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Review of Analytical Method for Quantitative Estimation of Metformin Hydrochloride and Evogliptin Tartrate, A New DPP-4 Inhibitor in Pharmaceutical Dosage Form

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Rajasekaran Aiyalu¹, I.Ponnilavarasan², Nidhil Rajan^{3*}, Haribhuvanesh⁴

1 Professor, Department of Pharmaceutical Analysis, KMCH College of Pharmacy, Coimbatore-641048, Tamilnadu, India.

2Associate Professor, Department of Pharmaceutical Analysis, KMCH College of Pharmacy, Coimbatore-641048, Tamilnadu, India.

3, 4 Research Students, Department of Pharmaceutical Analysis, KMCH College of Pharmacy, Coimbatore-641048, Tamilnadu, India.

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ABSTRACT

Metformin Hydrochloride, also known 3as (diaminomethylidene)-1,1dimethylguanidine; hydrochloride, is an oral antihyperglycemic agent and an effective biguanide. Metformin hydrochloride is primarily used as a first-line treatment for type II diabetes mellitus to control blood glucose levels (non-insulin-dependent). Evogliptin tartrate is a Dipeptidal peptidase-4 inhibitor that is taken orally. It is also known chemically as (3R) -4-[(3R) -3-amino - butanoyl-4-(2,4,5 trifluorophenyl)] [(2methylpropan-2-yl) ox methyl] -3-[(2-methylpropan-2-yl) ox methyl] piperazin-2-one;(2R,3R) Its chemical name is 2,3-dihydroxybutanedioic acid, and it is used to improve glycemic control primarily by stimulating glucose-mediated incretin increased insulin secretion and decreased glucagon release, resulting in a lower risk of hypoglycemia. The new combined strategy for type 2 diabetes mellitus medication adherence was not developed. This review focuses on recent advances in analytical techniques for estimating Evogliptin Tartrate and Metformin Hydrochloride, as there has been no approach for this combination described too far. However, for Metformin Hydrochloride alone and in combination with other medications, HPLC, UV, Stability indicating HPTLC and RP-HPLC methods have been described, however for Evogliptin Tartrate, just one HPLC and UV Spectrophotometric method has been reported recently.

INTRODUCTION

Type 2 diabetes is also known as Non-Insulin-Dependent Diabetes, and it affects 90-95 percent of diabetic patients. Metformin Hydrochloride is recommended as the first-line therapy for type 2 diabetes, followed by the addition of second-line medicines to Metformin Hydrochloride for individuals with insufficient control of hyperglycemia. DPP-4 inhibitors are a very new and developing class of therapy option among the added second-line medications. Example of DDP-IV inhibitors are Vildagliptin, Sitagliptin, Saxagliptin, Linagliptin, Gemigliptin, Anagliptin, Teneligliptin, Alogliptin, Trelagliptin, Omarigliptin, Evogliptin.

Metformin Hydrochloride, also known as 3-(diaminomethylidene)-1,1-dimethylguanidine; hydrochloride, is an effective biguanide class oral antihyperglycemic medication. Metformin hydrochloride has long been considered the first-line medication for non-insulin-dependent diabetic mellitus (type II) blood glucose control.

Metformin hydrochloride works by activating the enzyme AMP-activated protein kinase (AMPK), which reduces hepatic glucose synthesis (gluconeogenesis) and hence lowers blood glucose levels. It reduced glucose absorption in the intestine while improving insulin sensitivity, which improved peripheral glucose uptake and utilization. It disrupts the mitochondrial respiratory chain and increases anaerobic glycolysis for peripheral glucose utilization. It encourages weight loss rather than weight gain and is used to reduce the risk of macrovascular and microvascular complications in people with diabetes. ^[1,2]



Figure no 1: Classification of Antidiabetic Drug.

Dong-A ST recently discovered Evogliptin Tartrate, a new oral DPP-4 inhibitor for the treatment of type 2 diabetes. Chemically, it's known as (3R)-4-[(3R)-3-amino-4-(2,4,5-trifluorophenyl) butanoyl]-3-[(2-methylpropan-2-yl) oxy methyl] piperazin-2-one;(2R,3R)-2,3-dihydroxybutanedioic acid. Evogliptin Tartrate is used to improve glycaemic control by stimulating glucose-mediated incretin secretion, resulting in increased insulin secretion and decreased glucagon release with a lower risk of hypoglycemia. It also has a positive effect on metabolic abnormalities such as obesity, hypertension, and dyslipidemia, all of which are linked to type 2 diabetes (non-insulin-dependent diabetes mellitus).

