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# Sitagliptin: A literature review on analytical and bio-analytical methods

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**Abstract**
This review work is a collective data of previously published methods related to the analysis of Sitagliptin either in alone or in combination with other drugs. Many spectroscopic methods like derivative techniques, chromogenic techniques were used for. Newly developed as well as improved chromatographic method also available by using biological fluids and pharmaceutical formulations. Apart from these two techniques few LC-MS/MS and HPTLC methods also available. Now in this present analytical research world quality by design or design by expert technique is used to get improved method for method validation. This concise review work can guide an analyst to choose most appropriate method for a best analytical method development and validation.

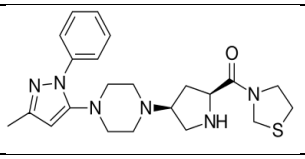
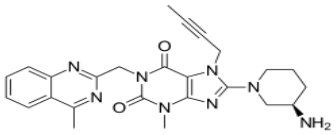
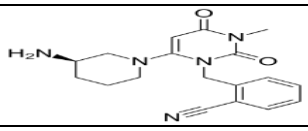
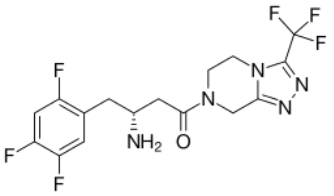
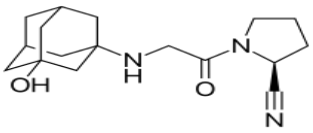
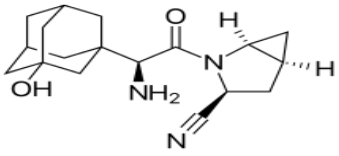
**Keywords:** Chromogenic, LC-ms/ms, HPTLC, Sitagliptin

## 1. Introduction
As pharmaceuticals developing every day, a revolution found in human health. These pharmaceuticals can show best activity if these are free from impurities and pure. At regular intervals various chemical and instrumental methods were developed to make drugs free from impurities. Impurities may develop in any stage, starting from manufacturing of bulk drug to packaging of finished product and further up to storage (degradation). Transportation and storage is the two stages where impurities may occur frequently. Hence in these condition impurities must be detected and quantitated. For detection and quantification analytical instrumentation and methods plays an important role [1].

For therapeutic process monitoring intermediate pharmaceutical analysis becomes an important tool as it includes different stages like testing of bulk drugs, intermediate products, drug formulations, degradation products, chemical stability of drugs and toxic contents of a drug materials. Now a day's poly pharmacy is a most worthy therapy for many diabetic patients. So for improving the poly pharmacy therapy quality control testing of combined formulations and assay of biological samples are important.

Defects in insulin secretion, insulin action, or both create diabetes which is characterized by hyperglycemia. Classification of Diabetes mellitus was widely accepted as IDDM or Type 1, and NIDDM or Type 2 which was published by WHO in 1980 [2]. DPP-4 inhibitors are the latest drugs which work by blocking the action of DPP-4, an enzyme which destroys the hormone in cretin which help the body produce more insulin only when it is needed and reduce the amount of glucose being produced by the liver when it is not needed [3]. The change in glucagon correlates linearly with improvement in glucose tolerance. Since these drugs improve insulin secretion in response to an increase in blood glucose, it seems appropriate to pair them with drugs that have a different mechanism of action, such as insulin sensitizers or Metformin [4]. During short-term clinical trials, no increased risk of acute pancreatitis has been observed with Sitagliptin, Vildagliptin, Saxagliptin, Alogliptin, and Linagliptin [5]. Linagliptin (Trajenta) is still included in black triangle scheme, while Sitagliptin (Januvia), Saxagliptin (Onglyza) and Vildagliptin (Galvus) were removed from the black triangle list in 2012 [6]. DPPIV inhibitors (Gliptins) include Saxagliptin, Linagliptin, Alogliptin, Sitagliptin, and Vildagliptin. Detail about the gliptin derivatives given in table no.1

