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VILDAGLIPTIN: A COMPREHENSIVE REVIEW ON ITS PHARMACOLOGICAL, PHARMACEUTICAL AND ANALYTICAL PROFILE

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ABSTRACT:

This review article presents a comprehensive and in-depth analysis of vildagliptin, a widely prescribed dipeptidyl peptidase-4 (DPP-4) inhibitor for the management of type II diabetes mellitus. The article synthesizes a wealth of information regarding the pharmacological, pharmaceutical, and analytical aspects of vildagliptin. The pharmacological profile encompasses its mechanism of action, clinical efficacy, safety, and potential interactions, offering a well-rounded understanding of its therapeutic impact. Furthermore, the pharmaceutical perspective delves into formulation strategies, dosage forms, and novel delivery methods, shedding light on the diverse approaches taken to optimize drug delivery and patient compliance. In parallel, the review addresses the analytical methods employed for Vildagliptin quantification, exploring advances in chromatographic, spectroscopic, and other techniques that ensure accurate and precise assessment of the drug in various matrices. This comprehensive synthesis of vildagliptin's multifaceted attributes serves as a valuable resource for clinicians, researchers, and pharmaceutical professionals, offering insights that can potentially inform future therapeutic advancements and research endeavours in the realm of diabetes management and drug development.

Keywords: Vildagliptin, Dipeptidyl peptidase-4 (DPP-4) inhibitor, Optimize drug delivery, Chromatography, Spectroscopy.

Introduction:

Vilidagliptin (LAF237) inhibits dipeptidyl peptidase-4 (DPP-4) selectively in the body to control blood sugar levels. A drug that inhibits GLP-1 secretion and insulinotropic effects is prescribed for the management of type II diabetes mellitus. Vildagliptin inhibits DPP-4, which leads to the destruction of glucose-dependent insulinotropic polypeptide (GIP), which is an incretin hormone that stimulates insulin secretion and regulates blood sugar levels. Consequently, GLP-1 and GIP levels are elevated, which leads to improved glycemic control. The risk of hypoglycemia associated with vildagliptin is relatively low in clinical trials. [1]

During 2008, the European Medicines Agency approved oral vildagliptin for treatment of adults with type II diabetes mellitus, either alone or in combination with metformin, sulfonylureas, or thiazolidinediones in patients who did not achieve adequate glycemic control with monotherapy. Galvus is the brand name for this drug. The fixed-dose formulation of vildagliptin, Eucreas, is also available for adults whose glycemic control is not adequate with vildagliptin alone. Vildagliptin is currently under investigation in the US.

Description:

Drug Profile:

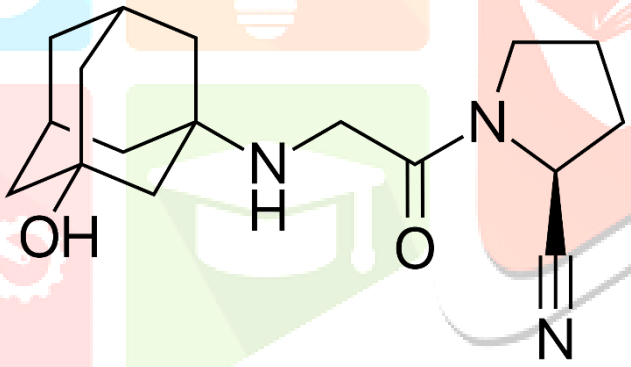

Figure 1: Chemical Structure of Vildagliptin

Table 1: Drug Profile of Vildagliptin [2]

DRUG	Vildagliptin
IUPAC Name	(2S)-1-{2-[(3-hydroxyadamantan-1-yl) amino] acetyl) pyrrolidine -2-carbonitrile
Chemical Formula	$C_{17}H_{25}N_3O_2$
Molecular Mass	303.3993 g/mole
Melting Point	153-l55°C
Physical State	Solid
Solubility	Soluble in Water and Methanol
pKa	14.71 and 9.03 Strongest acidic and basic respectively
t1/2	90 minutes
Therapeutic Use	Used to reduce hyperglycaemia in type II diabetes mellitus.

Pharmacology

Pharmacodynamics

Pharmacotherapeutic group:

Diabetes medications, dipeptidyl peptidase-4 inhibitors, ATC code: A10BH02 A potent and selective DPP-4 inhibitor, vildagliptin belongs to the islet enhancer class.

Pharmacodynamic effects

In addition to increasing endogenous levels of these incretin hormones, vildagliptin improves glucose-dependent insulin secretion by improving beta cell sensitivity. Treatment with vildagliptin 50-100 mg daily in patients with type 2 diabetes significantly improved markers of beta cell function including HOMA-β (Homeostasis Model Assessment–β), proinsulin to insulin ratio and measures of beta cell responsiveness from the frequently-sampled meal tolerance test. In non-diabetic (normal glycaemic) individuals, vildagliptin does not stimulate insulin secretion or reduce glucose levels.

As vildagliptin enhances endogenous GLP-1 levels, it also stimulates the secretion of glucose-sensitive glucagon by alpha cells.

