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Review Article

Analytical Techniques for the Assay of Gliptins - A Review

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Abstract

Gliptins are dipeptidyl peptidase-4 inhibitors. FDA had given approval for gliptin class of drugs which include Alogliptin, Linagliptin, Sitagliptin and Saxagliptin. Alogliptin acts by inhibiting the dipeptidyl peptidase 4 (DPP-4) which normally degrades the incretins glucose-dependent insulinotropic polypeptide and glucagon like peptide 1 which increases the amount of active plasma incretins which helps with glycemic control by stimulating the glucose dependent secretion of insulin in pancreatic beta cells. Linagliptin acts as a competitive, reversible DPP-4 inhibitor by stimulating the release of insulin from beta cells in the pancreas while inhibiting the release of glucagon from pancreatic beta cells. These effects together reduce the breakdown of glycogen in the liver and increase insulin release in response to glucose. Saxagliptin is an anti-diabetic used for the treatment of type 2 diabetes. It forms a reversible, histidine-assisted covalent bond between its nitrile group and the S630 hydroxyl oxygen on DPP-4. The inhibition of DPP-4 increases levels active of glucagon like peptide 1 which inhibits glucagon production from pancreatic alpha cells and increases production of insulin from pancreatic beta cells. Sitagliptin slows DPP-4 mediated inactivation of incretins which are released throughout the day and upregulated in response to meals as part of glucose homeostasis. Reduced inhibition of incretins increases insulin synthesis and decrease glucagon release in a manner dependant on glucose concentrations which leads to an overall increase in blood glucose control. A brief review of various analytical methods so far developed for the estimation of Gliptins was summarized in the present study.

Keywords: DPP-4; FDA; Gliptins

Introduction

Dipeptidyl peptidase-4 inhibitors are called Gliptins [1]. DPP-4 inhibitors are a class of compounds that act by affecting the action of natural hormones in the body called Incretins. Incretins decrease the blood sugar by increasing consumption of sugar by the body and especially by increasing the insulin production in the pancreas and there by reduce the production of sugar by the liver. DPP-4 is a membrane associated peptidase which is found in lymphocytes, many tissues and plasma. DPP-4 has two main mechanisms of action in which one mechanism is an enzymatic function and, in another mechanism, DPP-4 binds to adenosine deaminase, which conveys intracellular signals via dimerization when activated.

Alogliptin (CAS: 850649-61-5) is chemically 2-({6-[(3R)-3-Aminopiperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl} methyl) benzonitrile with molecular formula, $C_{18}H_{21}N_5O_2$ and molecular weight 339.39 g/mole. Linagliptin (CAS: 668270-12-0) is chemically 8-[(3R)-3-Amino piperidin-1-yl]-7-(but-2-yn-1-yl)-3-methyl-1-[(4-methyl quinazolin-2-yl) methyl]-3,7-dihydro-1H-purine-2,6-dione with molecular formula, $C_{25}H_{28}N_8O_2$ and molecular weight 472.54 g/mole. Sitagliptin (CAS: 486460-32-6) is chemically 7-[(3R)-3- amino-1-oxo-4-(2,4,5-trifluorophenyl) butyl]-5,6,7,8-tetrahydro-[3-(trifluoromethyl)-1,2,4-triazolo[4,3-a] pyrazine phosphate (1:1) monohydrate with molecular formula, $C_{16}H_{15}F_6N_5O$ and molecular weight 407.31 g/mole.

Saxagliptin (CAS: 361442-04-8) is chemically (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxy-1-adamantyl) acetyl]-2-azabicyclo [3.1.0] hexane-3-carbonitrile. The chemical structures of FDA approved gliptin class were shown in Figure 1.

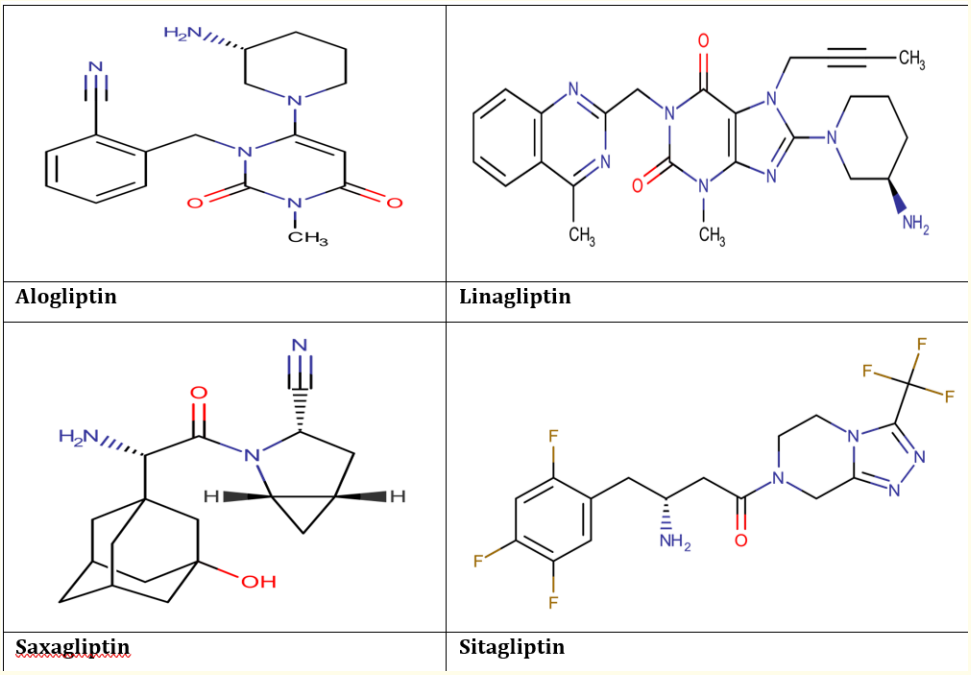

Figure 1: Chemical structures of A) Alogliptin B) Linagliptin C) Saxagliptin D) Sitagliptin.

