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Review Article

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A COMPREHENSIVE REVIEW ON ANALYTICAL APPROACHES FOR EVOGLIPTIN AND METFORMIN HYDROCHLORIDE

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ABSTRACT

Metformin, recognized as the primary first-line oral agent for managing type 2 diabetes, acts as a potent blood glucose-lowering agent. Operating as a biguanide drug, it exhibits efficacy by mitigating hepatic glucose production, impeding intestinal glucose absorption, and enhancing insulin sensitivity, resulting in a notable reduction in both basal and postprandial blood glucose levels. Concurrently, **Evogliptin,** a Dipeptidyl peptidase-4 (DPP-4) inhibitor, emerges as a novel oral antihyperglycemic agent, influencing insulin secretion and satiety through the reduction of endogenous glucagon-like peptide 1 (GLP-1) degradation. This review emphasizes recent advancements in analytical techniques for estimating Metformin Hydrochloride and Evogliptin Tartrate, considering both their combined and individual applications of evogliptin and Metformin Hydrochloride. Various methods, including UV spectroscopy, HPLC, Stability-Indicating RP-HPLC, and HPTLC, have been reported for both combined and individual estimations.

KEYWORDS

- RP-HPLC
- UV Spectrophotometry
- Type 2- Diabetes
- Metformin Hcl
- Evogliptin Tartarate

INTRODUCTION

Diabetes is a condition that happens when your blood sugar (glucose) is too high. It develops when your pancreas doesn't make enough insulin or any at all, or when your body isn't responding to the effects of insulin properly. Diabetes affects people of all ages. Most forms of diabetes are chronic (lifelong), and all forms are manageable with medications and/or lifestyle changes.[1]

A drug substance that helps a person with diabetes control their level of glucose (sugar) in the blood. Metformin is generally recommended as a first-line treatment for type 2 diabetes, as there is good evidence that it decreases mortality. It works by decreasing the liver's production of glucose, and increasing the amount of glucose stored in peripheral tissue.[2] Antidiabetic agents include insulin and the oral hypoglycaemic agents.[3] Evogliptin and metformin hydrochloride are the drugs used to treat diabetes and it is manufactured by a Alkem laboratories limited in Mumbai. Evogliptin and metformin hydrochloride combination was approved in 22.10.2018.[4]

DRUG PROFILE

a) Evogliptin Tartrate

Structure

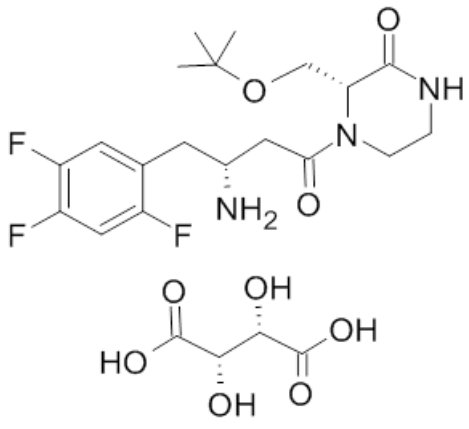

Fig. 1: Evogliptin Tartrate.

IUPAC Name: (3R)-4-[(3R)-3-Amino-4-(2,4,5 trifluorophenyl)butanoyl]-3-{[(2-methyl-2-propanyl)oxy]methyl}-2-piperazinone.
Molecular formula: $C_{19}H_{26}F_3N_3O_3$
Molar Mass: 401.430 g·mol^{-1}
Boiling Point: 571.5±50.0 °C at 760 mmHg.
Storage Condition: 4°C, sealed storage, away from moisture.
Pka: 13.69 (Strongest Acidic), 8.78 (Strongest Basic) [5].
Drug Category: It is antidiabetic drug in the dipeptidyl peptidase-4 inhibitor, Blood glucose lowering agents
Solubility: Evogliptin is very soluble in water and dilute methanol while freely soluble in organic solvents like ethanol, chloroform and ethyl acetate.
Mechanism of action: Reduce degradation of endogenous glucagon-like peptide 1 (glp-1) to increase insulin secretion and satiety and decrease glucagon [6].

b) Metformin Hydrochloride
Structure

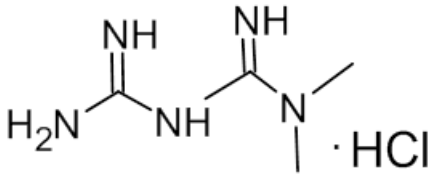

Fig. 2: Metformin Hydrochloride.

IUPAC Name: N, N-Dimethylimidodicarbonimidic diamide Hydrochloride.
Molecular formula: $C_4H_{12}ClN_5$
Molar Mass: 165.62 g/mol^{-1}
Boiling Point: 172.5±23.0 °C at 760 mmHg [7].
Storage Condition: Store at or below 25°C. Protect from heat, light and moisture.
Pka: 12.4.[8]
Drug Category: It is an oral anti-diabetic drug. used for the treatment of type 2 diabetes mellitus.
Solubility: Freely soluble in water, slightly soluble in alcohol.
Mechanism of action: Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.[9]

ESTIMATION OF DRUGS

1. METFORMIN HYDROCHLORIDE

DETERMINE BY LIQUID CHROMATOGRAPHY[10]

Stationary Phase: a stainless-steel column 30 cm x 4 mm, packed with octadecy1silane bonded to porous silica (10 µm),
Mobile phase: a solution containing 0.087 per cent w/v of sodium pentane sulphonate and 0.12 per cent w/v of sodium chloride, adjusted to pH-3.5 using 1 per cent w/v solution of orthophosphoric acid,
Flow rate: 1ml per minute,
Detection Wavelength: 218 nm,
Injection volume: 20 µl.