A decrease in fasting and postprandial hepatic glucose production results from an enhanced increase in the insulin/glucagon ratio during hyperglycaemia due to increased incretin hormone levels. The known effect of increased GLP-1 levels delaying gastric emptying is not observed with vildagliptin treatment.

Pharmacokinetics

Absorption

Vildagliptin is rapidly absorbed following oral administration in the fasting state, with peak plasma concentrations observed at 1.7 hours. AUC does not change when food is consumed, but the time to peak plasma concentration is delayed to 2.5 hours. Food-related administration of vildagliptin reduced Cmax (19%). Galvus can be taken with or without food, since the magnitude of the change is not clinically significant. There is an absolute bioavailability of 85%.

Distribution

Vildagliptin is poorly bound to plasma proteins (9.3%), and it is equally distributed between plasma and red blood cells. Upon intravenous administration of vildagliptin, the mean volume of distribution is 71 litres, indicating extravascular distribution.

Biotransformation

Vildagliptin is mainly eliminated by metabolism in humans, accounting for 69% of its dose. A major metabolite of BQS 867, LAY 151, is inactive and is formed during the hydrolysis of the cyano moiety. It accounts for 57% of the dose. The kidney may be an important organ in the hydrolysis of vildagliptin to its major inactive metabolite, LAY151, in vitro in human kidney microsomes. A study in vivo using rats with DPP-4 deficiencies found that DPP-4 contributes to the hydrolysis of vildagliptin. No quantifiable amount of vildagliptin is metabolized by CYP 450 enzymes. Consequently, co-medications that inhibit or induce CYP 450 should not affect the metabolic clearance of vildagliptin. During in vitro studies, vildagliptin was shown

not to inhibit or induce CYP 450 enzymes. The metabolism of co-medications metabolized by CYP 1A2, CYP 2C8, CYP 2C9, CYP 2C19, CYP 2D6, CYP 2E1 or CYP 3A4/5 is unlikely to be affected by vildagliptin.

Elimination

A dose of [14C] vildagliptin is excreted by approximately 85% in the urine and 15% in the feces following oral administration. Approximately 23% of the unchanged vildagliptin dose was excreted in the urine after oral administration. Vildagliptin has a total plasma clearance of 41 and a renal clearance of 13 l/h in healthy subjects after intravenous administration. A two-hour elimination half-life is typical after intravenous administration. The elimination half-life after oral administration is approximately 3 hours.

Linearity/non-linearity

As the therapeutic dose range for vildagliptin increased, the C_{max} and the area under the plasma concentration time curves (AUC) increased approximately dose proportionally.

Mechanism of action

It regulates blood glucose levels and maintains glucose homeostasis by acting on two incretin hormones, glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1). An oral glucose challenge is estimated to stimulate insulin responses through the action of GLP-1 and GIP by more than 70%. The GIP and GLP-1 receptors are G-protein-coupled and activate insulin secretion in a glucose-dependent manner. Additionally, GLP-1 promotes islet neogenesis and differentiation, and attenuates pancreatic beta-cell apoptosis in addition to its effects on insulin secretion. In type II diabetes mellitus, GLP-1 secretion is impaired, and the insulinotropic effect of GIP is significantly diminished. The incretin hormones also exert extra-pancreatic effects, such as lipogenesis and myocardial function.[1]

Vildagliptin lowers blood glucose by selectively inhibiting dipeptidyl peptidase-4 (DPP-4), an enzyme responsible for truncating and inactivating GLP-1 and GIP upon their release from intestinal cells. After the second amino acid from the N-terminal end, DPP-4 cleaves oligopeptides. As a result of the inhibition of DPP-4, GLP-1 and GIP half-lives are prolonged, increasing levels of active circulating incretin hormones.3 Vildagliptin inhibits DPP-4 for a dose-dependent duration.5 Vildagliptin reduces fasting and prandial glucose and HbA1c levels. It enhances the glucose sensitivity of alpha- and beta-cells and augments glucose-dependent insulin secretion. Fasting and postprandial glucose levels are decreased, and postprandial lipid and lipoprotein metabolism are also improved [3]. Mechanism of action of Vildagliptin was shown in Figure 2

