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Chromatographic Methods for Determination of Dipeptidyl peptidase-4 (DPP-4) inhibitors: A Review

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Abstract : Dipeptidyl peptidase-4 (DPP-4) inhibitors are a novel class of oral antidiabetics used in the treatment of type 2 of diabetes mellitus and work to enhance the effect of the incretin hormones. A wide range of analytical techniques that are useful in estimating DPP-4 inhibitors in biological matrices and pharmaceutical formulations are available. Analytical techniques such as ultraviolet spectrophotometry, Mass spectroscopy (MS), capillary electrophoresis, high Performance Liquid Chromatography (HPLC), high pressure thin layer chromatography (HPTLC), ultra-performance liquid chromatography (UPLC) and liquid chromatography-mass spectroscopy(LC-MS) have been reported for estimation of DPP-4 inhibitors in single and in combination with other drugs. This comprehensive review covers most of the chromatographic methods that are described for determination of alogliptin (ALG), vildagliptin (VIL) and linagliptin (LIN) in bulk, in different pharmaceutical dosage forms and biological matrices to till date. From the review it can be inferred that a large number of chromatographic methods have been developed, and HPLC-UV methods have been commonly used in the detection and evaluation of DPP-4 inhibitors.
Keywords: Alogliptin, Vildagliptin, Linagliptin, Chromatographic methods.

Introduction

In diabetes mellitus increased DPP-4 enzymatic activity in plasma and its release in visceral adipose tissues triggers incretin response. DPP-4 inhibitors are a newer class of oral antidiabetics that are used commonly due to modest effects on HbA1c, and lack of serious side effects. DPP-4 is one of the members of bound glycoprotein responsible for the catalytic degradation of incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose dependent insulinotropic polypeptide. DPP-4 is widely distributed in various body parts, such as

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pancreas, kidney, lungs, spleen and prostate gland [1]. Endothelial, epithelial and immune cells such as T cells and macrophages are highly expressed with DPP-4 enzyme. Disturbance in the expression of DPP-4 is generally observed in certain disorders such as autoimmune diseases, solid tumours, hepatitis-C, type 2 diabetes mellitus (DM) and obesity [2-4].

Mechanism of action of DPP-4 inhibitors

These are used for the treatment of Type 2 DM. The DPP-4 inhibitors selectively inhibit dipeptidylpeptidase-4 enzyme, and thereby increase the level of two known active incretin hormones, glucose dependent insulinotropic poly-peptide (GIP) and GLP-1. Incretin is a part of endogenous system involved in the physiological regulation of glucose homeostasis. GLP-1 and GLP increase synthesis and release of insulin from pancreatic beta cells when the glucose levels are normal or elevated. GLP-1 also lowers glucagon secretion from pancreatic alpha cell, thereby reducing hepatic glucose production. This mechanism is in contrast to that with sulfonylurea, which cause insulin release even when level of glucose is low, thus causing sulfonylurea induced hypoglycaemia in patients with type 2 DM and in normal subjects [5].

Pharmacokinetics

Gliptins show good oral bioavailability, adequately prolonged half-life and sustained DPP-4 enzyme inactivation which allows one single oral dose per day for the management of type 2 DM. But for VILDA (an only exception) because of a shorter half-life, a routine of twice-daily administration is recommended. DPP-4 inhibitors are not prone to a high risk of drug-drug interactions. They contribute to a good efficacy/safety ratio in the management of type 2 DM in clinical practice [6–10]. Summary of differences in the route of administration, bioavailability, plasma protein binding, metabolism, and excretion between the individual compounds is depicted in Table 1. The different physicochemical properties of DPP-4 inhibitors are represented in Table 2.