Evogliptin Tartrate has a long half-life (30 hours), and its pharmacokinetics are unaffected by meals, and its inhibitory effect on DPP-4 activity lasts for 24 hours. When compared to taking two individual component tablets, which reduce polypharmacy and improve patient compliance, the fixed-dose combination formulation of Metformin Hydrochloride and Evogliptin Tartrate may improve therapeutic effect in a patient with insufficient control of hyperglycemia by improving medication adherence.^[3]

DPP-IV inhibitors

DPP-IV (*dipeptidyl peptidase*-IV) inhibitors are a new type of diabetes medication. Patients with type 2 diabetes who haven't responded well to sulphonylureas or metformin are prescribed gliptins, also known as DPP-IV. Weight loss and blood glucose control are aided by dipeptidyl peptidase-IV inhibitors, but they've also been related to an increased risk of pancreatitis.

They function by inhibiting DPP-IV, an enzyme that breaks down incretins (a group of gastrointestinal hormones). Incretins help the liver reduce glucagon production when it's not needed (e.g., after eating) and stimulate insulin synthesis when it's needed (e.g., during digestion).

They also suppress hunger and cause digestion to take longer. DPP-IV inhibitors help to manage blood glucose levels by protecting incretins from destruction.^[4] They don't produce hypoglycemia unless they're taken with other hypoglycemic therapies.^[4,5] DPP-IV inhibitors can be used as a second or third-line treatment for patients with type -II diabetes after metformin and sulphonylureas, as an alternative to thiazolidinediones.^[5,6]



Figure no 2: Mechanism of DPP-4 inhibitors.

Pharmacology Pharmacokinetics

Absorption

Evogliptin has a bioavailability of greater than 50% after a single oral dosage. The administration of evogliptin with food does not affect its absorption. After a single oral administration of evogliptin at doses of 1.25-60 mg, the time to acquire maximum concentration (t C max) was 3–5.5 hours in healthy people.

After a single oral dosage of evogliptin, the maximum plasma concentration (C max) in healthy volunteers was 5.6 1.3 g/l at a dose of 5 mg. C max and the area under the concentration-time curve (AUC last) increase as the dose is increased.

After repeated oral administrations of evogliptin at dosages of 5 mg, 10 mg, and 20 mg once a day, a stable state was obtained by the third day of therapy.

After attaining a steady-state, Cmax of evogliptin was reported about 4-5 hours after drug administration.

Distribution

Evogliptin distribution in plasma and whole blood is nearly identical; roughly 46% of evogliptin binds to plasma proteins.

According to non-clinical research, evogliptin is rapidly disseminated in bodily tissues (except heart tissue and the mesentery). Evogliptin was discovered in the foetal bloodstream. Evogliptin was found to be absent in the milk of nursing rats.

Metabolism

The complete drug makes up the majority of evogliptin in circulation (more than 80 percent). The biotransformation pathway produces five metabolites that are primarily present in urine and plasma and have no inhibitory impact on DPP-IV.

CYP3A4 is frequently involved in the metabolism of evogliptin. Evogliptin did not stimulate CYP1A2, 2B6, 3A4 enzymes and did not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4 enzymes, according to in vitro tests.

Excretion

The average elimination half-life (t1/2) after a single administration of evogliptin ranged from 32.5 to 39.8 hours at doses of 1.25-60 mg.

After many administrations, the average excretion half-life ranged from 32.9 to 38.8 hours.

In healthy adult volunteers, 42.8 percent of the dosage is removed through feces (including metabolites), and 46.1 percent is eliminated by urine.

Dosing

Evogliptin is usually taken once a day by adults at a dose of 5 mg. Pediatric Use: The safety and efficacy in children have yet to be verified.

There hasn't been nearly enough research into the care of elderly individuals.

Because the elderly's physiological capabilities, such as renal and hepatic functions, are frequently compromised, caution should be exercised during administration while keeping an eye on the patient's health.