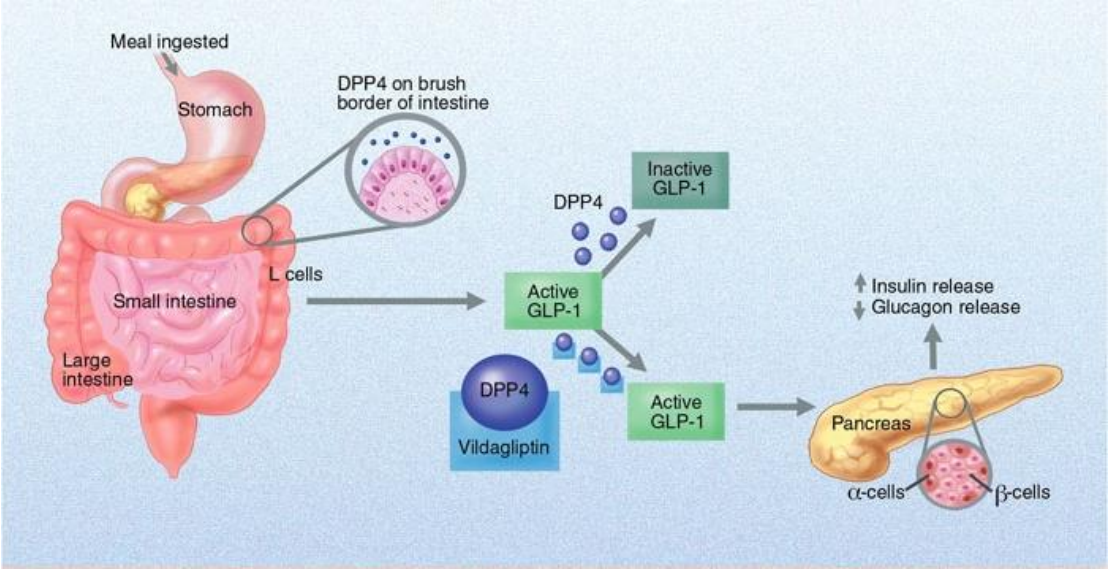

Figure 2: Mechanism of action of Vildagliptin [6]

Toxicity

The oral Lowest published toxic dose (TDLO) is 0.3 mg/kg in rats and 1 mg/kg in mice. [5]

There is limited information regarding overdose with vildagliptin. In one study, patients experienced muscle pain, mild and transient paresthesia, fever, edema, and a transient increase in lipase levels at a dose of 400 mg. At 600 mg, one subject experienced edema of the feet and hands and increases in creatine phosphokinase (CPK), aspartate aminotransferase (AST), C-reactive protein (CRP) and myoglobin levels. Supportive management is recommended in case of an overdose. There is no known antidote, and vildagliptin and its major metabolite cannot be removed via hemodialysis. [4]

Description of selected adverse reactions

Hepatic impairment

Rare cases of hepatic dysfunction (including hepatitis) have been reported. In these cases, the patients were generally asymptomatic without clinical sequelae and liver function returned to normal after discontinuation of treatment. In data from controlled monotherapy and add-on therapy trials of up to 24 weeks in duration, the incidence of ALT or AST elevations 3x ULN (classified as present on at least 2 consecutive measurements or at the final on-treatment visit) was 0.2%, 0.3% and 0.2% for vildagliptin 50 mg once daily, vildagliptin 50 mg twice daily and all comparators, respectively. These elevations in transaminases were generally asymptomatic, non-progressive in nature and not associated with cholestasis or jaundice.

Angioedema

Rare cases of angioedema have been reported on vildagliptin at a similar rate to controls. A greater proportion of cases were reported when vildagliptin was administered in combination with an angiotensin converting enzyme inhibitor (ACE-Inhibitor). The majority of events were mild in severity and resolved with ongoing vildagliptin treatment.

Hypoglycaemia

Hypoglycaemia was uncommon when vildagliptin (0.4%) was used as monotherapy in comparative controlled monotherapy studies with an active comparator or placebo (0.2%). No severe or serious events of hypoglycaemia were reported. When used as add-on to metformin, hypoglycaemia occurred in 1% of

vildagliptin-treated patients and in 0.4% of placebo-treated patients. When pioglitazone was added, hypoglycaemia occurred in 0.6% of vildagliptin-treated patients and in 1.9% of placebo-treated patients. When sulphonylurea was added, hypoglycaemia occurred in 1.2% of vildagliptin treated patients and in 0.6% of placebo-treated patients. When sulphonylurea and metformin were added, hypoglycaemia occurred in 5.1% of vildagliptin treated patients and in 1.9% of placebo treated patients. In patients taking vildagliptin in combination with insulin, the incidence of hypoglycaemia was 14% for vildagliptin and 16% for placebo.

Overdose

Symptoms

Information on the likely symptoms of overdose was taken from a rising dose tolerability study in healthy subjects given Galvus for 10 days. At 400 mg, there were three cases of muscle pain, and individual cases of mild and transient paraesthesia, fever, oedema and a transient increase in lipase levels. At 600 mg, one subject experienced oedema of the feet and hands, and increases in creatine phosphokinase (CPK), aspartate aminotransferase (AST), C-reactive protein (CRP) and myoglobin levels. Three other subjects experienced oedema of the feet, with paraesthesia in two cases. All symptoms and laboratory abnormalities resolved without treatment after discontinuation of the study medicinal product.

