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Review Article

Gliptin combinations: A Review on analytical methods

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Abstract

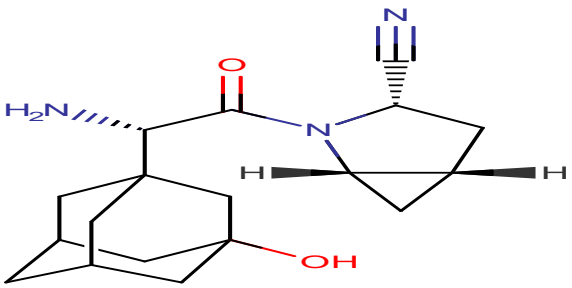
Diabetes mellitus is a metabolic disorder that causes high blood sugar levels. Several classes of drugs are used for the treatment. Gliptins inhibit the dipeptidyl peptidase 4 enzyme that prolongs the secretion of insulin in the pancreas and also improve the insulin secretion in response to increased blood glucose which may lead to improved glucose tolerance. Gliptins is an important class of drugs used for the treatment of diabetes in which many drugs such as Alogliptin, Linagliptin, Teneligliptin, Saxagliptin and Sitagliptin are incorporated by which the blood glucose can be controlled. In the present study the authors have summarized the analytical methods so far developed with the combination of Gliptins for the treatment of diabetes.

Keywords: Diabetes mellitus, Gliptins combinations, Analytical methods

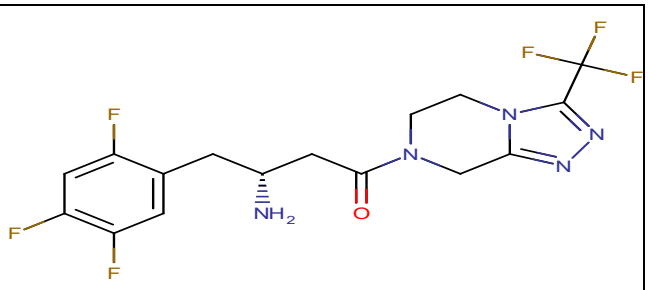
Introduction

Gliptin derivatives are used in the treatment of diabetes and the combination of Gliptins derivatives with other diabetic drugs are also useful in the treatment of diabetes[1]. Analytical methods such as spectrophotometry, HPLC and LC-MS methods are developed for the combination of Gliptin derivatives with other drugs. Some of the structures of Gliptins were shown in Figure 1.

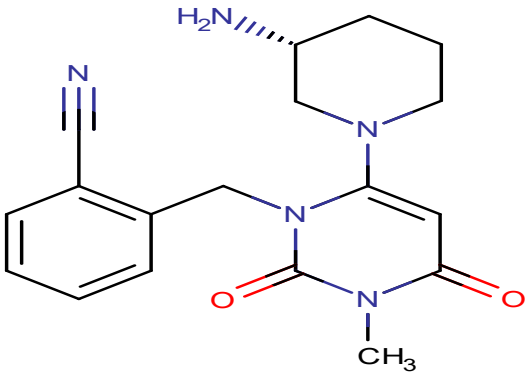
The liquid chromatographic methods so far developed for the combination of Alogliptin with Glibenclamide[2], Pioglitazone[3-5] and Metformin hydrochloride[6-10]; Linagliptin with Metformin HCl[11-16], Dapagliflozin[17], Empagliflozin[18-20] and with Metformin HCl as well as Empagliflozin together[21]; Saxagliptin with Dapagliflozin[22-29], Sitagliptin[30], Metformin HCl[31-33]; Sitagliptin with Metformin[34-37], Simvastatin[38-40] and Etruglifloxin[41-42] were summarized in Table 1.



