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ALOGLIPTIN: A REVIEW OF ANALYTICAL METHODS

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ABSTRACT
Dipeptidyl peptidase-4 (DPP-4) inhibitors, a new class of oral hypoglycemic agents, augment glucose-dependent insulin secretion and suppress glucagon levels through enhancement of the action of endogenous incretin by inhibiting DPP-4, an incretin-degrading enzyme. DPP-4 inhibitors are generally well tolerated because of their low risk of hypoglycemia and other adverse events. Moreover, with their potential to improve beta cell function, a core defect of type 2 diabetes, DPP-4 inhibitors are becoming a major component of treatment of type 2 diabetes. Alogliptin benzoate is a newly developed, highly selective DPP-4 inhibitor which has been approved in many countries throughout the world. This article examines published analytical methods reported so far in the literature for the determination of alogliptin in biological samples and pharmaceutical formulations. They include various techniques like electrochemical methods, spectrophotometry, capillary electrophoresis, high-performance liquid chromatography, liquid chromatography–electrospray ionization-tandem mass spectrometry and high-performance thin layer chromatography

KEYWORDS: Alogliptin, DPP-4 inhibitors, Gliptins, Analytical methods, HPLC.

INTRODUCTION

Alogliptin is an anti-diabetic drug which belong to the DPP-4 inhibitor class with a molecular formula of C18H21N5O2 and IUPAC name 2-({6-[(3R)-3-aminopiperidin-1-yl] -3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)- yl}methyl) benzonitrile .It is orally administered.[1] The major role of the drug is as an EC 3.4.14.5 (dipeptidyl-peptidase IV) inhibitor and a hypoglycemic agent.For the treatment of type 2 diabetes,it is used in the form of its benzoate salt.It is a nitrile, a member of piperidines, a member of pyrimidines and a primary amino compound.[2]

Dipeptidyl peptidase-4 (DPP-4) inhibitors, a new class of oral hypoglycemic agents, by inhibiting DPP-4, a degrading enzyme of incretin elevate glucose-dependent insulin secretion through enhancement of the action of endogenous incretin (ie, glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide).[3] DPP-4 inhibitors metabolize the insulin-increasing hormones glucagon-like peptide-1 (GLP-1) and glucosedependent insulinotropic peptide (GIP). By maintaining the blood levels of GLP-1 and GIP, secretion of glucagon is inhibited and the release of insulin from the pancreas is stimulated[4] Recently, DPP-4 inhibitors have been recommended in the treatment of diabetes mellitus to improve glycemic control and it is effective in controlling the metabolic syndrome and resulted in significant weight loss, a reversal of insulin resistance, islet and adipocyte hypertrophy, and alleviated hepatic steatosis.[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.

Chemically, alogliptin is prepared as a benzoate salt and exists predominantly as the R-enantiomer (>99%). It undergoes little or no chiral conversion in vivo to the (S)-enantiomer.[7] Physically ,the salt form is a white to off-white crystalline powder with a molecular weight I of 339.391 g/mol. It is administered orally soluble in dimethylsulfoxide; sparingly soluble in water, methanol; slightly soluble in ethanol; very slightly soluble in octanol, isopropyl acetate.[8] In the present review we have compiled the published analytical methods reported so far in the literature for determination of PIO in biological samples and pharma- ceutical formulations. Techniques like potentiometry, spectrophotome- try, capillary electrophoresis (CE), high-performance liquid chromatography (HPLC), liquid chromatography–mass spectrometry (LC–MS) and high-performance thin layer chromatography (HPTLC) have been used for analysis, from which HPLC methods are used most extensively.

This review paper focuses the analytical procedure available for the estimation of alogliptin i.e.

electrochemical methods, UV/VIS- spectrophotometric methods, HPLC/LC-MS, GC-MS, CE/CE-MS.

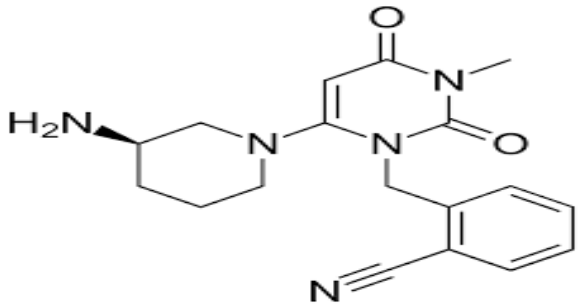

Fig. 1: Structure of Alogliptin.