Therapeutic Indication

If used as a monotherapy or in conjunction with metformin, for the treatment of type -II diabetes mellitus as an adjuvant to exercise and diet to improve glycaemic control.

Contraindication

Type 1 diabetes, intense ketosis, diabetic coma, or pre-coma are not approved for people who have a hypersensitivity to the medicine or any of its ingredients.

Side effects

Hypoglycemia with insulin or a sulfonylurea, throat irritation, and upper respiratory tract infection.

Safety Information ^[7]

1. Heart failure

The New York Heart Association (NYHA) has not approved the use of evogliptin in individuals with functional class II-IV due to a lack of clinical research in these patients.

2. Renal impairment

Around 46.1 percent of the administered radioactivity was removed in urine, while 42.8 percent was excreted in feces in healthy adults. It includes the original form as well as its metabolites.

3. Hepatic impairment

In patients with hepatic impairment, no research was done.

4. Acute pancreatitis

Acute pancreatitis has not been documented among evogliptin users. Acute pancreatitis can cause continual, strong abdominal discomfort, which patients should be aware of evogliptin should be stopped if pancreatitis is suspected; it should not be reintroduced if acute pancreatitis is confirmed. Patients who have had pancreatitis in the past should be handled with caution.

Use during Pregnancy and Lactation

Use in pregnant women

For pregnant women, there are no comparable research findings. In animal testing, evogliptin was discovered in the bloodstream of the fetus through the placenta is up to 61.7 percent of pregnant rats and 14.1 percent of pregnant rabbits two hours after injection. As a result, it is not recommended that pregnant women be used.

Use in nursing women

It has not been established how much evogliptin is excreted in human milk. Animal investigations have revealed that evogliptin is secreted in milk, hence it cannot be used by breastfeeding mothers.^[8]

Drug-Drug Interaction

The enzyme CYP3A4 is responsible for the majority of evogliptin metabolism. The CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4 enzymes were shown to be neither inhibitors nor inducers by evogliptin. Other medications that serve as substrates are unlikely to interact with evogliptin enzymes of this type.

Interaction of evogliptin with other drugs

Metformin: The pharmacokinetics of evogliptin 5 mg and metformin 1,000 mg twice daily (an OCT1 and OCT2 substrate) did not improve clinically appreciably until they reached a steady state^{. [8]}

Clarithromycin: When compared to multiple administration of potential CYP3A4 inhibitor clarithromycin at a daily dose of 1,000 mg until the steady concentration was reached, a single administration of evogliptin at a dose of 5 mg resulted in a 2.17 -fold increase in evogliptin Cmax and a 2.02-fold increase in evogliptin AUC. When given with a CYP3A4 inhibitor, the pharmacokinetic characteristics of evogliptin can rise, hence caution is advised. ^[9]

Physical and Chemical property

Metformin hydrochloride is a crystalline powder that is white or nearly white.

3-(diaminomethylidene)-1,1-dimethylguanidine is the IUPAC designation for metformin hydrochloride (Fig.1.). Metformin hydrochloride has the chemical formula C4H11N5, HCl.

165.6 gm/mol is the molecular weight. Water is easily soluble; alcohol is somewhat soluble, while ether, chloroform, acetone, and methylene chloride are practically insoluble.



Chemical structure of metformin hydrochloride ^[10]

Evogliptin Tartrate is a white powder that is used to treat diabetes. Evogliptin tartrate's IUPAC name is (3R)-4-[(3R)-3- amino-4-(2,4,5-trifluorophenyl) butanoyl]-3-[(2 methyl propan-2-yl) ox methyl] piperazin-2- one;(2R,3R)-2,3-dihydroxybutanedioic acid. Evogliptin tartrate has the chemical formula C23H32F3N3O9. The molecular weight of this compound is 551.5 gm/mol. It's soluble in water, dimethyl sulfoxide, and methanol, but essentially insoluble in acetone and chloroform.



Chemical structure of evogliptin tartrate ^[11]

Analytical methods

The creation and validation of analytical methods are critical in the discovery, development, and production of pharmaceutical products. The process of showing that an analytical method is suitable for measuring API content in certain compounded dosage forms is known as method development.