Table 1: Adverse reactions reported in patients who received vildagliptin as monotherapy or as add-on therapy in controlled clinical studies and in post-marketing experience. [4]

System organ class - adverse reaction	**Frequency**
Infections and infestations	
Nasopharyngitis	Very common
Upper respiratory tract infection	Common
Metabolism and nutrition disorders	
Hypoglycaemia	Uncommon
Nervous system disorders	
Dizziness	Common
Headache	Common
Tremor	Common
Eye disorders	
Vision blurred	Common
Gastrointestinal disorders	
Constipation	Common
Nausea	Common
Gastro-oesophageal reflux disease	Common
Diarrhoea	Common
Abdominal pain, including upper	Common
Vomiting	Common
Flatulence	Uncommon
Pancreatitis	Rare
Hepatobiliary disorders	
Hepatitis	Not known*
Skin and subcutaneous tissue disorders	
Hyperhidrosis	Common
Rash	Common
Pruritis	Common
Dermatitis	Common
Urticaria	Uncommon

Exfoliative and bullous skin lesions, including bullous pemphigoid	Not known*
Cutaneous vasculitis	Not known*
Musculoskeletal and connective tissue disorders	
Arthralgia	Common
Myalgia	Common
Reproductive system and breast disorders	
Erectile dysfunction	Uncommon
General disorders and administration site conditions	
Asthenia	Common
Oedema peripheral	Common
Fatigue	Uncommon
Chills	Uncommon
Investigations	
Abnormal liver function tests	Uncommon
Weight increase	Uncommon
* Based on post-marketing experience.	

Management

In the event of an overdose, supportive management is recommended. Vildagliptin cannot be removed by haemodialysis. However, the major hydrolysis metabolite (LAY 151) can be removed by haemodialysis.

Table 2: Available marketed formulations of Vildagliptin

Name	Dosage form	Strength	Route	Manufacturer
Galvus	Tablet	50 mg	Oral	Novartis India Ltd.
Jalra	Tablet	50 mg	Oral	USV Ltd.
Xiliarx	Tablet	50 mg	Oral	European Medicines Agency
Gliptagreat	Tablet	50 mg	Oral	Mankind Pharma Ltd
Vildazem	Tablet	50 mg	Oral	Zeelab Pharmacy Pvt Ltd
Zomelis	Tablet	50 mg	Oral	Eris Lifesciences Ltd

Table 3: List of Analytical methods available for Vildagliptin estimation

S. No.	Parameters		Results	
Method: UV				
1[7]	System	Shimadzu UV-1800 double beam spectrophotometer	Linearity range	2-32 µg/mL
			λ_{max}	268 nm
			accuracy	97.78%
			R^2	0.9997
			%RSD	1.27573%
			LOD	1.46053 µg/mL
			LOQ	3.46748 µg/mL
2[8]	System	UV-Vis double beam spectrophotometer	Linearity range	5-30 µg/mL
			R^2	0.9987
			LOD	2.54 µg/mL
			LOQ	4.69 µg/mL
			% RSD	0.85%

3[9]	System	Shimadzu 1800 spectronic UV-Visible spectrophotometric (Shimadzu corporation , japan)		
	λ_{max}	218.25 nm		
	Linearity range	60-100 µg/mL		
	R^2	0.998		
4[10]	System	UV-Visible spectrophotometer (Shimadzu UV-1800 spectrophotometer, Shimadzu, Japan)	Linearity range	8-32 µg/mL
			Wavelength	197 nm
			R^2	0.999
			LOD	0.247 µg/mL
			LOQ	0.748 µg/mL
			% RSD	< 2%
5[11]	System	UV-Vis spectrophotometer 1600 (shimadzu, japan)	Linearity range	1-60 µg/mL
			R^2	≥ 0.999
			Wavelength	207.2-230.6 Nm
			LOD	0.272 µg/mL
			LOQ	0.827 µg/mL
			% RSD	< ± 2%
6[12]	System	LABINDIA spectrophotometer	Linearity range	0.35-1.05 µg/mL
			Concentratioon range	0.7-1.0 µg/mL
			Wavelength	217 nm
			R^2	0.999
			LOD	0.023 µg/mL
			LOQ	0.225 µg/mL
			% RSD	< 2%
7[13]	System	Ultraviolet visible (UVVIS) spectrophotometer (Shimadzu model 18001 (Shimadzu, Kyoto, Japan))	Linearity range	10-40 µg/mL
			Wavelength	202.5 nm
			R^2	0.999
			LOD	0.055 µg/mL
			LOQ	0.166 µg/mL
			% RSD	<2%
Method: LC				
8[14]	System	Agilent liquid chromatography (Santa clara,CA)	Linearity	20-80 µg/mL
	Column	X Brdge analytical column C8 (130x4.6 mm I.d., 5 µm particle size) (waters)	Retention time	6.2 min
	Column temperature	Room temperature (23± 1^0C)	%RSD	0.61%
	Mobile phase	Acetonitrile and a solution of triethylamine 0.3% adjusted to pH 7.0 with phsphoric acid (15:85; v/v)	LOD	0.63 µg/mL
	Flow rate	1.0 mL /min	LOQ	2.82 µg/mL
	Injection volume	20 µL		
	Detector	Photo diode array detector		
	Detection wavelength	207 nm		