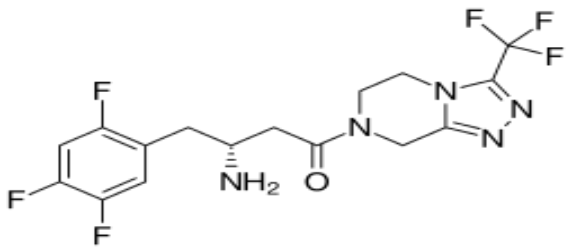
**Table I:** Details of Gliptin Derivatives

| Drug | Structure | IUPAC Name | Molecular weight | Solubility |
|---|---|---|---|---|
| Teneligliptin |  | {(2s,4s)-4-[4-(3-Methyl-1-phenyl-1-H pyrazole-5-yl) piperazin-1-yl] pyrrolidin-2-yl} (1,3-thiazolidin-3-yl) methanone hemipentahydrobromide hydrate | 426.58 g/mol | Soluble in DMSO, Methanol, Water |
| Linagliptin |  | 8-[(3R)-3-aminopiperidin-1-yl]-7-(but-2-yn-1-yl)-3-methyl-1-[(4-methylquinazolin-2-yl) methyl]-2, 3, 6, 7-tetrahydro-1H-purine-2,6-dione | 472.54 g/mol | It is very slightly soluble in water, IPA, Acetone, soluble in methanol, sparingly soluble in ethanol |
| Alogliptin |  | 2-((6-((3R)-3-aminopiperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)methyl) benzonitrile. | 339.39 g/mol | Soluble in Methanol; Insoluble in Acetonitrile |
| Sitagliptin |  | (3R)-3-amino-1-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3- a]pyrazin-7(8H)-yl]-4-(2,4,5-trifluorophenyl)butan-1-one phos-phate hydrate | 407.314 g/mol | It is soluble in water and N,N-dimethyl formamide; slightly soluble in methanol; very slightly soluble in ethanol, acetone, and acetonitrile; and insoluble in isopropanol and isopropyl acetate |
| Vildagliptin |  | (2*S*)-1-{2-[(3-hydroxy-1-adamantyl)amino]acetyl}pyrrolidine-2-carbonitrile | 303.399 g/mol | Slightly soluble in DMSO, Methanol |
| Saxagliptin |  | (1S, 3S, 5S)-2-[(2S)-2-Amino-2-(3 hydroxytricyclo [3.3.1.13, 7] dec-1-yl) acetyl]- 2-azabicyclo [3.1.0] hexane-3-carbonitrile | 315.41 g/mol | It is sparingly soluble in water, slightly soluble in ethyl acetate, and soluble in methanol, ethanol, isopropyl alcohol, acetonitrile, acetone |

**Sitagliptin**

From all these gliptin derivatives in this present journal about sitagliptin is discussed briefly.

Sitagliptin phosphate monohydrate (SPM) chemically, (3R)-3-amino-1-[3-(trifluoromethyl)-5, 6-dihydro [1, 2, 4] triazole [4,3-a] pyrazin-7 (8H)-yl]-4-(2,4,5-trifluorophenyl) butan-1-one phosphate hydrate (Fig. 1) is oral hypoglycemic drug belongs to dipeptidyl peptidase4(DPP4) inhibitor class [7]. DPP-4 inhibitors represent a new therapeutic approach to the treatment of type 2 diabetes that functions to stimulate glucose-dependent insulin release and reduce glucagons levels by the inhibition of the inactivation process of incretins, particularly glucagon-like peptide- 1 (GLP-1) and gastric inhibitory polypeptide (GIP), thereby improving glycemic control. Sitagliptin was approved by the U.S.



(7-[(3R)-3-amino-1-oxo-4-(2, 4,5trifluorophenyl) butyl] 5,6,7,8 tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo [4,3-a] pyrazine phosphate)

**Fig I:** Chemical structure and IUPAC name of Sitagliptin

Food and Drug Administration (FDA) on October 17, 2006, its bioavailability 87%, protein binding 38%, metabolism via hepatic, biological half-life 8 to 14 h and root of excretion through renal. Several analytical methods based on UV, RP-HPLC, LC-MS/MS was reported for the pharmacokinetic determination of Sitagliptin phosphate in plasma and urine of humans, rats and dogs.

This review paper focuses the analytical procedure available for the estimation of sitagliptin i.e. electrochemical methods, UV/VIS- spectrophotometric methods, HPLC/LC-MS, GC-MS, CE/CE-MS. The details about the previous studies are discussed in Table no. II, III and IV.

