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Newer Approaches for Analytical Method Validation of Anti Diabetic Agents: A Review

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Abstract:- Diabetes refers to a metabolic disorder identified by Hyperglycemia. Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) are also called as Gliptins are a relatively new class of antidiabetic drugs to treat type-2 diabetes. Analytical method development and validation play an indispensable role in analysis and manufacture of pharmaceuticals. The intent of this article is to study the reported analytical methods in the literature for assessment of Dipeptidyl peptidase- 4 inhibitors. This review covers divergent analytical methods for the estimation of these drugs. Many spectroscopic and chromatographic techniques are available for the determination and evaluation of these drugs in bulk and pharmaceutical preparation. Newly evolved and advanced chromatographic techniques are also available for the estimation of these drugs in biological fluids such as Liquid Chromatography-Tandem Mass Spectroscopy (LC- MS/MS), Gas Chromatography- Mass Spectroscopy (GC- MS), High Performance Liquid Chromatography- Mass Spectroscopy (HPLC-MS) and Ultra- Fast Liquid Chromatography (UFLC). The development and validation of analytical methods is imperative for drug development studies and even for the development of drug formulation including stability and degradation studies and also for the determination of pharmacokinetic data of these drugs. This review work summaries the current position of analytical methods for estimation of these antidiabetic drugs in bulk, dosage form and biological fluids.

I. INTRODUCTION

Diabetes is the most common non-communicable disease globally.[1] Diabetes is a heterogeneous metabolic disorder characterized by hyperglycemia due to defects in insulin secretion, insulin action, or both.[2] Types of diabetes includes type 1 diabetes, type 2 diabetes and in addition, gestational diabetes and due to other causes neonatal diabetes. Approximately 85-95% of all cases of diabetes are type 2 diabetes and the worldwide explosion of this disorder is a major healthcare burden.[1] In people with type 2 diabetes mellitus either pancreas does not produce enough insulin or pancreas produces insulin but cells don't use it this is also called insulin resistance.[3] When a cell becomes insulin resistance, it requires more insulin to convert glucose into energy and results into hyperglycemia or increased blood sugar level. The launch of a national program by the Indian Government for prevention and control of diabetes, cardiovascular disease and stroke (NPCDS) is a major step in strengthening the national capacity for coping with the diabetes epidemic. The most pressing need in India currently is the primary prevention of diabetes. Screening for glucose intolerance as a preventive measure, even in those younger than 30 years of age, is a requisite in Asian Indians because they develop hyperglycemia at a younger age.[1]

For the treatment of type 2 diabetes proper diet and exercise are essential along with antidiabetic drugs. Antidiabetic drugs are categorized into Biguanides, Thiazolidinediones, Sulfonylureas, α- Glucosidase inhibitors, Meglitinides and a newly emerging class Dipeptidyl Peptidase-IV inhibitors (DPP-IV inhibitors). Gliptins, also known as DPP-IV inhibitors are class of oral antidiabetic medication approved by food and drug administration (FDA) to treat type 2 diabetes mellitus in adults. DPP-IV inhibitors are given to those who have not responded well to sulfonylureas and metformin. DPP-IV is a ubiquitous enzyme that acts on incretin hormones, mainly GLP-1(glucagon-like peptide-1) and GIP (gastric inhibitory peptide), which maintain glucose homeostasis by increasing insulin secretion and decreasing glucagon secretion. GLP-1 is a hormone which lowers blood glucose by stimulating insulin secretion, reducing glucagon concentration and delaying gastric emptying. GIP is a hormone secreted in the stomach and proximal small intestine by neuro endocrine K-cell. DPP-IV inhibitors inhibit DPP-IV enzyme which results in increased level of GLP-1 and GIP, which in turn increase beta-cell insulin secretion in the pancreas. DPP-IV inhibitors are Sitagliptin, Linagliptin, Vildagliptin, Saxagliptin, Teneligliptin, Trelagliptin, Gemigliptin, Anagliptin, Alogliptin, Omarigliptin and Evogliptin.[4]

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Analytical techniques are used to determine chemical or physical property of analyte, chemical substance, chemical element or mixture. There are different types of analytical techniques used in pharmaceutical field for qualitative and quantitative estimation of drugs in biological fluids such as human plasma, human serum, human urine and its formulations such as tablet, capsule, bulk drug etc. The analytical techniques which are utilised for the estimation of these drugs involves UV-spectrophotometry, HPLC, HPTLC, LC-MS/MS, HPLC-MS, etc. [5] Spectrophotometry, one of the valuable techniques in pharmaceutical analysis, which find an important place in pharmacopoeias based on natural UV absorption and chemical reaction. These techniques such as ultra-violet, visible, infrared and atomic absorption spectroscopy are most commonly employed as in the analytical fields. Chromatography is a separation technique that separate mixture in to individual components by using mobile phase and stationary phase. HPLC is an advanced technique for liquid chromatography for the assay of bulk drug materials and biological samples. The specificity of HPLC method is excellent and simultaneously sufficient precision and accuracy are also achievable. HPTLC is an advanced form of instrumental TLC; it emerged as an important instrument in drug analysis. HPTLC is a fast separation technique and flexible enough to analyse a wide variety of samples.[6]