9[15]	System	Liquid Chromatography System	Retention time	Vildagliptin-5.41 min
	Column	Thermo Hypersil ODS C18 column (5 µm, 4.6x250 mm)	%RSD	1.32 and 1.53%
	Mobile phase	0.1M phosphate buffer (pH 3.5), Acetonitrile and methanol (65%:30%:5% v/v)	Linearity range	2.5-7.5 µg/mL
	Flow rate	0.8 mL/min)	R^2	0.9903
	Detector	PC 220 UV/visible Detector	LOD	0.13 µg/mL
	Detection wavelength	212 nm	LOQ	0.13 µg/mL
10[16]	Column	XBridge C8 (150x4.6 mm, 5 µm)	Linearity range	20-80 µg/mL
	Mobile phase	acetonitriletriethylamine 0.3%, pH 7.0 (15:85		
	Flow rate	1.0 ml/min		
	Detection wavelength	UV 207 nm	LOD	0.63 µg/mL
			LOQ	2.82 µg/mL
Method: HPLC				
11[17]	System	Shimadzu model LC2010CHT HPLC system	Linearity range	2-40 Ppm
			R^2	0.9997
	Column	Phenomenex Luna C18 (2) column (4.6mmx 250mm, 5µ)	LOD	0.715 Ppm
			LOQ	2.166 Ppm
	Wavelength	219.6 nm	% RSD	0.12%
12[18]	System	Shimadzu LC-20AT HPLC manual system	Linearity range	5-25 µg/mL
	Column	Phenomenex Luna C18 (250 x 4.6 mm, 5 µm)	Theoretical plates	2241.76 Plates
	Column temperature	25^0 C	Retention time	1.37 min
	Mobile phase	70:30 % v/v methanol: acetate buffer (adjusted to pH 5.6 using OPA)	R^2	0.9954
	Flow rate	1 mL/min	LOD	1.05 µg/mL
	Injection volume	20 µL	LOQ	3.90 µg/mL
	Detector	PDA detector	% RSD	0.22%
	Detection wavelength	210 nm		
13[19]	System	Waters HPLC	Linearity range	50-90 µg/mL
	Column	C18 (4.6 x 150mm, 5mm)	R^2	0.999
	Mobile phase	pH 8.2 buffer, acetonitrile and methanol	LOD	2.98 g/mL
	Flow rate	0.5 mL/min	LOQ	9.94g/mL
	Injection volume	10 µL	% RSD	>2%
	Detection wavelength	UV detection at 254 nm		
	Run time	10 min		

14[20]	System	1. Shimadzu chromatographic system 2. Jasco 2000 chromatographic system	Linearity range	10-100 µg/mL
	Column	C18 column (4.6 × 150 mm id., particle size 5 µm)	R^2	0.999
	Mobile phase	10 mM phosphate buffer (pH 4.6) and acetonitrile (85 : 15, v/v)	LOD	1 µg/mL
	Flow rate	1.0 mL / min	LOQ	3.2 µg/mL
	Detector	1. SPDM20A detector (PDA) 2. UV2070/2075 UVVis detector	% RSD	2.25%
15[21]	System	Dionex Ultimate 3000 System used	Linearity range	1.0 mg/mL
	Column	C18-WP, 100A^0, (250 mm×4.6 mm),5µm particle size column	Theoretical plates	13200
	Mobile phase Column temperature	A buffer solution and methanol (90:10) B methanol , degassed 40^{0}C	R^2	>0.99
	Column temperature Mobile phase	40^{0}C A buffer solution and methanol (90:10) B methanol , degassed	% RSD	< 1.5%
	Flow rate	1 mL/min	LOD	0.018 µg/mL
	Injection volume	100 µL	LOQ	0.066 µg/mL
	Detection wavelength	208 nm		
16[22]	System	Waters pump HPLC system	Linearity range	5-25 µg/mL
	Column	Lichrocart C18 column (250 x 4.60 x 5µm)	Retention rate	6.64 min
	Mobile phase	0.05 M KH2PO4 : Acetonitrile (70:30 v/v, pH 3.5 with Ortho Phosphoric Acid)	Theoretical plates	1.97 Plates
	Flow rate	1.0 mL/min	R^2	0.999
	Detector	UV-Visible detector	% RSD	0.057
	Detection wavelength	215 nm		
17[23]	System	HPLC machine (Agilent Technologies 1200 series)	Linearity range	10-60 µg/mL
	Column	ZORBAX Rapid Resolution HT C18 columns (150 mm x 4.6 mm)	Retention time	5.017 min
	Column temperature	30^{0}C	Theoretical plates	5790 Plates
	Mobile phase	Buffer: Acetonitrile in the ratio of 50:50 (v/v)	R^2	0.9996
	Flow rate	1.0 mL/min	LOD	0.025 µg/mL
	Injection volume	20 µL	LOQ	0.054 µg/mL
	Detection wavelength	UV detector at 220 nm	%RSD	0.68 %
	Run time	10 min		
18[24]	System	Waters Alliance e2695	Linearity range	0.2-100 µg/mL
	Column	Xbridge BEH C18 column (5 µm, 4.6 × 250 mm) (Waters® Corporation, Milford, MA, USA)	Retention time	4.5 min