**Table II:** Summery of methods related to HPLC technique

| S. No | Stationary Phase (Column) | Mobile Phase (with ratio) | pH | Wavelength | Flow rate | Reference |
|---|---|---|---|---|---|---|
| SITAGLIPTIN with METFORMIN | | | | | | |
| 1 | C18 (100 x 4.6 mm, 5 µm) | Mixture of Methanol: Acetonitrile: Phosphate buffer (20:35:45 %, v/v/v) | 8 | 254 nm | 1ml/min | 8 |
| 2 | CN (250 x 4.6 mm, 5 µm) | Mixture of OPA buffer: Acetonitrile (80:20 %, v/v) | --- | 205 nm | 1ml/min | 9 |
| 3 | ODS (250 x 4.6 mm, 5 µm) | Mixture of Ammonium di-hydrogen phosphate buffer: Acetonitrile (74:26 % v/v) | 4.3 | 246 nm | 1ml/min | 10 |
| 4 | C18 (250 x 4.6 mm, 5 µm) | Mixture of Water: Methanol (60:40 % v/v) | --- | 258 nm | 1ml/min | 11 |
| 5 | C18 (250 x 4.6 mm, 5 µm) | Mixture of Phosphate buffer: Methanol: Acetonitrile (50:30:20 %, v/v/v) | 4 | 253 nm | 0.8 ml/min | 12 |
| 6 | C18 (100 x 4.6 mm, 5 µm) | Mixture of Potassium dihydrogen orthophosphate buffer: Methanol (50:50 % v/v) | 8.5 | 215 nm | 1ml/min | 13 |
| 7 | C18 (250 x 4.6 mm, 5 µm) | Mixture of 0.02M Potassium dihydrogen phosphate buffer: Acetonitrile (60:40 % v/v) | 4 | 252 nm | 1ml/min | 14 |
| 8 | C18 (250 x 4.6 mm, 5 µm) | Mixture of Methanol: Phosphate buffer (60:40 % v/v) | --- | 258 nm | 1ml/min | 15 |
| 9 | C18 (250 x 4.6 mm, 5 µm) | Mixture of 0.01M dipotassium phosphate buffer: Acetonitrile (70:30 % v/v) | 7 | 223 nm | 1ml/min | 16 |
| 10 | C8 (250 x 4.6 mm, 5 µm) | Mixture of Methanol: Water (45:55 % v/v) | 3 | 267 nm | 1ml/min | 17 |
| SITAGLIPTIN with SIMVASTATIN | | | | | | |
| 11 | C8 (250 x 4.6 mm, 5 µm) | Mixture of Methanol: Water (70:30% v/v) | 3 | 253 nm | 1ml/min | 18 |
| 12 | C18 (250 x 4.6 mm, 5 µm) | Mixture of Water: Acetonitrile (30:70 % v/v) | 8 | 236 nm | 1ml/min | 19 |
| 13 | C18 (150 x 4.6 mm, 3.5 µm) | Mixture of phosphate buffer: Acetonitrile (30:70 % v/v) | 3.5 | 254 nm | 1ml/min | 20 |
| 14 | C18 (250 x 4.6 mm, 5 µm) | Mixture of Acetonitrile: Methanol: 10 mM Phosphate buffer (65:25:10 %, v/v/v) | 4 | 250 nm | 1.2 ml/min | 21 |
| 15 | C18 (250 x 4.6 mm, 5 µm) | Mixture of 10 mM Phosphate buffer: Acetonitrile: Methanol (45:35:20 % v/v) | 6.3 | 255 nm | 1ml/min | 22 |
| 16 | C8 (250 x 4.6 mm, 5 µm) | Mixture of Methanol: Water (25:75 % v/v) | 2.9 | 266 nm | 1ml/min | 23 |
| SITAGLIPTIN with GLICLAZIDE | | | | | | |
| 17 | C8 (250 x 4.6 mm, 5 µm) | Mixture of Water: Acetonitrile (40:60 % v/v) | --- | 253 nm | 1ml/min | 24 |
| SITAGLIPTIN AS SINGLE FORMULATION | | | | | | |
| 18 | C18 (250 x 4.6 mm, 5µm) | Methanol | --- | 248 nm | 1ml/min | 25 |
| 19 | C18 (150 x 4.6 mm, 5 µm) | Mixture of 0.01M Potassium dihydrogen orthophosphate buffer: Methanol (50:50 % v/v) | 2.5 | 267 nm | 0.7 ml/min | 26 |
| 20 | C18 (250 x 4.6 mm, 5 µm) | Mixture of Potassium dihydrogen phosphate buffer: Acetonitrile (35:65 % v/v) | 3 | 210 nm | 1ml/min | 27 |
| 21 | C18 (250 x 4.6 mm, 5µm) | Mixture of Acetonitrile: Water (60:40 % v/v) | --- | 272 nm | 1ml/min | 28 |