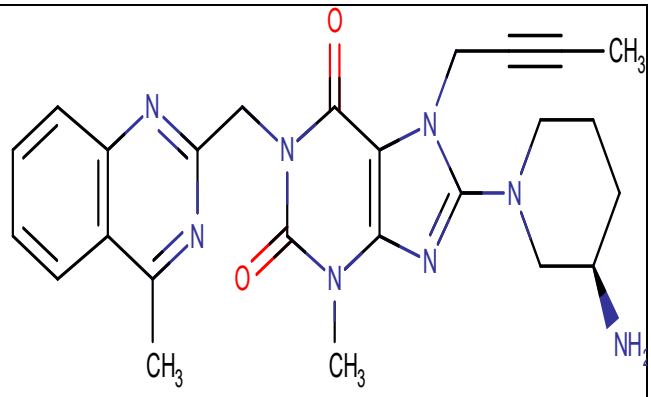
Saxagliptin (SX): (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxy-1-adamantyl) acetyl]-2-azabicyclo [3.1.0] hexane-3-carbonitrile



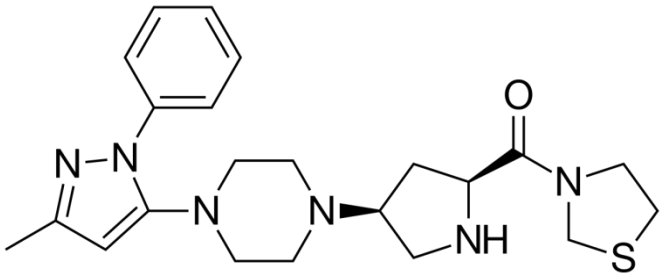
Sitagliptin (ST): 7-[(3R)-3- amino-1-oxo-4-(2,4,5-trifluorophenyl) butyl]-5,6,7,8-tetrahydro-[3-(trifluoromethyl)-1,2,4- triazolo[4,3-a] pyrazine phosphate (1:1) monohydrate



Alogliptin (AL): 2-({6-[(3R)-3-Aminopiperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl} methyl) benzonitrile



Linagliptin (LN): 8-[(3R)-3-Aminopiperidin-1-yl]-7-(but-2-yn-1-yl)-3-methyl-1-[(4-methylquinazolin-2-yl) methyl]-3,7-dihydro-1H-purine-2,6-dione



Teneligliptin: ((2S,4S)-4-(4-(3-Methyl-1-phenyl-1H-pyrazol-5-yl) piperazin-1-yl)pyrrolidin-2-yl)(thiazolidin-3-yl) methanone.

Figure 1: Chemical structures of Gliptins

Table 1: Liquid chromatographic methods

Combination	Mobile phase (v/v)	λ (nm)	Column	Linearity (µg/ml)	Ref
Alogliptin + Glibenclamide	Acetonitrile: Phosphate buffer (65:35)	240	Waters Xbridge C18	1-5 (AL) 10-50	2
Alogliptin + Pioglitazone	0.1 M Ammonium acetate: methanol (50:50)	248	Zorbax C8	6.25-18.75 (AL) 11.25-33.75	3
	Phosphate buffer: Methanol (45:55)	280	BEH C18	6.25-37.5 (AL) 15-90	4
	Acetonitrile: Methanol: Water (30:22:48)	268	Phenomenex C 18	10-50 (AL) 12-60	5
Alogliptin + Metformin hydrochloride	Buffer: Methanol (30:70)	254	Agilent C18	25-150	6
	Sodium dihydrogen ortho phosphate: Acetonitrile (70:30)	235	X-Terra C18	7.5- 17.5 (AL) 300-700	7
	Acetonitrile: Ammonium Phosphate buffer (70:30)	214	Water C18	6.25-18.75 (AL) 250-750	8
	Methanol: 10 mM Potassium dihydrogen phosphate (30:70)	224	Cosmosil C18	4.25-21.25 (AL) 125-625	9
	Potassium dihydrogen: Acetonitrile (80:20)	235	SPOLAR C_{18}	5-25 (AL) 50-250	10