	Mobile phase	acetonitrile and monopotassium phosphate buffer (1.36 g/L) 49:51 (v/v)	LOD	0.08 µg/mL
	Flow rate	1.2 mL/min	R^2	>0.999
	Injection volume	20 µL		
	Detector	photodiode array detector (model 2998) (Waters Corporation, Mildford, MA, USA)		
	Detection wavelength	236 and 297 nm		
19[25]	System	Shimadzu Corporation (LC-2010C HT) model	Linear range	10-1000 ng/mL
	Column	C18 column	R^2	0.9992
	Mobile phase	A 50 mM ammonium bicarbonate (pH 7.8) B 100% acetonitrile	LOD	10 ng/mL
	Injection volume	20 µL		
	Detection wavelength	UV detector 210 nm		
	Run time	20 min		
20[26]	System	Shimadzu (Tokyo, Japan)	Linearity range	2-10 µg/mL
	Column	Onyx C18 Monolithic column (100mm× i.d., 5µm)	Retention time	2.821 min
	Mobile phase	MeOH: ACN: KH_2PO_4 at pH 4.0	R^2	0.998
	Flow rate	0.4 mL/min	LOD	0,123 ng/mL
	Detection wavelength	220 nm	LOQ	0.374 ng/mL
	Run time	8 min	% RSD	< 2%
21[27]	System	HPLC-grade water system	Linearity range	1-100 ppm
	Column	Unisphere Aqua C18 (4.6 x 150 mm, 3µ) column	R^2	0.9998
	Column temperature	40^0C	LOD	1.173 ppm
	Mobile phase	Buffer(pH-6.50):Acetonitrile:Methanol -55:44:1	LOQ	3.555 ppm
	Flow rate	1.2 mL/min	% RSD	1.07 %
	Injection volume	20 µL		
	Detection wavelength	210 nm		
22[28]	System	Shimadzu prominence LC20AP (Shimadzu Corporation, Tokyo, Japan)		
	Column	InertSustainSwift C18 (G L Sciences, Eindhoven, Netherlands) 500 mm × 30 mm, 10 m particle size		
	Mobile phase	Water and acetonitrile		
	Flow rate	10 mL/min		
	Detection wavelength	210 nm		
23[29]	System	RP-HPLC Shimadzu (Tokyo,Japan)	Retention Time	5 min
	Column	C18 segment (100 x 4.6 mm id, 5 µm molecule size)	R^2	0.998

	Mobile phase	MeOH, ACN, 0.01mM KH_2PO_4 (pH 3.5 0.5)adjusted with freshly prepared 10% orthophosphoric acid	LOD	0.013 µg/mL
	Flow rate	0.3-0.5 mL/min	LOQ	0.039 µg/mL
	Injection volume	20 µL		
	Detector	SPD-M20A prominence diode array detector		
	Detection wavelength	210 nm		
24[30]	System	Waters 2695 HPLC framework system	R^2	0.999
	Column	C18 section (150x4.6mm, 5 µm)	%RSD	0.649 %
	Column temperature	25 ^{0}C	LOD	0.25 µg/mL
	Mobile phase	Phosphate cushion, Acetonitrile and Menthol in the proportion of 30:05:65)	LOQ	0.08 µg/mL
	Flow rate	1 mL/min		
	Detector	UV locator and Engage 2 programming Detector are used		
	Detection wavelength	249 nm		
25[31]	System	Agilent 1260 Infinity system (Agilent Technologies, USA)	Linearity range	20-320 µg/mL
	Column	Inertsil ODS-3,4.6x250 mm,5 µm porosity (GL Science, Japan)	Recovery range	40-120 µg/mL
	Column temperature	34^0 C	%RSD	1.0-1.4%
	Mobile phase	MeOH ad TFA (0.1%v/v) in the proportion 52:48(v/v)	LOD	0.06 µg/mL
	Injection volume	20 µL	LOQ	0.20 µg/mL
	Detector	Diode array detector		
	Detection wavelength	321 nm		
26[32]	System	RP-HPLC System	Retention time	4.296 min
	Column	Kromsil C18 (4.6x250 mm, 5 mm) column	LOD	0.1 µg/mL
	Mobile phase	Phosphate buffer pH-5.8 and Acetonitrile in ratio of 80:20	LOQ	0.4 µg/mL
	Flow rate	1 mL/min	Percentage assay	99.2%
	Detector	Electronspray ionization- tandem mass spectrometry	Percentage recovery	100.1%