Table 1: Analytical Methods Study for Estimation of Anti-Diabetic Agents

Sr. No.	Drug Name	Instrumental Method Used for Analysis	Solvent System	Ref. No.
1	Sitagliptin	UV- Spectrophotometry Absorption ratio Area under curve	Water	7
2	Sitagliptin	UV- Spectrophotometry Absorption ratio Area under curve	Methanol & water	7
3	Sitagliptin	Spectrofluorimetric method	Water	7
4	Sitagliptin	Spectrofluorimetric method	Deionized water	7
5	Sitagliptin	Visible method	Water Colouring agent: O- phosphoric acid, NAC & Borate buffer	7
6	Sitagliptin	Visible method	Water Colouring agent: Acetyl acetone & Formaldehyde	7
7	Sitagliptin	UV- Spectrophotometry Zero order, First order, Second order	Methanol	8
8	Sitagliptin	UV- Spectrophotometry First order	Water	7
9	Sitagliptin	HPLC (Human plasma)	0.5% V/V Triethylamine: Acetonitrile (77: 23 V/V)	7
10	Sitagliptin	RP- HPLC (Stability indicating)	Methanol: Phosphate potassium buffer (pH- 6.8) (60: 40 V/V)	9
11	Sitagliptin	RP- HPLC (Stability indicating)	Gradient elution 5m M Ammonium acetate & Acetonitrile	10
12	Sitagliptin	RP- HPLC (Stress- study sample analysis)	1) 0.1% Ortho phosphoric acid in water 2) 0.1% Ortho phosphoric acid in acetonitrile	10
13	Sitagliptin	RP- HPLC (Isolation of degradation product)	5m M Ammonium acetate in water & Acetonitrile	10
14	Sitagliptin	HPLC	Acetonitrile: 0.01 N Potassium dihydrogen phosphate (pH- 5.0) (70: 30% V/V)	11
15	Sitagliptin	RP- HPLC (Human plasma)	Acetonitrile: 0.5% Triethanolamine (pH- 6.5) (20: 80 V/V)	12
16	Sitagliptin	RP- HPLC (Human plasma)	Potassium dihydrogen phosphate: Acetonitrile: Methanol (pH- 4.9) (30: 50: 20 V/V/V)	13
17	Sitagliptin	HPLC	Phosphate buffer: Acetonitrile (pH- 7.2 ± 0.05) (60: 40 V/V)	14
18	Sitagliptin	RP- HPLC (Rat urine)	Potassium dihydrogen phosphate: Acetonitrile (pH- 3.0) (70: 30 V/V)	15
19	Sitagliptin	RP- HPLC (Human plasma)	Acetonitrile: Methanol: Buffer (pH- 4.0) (2: 3: 5 V/V/V)	16
20	Sitagliptin	RP- HPLC	Methanol: 10m M Phosphate buffer (pH- 4.8) (60: 40 V/V)	17
21	Sitagliptin	HPLC	Methanol	8

22	Sitagliptin	HPLC	Potassium dihydrogen phosphate: Acetonitrile (pH- 3.0) (35: 65 V/V)	8
23	Sitagliptin	RP- HPLC	Acetonitrile: Phosphate buffer (pH- 4.0) (60: 40 V/V)	18
24	Sitagliptin	RP- HPLC	0.05 M Phosphate buffer: Acetonitrile (pH- 2.8) (30: 70 V/V)	19
25	Sitagliptin	HPLC (Rat serum)	Phosphate buffer: Methanol (pH- 3.9) (65: 35 V/V)	20
26	Sitagliptin	RP- HPLC (Stability indicating)	10m M phosphate buffer: Acetonitrile (pH- 3.5) (60: 40 V/V)	21
27	Sitagliptin	RP- UHPLC	Phosphate buffer: Acetonitrile (pH- 6.0) (70: 30 V/V)	22
28	Sitagliptin	UHPLC- MS/ MS (7-nitroso impirity)	Gradient elution 1) 0.12% Formic acid in water 2) 0.12% Formic acid in Methanol	23
29	Sitagliptin	LC- MS/ MS (Human plasma)	0.1 v/v Formic acid: Methanol (45: 55 V/V)	24
30	Sitagliptin	LC- MS/ MS (Human plasma)	Methanol: Water (85: 15 V/V)	25
31	Sitagliptin	LC- MS/ MS (Human plasma)	Acetonitrile: Water Containing 10m M Ammonium acetate (80: 20 V/V) (pH- 4.7)	7
32	Sitagliptin	LC assay (Degradation product)	Solution of 0.3 % Triethylamine: Acetonitrile (pH- 4.0) (75: 25 V/V)	26
33	Sitagliptin	HPTLC (Stability indicating)	Toluene: Ethyl acetate: Methanol (3: 6: 1 V/V/V)	27
34	Sitagliptin	TLC/ HPTLC	Toluene: Methanol (8: 2 V/V)	28
35	Sitagliptin Phosphate	UV- Spectrophotometer Zero order	Distilled water	29
36	Sitagliptin Phosphate	UV- Spectrophotometry Zero order	Methanol	16
37	Sitagliptin Phosphate	UV- Spectrophotometry Zero order	0.1 N HCl	16
38	Sitagliptin Phosphate	UV- Spectrophotometry First order	Methanol & water	16
39	Sitagliptin Phosphate	UV- Spectrophotometry Absorption ratio Area under curve	Methanol	8
40	Sitagliptin Phosphate	RP- HPLC	Acetonitrile: Water (60: 40 V/V)	30
41	Sitagliptin Phosphate	RP- HPLC	0.01 M Potassium dihydrogen phosphate: Methanol (pH- 4.5) (50: 50 V/V)	31
42	Sitagliptin Phosphate	RP- HPLC	Methanol: 0.1% Perchloric acid solution (32: 68 V/V)	32
43	Sitagliptin Phosphate	HPLC (Stability indicating)	0.1 M Potassium dihydrogen phosphate: Methanol (pH- 4.5) (1: 1 V/V)	33
44	Sitagliptin Phosphate	RP- HPLC	Methanol: Water (pH- 3.0) (50: 50 V/V)	34
45	Sitagliptin Phosphate	RP- HPLC (Chiral separation)	n- haptane: Ethanol: Diethylamine (35: 65: 0.1 V/V/V)	35
46	Sitagliptin Phosphate	RP- HPLC (Rat plasma sitagliptin enantiomers Fluorescence)	Phosphate buffer: Methanol (45: 55 V/V)	36
47	Sitagliptin Phosphate	UPLC- MS/ MS (Rat plasma)	Gradient elution 1) 0.05% Formic acid in Acetonitrile 2) 0.05% Formic acid in water	38
48	Sitagliptin Phosphate	LC- UV (Stability indicating)	0.025 M Phosphate buffer: Acetonitrile (pH- 6.8) (60: 40 V/V)	39
49	Sitagliptin monophosphate	HPLC (Human plasma)	0.01 M Phosphate buffer: Acetonitrile (pH- 4.5) (73: 27 V/V)	37
50	Sitagliptin	UV- Spectrophotometry	Methanol	8

