIAN TRADEMARKS TABLETS FORMULATIONS

Trade name	Company	Dose (mg/tab)	$\bar{x}$ n = 5 (mg/dose)	RSD (%)	Recovery (%)
Sitacretin 100	Ibn Alhaytham	100	101.096	1.159	101.856
Sitacretin 50	Ibn Alhaytham	50	50.266	1.236	101.173
Janu asia 100	Asia	100	100.962	1.247	100.225
Janu asia 50	Asia	50	50.008	1.439	100.944
Gliptin 50	Ultra Medica	50	49.768	1.101	99.520

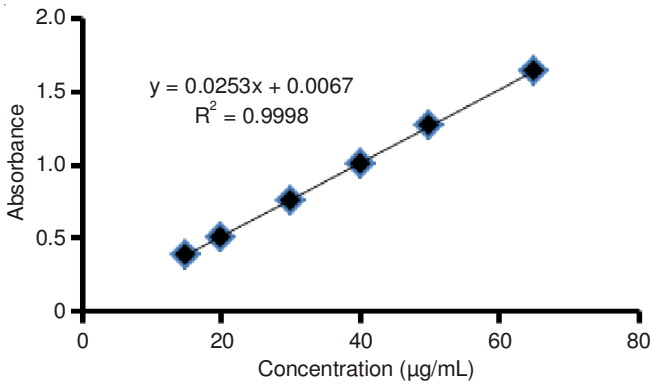


Fig. 8. Linearity of sitagliptin

Limit of detection, limit of quantification, linearity and the optimal parameters of sitagliptin are presented in Table-1.

TABLE-1
OPTIMAL SPECTROPHOTOMETRIC PARAMETERS OF SITAGLIPTIN

Parameters	STG
λ_{max} (nm)	580
Beer's law limit (µg/mL)	15-65
Molar absorptivity (L/mol cm)	10561.16
Sandell's sensitivity (µg/cm^2)	0.0771
Linear regression equation	m = 0.0253
Y = mx + b	b = 0.0067
Correlation coefficient r^2	0.9998
LOD (µg/mL)	0.7155
LOQ (µg/mL)	2.1683

Pharmaceuticals samples: Sitagliptin was determined in three Syrian trade mark products: Sitacretin (Ibn Alhaytham), Janu Asia (Asia), Gliptin (Ultra Medica). The obtained results were presented in Table-2.

Conclusion

Sitagliptin can be directly determined in tablets in the presence of excipients without any interferences by spectrophotometry. The charge-transfer reaction between sitagliptin and Quinalizarin was enhanced in dimethyl sulfoxide medium. Also, the reaction was immediately formed in DMSO solvent, which allowed the absorbance measurement to be available for chosen time 5 min. Linear analytical curves were obtained in the range of 15-65 µg/mL and the limits of detection and quantification were 0.7155 and 2.1683 µg/mL, respectively. The method is simple as it does not involve adjustment of critical conditions like temperature, pH or tedious sample preparation. This method has many advantages over other analytical methods due to its simplicity, sensitivity, rapidity, low cost instrumentation, accuracy. Due to these advantages this method can be used for quality control and routine analysis.

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