Every year, the number of pharmaceuticals that are added to the market grows. Because these medications may be a novel moiety or a structural alteration of an existing one, analytical

methodologies for the new drugs may not be available in pharmacopeias. As a result, newer analytical methods for such medications are required. Quality control laboratories utilize official test procedures to assure the identification, purity, potency, and performance of drug goods. UV Spectrophotometry, High-Performance liquid chromatography, High-Performance thin layer chromatography, Ultra performance liquid spectrometry, and Stability indicating High-Performance liquid chromatography, BC-MS/MS, spectrofluorimetry, GC/MS, etc. are some of the technologies used to analyze the analyte. ^[12-13]

After doing a literature review on the development and validation of analytical methods for Metformin Hydrochloride and Evogliptin Tartrate, it was discovered that no method has been reported for this combination to date. However, for Metformin Hydrochloride alone and in combination with other medications, UV, HPLC, Stability indicating RP- HPLC and HPTLC methods have been described, however for Evogliptin Tartrate, only one UV Spectrophotometric method has been documented.

Sr. no.	Official in	Methods	Description	Ref. no.
1	Indian Pharmacopoeia 2018	Liquid Chromatogra	 Stationary Phase: A stainless steel column 30 cm x 4 mm, packed with octadecylsilane bonded to porous silica (10 μm) Mobile Phase: A solution containing 0.087 % w/v of Sodium pentane sulphonate and 0.12% w/v of sodium chloride, adjusted to pH 3.5 using 1% v/v solution of orthophosphoric acid. Flow rate: 1 ml/min. 	[14]
		r J	Wavelength: 218 nm Injection volume: 20µ1	

 Table no. 1: Official methods for estimation of metformin hydrochloride.

			Stationary phase:	
			Size = $0.25 \text{ m}, \emptyset = 4.6 \text{ mm}$	
			Stationary phase: irregular, porous silica gel to which	
			benzenesulphonic acid groups have been chemically	
			bonded (10 μm)	
			Or	
	Duitich	Liquid	Size = 0.11 m , Ø = 4.7 mm ;	
	Dhamaaanaaia	Chromotogra	Stationary phase: regular, porous silica gel to which	
2		chromatogra	benzenesulphonic acid groups have been chemically	[15]
	2003	рпу	bonded (5 μm).	
			Mobile phase: 17 g/l solution of ammonium	
			dihydrogen phosphate R adjusted to pH 3.0 with	
			phosphoric acid R	
			Flow rate: 1 ml/min	
			Wavelength: 218 nm	
			Injection volume: 20µ1	



Sr. Method Description Ref. no. no. Development and Validation of UV Model: Spectrophotometric Method for Shimadzu UV-1800 240V [16] 1 Estimation of **Metformin** in Bulk and Solvent: Distilled water Tablet Dosage Form. Wavelength: 234 nm **Linearity:** 10-50 µg/ml Development and validation of UV Model: spectroscopic method for the [17] 2 determination of Metformin Shimadzu UV mini 1700 **Hvdrochloride** in tablet dosage Solvent: 0.01N NaOH form. Wavelength: 233\nm **Linearity:** 1-25 µg/ml Model: ShimadzuUV1700 Method Development and Validation of Solvent: Methanol [18] Metformin Hydrochloride in Tablet 3 Wavelength: 233 nm Dosage Form. **Linearity:** 8-13 µg/ml Stability Indicating UV Spectroscopic Model: Method for The Estimation of Shimadzu 1800 Metformin Hydrochloride in Bulk and 4 Solvent: Methanol Tablets. Wavelength:232.2m **Linearity:** 2-10 µg/ml %Degradation: [19] Sr.no. Condition % Degradation Acid 15.84 2 Alkali 18.94 3 Thermal 3.31 4 UV(254nm) 9.51 5 UV(365nm) 212.12 22.14 3% H₂O₂ Model: Shimadzu1700 Method development and validation of Forced degradation studies of Solvent: Methanol 5 Metformin Hydrochloride by using Wavelength:237 nm Linearity: 1-10 µg/ml UV spectroscopy. [20] %Degradation: Sr.no Condition Time % Degradation 0.1N NaOH 60min 8.07 1 90min 11.95 9.75 60 min 2 3N HCl 90min 12.79 30% H₂O₂ 12.65 3 15 min 4 Dry Heat 48 hrs 20.94 (70°C) 5 Photolytic 3 hrs 10.53

Table no. 2: Reported methods for estimation of metformin hydrochloride.