Table 1: Pharmacokinetic properties of DPP-4 inhibitors

Pharmacokinetic parameter	ALG	VIL	LIN
Administrative route	Oral	Oral	Oral
Bioavailability (%)	100	85	30
Metabolism	Excreted unchanged	Hepatic to LAY151	90 % Excreted unchanged
Plasma protein binding	20	9.3	70–80
Elimination half life	12.4–21.4	1.5	>100
Excretion	Urine	Urine	Enterohepatic or urine

Table 2: Physicochemical properties of DPP-4 inhibitors

Drug	pKa	Solubility	λmax (nm)
Alogliptin (ALG)	9.5	Soluble in methanol and dimethyl sulfoxide, sparingly soluble in water as well as ethanol.	222
Linagliptin (LIN)	8.6	Soluble in methanol, sparingly Soluble in ethanol and slightly soluble in isopropanol and acetone	242
Vildagliptin (VIL)	14.7	Soluble in methanol, water and dimethyl sulfoxide	217

REPORTED CHROMATOGRAPHIC METHODS

High performance thin layer chromatography

A validated HPTLC method for estimation of ALG in bulk drugs and tablet dosage forms has been developed and reported [11]. HPTLC method demonstrating the degradation behaviour of ALG as bulk drug and in tablet dosage form has also been reported [12, 13]. HPTLC methods for simultaneous estimations of ALG in combination with pioglitazone hydrochloride (PIO) and MET as bulk and in fixed dose combination tablets have been developed and validated [14-16]. Estimation of ALGP in combination with MET in tablets is reported by stability indicating HPTLC method [17]. Whereas, a method proposing application of accelerated stability studies of LIN by HPTLC have been developed [18]. Validated stability indicating methods for the simultaneous determination of LIN with EMP and MET in their respective combined pharmaceutical formulations have been developed and reported [19-23]. Also, stability indicating HPTLC methods for the estimation of VIL as bulk and in tablet dosage form have been reported [24, 25]. Stability indicating HPTLC method for simultaneous estimation of VIL with MET in their pharmaceutical dosage forms have been reported in two articles [26, 27]. The summary of reported HPTLC-densitometric methods for separation and estimation of DPP-4 inhibitors in bulk and pharmaceutical dosage forms is listed in table 3.

Table 3: Reported HPTLC-densitometric methods

Drug(S)	Mobile Phase	Detection Wavelength, nm	Ref. No.
ALG	Acetonitrile:1% ammonium acetate in methanol (4.5: 5.5, v/v)	277	11
ALG	n-butanol: water: acetic acid (7: 2: 1, v/v/v)	233	12
ALG	Benzene: ethyl acetate: triethylamine (7.5: 2: 0.5, v/v/v)	222	13
ALG with PIO	Acetonitrile:1% ammonium acetate in methanol (4.5: 5.5, v/v)	254	14
ALG with MET	Acetonitrile: 1% ammonium acetate in methanol (4.5: 5.5, v/v)	253	15
ALG with MET	Chloroform: methanol: 0.5 % ammonium sulphate (4: 4: 2, v/v/v)	254	16
ALG with MET	Methanol: chloroform: 0.5% ammonium sulphate (4: 4: 2, v/v/v)	254	17
LIN	n-butanol: water: glacial acetic acid (6: 3: 1, v/v/v)	242	18
LIN	Methanol: toluene (7: 3, v/v)	295	19
LIN with EMP	Methanol: toluene: ethyl acetate (2: 4: 4, v/v/v)	229	20
LIN with MET	Acetone: methanol: toluene: formic acid (4 : 3 : 2 : 1, v/v/v/v)	259	21
LIN with MET	Acetone: methanol: chloroform: formic acid (3: 1: 5: 1, v/v/v/v)	230	22
LIN with MET, EMPA	n-butanol: water: glacial acetic acid (6: 3: 1, v/v/v)	223	23
VIL	Ethyl acetate: methanol (8.5 : 1.5, v/v)	217	24

VIL	Chloroform: n-butanol: methanol (5: 2: 3, v/v/v)	227	25
VIL with MET	Hexane: ethanol: acetonitrile: glacial acetic acid (2: 3.5: 2.5: 0.2, v/v/v/v)	217	26
VIL with MET	Ammonium acetate in methanol (1% w/v): Toluene (10: 0.5, v/v)	214	27

High performance liquid chromatography

High performance liquid chromatography has been widely used for determination of studied DPP-4 inhibitors. Also, HPLC come out to be a method frequently regularly used in all fields of DPP-4 inhibitors. The various reported HPLC methods [28-95] based on use of different stationary phases (silica C8, C18, cyanopropyl), mobile and using UV, fluorescence or tandem mass spectrometry for detection and quantitative determination of DPP-4 inhibitors either as single or in combination with other drugs in pure, pharmaceutical dosage forms and biological fluids are shown in table 4.