Sample Preparation

Solubility

Alogliptin is considered Biopharmaceutics Classification System (BCS) Class I (high solubility, high permeability)[9]

Sample preparation strategies

Sample preparation is an integral part of analytical methodology, and it was reported that about approximately 30% error generated in sample analysis was due to sample preparation.[10] The sample preparation techniques for the extraction of ALO from biological matrices (plasma, serum and urine) include protein precipitation with acetonitrile, liquid–liquid extraction using diethyl ether, dichloromethane, ethyl acetate, methyl t-butyl ether and n-butyl ether; hollow fiber liquid phase micro-extraction using di n-hexyl ether; and solid phase extraction.

Analytical methods

Electrochemical Methods

Al-Bratty M et al[11] As conductometric analysis has been considered to be relatively inexpensive analytical technique offering fast analysis of drugs, in this study our aim was to develop a rapid and cost-effective method for quantitative determination of sitagliptin, linagliptin, vildagliptin and alogliptin in bulk and dosage forms. The test drugs were allowed to complex with metal ion (Cu2+) in the titration cell, which resulted in the change of conductance of the solution. The corrected conductance was calculated and graph was plotted between corrected conductance and the volume of the analyte solution added. The point of maximum change in the corrected conductance was considered as end point of the titration. The method was found to be linear in the concentration range of 1.0 – 1.4 mM for all analytes with good correlation coefficient (R2 > 0.999). The %RSD of the corrected conductance values were in the range of 0.046-1.837, while the recovery of analytes were within 100 ± 2%, indicating that the method was precise and accurate.

Table 1: Summary of methods related to HPLC technique.

S. No	Stationary Phase (Column)	Mobile Phase (with ratio)	pH	Wavelength	Flow rate	Reference
ALOGLIPTIN with METFORMIN						
1	C18 (100 x 4.6 mm, 5 µm)	Mixture of Acetonitrile: Phosphate buffer (62:38 %, v/v)	3.4	275 nm	1ml/min	[12]
2	C18 (100 x 4.6 mm, 5 µm)	Mixture of OPA buffer: Methanol (30:70 %, v/v)	6	254 nm	1ml/min	[13]
3	C18 (100 x 4.6 mm, 5 µm)	Mixture of Acetonitrile: Phosphate buffer (65:35 % v/v)	3.6	235 nm	1ml/min	[14]
4	C18 (100 x 4.6 mm, 5 µm)	Mixture of Buffer: Methanol: Acetonitrile (20:60:20%v/v/v)	3	290 nm	1ml/min	[15]
5	C18 (100 x 4.6 mm, 5 µm)	Mixture of Phosphate buffer : Acetonitrile (48:52 % v/v)	4.8	210 nm	1ml/min	[16]
6	C18 (150 x 4.6 mm, 5 µm)	Mixture of OPA buffer: Methanol (20:80 %, v/v)	3	242 nm	0.7 ml/min	[17]
7	C18 (250 x 4.6 mm, 5 µm)	Mixture of OPA buffer: Methanol (30:70 %, v/v)	3	242 nm	0.7 ml/min	[18]
ALOGLIPTIN with PIOGLITAZONE						
8	C18 (150 x 4.6 mm, 5 µm)	Mixture of Acetonitrile: Methanol: Water: (30:22:48 % v/v)	3	268 nm	1ml/min	[19]
9	C8 (150 x 4.6 mm, 5 µm)	Mixture of 0.1 M ammonium acetate and methanol (50:50, v/v)	---	248 nm	1ml/min	[20]
10	C18 (150 x 4.6 mm, 5 µm)	Mixture of Phosphate buffer: Acetonitrile (20:80 % v/v)	4	278 nm	1ml/min	[21]
11	C18 (2.1× 50 mm, 1.7 µ)	Mixture of Phosphate buffer : Methanol (45:55% /v/v)	3	280 nm	0.3 ml/min	[22]
ALOGLIPTIN with GLIBENCLAMIDE						
12	C8 (250 x 4.6 mm, 5 µm)	Mixture of Acetonitrile: Phosphate buffer (65:35 % v/v)	3.6	240 nm	1ml/min	[23]
ALOGLIPTIN AS SINGLE FORMULATION						
13	C18 (250 x 4.6 mm, 5µm)	Mixture of Acetonitrile : Ammonium carbonate buffer (55:45% v/v)	---	277 nm	1ml/min	[24]
14	C18 (250 x 4.6 mm, 5 µm)	Mixture of Water :Methanol (75:25 % v/v)	---	225 nm	1ml/min	[25]
15	C18 (250 x 4.6 mm, 5µm)	Mixture of Methanol: Double distilled water (80:20 % v/v)	---	222 nm	1ml/min	[26]

Table 1: Summary of methods related to UV techniques.