		Model: Elico SL 210 Solvent:	
6	Development and validation of UV	Methanol and Water	
	spectrophotometric method for	Wavelength	
	simultaneous estimation of	Simultaneous equation method:	
	Empagliflozin and Metformin	Empagliflozin: 224 nm	
	Hydrochloride in combined dosage	Metformin Hydrochloride: 233 nm	[21]
	torm.	Absorbance ratio method:	
		Iso-absorptive Point: 266 nm	
		Metformin Hydrochloride: 233 nm	
		Linearity:	
		Empagliflozin: 0.1-25 µg/ml	
		Metformin Hydrochloride: 0.5-25 µg/ml	
	Development and validation of UV-	Model: Jasco V-630	
7	Visible spectroscopy method for	Solvent: Methanol and Distilled water	
	simultaneous estimation of Saxagliptin	Wavelength	
	Hydrochloride and Metformin	Metformin Hydrochloride: 231 nm	[22]
	Hydrochloride in tablet dosage form.	Saxagliptin: 274 nm	[]
	· c	Linearity:	
		Metformin Hydrochloride: 2-10 µg/ml	
		Saxagliptin: 50-90 µg/ml	
	Development and Validation of UV	Model: Shimadzu 1800s	
8	Spectrophotometric Method for	Solvent: Distilled water	
	Simultaneous Estimation of	Wavelength	
	Metformin and Glipizide in Tablet	Metformin Hydrochloride: 272 nm	[23]
	dosage form.	Glipizide: 232 nm	[=0]
		Linearity:	
		Metformin Hydrochloride: 5-25 µg/ml	
		Glipizide: 20-50 µg/ml	
	Analytical method development and	Model: Shimadzu 1800	
9	validation for simultaneous estimation of	Solvent: Methanol	
	Teneligliptin Hydrobromide Hydrate	Wavelength	
	and Metformin Hydrochloride from its	Simultaneous equation method:	
	pharmaceutical dosage form by three	Metformin Hydrochloride: 237 nm Teneligliptin	
	different UV spectrophotometric	Hydrobromide Hydrate: 246 nm Absorbance	
	methods.	ratio method:	
		Iso-absorptive Point: 247.5 nm	[24]
		Metformin Hydrochloride: 237 nm	
		First derivative method:	
		Zero-crossing Points:	
		Metformin Hydrochloride: 237 nm Teneligliptin	
		Hydrobromide Hydrate: 246 nm Linearity:	
		Metformin Hydrochloride: 1-20 µg/ml	
		Teneligliptin Hydrobromide Hydrate: 1-20 µg/ml	

	Development and validation of	Model: Shimadzu 1800	
10	analytical method for simultaneous	Solvent: 0.01N NaOH	
	estimation of Glibenclamide and	Wavelength	
	Metformin Hydrochloride in bulk	Metformin Hydrochloride: 233 nm	[25]
	and tablets using UV-Visible	Glibenclamide: 226.60 nm	
	spectroscopy.	Linearity:	
		Metformin Hydrochloride: 2-10 µg/ml	
		Glibenclamide: 3-15 µg/ml	
	Simultaneous UV Spectrophotometric	Model: Shimadzu 1800	
11	Methods for Estimation of	Solvent: Methanol	
	Metformin HCl and Glimepiride in	Wavelength	
	Bulk and Tablet Dosage Form.	Absorbance maxima method.	
		Metformin Hydrochloride: 236 nm	[26]
		Glimeniride: 228 nm	[20]
		A rea under curve method: Metformin	
		Hydrochloride: 217-247 nm Glimeniride:	
		213 230 nm	
		$\mathbf{Linearity:} 5.25 \mu_{\rm G}/m^{1}$	
		Madala Shimadan 1900	
10	Development and validation of UV	viodei: Snimadzu 1800	
12	spectrophotometric method for	Solvent: Methanol	
	simultaneous estimation of	Wavelength	
	Mattermin Hudrochlanide and	Simultaneous equation method:	
	Vietorinin Hydrochioride and	Metformin Hydrochloride: 232 nm	
	Alogiptin Benzoate in bulk drugs	Alogliptin Benzoate: 277nm	[27]
	and combined dosage forms.	Absorbance ratio method:	
		Iso-absorptive Point: 250 nm	
		Metformin Hydrochloride: 277 nm	
		Linearity:	
		Metformin Hydrochloride: 1-10 µg/ml	
		Alogliptin: 5-25 µg/ml	
	Method development of	Model: Shimadzu 1800	
13	simultaneous estimation of	Solvent: Distilled water	
_	Sitagliptin and Metformin	Wavelength	
	Hydrochloride in pure and tablet	Metformin Hydrochloride: 231 nm	[28]
	dosage form by UV-VIS	Sitagliptin: 267 nm	[20]
	spectroscopy	Linearity:	
		Metformin Hydrochloride: 2-10 µg/ml	
		Sitaglintin: 20-60 ug/ml	
	Analytical Method Development and	Stationary phase: Cosmosil C ₁₀	
14	Validation of Metformin	$(250 \text{mm x 4 6 mm \cdot 5 \mu m})$	
14	Hydrochloride by using PD HDI C	Mohile nhase. Methanol: Phoenhate huffer (nH 2)	
	with ICH Guidelines	(70.30 % y/y)	
		(70.30%)(7)	[29]
		Flow fate: 1 III/IIII	
		wavelength: 238 nm	
		Linearity: $10-50 \ \mu g/ml$	
		Ketention time: 4.2 min	