	phosphate monohydrate	Zero order		
51	Sitagliptin phosphate monohydrate	RP- LC	Potassium dihydrogen phosphate buffer: Acetonitrile (pH- 7.8) (70: 30 V/V)	40
52	Sitagliptin phosphate monohydrate	LC- MS/ MS (N- nitrosamine impurity)	Gradient elution 1) 0.01 mol/L Ammonium formate in water 2) 0.01 mol/L Ammonium formate in acetonitrile	41
53	Linagliptin	UV- Spectrophotometry Zero order	Methanol	42
54	Linagliptin	UV- Spectrophotometry Zero order	Methanol & water	43
55	Linagliptin	UV- Spectrophotometry Zero order	Acetonitrile	44
56	Linagliptin	UV- Spectrophotometry AUC Zero order, First order, Second order	Methanol	45
57	Linagliptin	UV- Spectrophotometry Visible method	Method A= 3- methyl- 2 benzothiazoline hydrazine in presence of ferric chloride Method 2= Picric chloride.	46
58	Linagliptin	UV- Spectrophotometry Calibration graph method AUC method	0.1 M HCl	47
60	Linagliptin	Spectrofluorometry Human plasma	4- chloro-7 nitrobenzofuran	48
61	Linagliptin	Spectrofluorometry Spectrofluorimetric method	Fluorescamine reagent with aqueous borate buffer (Ph- 8.5)	49
62	Linagliptin	HPLC	Potassium dihydrogen buffer (pH- 4.6): Acetonitrile (20: 80 V/V)	50
63	Linagliptin	RP- HPLC	Acetonitrile: Water: Methanol (25: 50: 25 V/V/V)	51
64	Linagliptin	RP- HPLC	Phosphate buffer: Acetonitrile (pH- 3.0) (35: 65 V/V/V)	52
65	Linagliptin	RP- HPLC	Methanol: Water (pH- 4.1) (83: 17 V/V)	52
66	Linagliptin	RP- HPLC	Phosphate buffer: Methanol (pH- 7.2) (70: 30 V/V)	52
67	Linagliptin	RP- HPLC	Methanol: Water (pH- 4.5) (40: 60 V/V)	52
68	Linagliptin	RP- HPLC	0.02 M Potassium dihydrogen phosphate: Acetonitrile (pH- 5.0) (70: 30 V/V)	52
69	Linagliptin	RP- HPLC	Methanol: Water (70: 30 V/V)	52
70	Linagliptin	RP- HPLC	Phosphate buffer: Methanol (pH- 3.0) (50: 50 V/V)	52
71	Linagliptin	UPLC	Acetonitrile: 0.01 M Potassium phosphate buffer (pH- 4.0) (70: 30 V/V)	52
72	Linagliptin	HPLC	Methanol: Water containing 0.3% triethylamine (pH- 4.5) (40: 60 V/V)	53
73	Linagliptin	RP- HPLC	Phosphate buffer: Acetonitrile (pH- 6.8 ± 0.2) (70: 30 V/V)	54
74	Linagliptin	HPLC (Rat plasma)	Methanol: 0.1% Formic acid (pH- 4.1) (75: 25 V/V)	55
75	Linagliptin	RP- HPLC	Acetonitrile: Phosphate buffer (pH- 8.0) (60: 40 V/V)	47
76	Linagliptin	LC Stability indicating	A= 0.1% v/v Formic acid (pH-3.5) B= Acetonitrile	56
77	Linagliptin	HPLC	40m M Potassium dihydrogen phosphate (pH- 3.0): Acetonitrile (70: 30 V/V)	57
78	Linagliptin	HPLC & UPLC Stability indicating	A= 0.02 M Potassium dihydrogen phosphate (pH- 3.0)	58