Table 4: Reported HPLC methods

Drug(s)	Column	Mobile phase	Analytical wavelength, nm	Ref. No.
ALG	Agilent zobrax SB-CN	Solvent A : water: acetonitrile: trifluoroacetic acid (1900 : 100:1, v/v/v) Solvent B : acetonitrile : water : trifluoroacetic acid (1900:100: 1)	278	28
ALG	Symmetry cyanide	Potassium dihydrogen phosphate buffer pH 4.6 : acetonitrile (20: 80, v/v)	215	29
ALG	Lux cellulose 2	Ethanol: diethyl amine (100: 0.5, v/v)	230	30
ALG	Finepaksil C18	Methanol : double distilled water (80:20, v/v)	222	31
ALG	Phenomenex gemini C18	Acetonitrile : ammonium carbonate buffer (55: 45, v/v)	227	32
ALG	Shiseido C18	Acetonitrile : 1-octasulphonic acid pH 5 (60 : 40, v/v)	220	33
ALG	Phenomenex lux cellulose-2	Water : methanol (75:25, v/v)	225	34
ALG	Hypersil ODS C18	Methanol: 0.01% formic acid (70: 30, v/v)	230	35
ALG	Agilent C18	Phosphate buffer pH 2.5 : acetonitrile (70:30 v/v)	210	36
ALG with MET	Xterra C18	Buffer : methanol (30: 70, v/v)	254	37
ALG with MET	Enable C18	Potassium dihydrogen phosphate buffer pH 4 : acetonitrile (70:30, v/v)	235	38
ALG with PIO	Agilent C18	Phosphate buffer pH 3.6 : acetonitrile (35: 65, v/v)	268	39
ALG with MET	X Bridge C18	Water: Methanol (70: 30, v/v)	242	40

ALG with MET	Xterra C 18	Buffer : Methanol: acetonitrile (20: 60: 20 v/v/v)	290	41
ALG with MET	Hypersil BDS C18	Potassium dihydrogen phosphate buffer pH 4 : acetonitrile (70: 30, v/v)	235	42
ALG with PIO	Xterra C 18	Phosphate buffer pH 4 : acetonitrile (70: 30, v/v)	215	43
ALG with MET	Symmetry C18	Sodium dihydrogen phosphate pH 4: acetonitrile (70: 30 v/v)	235	44
ALG with MET	Inertsil ODS C18	Acetonitrile : Phosphate buffer (62: 38, v/v)	275	45
ALG with MET, REP	Hypersil Gold BDS C18	Acetonitrile : Phosphate buffer pH 2.5 : 0.3 % sodium heptane sulfonate in water (60: 20: 20, v/v/v)	220	46
ALG with OMR, TRE	Symmetry C18	Acetonitrile :phosphate buffer (50: 50, v/v)	274 240	47
LIN	X Bridge C18	Methanol: water (83: 17, v/v)	241	48
LIN	Symmetry kromosil C18	Phosphate buffer pH 3.4: acetonitrile (70: 30, v/v)	240	49
LIN	kromosil C18	Acetonitrile: water: methanol (25: 50: 25, v/v/v)	238	50
LIN	C18	0.02 M Potassium dihydrogen phosphate pH 5: acetonitrile (70: 30, v/v)	226	51
LIN (stability study)	Zorbax XDB C18	Methanol : phosphate buffer (70: 30, v/v)	218	52
LIN	C18	Methanol : formic acid 0.1 % 4.1 (75: 25, v/v)	254	53
LIN	C8	Phosphate buffer (pH 6.8 ± 0.2) : acetonitrile (70: 30, v/v)	239	54
LIN with MET	Hypersil BDS C18	Acetonitrile: water: methanol (25: 50: 25, v/v/v)	243	55
LIN with MET	Grace vyadyec genesis CN	Phosphate buffer pH 5.6: methanol: acetonitrile (40: 5: 55, v/v/v)	233	56
LIN with MET	Phenomenex Luna RP C18	Acetonitrile : dipotassium hydrogen phosphate (75: 25, v/v)	237	57
LIN with MET	Agilent Zorbax SB C18	Phosphate buffer: methanol: acetonitrile (65: 10: 25, v/v/v)	231	58
LIN with MET	Inertsil ODS 3V C18	Potassium dihydrogen phosphate: acetonitrile (40: 60, v/v)	250	59
LIN with MET	Symmetry Waters C18	Potassium dihydrogen phosphate: acetonitrile (40: 60, v/v)	236	60
LIN with MET	Waters X-Bridge C18	Phosphate buffer pH 4.5 : acetonitrile (60: 40, v/v)	280	61
LIN with MET	C 18	Potassium dihydrogen phosphate: buffer (pH 4.6): Methanol (30: 70, v/v)	260	62
LIN with MET	Equisil BDS C 18	Acetonitrile: Phosphate buffer pH 5 (35: 65, v/v)	225	63
LIN with MET	Symmetry C18	Methanol: KH2PO4 pH 4.6 (70: 30, v/v)	267	64