	RP-HPLC Analytical Method	Stationary phase: Hypersil ODS C ₁₈ (250mm x	
15	Development and Validation of	4.6mm: 5um)	
	Metformin Hydrochloride	Mobile phase: Acetonitrile: Phosphate buffer	
	Tablets Assav	(pH-5.75) (65:35 % v/v)	
		Flow rate: 1.0 ml/min	[30]
		Wavelength: 233 nm	
		Linearity: 50-150 µg/ml	
		Retention time: 7.168 min	
	Development and Validation of a	Stationary phase: Zorbax-SCX C18,	
16	RP-HPLC Method for the	(250mm x 4.6mm; 5µm)	
	Determination of Metformin	Mobile phase: Ammonium-dihydrogen	
	Hydrochloride in Pharmaceutical	phosphate buffer (pH-3): Acetonitrile (50:50	[31]
	Dosage Forms.	% v/v)	
		Flow rate: 1 ml/min	
		Wavelength: 218 nm	
		Linearity: 20-60 µg/ml	
		Retention time: 11.12 min	
	Simple and sensitive analytical	Stationary phase: Inertsil-Extend C ₁₈ ,	
17	method development and	(250mm x 4.6mm; 5µm)	
	validation of Metformin	Mobile phase: 1-Octane sulfonic acid:	
	Hydrochloride by RP-HPLC.	Acetonitrile (80:20 %v/v)	[32]
		Flow rate: 1 ml/min	
		Wavelength: 232 nm	
		Linearity: 1-250 µg/ml	
		Retention time: 10.78 min	
		Stationary phase: Cosmosil C ₁₈ ,	
	Development and validation of	(250mm x 4.6mm; 5µm)	
18	RP- HPLC method for	Mobile phase: Methanol: Water (60:40 % v/v) (pH 3	
	simultaneous estimation of	adjusted with orthophosphoric acid)	
	Metformin Hydrochloride and	Flow rate: 0.8ml/min	
	Glipizide in bulk and	Wavelength: 226 nm	[33]
	pharmaceutical dosage form.	Linearity:	
		Glipizide: 1-5 µg/ml	
		Metformin Hydrochloride: 100-500 µg/ml	
		Retention time:	
		Glipizide: 5.571 min	
		Metformin Hydrochloride: 4.159 min	
	Development and validation of a	Stationary phase: Alltima CN	
19	new analytical HPLC method for	$(250 \text{mm} \times 4.6 \text{mm}; 5 \mu \text{m})$	
	simultaneous determination of the	Mobile phase: 20 mM ammonium formate	
	antidiabetic drugs, Metformin and	buffer (pH 3.5): Acetonitrile (45:55 %v/v)	
	Gliclazide.	Flow rate: 1 ml/min	
		Wavelength: 227nm	[34]
		Linearity:	
		Metformin: 2.5-150 µg/ml	
		Gliclazide: 1.25-150µg/ml	
		Retention time: Metformin:	
		6.9 min	
		Gliclazide: 4.1 min	