	Detection wavelength	215 nm		
27[33]	System	HPLC water 2469 system	Run time	10 min
	Column	C8 column 150x4.6 mm, 5 µm column	Retention time	6.5 min
	Column temperature	25 ^{0}C		
	Mobile phase	Buffer pH-3.0 and (ACN:Methanol) in the ratio of (80:19:1)		
	Flow rate	1.2 mL/min		
	Injection volume	10 µL		
	Detector	UV/PDA detector		
28[34]	System	Waters Alliance 2690 or 2795 HPLC system (water, Milford, MA)		
	Column	YMC ODS-AR C18 column (3 µm, 4.6x150 mm)		
	Column temperature	35 ^{0} C		
	Mobile phase	5 mM ammonium acetate containing 0.1% trifluoroacetic acid (pH-2.3)		
	Flow rate	1.0 mL/min		
	Injection volume	10 µL		
	Detector	Radioactivity detector with 250- µL liquid cell (INUS B- RAM, Tampa, FL)		
Method: HPLC-MS/MS				
29[35]	HPLC-MS/MS Plates	Oasis HLB 96-Well extraction plates using an automated system	LLOQ 2.0 ng/mL	
	Column	X Tera MS C18 5 µm column (150x2.1 mm; waters corp; Milford, MA, USA)		
	Mobile phase	(A): 40% (10 mmol/L ammonium acetate (pH 8) methanol (95:5, v/v)		
	Flow rate	0.2 mL/min		
	Detector	API 3000 electrospray ionization mass spectrophotometer (Applied Biosystems, Foster city, CA, USA)		
30[36]	System	6460 triple quadrupole mass spectrometer.	Retention time	5.3 min
	Column	C18 column (250 × 4.6 mm, 5-Hypersil Gold)	R^2	0.9999
	Mobile phase	acetonitrile and water (40:60)	Linearity range	2-12 µg/mL
	Flow rate	1 mL/min	LOD	3.61 ug/mL
	Detection wavelength	220 nm	LOQ	10.96 ug/mL
Method: UHPLC				
31[37]	System	Agilent 1290 series Ultra High-Performance Liquid Chromatography (US-CA)	Linearity range	20-100 µg/mL

	Column	Agilent Zorbax Eclipse Plus C18 (150×4.6mm, 5µm) column	R^2	0.999
	Column temperature	30^0C	LOD	2.20 µg/mL
	Mobile phase	Acetonitrile and Potassium dihydrogen phosphate buffer (80:20, v/v)	LOQ	7.33 µg/mL
	Flow rate	0.6 mL/min	% RSD	< 2%
	Injection volume	5 µL		
	Detector	DAD detection		
	Detection wavelength	270 nm		
Method: UHPLC-MS				
32[38]	System	Dionex Ultimate 3000RS device (Dionex, Sunnyvale, CA, USA)		
	Column	Kinetex XB-C18 column (150 × 2.1 mm, 1.7 µm)		
	Column temperature	25^0C		
	Mobile phase	A : 0.1% formic acid in deionized water B : 0.1% formic acid in acetonitrile		
	Flow rate	0.3 mL/min		
	Detection wavelength	190-450 nm		
Method: UPLC				
33[39]	System	Highly sensitive UPLC System	Linearity range	2.5-15 µg/mL
	Column	Acquity UPLC BEH C18 (2.1 × 50 mm, 1.7 µm) column	Theoretical plates	9417 Plates
	Colum temperature	25^0C		
	Mobile phase	0.05 M ammonium acetate buffer at pH 5.1 and methanol in the ratio of 45:65 (v/v)	Retention time	3.84 min
	Flow rate	0.3 mL/min	R^2	0.9995
	Detector	PDA detector	LOD	0.03 µg/mL
	Detection wavelength	215 nm	LOQ	0.01 µg/mL
Method: UPLC-MS/MS				
34[40]	System	Tandem Triple quadrupole mass spectrometer (AQUITY TQD)	Linearity	2-16 ng/mL
	Column	C18 (50x2.1 mm, 1.7 µm) column	LOD	1 mL/min
	Column temperature	15-20^0 C	LLOQ	100± 20 % accuracy or 20 ng/mL
	Mobile phase	0.5% Acetic acid in Methanol and 0.02M aqueous Ammonium Acetate (10:90, v/v)	Accuracy	99.78±0.78