			B= Acetonitrile: Methanol (90: 10 V/V)	
79	Linagliptin	HPLC & UPLC Stability indicating	Acetonitrile: Methanol (50: 50 V/V)	58
80	Linagliptin	HPLC & UPLC Stability indicating	A= 0.1% Acid (pH- 3.5) B= Acetonitrile	58
81	Linagliptin	RP- HPLC	Methanol: Water containing 0.1% O-phosphoric acid (70: 30 V/V)	59
82	Linagliptin	RP- HPLC N, N- dimethylamine impurity	Acetonitrile: Water containing 25.0m M Ammonium acetate (75: 25 V/V)	60
83	Linagliptin	HILIC- UV 3-aminopyridine impurity	Water: Acetonitrile containing 10m M Ammonium acetate (Ph- 6.0) (10: 90 V/V)	61
84	Linagliptin	HILIC 4- dimethylaminopyridine	Water: Acetonitrile containing 10m M Ammonium acetate (pH- 6.2) (15: 85 V/V)	62
85	Linagliptin	RP- HPLC/ UPLC	Ethanol: Methanol: Diethylamine (90: 10: 0.1 V/V/V)	58
86	Linagliptin	LC- MS/ MS plasma	Acetonitrile: 0.1% Formic acid (90: 10 V/V)	58
87	Linagliptin	LC- MS/ MS plasma	10m M Ammonium formate: Methanol (20: 80 V/V)	58
88	Linagliptin	UHPLC- MS/ MS	10m M Ammonium formate: Methanol (20: 80 V/V)	63
89	Linagliptin	UPLC- MS/ MS Rat plasma	A= Acetonitrile B= 0.1% Formic acid in water	64
90	Linagliptin	HPTLC Stability indicating	Ethyl acetate: IPA: Ammonia (7: 3: 0.4 V/V/V)	65
91	Linagliptin	HPTLC	Methanol: Toluene (7: 3 V/V)	66
92	Saxagliptin	UV- Spectrophotometry Zero order (Gastric medium)	Solvent= Methanol: Water (15: 85 V/V) Diluent= Methanol: 0.1 N HCl (15: 85 V/V)	67
93	Saxagliptin	UV- Spectrophotometry Calibration curve method	Methanol	68
94	Saxagliptin	UV- Spectrophotometry Zero order	Acetonitrile	69
95	Saxagliptin	Spectrofluorimetry	Method A= 0.5% 1- 1- naphthoquinone-4- sulfonic acid sodium salt (NQS) in distilled water (pH- 10 with borate buffer) Method B= 0.2% 4- chloro- 7-nitrobenzofuran (NBD- Cl) in methanol (pH- 9 with borate buffer)	70
96	Saxagliptin	Spectrofluorimetry	Method A= Tetrachloro-1, 4-benzoquinone (P- chloranil) Method B= Formaldehyde and acetyl acetone	71
97	Saxagliptin	AAS Spectrophotometer & AES Spectrophotometer (AAS & ICP- AES)	Method A= Using $[HgI4]^{-2}$ Method B= Using $[Cr(NH3)2(SCN)4]^{-1}$	72
98	Saxagliptin	RP- HPLC	Acetonitrile: 0.02 M Potassium dihydrogen phosphate (pH- 4.5) (30: 70 V/V)	73
99	Saxagliptin	RP- HPLC	0.05 M Ammonium acetate buffer: Methanol (47: 53 V/V)	74
100	Saxagliptin	RP- HPLC	Acetonitrile: Water (90: 10 V/V)	75
101	Saxagliptin	RP- LC (Stability indicating)	0.1% Phosphoric acid (Ph- 3.0) : Methanol (70: 30 V/V)	76
102	Saxagliptin	RP- HPLC (Human plasma)	Acetonitrile: Potassium dihydrogen phosphate (Ph- 3.5) (28: 72 V/V)	77
103	Saxagliptin	RP- HPLC	Methanol: Water (70: 30 V/V)	78
104	Saxagliptin	RP- HPLC	Acetonitrile: Phosphate (13: 87 V/V)	72

105	Saxagliptin	RP- HPLC	Orthophosphoric acid: Methanol: Acetonitrile (70: 10: 20 V/V/V)	72
106	Saxagliptin	HPLC	Phosphate buffer (pH- 4.5) : Methanol (65: 35 V/V)	28
107	Saxagliptin	LC	0.02 M Sodium dihydrogen phosphate (pH- 3) with OPA: Methanol: Acetonitrile (45: 20: 35 V/V/V)	70
108	Saxagliptin	HPLC	Acetonitrile: Water (pH- 3.0) (20: 80 V/V)	79
109	Saxagliptin	HPLC	Methanol: Phosphate buffer (pH- 4.8) (70: 30 V/V)	79
110	Saxagliptin	HPLC/ UV (Animal serum)	Phosphate buffer (pH-4): Methanol (70: 30 V/V)	80
111	Saxagliptin	HPLC (Human plasma)	A= 0.1% Formic acid in water B= 0.1% Formic acid in acetonitrile	81
112	Saxagliptin	RP- HPLC (Simple stability study)	Solvent A= 1.20g Sodium dihydrogen phosphate in 100ml water (pH- 5) Solvent B= Acetonitrile	82
113	Saxagliptin	HPLC (Sulphonate ester impurity)	A=0.10% Orthophosphoric acid in Milli-Q water B= 10% Acetonitrile	83
114	Saxagliptin	HPLC (Degradation related impurity)	Solvent A= Water Solvent B= Acetonitrile	84
115	Saxagliptin	LC- MS/ MS	Methanol: Acetonitrile: Formic acid (50: 50: 0.1 V/V/V)	72
116	Saxagliptin	LC- MS	Potassium dihydrogen phosphate (pH- 4.6) : Acetonitrile: Methanol (40: 30: 30 V/V/V)	79
117	Saxagliptin	LC- MS/ MS (Human plasma)	0.1% Acetic acid in 5m M ammonium acetate and Acetonitrile (30: 70 V/V)	85
118	Saxagliptin	LC- ESI- MS/ MS (Degradation product)	10m M Ammonium formate and Methanol in gradient elution	86
119	Saxagliptin	UPLC- MS/ MS (Rat plasma)	Methanol: 0.1% Formic acid (40: 60 V/V)	87
120	Saxagliptin	HPTLC HPTLC	Hexane: Methanol: Ethyl acetate (4: 2: 2 V/V/V)	72
121	Saxagliptin	HPTLC	Methanol: Chloroform (6: 4 V/V)	79
122	Saxagliptin	HPTLC	1% Methanolic ammonium acetate: Toluene (5: 5 V/V)	79
123	Saxagliptin	HPTLC	Toluene: Methanol: Ammonia (6: 4: 0.2 V/V/V)	79
124	Saxagliptin HCl	HPLC RP- HPLC	Methanol: Water (80: 20 V/V)	88
125	Saxagliptin HCl	RP- HPLC	Phosphate buffer (pH- 2.70): Acetonitrile (80: 20 V/V)	89
126	Vildagliptin	UV- Spectrophotometry Zero order	Water	90
127	Vildagliptin	UV- Spectrophotometry Zero order	0.1% NAOH	91
128	Vildagliptin	UV- Spectrophotometry Zero order (gastric medium)	0.1 N HCl	92
129	Vildagliptin	UV- Spectrophotometry Second order derivative	Purified water	93
130	Vildagliptin	Visible Spectrophotometry	Method based on formation of Schiff's base with p-dimethylaminobenzaldehyde in acidic ethanol	94
131	Vildagliptin	RP- HPLC	Buffer (pH- 2.6): Acetonitrile (72: 28 v/v)	95
132	Vildagliptin	HPLC	Buffer (Perchloric acid): Acetonitrile:	96