LIN with EMP	Grace cyano	Methanol: water (40: 60, v/v)	294 224	65
LIN with MET	C18	Methanol : 10 mM ammonium formate buffer (95:5, v/v)	240	66
LIN with MET	Zobrax SB-Aq	25 Mm ammonium bicarbonate buffer: acetonitrile (65:35, v/v)	207	67
LIN with EMP	Phenomenex Luna C18	Buffer : acetonitrile (68: 32, v/v)	218	68
LIN with MET	X-Bridge Shield C18	A- KH_2PO_4 Buffer pH 3 Adjusted with OPA B- ACN: Methanol (90 :10, v/v)	240	69
LIN with EMP	Shimpack VP-ODS	A: 10 mM potassium dihydrogen orthophosphate pH 3 B: Acetonitrile : methanol (55: 45, v/v)	225	70
VIL	Xterra Waters C18	A : 50 mM ammonium bicarbonate pH 7.8 B: Acetonitrile	210	71
VIL	C18	0.02 M phosphate buffer (pH 4.6): acetonitrile (80: 20, v/v)	210	72
VIL	Altima C18	Aqueous phase (25 % ammonium hydroxide in 1000 ml of water, (pH adjusted to 9.5) : organic phase (methanol) (60: 40, v/v)	210	73
VIL	Symmetry C18	Buffer: acetonitrile (50: 50, v/v)	220	74
VIL	Shimpack VP-ODS C18	o-phosphoric acid buffer pH 2.6 ± 0.5 : acetonitrile (72: 28, v/v)	266	75
VIL	Altima C18 (150 µm x 4.6 mm)	Methanol: 10 mM ammonium acetate buffer (30: 70, v/v)	220	76
VIL	Hypersil ODS C18	0.01 M phosphate buffer (pH 5.3) : acetonitrile (30: 70, v/v)	210	77
VIL	Kromosil C18	Dilute phosphoric acid solution pH 2.6 as buffer solution : ACN (40: 60, v/v)	210	78
VIL with MET	Kromosil C18	0.1 M potassium hydro phosphate: acetonitrile (60: 40, v/v)	263	79
VIL with MET	Waters C18	Phosphate buffer pH 5.8 : acetonitrile (80: 20, v/v)	215	80
VIL with MET	Monolithic	Dipotassium mono hydrate phosphate : acetonitrile (80: 20, v/v)	250	81
VIL with MET	Phenomenex C18	Phosphate buffer pH 7: acetonitrile (70:30,v/v)	263	82
VIL with MET	Phenomenex	Acetonitrile: sodium dihydrogen phosphate and sodium dodecyl sulfate with pH 4.5 ± 0.2 (30: 70, v/v)	208	83
VIL with MET	ZODIAC	Phosphate buffer pH 7 : methanol (65: 35 ,v/v)	225	84
VIL with MET	Lichrocart C18	Phosphate buffer: Acetonitrile (7: 25 ,v/v)	260	85
VIL with MET	Inertsil C18	Disodium hydrogen phosphate pH 3.5 : methanol (7.5: 26.5, v/v)	200	86
VIL with MET	Sunfire BDS C8	Potassium dihydrogen phosphate: acetonitrile (70: 30, v/v) A : 0.1% ortho phosphoric acid B: Acetonitrile : methanol (95: 5, v/v)	215	87