Various analytical techniques such as spectrophotometry, liquid chromatography and LC-MS techniques have been developed for the Gliptin class of drugs such as Alogliptin, Linagliptin, Sitagliptin and Saxagliptin. Table 1 describes the various parameters employed for the liquid chromatographic methods [2-21] and the spectrophotometric methods [22-36] so far developed for the estimation of Gliptin class of drugs were summarized in Table 1. Table 3 describes the LC-MS methods [37-41] performed by various authors for the determination of Gliptin class of drugs.

Table 1: Liquid chromatographic methods.

Mobile phase (v/v)	λ(nm)	Column	Linearity (µg/ml)	Ref
Solution A: Water: Acetonitrile: Trifluoracetic acid (1900:100:1) Solution B: Acetonitrile: Water: Trifluoracetic acid (1900:100:1) (Gradient mode)	278	Agilent Zobax SB-CN	0.05-1.0	[2]
Acetonitrile: Ammonium carbonate buffer (55: 45)	277	Hypersil Gold Thermo Scientific C18	85-306	[3]
Acetonitrile: Water (40:60)	277	Agilent, TC C18	5-50	[4]
Phosphate Buffer: Acetonitrile (60:40)	237	Phenomenex Luna C18	10–50	[5]
Acetonitrile:1-octasulphonoic acid [0.005mM] (60:40)	220	Phenomenex Gemini-NX, LC Column	2-10	[6]
Water and Acetonitrile (70:30)	252	Intertsil Extend C18	1-25	[7]
Methanol: Formic acid 0.1% (75:25)	254	Zorbax Eclispe XDB C18	0.005-1.0	[8]
OPA: Methanol (30:70)	238	C18	10-50	[9]

Methanol: 0.2% Orthophosphoric acid (50:50)	227	Luna C18	2-12	[10]
Phosphate buffer: Acetonitrile (70:30)	239	C18	40-60	[11]
Methanol: 0.3% TEA aq(40:60)	225	C18	1-50	[12]
Methanol: Water (70:30)	212	Cosmosil C18	10-50	[13]
Methanol: Water (80:20)	212	Grace C18	10-50	[14]
Phosphate buffer: Acetonitrile (80:20)	210	C18	100-300	[15]
0.01M KH_2PO_4: Methanol (50:50)	267	Zorbax Eclipse XDB C18	5-30	[16]
0.01M Phosphate: Acetonitrile (73:27)	267 and 310	C18	0.1-3	[17]
Methanol: 0.1% Perchloric acid solution (32:68)	268	Symmetry C_{18}	0.5-500	[18]
Methanol: Water: Triethylamine: Acetic acid (60:40:0.1:0.1)	268	Poroshell 120 EC-C18, Pursuit 5PFP, Chromolith	100-1000	[19]
(0.05M) Phosphate Buffer: Acetonitrile (30:70)	255	Develosil ODS HG-5 RP C18	30-70	[20]
Potassium dihydrogen phosphate solution: acetonitrile (70:30)	267	Enable C18	1-150	[21]

Table 2: Spectrophotometric methods.

Reagent	Linearity (µg/ml)	λ_{max} (nm)	Ref
Method A: Bromine Method B: methylene blue	1–10 2.5–12.5	505 720	[22]
Methanol	1-50	243	[23]
Distilled water	1-10	295	[24]
Acetonitrile	1-10	296	[25]
Methanol	5-40	228	[26]
Method A: 3-methyl-2-benzothiazoline hydrazineMethod B: picric acid	2–12 1–25	660 490	[27]
Methanol: water (1:1)	0-40	211	[28]
Interference with no excipients and solvents	5-25	578	[29]
Methanol: Water (15:85)	2-10	204	[30]
Water	2-10	267	[31]
Methanol	35-85	272.5	[32]
Phosphate buffer, Acetate buffer 0.1N NaOH and Borate buffer	5-100	267	[33]
0.1N HCl	20-100	267	[34]
Acetyl acetone and Formaldehyde	5-25	430	[35]
2, 4 DNP, 0.1N Sulphuric acid and Methanol	2-10	400	[36]

Table 3: LC-MS methods.

Drug	Mobile Phase (v/v)	Linearity (ng/ml)	Ref
Alogliptin	(30: 70) 0.1% Formic acids: Organic Mixture (Acetonitrile: Methanol 80:20)	4-600	[37]
Linagliptin	Acetonitrile: 0.1% Formic acid (90:10)	10-5000	[38]
	10m M Ammonium formate buffer: Methanol (15:85)	0.0995- 1.0045	[39]
Saxagliptin	0.1% Acetic acid in 5 mM Ammonium acetate: Acetonitrile (30:70)	0.05-100	[40]
	Potassium dihydrogen phosphate buffer (pH 4.6): acetonitrile: Methanol (40: 30: 30)	25-400	[41]

Conclusion

The present study represents a detailed review of the analytical methods so far developed for the Gliptin class of drugs such as Alogliptin, Linagliptin, Sitagliptin and Saxagliptin in pharmaceutical formulations as well as biological fluids.

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