			Methanol (87: 10:3 v/v/v)	
133	Vildagliptin	HPLC	A= 50m M Ammonium bicarbonate pH-7.8 B= Acetonitrile	97
134	Vildagliptin	HPLC	0.02 M Phosphate buffer (pH- 4.6) : Acetonitrile (80: 20 v/v)	97
135	Vildagliptin	HPLC	25% Ammonium hydroxide in 1000 ml water (pH 9.5): Methanol (60: 40 v/v)	97
136	Vildagliptin	HPLC	Buffer: Acetonitrile (50: 50 v/v)	97
137	Vildagliptin	HPLC	Orthophosphoric acid buffer (pH-2.6 ± 0.5): Acetonitrile (72: 28 v/v)	97
138	Vildagliptin	HPLC	Methanol: 10m M Ammonium acetate buffer (30: 70 v/v)	97
139	Vildagliptin	HPLC	0.01 M Phosphate buffer (pH- 5.3): Acetonitrile (30: 70 v/v)	97
140	Vildagliptin	HPLC	Dilute phosphoric acid solution (pH-2.6): Acetonitrile (40: 60 v/v)	97
141	Vildagliptin	RP- HPLC (Stability indicating)	Sodium dihydrogen phosphate buffer (pH-6.5): Acetonitrile (50: 50 v/v)	98
142	Vildagliptin	RP- HPLC	Dilute phosphoric acid solution (pH-2.6 ± 0.5): Acetonitrile (40: 60 v/v)	99
143	Vildagliptin	RP- HPLC	10m M Phosphate buffer (pH- 4.6): Acetonitrile (85: 15 v/v)	100
144	Vildagliptin	RP- HPLC	Buffer (pH-8.2): Acetonitrile: Methanol (450: 480: 70 v/v/v)	101
145	Vildagliptin	RP- HPLC	Buffer (pH-6.0): Acetonitrile: Methanol (70: 10: 20 v/v/v)	102
146	Vildagliptin	RP- HPLC	0.1 M Phosphate buffer: Acetonitrile (85: 15 v/v)	103
147	Vildagliptin	RP- HPLC	Methanol: Water (pH- 4.5) (60: 40v/v)	104
148	Vildagliptin	RP- UHPLC	Phosphate buffer (pH-6.8): Acetonitrile (67: 33 v/v)	105
149	Vildagliptin	UFLC (Chiral)	20m M Borax buffer (pH-9.0 ± 0.05): Acetonitrile: 0.1% Triethylamine (50: 50: 0.1 v/v/v)	106
150	Vildagliptin	RP- HPLC (Stability indicating)	Acetonitrile: 0.3% Triethylamine (pH-7.0) (15: 85 v/v)	107
151	Vildagliptin	LC- MS/ MS (Rat plasma)	Ammonium acetate buffer: Acetonitrile (20:80 v/v)	108
152	Vildagliptin	LC- MS (Degradation products)	Ammonium acetate buffer (pH- 7.5): Methanol	109
153	Vildagliptin	LC- MS/ MS (Diabetic rats)	Methanol: Ammonium acetate 5m M (95: 5 v/v)	110
154	Vildagliptin	LC- MS/ MS	0.1% Ammonium acetate solution: Acetonitrile (90: 10 v/v)	97
155	Vildagliptin	LC- MS/ MS	Acetonitrile: 2m M Ammonium acetate (90: 10 v/v)	97
156	Vildagliptin	HPLC- MS (Stability indicating)	Acetonitrile: Water (40: 60 v/v) (pH-7.0)	111
157	Vildagliptin	HPLC- MS (Genotoxic impurities)	Mobile phase- A mixture of water–methanol (55: 45 v/v) containing 2.5m M ammonium acetate and 0.1% formic acid.	112
158	Vildagliptin	HPTLC (Stability indicating)	Ethyl acetate: ethanol (8.5: 1.5 v/v)	113
159	Vildagliptin	HPTLC	Isopropyl alcohol: Methanol: Ammonia Solution (6: 4: 0.2 v/v/v)	114
160	Vildagliptin	HPTLC	Chloroform: n-butanol: Methanol (5: 2: 3 v/v/v)	115
161	Alogliptin	Visible method	Method A= 0.4% Picric acid Method B= 0.1% 2, 4 dinitrophenol	116