Linagliptin + Metformin	Methanol: 0.05 M Potassium dihydrogen orthophosphate (70:30)	267	C18	2-12 (LN) 400-2400	11
	Acetonitrile: 0.02M Phosphate buffer (35:65)	225	Water's X-Bridge C18	1.25-12.5 (LN) 250-2500	12
	Acetonitrile: Water: Methanol (25:50:25)	243	C8	5-30 (LN) 10-100	13
	Di-ammonium hydrogen phosphate buffer: Acetonitrile: Methanol (60:20:20)	272	C18	1.25-10 (LN) 250-2000	14
	Methanol: Water (0.05% O-phosphoric acid) (50:50)	238	C8 Primesile	1-5 (LN) 200-1000	15
	Methanol: 0.05 M Potassium dihydrogen orthophosphate (70:30)	267	LiChrosphere 100 RP 18e	1-6 (LN) 200-1200	16
Linagliptin + Dapagliflozin	Mobile Phase A: Phosphate Buffer: Acetonitrile (900:100) Mobile Phase B: Phosphate Buffer: Acetonitrile (300:700)	230	X-Bridge C18	6-28 (LN) 12-74	17
Linagliptin + Empagliflozin	Methanol: water (60:40)	270	Waters acquity C18	25-75 (LN) 50-150	18
	0.1% Perchloric acid: Acetonitrile (60:40)	230	C18	12.5-75 (Both drugs)	19
	Potassium dihydrogen: Methanol (70:30)	240	THERMO® C18	50-150 (Both drugs)	20
Linagliptin + Metformin + Empagliflozin	Methanol: 0.1 % OPA Water (30:70)	224	C18 (COSMOSIL)	0.4-2 (LN) 2-10 (Empagliflozin) 80-400 (Metformin)	21
Saxagliptin + Dapagliflozin	Acetonitrile: Water (60:40)	248	Xterra RP18	50-250 (SX) 100-500	22
	0.1% Ortho phosphoric acid: Acetonitrile (50:50)	254	Eclipse XDB C18	0.01-0.5 (SX) 0.05- 2	23
	Buffer: Acetonitrile (53: 47)	230	Xterra C-18	2-14 (Both drugs)	24
	Buffer: Acetonitrile (70:30)	221	Symmetry C8	12.5-62.5 (SX) 25-125	25
	Methanol: Potassium dihyrogen (45:55)	210	Inertsil-ODS, C18	20-70 (Both drugs)	26
	Methanol: 20 mM Phosphate buffer (70:30)	225	Phenomenex Hyperclone C18	2-12 (SX) 4-24	27
	Phosphate buffer: Acetonitrile (50:50)	225	XTerra C18	20-60 (SX) 10-120	28
	Potassium dihydrogren phosphate Buffer: Acetonitrile (45:55)	247	C18	5-30 (SX) 10-60	29
Saxagliptin + Sitagliptin	Methanol: Water (70:30)	212 255	Cosmosil C18 Develosil ODS	10-50 (SX) 30-70 (ST)	30

Saxagliptin + Metformin HCl	Potassium dihydrogen orthophosphate buffer: Acetonitrile (85:15)	220	BEH C18	10-60 (SX) 100-600	31
	0.1M KH_2PO_4 buffer: Methanol (65:35)	256	C18	50-150 (Both drugs)	32
	50mM Sodium dihydrogen phosphate buffer: Methanol (80:20)	242	Kromasil- C18	0.5-3.0 (SX) 50-300	33
Sitagliptin + Metformin	Acetonitrile: Phosphate (40:60)	257	C8	1-8 (ST) 10-80	34
	Methanol: Water (45:55)	267	C8	10-150 (ST) 50-450	35
	Water: Methanol (60:40)	258	Intersil-BDS C_{18}	20-80 (Both drugs)	36
	OPA buffer: Acetonitrile (80:20)	205	AGILENT CN	3-75 (ST) 25-750	37
Sitagliptin + Simvastatin	Acetonitrile: 10mM Potassium dihydrogen orthophosphate (85:15)	225	Cosmosil C18	20-100 (ST) 0.4-20.0	38
	Methanol: Water (70:30)	253	C_8 (Qualisil BDS)	20-150 (ST) 8-60	39
	Acetonitrile: methanol:10 mM Phosphate buffer (65:25:10)	250	Hi-Q Sil C18	100-600 (ST) 20-120	40
Sitagliptin + Etruglifloxin	Phosphate buffer: Acetonitrile (45:55)	260	Discovery C18	25-150 (ST) 3.75-22.5	41
	OPA 0.2: Acetonitrile (60:40)	250	Waters RP-C18	216.50-649.50 (ST) 32.50-97.50	42

The spectrophotometric methods developed for the combination of Alogliptin with Pioglitazone hydrochloride[43] and Metformin hydrochloride[44-45]; Linagliptin with Metformin HCl[46-48], Empagliflozin[49-50]; Saxagliptin with Dapagliflozin[51-53]; Sitagliptin with Metformin[54], Simvastatin[55] were summarized in Table 2.