	Flow rate	0.5 mL/min		
	Injection volume	10 µL		
	Detector	Tandem mass detector		
35[41]	System	ACQUITY UPLC sysem from waters corp.(Milford)	%RSD	Less than 5.0 %
	Column	ACQUITY UPLC BEH C8 column (2.1x50 mm , 1.7 µm, waters)	R^2	0.998
	Column temperature	35^0C	LOD	0.015 µg/mL
	Mobile phase	(A): water with 0.1% formic acid (B): methanol containing o.1% formic acid	LOQ	0.03 µg/mL
	Flow rate	0.3 mL/min	Accuracy	14.1 µg/mL
	Injection volume	1 µL		
	Detector	Xevo G2 Q-TOR mass spectrometer (waters) was equipped with an electrospray ionization source (ESI)		
	Detection wavelength	220 nm		
36[42]	System	HPG-3400 pump (Dionex UltiMate 3000 RSLC, Thermo Fisher Scientific, Germany)	Linearity range	0.025-1 µg/L
	Column	1.Acclaim RSLC C18 column (2.1 × 100 mm, 2.2 µm) from Thermo Fisher Scientific (Dreieich, Germany) 2.ACQUITY UPLC BEH C18 1.7 µm, VanGuard Pre-Column, Waters (Ireland)		
	Column temperature	30^0C	R^2	0.98
	Mobile phase	A H2O:MeOH (90:10) with 5 mM ammonium formate and 0.01 % formic acid B MeOH with 5 mM ammonium formate and 0.01 % formic acid		
	Injection volume	5 µL	% RSD	< 20%
Method: LC-MS				
37[43]	System	Model 515 pump system used	Linearity range	40-190 µg/mL
	Column	Purospher RP-18 end capped column (125 × 4.0 mm, 5 µm)	R^2	0.9997
	Mobile phase	2 mM ammonium acetate-acetonitrile (80:20, v/v)	LOD	2.99 µg/mL
	Flow rate	1.2 mL/min	LOQ	9.09 µg/mL
	Detector	model 2487 UV DAD detector	% RSD	0.26-0.55%
	Detection wavelength	210 nm		
38[44]	System	Shimadzu, Nexera-X2 (Shimadzu Corporation, Japan)		
	Column	Waters X Bridge C-18, 250 mm × 4.6 mm, 5.0 m (Milford, MA, USA) column		

	Column temperature	45^0C		
	Mobile phase	Solvent A 0.05% of ammonia solution, pH - 9.2 with 5 M acetic acid (v/v), Solvent-B: mixture of methanol-acetonitrile (50:50, v/v)		
	Flow rate	0.6 mL/min		
	Detection wavelength	210 nm		
39[45]	System	API3000 (Applied biosystems foster city, calif)	LOQ	2 ng/mL in 0.2 mL
	Column	X Terra MS C18 5 µm(150x2.1 mm) column		
	Column temperature	30 ^{0}C		
	Mobile phase	A(40%) : 10 mM Ammonium acetate-Methanol (95:5,v/v), pH8 B(60%) : Acetonitrile- Methanol (95:5,v/v)		
	Flow rate	0.2 mL/min		
	Detector	Quantum Discovery (Thermo finnigan, San Jose, calif) mass spectrometer		
40[46]	System	Micromass Quattro LC water		
	LC/MS/MS Plates	96-well polypropylene plate		
	Column	Polaris 5- µm C18-A 50x2.0 mm column		
	Column temperature	45^0 C		
	Mobile phase	(A): Methanol/10mM Ammonium acetate, pH 8.0 (5:95, v/v) (B): acetonitrile/Methanol (10:90, v/v)		
	Flow rate	0.2mL/min		
	Injection volume	10 µL		
41[47]	System	LC-MS system		
	Column	X Terra Ms C18 High- Performance liquid chromatography (HPLC) column (150x2.1 mm, waters Corp; Milford,MA, USA)		
	Mobile phase	(A): 40% (10 m mol/L ammonium acetate (pH-8): Methanol (95:5, v/v) (B): 60% (Acetonitrile: Methanol (10:90, v/v))		
	Flow rate	0..2 mL/min		
	Injection volume	10 µL		

	Detector	API 4000 electrospray ionization mass spectrometer (Applied Biosystems, Foster city, CA, USA)		
Method: GC-MS				
42[48]	System	6890 N Agilent GC	Linearity range	3.5-300 ng/mL
	Column	5973 N mass selective detector	LOD	1.5 ng/mL
	Injection volume	1 µL	LOQ	3.5 ng/mL
	Detector	5% phenyl methylpolysiloxane capillary column (30 m× 0.25 mm i.d. with 0.25 µm film thickness, Agilent Technologies, USA)		
	Run time	6 min		

CONCLUSION:

In conclusion, this comprehensive review has delved into the multifaceted aspects of vildagliptin, encompassing its pharmacological, pharmaceutical, and analytical attributes. Through a meticulous analysis of existing literature, we have gained a profound understanding of vildagliptin's mechanisms of action, therapeutic indications, and clinical efficacy in managing type II diabetes mellitus. The review has also highlighted the critical role of formulation strategies in ensuring the drug's stability, bioavailability, and patient compliance. As we conclude this review, it is evident that vildagliptin holds a prominent place in the therapeutic landscape for type II diabetes management. Its unique mechanism of action and favourable safety profile make it an attractive option for clinicians and patients alike. Furthermore, advancements in pharmaceutical formulations and analytical techniques continue to enhance our understanding of vildagliptin's characteristics and optimize its administration. The analytical methods discussed herein underscore the significance of accurate and sensitive techniques in assessing vildagliptin's presence and concentration. These methodologies not only aid in quality control during pharmaceutical production but also contribute to bioequivalence studies and pharmacokinetic investigations, thereby promoting the drug's safe and effective use.

This comprehensive review serves as a valuable resource for researchers, clinicians, and pharmaceutical professionals, offering a consolidated understanding of vildagliptin's multifaceted nature and inspiring further scientific inquiry in the realm of diabetes therapeutics.

CONFLICT OF INTEREST:

All the authors have no conflict of interest.

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