			(Solvent- chloroform)	
162	Alogliptin	Visible method	Bromate- bromide solution (Solvent- methanol+ water)	117
163	Alogliptin	Spectrofluorometry	Eosin Y	118
164	Alogliptin	Spectrofluorometry	Fluorescamine (alkaline medium) (borate buffer, pH- 8.8)	119
165	Alogliptin	Spectrofluorometry	Acetylacetone and formaldehyde (Hantzsch condensation reaction)	120
166	Alogliptin	RP- HPLC	Methanol: Double distilled water (80: 20 V/V) (pH-6.8)	121
167	Alogliptin	RP- HPLC	Potassium dihydrogen phosphate (pH- 2.9): Acetonitrile (60: 40 V/V)	122
168	Alogliptin	RP- HPLC	0.1% Trifluoroacetic acid in water: Acetonitrile (62: 38 V/V)	123
169	Alogliptin	LC	Potassium dihydrogen phosphate (pH- 4.6): Acetonitrile (20: 80 V/V)	124
170	Alogliptin	LC- CAD & LC- UV	Acetonitrile: 10m M Ammonium acetate buffer (pH- 3.5) (90: 10 V/V)	125
171	Alogliptin	RP- HPLC	Acetonitrile: 1-octasulphonic acid (0.005m H) (pH- 5.0) (60: 40v/v)	126
172	Alogliptin	RP- HPLC	Water: Acetonitrile (70: 30 V/V)	127
173	Alogliptin	RP- HPLC	Potassium dihydrogen phosphate (pH- 3.1): Methanol (60: 40 V/V)	128
174	Alogliptin	HPLC	Methanol: 0.01% Formic acid (70: 30 V/V)	97
175	Alogliptin	HPLC/ UV (Process related impurities)	A= 0.1% Perchloric acid (pH- 3): Acetonitrile (90: 10 V/V) B= 0.1% Perchloric acid (pH- 3): Acetonitrile (40: 60 V/V)	129
176	Alogliptin & Alogliptin D_3 (IS)	LC- MS/ MS (in rabbit plasma)	0.1% Formic acid: Acetonitrile: Methanol (30: 56: 14 V/V/V)	130
177	Alogliptin & Alogliptin D_3 (IS)	LC- ESI/ MS/ MS (spiked human plasma)	A binary mixture of 0.3% formic and acetonitrile (20: 80 V/V)	131
178	Alogliptin & Alogliptin D_3 (IS)	UPLC- MS/ MS (in rat plasma)	A= 0.1% Formic acid B= Acetonitrile	132
179	Alogliptin & Alogliptin D_3 (IS)	RP- HPLC- MS (genotoxic impurities)	Mobile phase a mixture containing water- methanol (55: 45 V/V) 2.5m M ammonium acetate and 0.1% formic acid	133
180	Alogliptin & Alogliptin D_3 (IS)	HPTLC	Benzene: Ethyl acetate: Triethylamine (7.5: 2: 0.5 V/V/V)	134
181	Alogliptin benzoate	UV- Spectrophotometry Zero order	Methanol	135
182	Alogliptin benzoate	UV- Spectrophotometry First order derivative	0.1M HCl + double distilled water	136
183	Alogliptin benzoate	Spectrofluorometry (biofluids)	4- chloro- 7-nitrobenzofuran (NBD- Cl) (borate buffer, pH- 8.5)	137
184	Alogliptin benzoate	HPLC (impurities)	A= Water: Acetonitrile: Trifluoroacetic acid (1900: 100: 1 V/V/V) B= Acetonitrile: Water: Trifluoroacetic acid (1900: 100: 1 V/V/V)	138
185	Alogliptin benzoate	HPLC	Acetonitrile: Ammonium carbonate buffer (55: 45 V/V)	139
186	Alogliptin benzoate	RP- HPLC (Process related impurities & force degradation products)	A= 0.1% Perchloric acid (pH- 3.0 with triethyl amine) B= Acetonitrile	140
187	Alogliptin	HPLC/ UV (Human plasma)	50m M Phosphate buffer (pH- 2.5) :	141