Table 2: Spectrophotometric methods

Drug	Reagent	Linearity (µg/ml)	λ_{max} (nm)	Ref
Alogliptin benzoate + Pioglitazone hydrochloride	Methanol Method A: Ratio difference spectroscopic method Method B: First derivative of ratio spectra method Method C: Area under curve method	0.5-5 (AL) 1.8-18	288-291 (AL) 236 -245 290 (AL) 276.8 276 ± 10 (AL) 267.8 ± 10	43
Alogliptin+ Metformin hydrochloride	Methanol	5–25 (AL) 4–20	231(AL) 276	44
	Methanol Method A: Simultaneous equation method Method B: Absorption ratio method	0.5-2.5 5-25	277 (AL) 232 (Both methods)	45
Linagliptin+ Metformin	Distilled water	10-40 (LN) 2-14	294.4 (LN) 230.4	46

	Inference with no excipients and diluents	1-11 (LN) 3-13	227 (LN) 232	47
	Methanol: water (40:60)	3-11 (Both drugs)	295 (LN) 234	48
Linagliptin+ Empagliflozin	Inference with no excipients and diluents	5-80 (Both drugs)	293 (LN) 276	49
	2M Ammonium acetate: 2M Sodium citrate (50:50)	5-25 (LN) 10-50	294 (LN) 270	50
Saxagliptin+ Dapagliflozin	10ml Methanol	2-10 (SX) 4-20	224 (SX) 274	51
	Phosphate buffer	5-25 (Both drugs)	222 (SX) 276	52
	Method 1: Water Method 2: Phosphate buffer	1-10 (Both drugs)	222 (SX) 274	53
Sitagliptin+ Metformin	Distilled water Method A: Absorption Maxima Method Method B: Area under Curve Method	25-225 (ST) 2-12	266 (ST) 232 244-279 (ST) 222-240	54
Sitagliptin+ Simvastatin	Methanol: Water (90:10)	10-50 (ST) 5-25	267 (ST) 238	55

The Liquid chromatography-mass spectrophotometric methods so far developed for the combination of Alogliptin with Voglibose[56] and Metformin hydrochloride[57]; Linagliptin with Metformin HCl[58] and Empagliflozin[59-60]; Saxagliptin with Dapagliflozin[61-63] were summarized in Table 3.

Table 3: Liquid chromatography-Mass spectrophotometric methods

Drug	Mobile Phase (v/v)	Linearity (ng/ml)	Ref
Alogliptin+ Voglibose	5mM Ammonium formate: Acetonitrile (50:50)	5.09-509 (AL) 2.03-203	56
Alogliptin+ Metformin	Acetonitrile: 0.2% Formic acid	5- 400 (AL) 25-2000	57
Linagliptin+ Metformin	Methanol: 10 mM Ammonium formate buffer (95:5)	0.25-10 (LN) 25-2000	58
Linagliptin+ Empagliflozin	0.1 % aq. Formic acid: Acetonitrile (50:50)	25 - 800 (LN) 50 - 1600	59
	2 mM Ammonium acetate buffer: Acetonitrile	0.01–10	60
Saxagliptin+ Dapagliflozin	0.1% Formic acid: Acetonitrile (25:75)	2-2000 (SX) 0.5-1500	61
	10 mM Ammonium acetate: Methanol (20:80)	50-10000 (pg/mL) (Both drugs)	62
	Acetonitrile: 5 mM Ammonium acetate buffer (70:30).	0.502-227 (SX) 0.103-76.402	63

Conclusion

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

Consent and ethical Approval: It is not applicable.

Conflict of Interest: None.

Funding Source: None.

Author Contributions: All authors have equal contribution in the preparation of manuscript and compilation.

Source of Support: Nil.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data supporting in this paper are available in the cited references.

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