20 Bevelopment and validation of malytical method for simultaneous Stationary phase: Waters Cs, (250mm x 4.66mm;5µm) [33] 20 estimation of Saxaglipfin and Metformin Hydrochloride by using RP-HPLC method. Mobile phase: Methanol: Phosphate buffer (pH-5.0) (70:30 %/v) [33] 21 Method development and validation of simultaneous estimation of Alogliptin and Metformin Hydrochloride: 2.5 L2.5 µg/ml Retention time: Metformin Hydrochloride: 2.8 min Saxagliptin: 2.5 L2.5 µg/ml Retention time: Metformin Hydrochloride: 2.8 min Saxagliptin: 4.9 min [36] 21 Method development and validation of simultaneous estimation of Alogliptin and Metformin Hydrochloride by RP-HPLC. Stationary phase: Agilent C1s G (50mm x 4.6mm; 5µm) Mobile phase: Phosphate buffer (pH-3.0 adjusted with 0.1% 0PA): methanol (20:80 %v/v) [36] 22 Method development and validation for the Simultaneous Form. Stationary phase: ODS (250mm x 4.6mm; 5µm) Mobile phase: DDS (250mm x 4.6mm; 5µm) [37] 22 Estimation of Metformin and Canagliflozin in Tablet Dosage Form. Forw rate: 1 m/min Wavelength: 212 nm Linearity: Metformin: 5-30 µg/ml Retention time: Metformin: .2.783 min Canagliflozin: 5.781 min Stationary phase: Hypersil BDS C1s. [37] 23 Development and Validation of RP- Form adjuitin in Combined Pharmaceutical Dosage Form. Stationary phase: Hypersil BDS C1s. [38] 24 Development and Validation of RP- Form adjuitin in Combined Pharmaceutical Dos				
20 eximativical method for simultaneous estimation of Saxagliptin and Metformin Hydrochloride by using RP-HPLC method. (250mm x 4.6mm;5µm) [35] 21 Metformin Hydrochloride by using RP-HPLC method. Flow rate: 1 ml/min Wavelength: 225 nm Linearity: Metformin Hydrochloride: 250-1250 µg/ml Saxagliptin 2.5-12.5 µg/ml Retention time: Metformin Hydrochloride: 2.8 min Saxagliptin 4.9 min Metformin Hydrochloride: 2.8 min Saxagliptin 4.9 min Metformin Hydrochloride: 2.8 min Saxagliptin 4.9 min Metformin Hydrochloride: 2.8 min Saxagliptin 2.9 min Mobile phase: Agilent C1s G (150mm x 4.6 mm; 5µm) Mobile phase: Agilent C1s G (150mm x 4.6 mm; 5µm) Mobile phase: Agilent C1s G (150mm x 4.6 mm; 5µm) Mobile phase: Agilent C1s G (150mm x 4.6 mm; 5µm) Mobile phase: Phosphate buffer (pH-3.0 adjusted with 0.1% OPA): methanol (20:80 %v/v) Flow rate: 0.7 min/ml Wavelength: 242 nm Linearity: 10-30 µg/ml Retention time: Metformin Hydrochloride: 1.727 min Alogliptin 2.9 min Stationary phase: ODS (250mm x 4.6 mm; 5µm) Mobile phase: Buffer : Acetonitrile : methanol (40:40:20 %v/v) [36] 21 RP-HPLC Method development and validation for the Simultaneous Estimation of Metformin and Canagliflozin in Tablet Dosage Form. Stationary phase: ODS (250mm x 4.6 mm; 5µm) Mobile phase: Buffer : Acetonitrile : methanol (40:40:20 %v/v) [37] 22 Estimation of RP-Form. Stationary phase: Agilent Cise G (2.7 min Alogliptin: 3.7 min Canagliflozin: 5.7 30 µg/ml Retertion time: Metformin: 2.783 min Canagliflozin: 3.781 min Mavelength: 212 nm Hinearity: Metformin: 2.783 min Canagliflozin: 3.781 min Mavelength: 212 nm Hinearity: Metformin: 2.783 min Canagliflozin: 3.781 min Mavelength: 2.783 min Canagliflozin: 3.781 min Mobile phase: Phyersil BDS C1s. (250mm x 4.6 mm; 5µm) M		Development and validation of	Stationary phase: Waters C ₈ ,	
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Hydrochloride by RP-HPLC.Flow rate: 0.7 min/ml[159]Wavelength: 242 nmLinearity: 10-30 µg/mlRetention time:Retention time:Metformin Hydrochloride: 1.727 min Alogliptin: 2.9 minMetformin Tydrochloride: 1.727 min Alogliptin: 2.9 min22RP-HPLC Method development and validation for the SimultaneousStationary phase: ODS (250mm x 4.6mm; 5µm) Mobile phase: Buffer : Acetonitrile : methanol (40:40:20 %/v/v)[37]22Estimation of Metformin and Canagliflozin in Tablet Dosage Form.Flow rate: 1 ml/min Canagliflozin: 5-30 µg/ml Retention time: Metformin: 2.783 min Canagliflozin: 3.781 min[37]23Development and Validation of RP- HPLC Method for Simultaneous Estimation of Metformin and Estimation of Metformin and Canagliflozin: 3.781 minStationary phase: Hypersil BDS C18, (250mm x 4.6mm; 5µm)23Development and Validation of RP- HPLC Method for Simultaneous Estimation of Metformin and Linagliflozin: 3.781 minMobile phase: Potassium dihydrogen phosphate (KH_2PO_4): Acetonitrile (40:60 %v/v)23Pharmaceutical Dosage Form.Flow rate: 1 ml/min Wavelength: 250 nm Linearity: Metformin Hydrochloride: 100-600 µg/ml		Alogliptin and Metformin	with 0.1% OPA) : methanol (20:80 %v/v)	12.01
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Linagliptin in Combined(KH2PO4): Acetonitrile (40:60 %v/v)[38]Pharmaceutical Dosage Form.Flow rate: 1 ml/minWavelength: 250 nmLinearity: Metformin Hydrochloride: 100-600 μg/mlMagement		Estimation of Metformin and	Mobile phase: Potassium dihydrogen phosphate	
Pharmaceutical Dosage Form. Flow rate: 1 ml/min Wavelength: 250 nm Linearity: Metformin Hydrochloride: 100-600 μg/ml		Linagliptin in Combined	(KH ₂ PO ₄): Acetonitrile (40:60 $\%$ v/v)	[38]
Wavelength: 250 nm Linearity: Metformin Hydrochloride: 100-600 μg/ml		Pharmaceutical Dosage Form.	Flow rate: 1 ml/min	
Linearity: Metformin Hydrochloride: 100-600 μg/ml			Wavelength: 250 nm	
Metformin Hydrochloride: 100-600 µg/ml			Linearity:	
			Metformin Hydrochloride: 100-600 µg/ml	