	benzoate		Acetonitrile (70: 30 V/V)	
188	Alogliptin benzoate	Chiral HPLC	Ethanol: Diethylamine (100: 0.5 V/V)	142
189	Alogliptin benzoate	HPLC (Stability indicating)	Water: Acetonitrile (80: 20 V/V) (pH-4.5)	143
190	Alogliptin benzoate	RP- HPLC	Methanol: 10m M Ammonium acetate buffer (pH- 5.0) (80: 20 V/V)	135
191	Alogliptin benzoate	RP- HPLC	Acetonitrile: Water (40: 60 V/V)	144
192	Alogliptin benzoate	LC- QTOF/ MS (Related substance and major degradation products)	A= 0.2% Formic acid -0.2% Ammonium acetate in water B= Acetonitrile and methanol (60: 40 V/V)	145
193	Alogliptin benzoate	HPTLC	Acetonitrile: 1% Ammonium acetate in methanol (4.5: 5.5 V/V)	146
194	Alogliptin benzoate	HPTLC (Degradation study)	Chloroform: Methanol: Ethyl acetate: Triethylamine (9: 1: 1: 5 V/V)	147
195	Alogliptin benzoate	HPTLC	Chloroform: Methanol (3: 7 V/V)	148
196	Alogliptin benzoate	HPTLC (Stability indicating)	Acetic acid: Water: n-butanol (1: 2: 7 V/V/)	143
197	Alogliptin phosphate monohydrate	RP- HPLC	Water: Methanol (75: 25 V/V)	149
198	Teneligliptin	UV- Spectrophotometry Zero order	Methanol	150
199	Teneligliptin	UV- Spectrophotometry Zero order (Stress degradation study)	Methanol	151
200	Teneligliptin	UV- Spectrophotometry Zero order	DMSO (dimethyl sulfoxide)	152
201	Teneligliptin	UV- Spectrophotometry AUC	Methanol & Water (50: 50 V/V)	153
202	Teneligliptin	Colorimetry	Solvent: Ethanol Method A= Potassium thiocyanate & ferric chloride Method B= Ferric chloride & 2, 2 bipyridyl	154
203	Teneligliptin	RP- UFLC	Methanol: Acetonitrile (60: 40 V/V)	155
204	Teneligliptin	RP- HPLC	Methanol: Potassium dihydrogen phosphate (pH-3) (70: 30 V/V)	156
205	Teneligliptin	RP- HPLC	Mobile phase A= Acetonitrile, water, trifluoroacetic acid B= Acetonitrile and trifluoroacetic acid	157
206	Teneligliptin	RP- HPLC	0.05 M Potassium dihydrogen phosphate (pH-4.0): Acetonitrile (80: 20 V/V)	158
207	Teneligliptin	RP- HPLC (Stability studies)	Phosphate buffer (pH- 6.0): Acetonitrile (60: 40 V/V)	159
208	Teneligliptin	UFLC (RP- HPLC) (Stability indicating)	0.1% Formic acid: Methanol: 0.1% Acetic acid (25: 75: 0.1 V/V/V)	160
209	Teneligliptin	HPLC (Chiral HPLC)	Ethanol: Acetonitrile: Ethanolamine (90: 10: 0.1 V/V/V)	161
210	Teneligliptin	RP- HPLC (assay)	Phosphate buffer (pH- 3.5): Acetonitrile (50: 50 V/V)	162
211	Teneligliptin	RP- HPLC (Rabbit plasma)	Methanol: 5m M Potassium dihydrogen phosphate (60: 40 V/V)	163
212	Teneligliptin	HPLC	Methanol: Potassium dihydrogen phosphate (60: 40 V/V) (pH- 3)	164
213	Teneligliptin	HPLC	A= Acetonitrile: Water: Trifluoroacetic acid (60: 1940: 2 V/V/V)	164

			B= Acetonitrile: Trifluoroacetic acid (2000: 2 V/V)	
214	Teneligliptin	HPLC	Acetonitrile: Methanol: Water (30: 40: 30 V/V/V)	164
215	Teneligliptin	UFLC	Methanol: Acetonitrile: Potassium dihydrogen orthophosphate (pH- 4.6) (40: 20: 40 V/V/V)	164
216	Teneligliptin	LC	Methanol: Formic acid (75: 25 V/V)	165
217	Teneligliptin	LC- MS/ MS	A= 0.1% Formic acid in milli- q water B= 0.1% Formic acid in acetonitrile	164
218	Teneligliptin	LC- MS/ MS (rats)	A= 10m M Ammonium formate B= Acetonitrile	166
219	Teneligliptin	UPLC- MS/ MS (Identification of degradation products)	A= 10% Acetonitrile in water with 0.1% formic acid B= 90% Acetonitrile with 0.1% formic acid	159
220	Teneligliptin	HPTLC	Butanol: Water: Glacial acetic acid (6: 2: 2 V/V/V)	167
221	Teneligliptin	HPTLC	0.25% Ammonium sulphate in water: Ethyl acetate: Methanol (10: 2.5: 2.5 V/V/V)	168
222	Teneligliptin	HPLTC	Methanol: Toluene: Triethylamine (1: 3: 1 V/V/V)	169
223	Teneligliptin	HPTLC	Toluene: Methanol: Glacial acetic acid: Triethylamine (5: 4: 0.5: 0.5 V/V/V/V)	164
224	Teneligliptin	HPTLC	Methanol: Ammonium sulphate: Triethylamine (9: 2.7: 0.5 V/V/V)	164
225	Teneligliptin	HPTLC	Methanol: Toluene: Triethylamine (1: 3: 1 V/V/V)	164
226	Teneligliptin	GC- MS GC- MS (Genotoxic sulphonate ester impurities)	DCM used as diluent Carrier gas-helium	170
227	Teneligliptin hydrobromide	UV- Spectrophotometry Zero order	Methanol + water	171
228	Teneligliptin hydrobromide	UV- Spectrophotometry Zero order	Water	172
229	Teneligliptin hydrobromide	HPLC	Methanol: Buffer (pH- 3.5) (72: 28 V/V)	173
230	Teneligliptin hydrobromide	HPTLC	Toluene: Chloroform: Ethanol: Diethylamine (4: 4: 1: 1 V/V/V/V)	172
231	Teneligliptin hydrobromide hydrate	UV- Spectrophotometry Zero order, First order derivative Area under curve	Distilled water	174
232	Teneligliptin hydrobromide hydrate	RP- HPLC	Methanol: Phosphate buffer (pH- 7.2) (70: 30 V/V)	175
233	Teneligliptin hydrobromide hydrate	RP- HPLC	Phosphate buffer (pH-5.5): Methanol (75: 25 V/V)	176
234	Teneligliptin hydrobromide hydrate	LC- MS/ MS (impurities)	Methanol: Ammonium formate (80: 20 V/V)	177
235	Teneligliptin hydrobromide hydrate	HPTLC	Toluene: Methanol: Triethylamine (8: 2: 0.2 V/V)	178
236	Trelagliptin	UV- Spectrophotometry	Methanol	179