**Table III:** Summery of methods related to HPLC technique with plasma

| S. No | Stationary Phase (Column) | Mobile Phase (with ratio) | pH | Wavelength | Flow rate | Reference |
|---|---|---|---|---|---|---|
| Sitagliptin AS Single Formulation | | | | | | |
| 1 | C18 (150 x 4.6 mm, 5 µm) | Mixture of acetonitrile: methanol: buffer (2:3:5 % v/v/v) | 4 | 267 nm | 1ml/min | 29 |

**Table IV:** Summery of Analysis of Sitagliptin by UV-Spectroscopy methods.

| S. No | Drug | Method | Description | Reference |
|---|---|---|---|---|
| 1 | Estimation Sitagliptine Phosphate Monohydrate in Pure and Tablet Dosage Form | Spectroscopic Method | Detection wavelength: 267 nm in Methanol Linearity range: 20-60 µg/ml Co-relation Co-efficient: 0.991 % Recovery range: 99.62-100.48 % %RSD: ≤2% | 30 |
| 2 | Estimation Sitagliptine by derivative spectroscopy | UV- Spectroscopic Method First order and Second order derivatives | Detection wavelength: Zero order derivative λ max: 267 nm in Methanol First order derivative λ max: 213 nm in Methanol Second order derivative λ max: 276 nm in Methanol Linearity range: 20-60 µg/ml Co-relation Co-efficient: 0.991 % Recovery range: Near 100% %RSD: ≤2% | 31 |
| 3 | Estimation of Metformin amd Sitagliptin | UV- Spectroscopic Simultaneous equation Method | Detection wavelength: 266 nm for Sitagliptin & 232 nm for Metformin Linearity range: 20-80 µg/ml for Sitagliptin & 10-50 µg/ml for Metformin Co-relation Co-efficient: 0.9992 for Metformin & 0.9997 for Sitagliptin % Recovery range: 99.62-100.48 % %RSD: ≤2% | 32 |
| 4 | Estimation Sitagliptine Phosphate | Absorption Ratio and Area under curve Method | Detection wavelength: 267 nm in Methanol Linearity range: 20-160 µg/ml Co-relation Co-efficient: 0.991 % Recovery range: 99.62-100.48 % %RSD: ≤2% | 33 |

**Quality by Design**

For improving the analytical method presently Quality by Design technique is used widely. Quality by design (QBD) which is discussed in ICH Q8, [1] Q9 and Q2 is well established for the development and manufacture of pharmaceuticals [34].

**Benefits of Quality by Design Method**

It helps in the development of a robust method. As per design setup sources of variability can be better controlled. Method Transfer success is greater when a method is transferred from research level to quality control department. This technique gives a space for the invention of new techniques by continuous improvement throughout the lifecycle [35].

**Conclusion**

This review depicts the reported Spectrophotometric and Chromatographic methods; developed and validated for estimation of Sitagliptin. According to this review it was concluded that for Sitagliptin different Spectroscopic & Chromatographic methods are available for single component as well as for combination and also it was found that the mobile phase containing phosphate buffer, methanol and acetonitrile were common for most of the chromatographic method to provide more resolution. It was observed that most common combination of Sitagliptin was with Metformin (ex. JANUMET). For chromatographic method flow rate is observed in the range of 0.8-1.5 ml/min to get good retention time. For most of the Spectroscopic methods common solvent is Methanol. Hence this all methods found to be simple, accurate, economic, precise, and reproducible in nature. But from this review it was clear that available methods can be improved by using Design of Expert (DOE) technique, which will give more accurate and precise result.

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