Table 1 Representative spectrophotometric methods for the analysis of ALO.					
Compounds	**Method**	**λmax**	**Solvent/procedure**	**LOD (µg/mL)**	**Ref.**
PIO, ALO	Second order derivative	267, 278	Methanol	0.009	[27]
ALO	First order derivative	278	0.1 M HCl	–	[28]
ALO, MET	Multi-wavelength spectroscopy	274,284	Methanol	3.96,0.96	[29]
ALO, MET	Absorption ratio	277,242	Methanol	1.2	[30]
	Method				
ALO	–	276	Methanol	0.8,2.6	[31]
ALO, MET	Vierodt's Method	277,232	Methanol	0.014, 0.043	[32]
	Second order derivative	277.232		0.229, 0.699	
ALO, MET	Vierodt's method	277,232	Methanol	–	[33]
	Absorption ratio method	250,277		0.05	
	Absorption correction	267		3	
Method					

LCMS

LC/MS/MS method was developed by Mowaka et al.[34] for simultaneous estimation of alogliptin (AG) and metformin (MF) in plasma using sitagliptin (SG) as an internal standard (IS). Samples were extracted by using gradient elution of acetonitrile and 0.2% formic acid solution. Selected reaction monitoring (SRM), with transitions of 340.33 → 116.32 (*m/z*), 130.12 → 71.32 (*m/z*) and 408.12 → 235.24 (*m/z*), was used to quantify AG, MF and SG (IS), respectively on a triple quadropole mass spectrometer in positive ion mode. Enhanced sample preparation involved direct precipitation and an evaporation technique.

Another LC/MS/MS study was reported by Abdel-Ghany et al.[35] where a new fast LC–MS/MS method was developed for determination of alogliptin and pioglitazone in human plasma. Linearity ranges of 10–400 ng mL^{-1} for alogliptin and 25–2000 ng mL^{-1} for pioglitazone, were found to be suitable for their bioanalysis covering the C_{min} and C_{max} values of the drugs. Direct precipitation technique was used for simultaneous extraction of the drugs successfully from human plasma samples. Chromatographic separation was achieved on a BEH C_{18} column (50 mm × 2.1 mm, 1.7 µm) with 0.1% aqueous formic acid: acetonitrile (40:60, *v/v*) at a flow rate of 0.3 mL min^{-1}.

HPTLC

Shah et al.[36] reported a method in which ALO and PIO using the mobile phase selected was n-butanol : water : acetic acid (6 : 3 :1 v/v/v). The separated spots were densitometrically analyzed at 270 nm. The Rf value of PIO and ALO were found to be 0.70 and 0.39, respectively. The calibration curve of PIO and ALO were plotted in the range of 400 – 1600 ng/band. Sharma et al.[37] proposed a simple HPTLC method for simultaneous estimation of ALO and PIO using mobile phase consisting Acetonitrile : 1% ammonium acetate in Methanol (4.5:5.5 v/v). Densitometric quantification was performed at 254 nm. The Rf value of ALO and PIO was found to be 0.43 and 0.88 respectively and the method was linear in the range of 500- 3000ng/spot. Deshpande et al [38] gave a HPTLC method in which ALO was estimated using the mobile phase Benzene: Ethyl acetate: Triethylamine (7.5: 2: 0.5, v/v/v). The retention factor for Alogliptin Benzoate was found to be 0.62 ± 0.10 .Linearity was found to be in the concentration range of 250-1500 ng band.

CONCLUSION

This review delineates the reported Spectrophotometric and Chromatographic methods which are developed and estimated for the drug Alogliptin. In conclusion, a broad range of techniques are available for the analysis of ALO in biological samples and pharmaceutical formulations. According to the review it can be concluded that different methods of estimation for both single component as well as in combination are available.The analysis of the published data revealed that the HPLC was extensively used for the determination of ALO where methanol,acetonitrile and buffer solutions were used as the major solvents in the review of data.Drugs like Metformin, Pioglitazone and Glibenclamide were used incombination for many estimations. This review carried out an overview of the current state-of analytical methods for the determination of ALO.

Abbreviation

DPP4- Dipeptidyl peptidase, BCS-Biopharmaceutics Classification System.

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