Official method for estimation of evogliptin tartrate

There is no official method for Evogliptin tartrate in any pharmacopeia.

Table no. 3: A reported method for estimation of evogliptin tartrate.

Sr. no.	Method	Description	Ref. no.
1	Development and Validation of RP- HPLC Method for estimation of Evogliptin in Pharmaceutical Dosage Form.	Stationary phase: Column C18, 5 μm, (250 X 4.6 mm) Mobile Phase: methanol:water:acetonitrile (70:20:10) Wavelength: 265 nm Linearity: 10–30 μg/ml. 80775 X – 21004, Rf value: 0.99	[39]
2	Development and Validation of Novel UV Spectrophotometric Method for the Determination of Evogliptin tartrate in Pharmaceutical Dosage Form.	Solvent: Deionized water Wavelength: 267 nm Linearity: 10-100 μg/ml	[40]

SUMMARY

The analysis of published data revealed that there was no method reported for Metformin Hydrochloride and Evogliptin Tartrate fixed-dose combination. According to the literature review, it has been concluded that different spectroscopic methods like UV, HPLC, Stability indicating RP-HPLC, and HPTLC methods have been reported for Metformin Hydrochloride individual and along with other drugs and for Evogliptin Tartrate only one UV Spectrophotometric method has been reported. So there is scope to develop different analytical methods for the combination of Metformin Hydrochloride alone and Evogliptin Tartrate. This review carried out an overview of the current state-of-art analytical methods for the determination of Metformin hydrochloride and Evogliptin tartrate, which will be supportive for further research on this combination. The review would also help to know the key solvents and their available set of instruments in the analytical laboratory. The methods are also helpful for in-process evaluation during the manufacturing of API.

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