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Review Article

Linagliptin: A Review on Bio-analytical and Analytical Methods

Kirtimaya Mishra*, Balamurugan K[1], Suresh R[1]

[1]*Department of Pharmacy, Annamalai University, Chidambaram, Tamilnadu-608002, India.*
[2]*Annamalai University, Chidambaram, Tamilnadu-608002, India*

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ABSTRACT
This is a collective data for Linagliptin from previously published methods either in alone or in combination with Metformin or Empagliflozine . Many spectroscopic methods like derivative techniques, chromogenic techniques were used for newly developed as well as improved chromatographic methods were reported for 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 of Linagliptin alone or in combination with Metformin or Empagliflozine.

Keywords: Linagliptin, Quality by design, Analytical method.

INTRODUCTION

Every day in human health a revolution found as pharmaceuticals developing. 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. Various methods are available to validate bulk drugs and pharmaceuticals such as, HPLC, GC, Titration, UV-Vis spectrophotometry, IR, NMR, Polarimetry, Fluorimetry, AAS, Polarography, Microbiological assay etc[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 polypharmacy is a most worthy therapy for many diabetic patients. So for improving the polypharmacy 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 incretin 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

Linagliptin

In this present review work linagliptin is discussed briefly from all these gliptin derivatives.

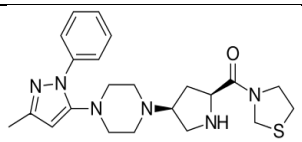
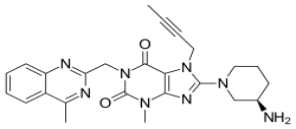
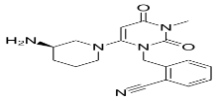
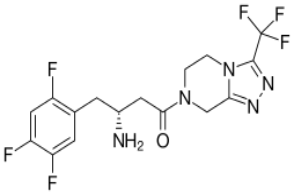
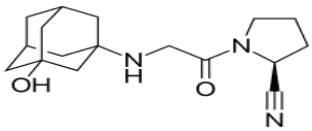
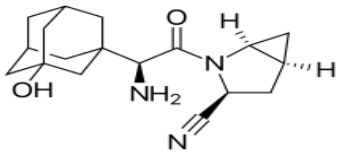
Linagliptin (LINA) is chemically known as 1HPurine-2,6-dione, 8-((3R)-3 aminopiperidin-1-yl)- 7-(2-butyn-1-yl)-3,7-dihydro-3-methyl-1-((4-methylquinazolin-2-yl) methyl) (Fig. 1) is oral hypoglycemic drug belongs to dipeptidyl peptidase4(DPP4) inhibitor class (7). DPP-4 inhibitors represent a new therapeutic 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. Linagliptin was approved by the U.S. Food and

*Author for Correspondence: kirtimishra.pharma@gmail.com

Drug Administration (FDA) on 2 May 2011 for treatment of type 2 diabetes

its bioavailability 30%, protein binding 75-99%, metabolism via hepatic, biological half-life 12 h and root

Table 1: 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

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, IV and V.

Quality by Design

Table 2: Summery of methods related to HPLC technique.

Sl.No	Stationary Phase (Column)	Mobile Phase (with ratio)	pH	Wavelength	Flow rate	Reference
		LINAGLIPTIN with METFORMIN				
1	C18 column (150×4.6mm, 5µm)	Mixture of Acetonitrile : 0.02M phosphate buffer (35:65% v/v)	5	225 nm	1ml/min	8
2	C18 column (250 × 4.6 mm, 5µm)	Mixture of Phosphate buffer : Methanol : Acetonitrile (40:5:55 % v/v/v)	5.6	233 nm	1ml/min	9
3	C18 column (250 × 4.6 mm, 5µm)	Mixture of Acetonitrile : 0.02M phosphate buffer (60:40% v/v)	4	250 nm	1ml/min	10
4	C18 column (150×4.6mm, 5µm)	Mixture of Phosphate buffer : Methanol : Acetonitrile (65:10:25 % v/v/v)	5.6	231 nm	1ml/min	11
5	C18 (125× 4.0 mm, 5 µm)	Mixture of Methanol : 0.05 M potassium dihydrogen orthophosphate (70:30% v/v)	4.6	267 nm	0.6 ml/min	12
6	C8 column (250 × 4.6 mm, 5µm)	Mixture of Acetonitrile : Water : Methanol (25:50:25% v/v/v)	4.1	243 nm	1ml/min	13
7	C18 column (250 × 4.6 mm, 5µm)	Mixture of Phosphate buffer : Acetonitrile (50:50% v/v)	6.5	248 nm	1ml/min	14
8	C18 column (150×4.6mm, 5µm)	Mixture of Phosphate buffer : Methanol : Acetonitrile (45:25:30 % v/v/v)	3	237 nm	0.8 ml/min	15
9	C18(125 × 4.0 mm, 5 µm)	Mixture of methanol : 0.05 M potassium dihydrogen orthophosphate (70:30% v/v)	4.6	267 nm	0.6 ml/min	16
		LINAGLIPTIN with EMPAGLIFLOZINE				
10	ODS column (250 x 4.6mm, 5µm)	Mixture of Phosphoric acid buffer : Acetonitrile (45:55% v/v)	---	245 nm	1ml/min	17
		LINAGLIPTIN AS SINGLE FORMULATION				
11	C8 (250 x 4.6 mm, 5µm)	Mixture of Phosphate buffer : Acetonitrile (35:65% v/v)	3	227 nm	1ml/min	18
12	C18 (250 x 4.6 mm, 5 µm)	Mixture of Methanol : Water (83:17 % v/v)	4.1	241 nm	1ml/min	19
13	C18 (150 x 4.6 mm, 5 µm)	Mixture of Phosphate buffer : Methanol (70:30 % v/v)	7.2	292 nm	1ml/min	20
14	C18 (150 x 4.6 mm, 5µm)	Mixture of Methanol : Water (40:60 % v/v)	4.5	225 nm	1ml/min	21
15	C18 (150 x 4.6 mm, 5µm)	Mixture of 0.02 M potassium dihydrogen phosphate : Acetonitrile (70:30% v/v)	5	226 nm	1.2 ml/min	22
16	C18 (100 x 2.5 mm, 3µm)	Mixture of Methanol : Water (70:30% v/v)	---	296 nm	0.8 ml/min	23
17	C18 (100x4.6 mm, 5 µm)	Mixture of Phosphate buffer : Methanol (50:50 % v/v)	3	238 nm	0.8 ml/min	24