VIL with MET, SITP	Phenomenex C18	A : 0.1% ortho phosphoric acid B: Acetonitrile : methanol (95: 5, v/v)	217	88
VIL with MET	Xterra C 18	Disodium hydrogen phosphate pH 7: Acetonitrile (60: 40, v/v)	263	89
VIL with MET	Hypersil ODS C18	Potassium dihydrogen phosphate : acetonitrile (70: 30, v/v)	220	90
VIL with MET	Kromosil C18	Acetonitrile :phosphate buffer pH 6: water (65: 20: 15, v/v/v)	239	91
VIL with MET	Primesil C18	Methanol: acetonitrile : phosphate buffer (5: 35: 65, v/v/v)	212	92
VIL with MET	Inerrtsil CN-3	Potassium dihydrogen phosphate buffer: acetonitrile (80: 20, v/v)	263	93
VIL with MET	Finepaksil C18	Acetonitrile: Potassium phosphate buffer pH 3.2 (40: 60, v/v)	225	94
VIL with SAXG	Phenomenex gemini C18	Potassium dihydrogen phosphate buffer pH 4.6 (40: 60, v/v)	208	95

Liquid Chromatographic-mass spectrophotometry

A method employing Liquid-Liquid extraction technique have demonstrated a liquid chromatography-tandem mass spectrophotometric (LC-MS/MS) method for the estimation of ALGP in rabbit plasma. Internal standard used was Alogliptin D3. A column of Inertsil ODS 5 µm C18, 50 × 4.60 mm was employed for chromatographic separation, with 30:70 v/v of 0.1% formic acids: Organic Mixture (acetonitrile: methanol, 80:20% v/v) as a mobile phase with a flow rate of 1.0 ml/min. Instruments used viz.- LC-MS/MS used for the study - Shimadzu LC-20ADvp coupled with Tandem mass spectrometer (Applied Biosystem sampler Sciex API 4000). Quantitation was achieved employing turbo ion spray interface through negative ion mode at 400ºC. For detection multiple-reaction monitoring mode (MRM) was employed. Operating parameters- ion spray voltage -5500 V. The source parameters viz., the nebulizer-8 psi, curtain-10 psi and CAD gas 6 psi were set respectively. The compound parameters - the declustering potential (DP) - 18 V, collision energy (CE) 10V, entrance potential (EP)-10V and collision cell exit potential (CXP) 10V etc. were set for both alogliptin and alogliptin-D3 were similar [96]. A liquid chromatographic method (LC-MS/MS) method has been described for estimation of ALGP in Human plasma. Deuterated analogue alogliptin 13C D3 was used as internal standard (IS). Kromasil 100-5 C18 (100 mm × 4.6 mm) column along with a binary pump and a 96–vial autosampler was used for chromatographic separation. While, a mobile phase of 5mM ammonium formate, methanol and acetonitrile (20:40:40, v/v/v) at a flow rate of 0.4 mL/min was used for the same. A Waters XEVO TQ–S mass spectrometer was used for quantification. ESI-MS was kept in the positive mode and the cone voltage, collision energy and capillary voltage were 30 V, 30 V & 3.5 V for alogliptin and 25 V, 34 V & 3.5 V for the IS. The retention time for ALGP was 2.5 min [97].

A HPLC-tandem mass spectrometry (MS/MS) method that allows the simultaneous quantification of ALGP, and PIO in human plasma have been developed. In this method, instruments used were-viz for purpose of Analysis- Agilent HPLC system coupled to a triple quadrupole API spectrometric detection was done using a 4500. Chromatographic separation was carried out using an Kinetex column C8 (50 × 4.6 mm) column which was maintained at 400 C. Methanol and 0.1% formic acid in a gradient mode was used as a mobile phase with 0.7ml/min flow rate. Analyte quantification was achieved using multiple reactions monitoring, whereas, the MS ESI source operated in positive ion mode. The source parameters were as follows: medium temperature, 600 ◦C, collision gas, 8 psi, curtain gas, 30 psi, ion source gas one 30 psi and gas two, 45 psi, ion spray voltage, 2000 V [98].