		Zero order		
237	Trelagliptin	HPLC (Chiral)	Hexane: Ethanol: Diethylamine (70: 30: 0.1 V/V/V)	180
238	Trelagliptin	Chiral LC	n- hexane: 2- propanol (90: 10 V/V)	181
239	Trelagliptin	UPLC- UV	Acetonitrile: 0.05 M Potassium dihydrogen phosphate (pH- 3.5) (50: 50 V/V)	179
240	Trelagliptin	UPLC- MS/ MS	Acetonitrile: 0.1% Formic acid (80: 20 V/V)	179
241	Trelagliptin	UHPLC- MS/ MS (Rat plasma)	A= Acetonitrile B= 0.1% Formic acid	182
242	Trelagliptin	LC- MS/ MS (Beagle dog plasma)	A= Acetonitrile B= 5 Ammonium carbonate	183
243	Trelagliptin succinate	HPLC	A= 0.05% Trifluoroacetic acid in water B= 0.05% Trifluoroacetic acid in acetonitrile	184
244	Trelagliptin succinate	HPLC (impurities)	Acetonitrile & 20m M Potassium dihydrogen phosphate with 0.25% triethylamine (pH- 3.5)	185
245	Trelagliptin succinate	HPLC	A= Buffer B= Mixture of buffer: Acetonitrile (20: 80 V/V)	186
246	Omarigliptin	Spectrofluorometry	0.5% w/v Tween 80 + 0.2 M Phosphate buffer (pH-3.5) Diluent: Water	187
247	Omarigliptin	HPLC (Degradation study)	10µ M Phosphate buffer: Methanol (45: 55 V/V)	188
248	Omarigliptin	HPLC	Phosphate buffer (pH- 3.5): Acetonitrile (80: 20 V/V)	189
249	Omarigliptin	HPLC/ DAD	First condition: 0.1% Phosphoric acid & Acetonitrile Second condition: 10m M Potassium dihydrogen phosphate (pH- 7) & methanol	190
250	Omarigliptin	LC- MS	A= Water, 0.06% Trifluoroacetic acid B= Acetonitrile, 0.05% Trifluoroacetic acid	190
251	Omarigliptin	LC- MS/ MS (Human plasma)	Acetonitrile: 0.3% Formic acid (90: 10 V/V)	191
252	Omarigliptin	UHPLC- MS/ MS (Rat plasma)	A= 0.1% Formic acid B= Acetonitrile	192
253	Omarigliptin	TLC	Methanol: Ethyl acetate: 3% Ammonia (2: 8: 1 V/V/V)	189
254	Anagliptin phosphate	UV- Spectrophotometry Method 1: Zero order spectrometry using AUC Method 2: First-order derivative using amplitude Method 3: First-order derivative using AUC Method 4: Second-order derivative using amplitude Method 5: Second-order derivative using AUC	Water	193
255	Anagliptin phosphate	RP- HPLC (Stability indicating)	A= Acetate buffer (10m M, pH- 5): Methanol: Acetonitrile (90: 5: 5 V/V/V) B= Acetate buffer (10m M, pH- 5): Methanol: Acetonitrile (50: 25: 25 V/V/V)	194
256	Anagliptin phosphate	Chiral HPLC	Hexane: Ethanol: Diethylamine (80: 20: 0.1 V/V/V)	195

257	Anagliptin phosphate	NP- HPTLC	Dichloromethane: Methanol (9.2: 0.8 V/V)	196
258	Evogliptin tartrate	UV- Spectrophotometry Zero order	Deionized water	197
259	Evogliptin tartrate	RP- HPLC	Buffer (pH- 4.5): Methanol (45: 55 V/V)	198
260	Evogliptin tartrate	RP- HPLC (Stability indicating)	Methanol: Water: Trifluoroacetic acid (70: 30: 0.1 V/V/V)	199
261	Evogliptin tartrate	RP- HPLC	Methanol: Water: Acetonitrile (70: 20: 10 V/V/V)	200
262	Evogliptin tartrate	RP-HPLC	Phosphate buffer (pH=4.5) : Methanol (60: 40 % v/v)	201
262	Gemigliptin	Visible method	Ninhydrin (alkaline medium, pH- 10 with borate buffer)	202

II. CONCLUSION

Globally, diabetes is a minacious disorder which is remarkably influencing the human population. Research and development for DPP-4 inhibitors have been one of the largest activities in the pharmaceutical field. This review represents the reported spectrophotometric and chromatographic methods developed and validated for estimation of DPP-4 inhibitors. A vast range of techniques are available for determination of DPP-4 inhibitors in bulk, pharmaceutical dosage form and in biological fluids. It is found that different types of DPP-4 inhibitors are investigated by using variety of methods like UV-Vis spectrophotometry, spectrofluorometric, HPLC, UFLC, LC-MS, LC-MS/MS, HPLC-MS, GC-MS and HPTLC. The evaluation of published literature revealed that amongst the available methods UV-Spectrophotometric and HPLC are the most common techniques employed for investigation of DPP-4 inhibitors in bulk and in dosage form. It also concluded that HPLC is also considerably used for stability and degradation studies. This literature assessment pointed up that hyphenated techniques such as LC-MS, LC-MS/MS, UHPLC-MS/MS and GC-MS are versatile tools for separation and quantitation of metabolites of DPP-4 inhibitors in biological fluids and to obtain essential pharmacokinetic data. Analytical method development allows analyst to gain the data for certain problems such as sensitivity, accuracy and range etc. The methods which are stated in this review can be developed on this basis and can be implemented to pharmaceutical fields like drug testing and daily regular analysis in biological analysis and in quality control of these drugs.

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