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[33]. Most of the already reported methods have not used Quality by Design/Design of Expert except two one using Box-Behnken design[34] and another is Two-level factorial design for enantio-separation of Linagliptin[35].

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

Table 3: Summery of methods related to HPLC technique with plasma.

Sl.No	Stationary Phase (Column)	Mobile Phase (with ratio)	pH	Wavelength	Flow rate	Reference
		LINAGLIPTIN AND METFORMIN				
1	CN (150 × 4.6 mm, 4 µm)	Mixture of Acetonitrile : 0.01M di-potassium hydrogen phosphate buffer (75:25% v/v)	7	237 nm	1ml/min	25

Table 4: Summery of methods related to UPLC technique.

Sl.No	Stationary Phase (Column)	Mobile Phase (with ratio)	pH	Wavelength	Flow rate	Reference
		LINAGLIPTIN AS SINGLE FORMULATION				
1	SB-C18 (50 × 2.1 mm, 1.8 µm)	Mixture of Acetonitrile : 0.01M Potassium phosphate buffer (70:30% v/v)	4	292 nm	0.3 ml/min	26

Table 5: Summery of Analysis of Linagliptin by UV-Spectroscopy methods.

Sl.No	Drug	Method	Description	Reference
1	Assay of Linagliptine in Bulk and Marketed Dosage Form.	Spectroscopic Method	Detection wavelength: 294 nm in Methanol Linearity range: 5-30 µg/ml Co-relation Co-efficient: 0.999 % Recovery range: 99.43-100.01 % %RSD: ≤2%	27
2	Determination of Linagliptine in Bulk and Pharmaceutical Dosage Forms.	UV-Spectroscopic Method	Detection wavelength: 294 nm in Methanol Linearity range: 5-25 µg/ml Co-relation Co-efficient: 0.999 % Recovery range: 99.76-100.22 % %RSD: ≤2%	28
3	Estimation of Metformin and Linagliptin	Stability Indicating UV-Spectroscopic Method	Detection wavelength: 294.4 nm for Linagliptin & 230.4 nm for Metformin Linearity range: 10-40 µg/ml for Linagliptin & 2-14 µg/ml for Metformin Co-relation Co-efficient: 0.999 for Metformin & 0.999 for Linagliptin % Recovery range: 96.66-100.75 % %RSD: ≤2%	29
4	Estimation Linagliptine	UV-Spectroscopic Method	Detection wavelength: 241 nm in Methanol and Water (50;50) Linearity range: 10-35 µg/ml Co-relation Co-efficient: 0.999 % Recovery range: 99.60-100.65 % %RSD: ≤2%	30
5	Estimation of Empagliflozin and Linagliptin	UV-Spectroscopic Method	Detection wavelength: 277 nm for Linagliptin & 233 nm for Empagliflozin Linearity range: 2-6 µg/ml for Linagliptin & 5-15 µg/ml for Empagliflozin Co-relation Co-efficient: 0.999 for Empagliflozin & 0.999 for Linagliptin % Recovery range: 98-101 % %RSD: ≤2%	31

6	Estimation of Empagliflozin and Linagliptin	UV-Spectroscopic Method	Detection wavelength: 238 nm for Linagliptin & 221 nm for Empagliflozin Linearity range: 2.5-30 µg/ml for Linagliptin & 2.5-30 µg/ml for Empagliflozin Co-relation Co-efficient: 0.999 for Empagliflozin & 0.999 for Linagliptin % Recovery range: 99.8-100.3 % %RSD: ≤2%	32

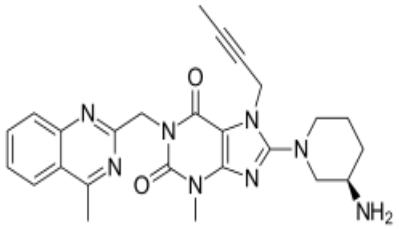


Figure 1: Chemical structure and IUPAC name of Linagliptin
1HPurine- 2,6-dione, 8-((3R)-3 aminopiperidin-1-yl)-7-(2-butyn-1-yl)-3,7-dihydro-3-methyl-1-((4-methylquinazolin-2-yl) methyl)

of new techniques by continuous improvement throughout the lifecycle[36].

CONCLUSION

This review depicts the reported Spectrophotometric and Chromatographic methods; developed and validated for estimation of Linagliptin alone or on combination with Metformin or Empagliflozine. According to this review it was concluded that for Linagliptin 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 Linagliptin was with Metformin (ex. JENTADUETO, TRAJENTA). For chromatographic method flow rate is observed in the range of 0.6-1.2 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. From this elaborate literature review it was found that, till date there is no RP-HPLC method available for the determination of Linagliptin with Metformin or Empagliflozine using Design of Expert or Quality by Design.

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