A liquid chromatography tandem mass spectroscopic method (UPLC-MS/MS) was developed and reported for simultaneous determination of Alogliptin and Voglibose in human plasma in Human Plasma. Alogliptin D3 and Miglitol were used as internal standard (IS). Chromatographic separation was achieved using an Welchrom XB

C18, with specifications of (50 × 4.6 mm) column, using a mobile phase of 5 mM Ammonium formate: Acetonitrile in the ratio 50:50 v/v. at a flow rate of 0.7 mL/min. The retention time of Voglibose, Alogliptin, Alogliptin D3 and Miglitol occurred at 0.8, 1.03, 0.8 and 0.81 min respectively. The analytes and IS were detected using MDS Sciex, API-4000 Mass spectrometer equipped with a Turbo ion spray interface (set in positive ion mode). Temperature was maintained at 500°C and ion spray voltage of 5500 V was fixed. The source parameters were maintained at pressure of 50 psi (GS1) and 60 (GS2) psi [99]. Apart from these above methods the summary of other reported LC MS/MS methods for separation and estimation of DPP-4 inhibitors as single or in combination with other drugs in pure, pharmaceutical dosage forms and biological fluids are listed in Table 5.

Table 5: Reported LC MS/MS methods

Drug(s)	Column	Mobile phase	Ionization	Ref. No.
ALG with PIO	BEH C18	0.1% aqueous formic acid and acetonitrile in the ratio of (40: 60, v/v)	Electrospray ionization (ESI) positive mode	100
ALG with MET	Hypersil Gold	Acetonitrile (A) and 0.2% formic acid solution (B)	Turbo ion spray positive mode	101
LIN	Kinetex Phenyl	10 mM Ammonium formate buffer (pH 6.5 ± 0.5): methanol (15: 85, v/v)	Turbo ion spray positive mode	102
LIN	Waters X-Bridge C18	Acetonitrile: 0.1 % formic acid (90: 10, v/v)	Turbo ion spray positive mode	103
LIN with MET, SAX	C 18	Methanol: ammonium acetate buffer pH 4.5 (85: 15, v/v)	Turbo ion spray positive mode	104
VIL	Athena C18	0.1% ammonium acetate solution: acetonitrile (90: 10, v/v)	Electrospray ionization (ESI) positive mode	105
VIL	Betasil C18	Acetonitrile: 2 mM ammonium acetate (90: 10, v/v)	Electrospray ionization (ESI) positive mode	106
VIL with GCZ, GMP, MET	Acquity UPLC1 HSS Cyano	Water: acetonitrile	Electrospray ionization (ESI) positive mode	107
VIL with MET	UPLC (BEH) C18	0.5% acetic acid in methanol: 0.02 M aqueous ammonium acetate (10: 90, v/v).	Electrospray ionization (ESI) positive mode	108
VIL with MET	C8 column	Acetonitrile: water: formic acid (20: 80: 0.1, v/v/v)	electrospray ionization (ESI) positive mode,	109

Conclusion

This review focuses on different chromatographic methods which are reported for the determination of three DPP-4 inhibitors viz. Alogliptin, Vildagliptin, Linagliptin, in bulk, different pharmaceutical dosage forms and biological matrices. Certain LC-MS/MS methods that proposes small analysis time and higher sensitivity have also been developed and validated for quantification of DPP-4 inhibitors in human plasma. The studied data revealed that HPLC was comprehensively used for the quantitative determination of DPP-4 inhibitors as it offers excellent specificity and adequate precision. We recommend the HPLC-MS/MS method for the determination of DPP-4 inhibitors because it combines the HPLC separation capacity with MS sensitivity and selectivity that allows the unequivocal identification of DDP-4 inhibitors and their metabolites. For determination of DPP-4 inhibitors in pharmaceutical formulations, HPLC with UV detection can be used because of accuracy in results and low cost as compared to advanced detection techniques.

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