2. EVOGLIPTIN TARTARATE

The Indian pharmacopoeia, British pharmacopoeia or other official books not provide an official estimation, for evogliptin, but various researchers have conducted estimations independently.

ANALYTICAL METHODS

Analytical methods are paramount for estimating and independently uncovering the identity of unknown agents. Various techniques, including UV spectroscopy, IR spectroscopy, NMR spectroscopy, mass spectrometry, TLC, HPLC and HPTLC, are available for analysing these mysterious substances.

1. Chromatographic Estimations

Organic chemical analysis heavily depends on chromatography as a critical tool for isolating diverse chemical mixtures into their individual components. Various chromatographic techniques, such as gas chromatography (GC), liquid chromatography (LC), thin-layer chromatography (TLC), and high-performance liquid chromatography (HPLC), contribute to the effective separation of compounds.

Table 1: Chromatographic Estimation of Evogliptin and Metformin Hydrochloride.

S.No	Title	Method	Column	Mobile Phase (M.P), Flow rate (F.R) & Injection Volume (I.V)	Retention time & Wavelength	Ref. No
1.	Development and validation of stability indicating RP-	RP- HPLC	Hypersil BDS C18 column (250mm X	**MP:** Buffer (pH- 4.5): Methanol (45:55% v/v)	**RT:** 5.310 mins (Evogliptin)	[11]

	HPLC method for the estimation of **evogliptin tartrate** in pharmaceutical dosage form.		4.6mm, Hypersil BDS C18 column (250mm X 4.6mm, 5µm) 5µm)	**FR:** 1mL/min **IV:** 20 µl	**W:** 265nm	
2.	Development and validation of RP-HPLC method for estimation of **evogliptin** in pharmaceutical dosage form.	RP-HPLC	ODS 5 µm, (4.6mm X 250mm) C18 column	**MP:** methanol:water:acetonitrile (70:20:10) **FR:** 1mL/min **IV:** 20µl	**RT:** 3.6 mins (Evogliptin) **W:** 265nm	[12]
3.	Box-Behnken design assisted optimization of RP-HPLC method for the estimation of **evogliptin tartrate** by analytical quality by design.	RP- HPLC By QBD	C18 column (150mm X 4.6mm, 5 µm)	**MP:** Methanol:Phosphate buffer (pH- 4.5) (60:40% v/v) **FR:** 1mL/min **Software:** Design Expert software trail version 13.0	**Method:** Box-Behnken experimental design **W:** 267nm	[13]
4.	Development and validation of RP-HPLC method for estimation of **evogliptin** in formulation.	RP-HPLC	ACCLAIMED mix mode HILIC-1 (5 µ, 150 X 4.6mm)	**MP:** 15 ml Ammonium acetate:Acetonitrile (30:70 v/v) **FR:** 1mL/min	**RT:** 4.8 mins (Evogliptin) **W:** 205nm	[14]
5.	Novel method development, validation, and stability indicating assay method for **evogliptin tartrate** in pharmaceutical dosage form.	RP- HPLC	Hypersil BDS C18 (250mm x 4.6mm, 5µ**)** column in isocratic mode	**MP:** methanol:water:TFA mixture (70:30:0.1% v/v) **FR:** 1mL/min **IV:** 20 µl	**RT:** Evogliptin API: 4.03 mins Tablets: 4.02 mins **W:** 264nm	[15]
6.	Development and Validation of RP-HPLC method for the analysis of **Metformin**	RP-HPLC	OD-5-100, C_{18} µ-bondapack column (0.4 x 25cm) with 0.5 µm particle size.	**MP:** Gradient elution water:methanol (70:30) **FR:** 0.5mL/min **IV:** 20 µl	**RT:** 4.4 mins **W:** 233 nm	[16]
7.	Development and Validation of A Reverse Phase HPLC Method for the Determination of **Metformin HCl** in Pharmaceutical Dosage Forms	RP-HPLC	Zorbax-SCX, C 18, 250 mm × 4.6 mm, 5 mm	**MP:** Buffer (pH 3.0) with ammonium dihydrogen phosphate: acetonitrile [50: 50, v/v] **FR:** 1.0mL/min	**RT:** 11.12 mins **W:** 218 nm	[17]
8.	RP-HPLC Analytical Method Development and Validation of **Metformin Hydrochloride** Tablets Assay	RP-HPLC	Hypersil ODS C18, 25cm x 4.6mm x 5µm	**MP:** 65% acetonitrile and 35% phosphate buffer and P H was adjusted to 5.75 with 85v/v Ortho phosphoric acid **FR:** 1.0mL/min	**RT:** 7.168 mins **W:** 233 nm	[18]
9.	Analytical Method Development and Validation of **Metformin Hydrochloride** by using RP-HPLC with ICH Guidelines	RP-HPLC With ICH	C18 column [4.6x250mm, particle size 5µm]	**MP:** 70:30 (Methanol: Phosphate buffer pH-3). **FR:** 1.0mL/min **IV:** 20 µl	**RT:** Approx. 4.2 min **W:** 238 nm	[19]
10.	Simple and sensitive analytical method development and validation of **metformin hydrochloride** by RP-HPLC	RP-HPLC	Inertsil-Extend C18 (250 × 4.6mm, packed with 5µm) is suitable	**MP:** 1-Octane sulfonic Acid: Acetonitrile (80:20) **FR:** 1.0mL/min **IV:** 5 µl	**RT:** 10.785 min **W:** 232 nm	[20]
11.	Development and analytical method validation for stimultaneous estimation of **evogliptin tartrate and metformin hydrochloride** in combine dosage form.	RP- HPLC	Phenomenex luna C18 column @ 25^{o} C	**MP:** water:acetonitrile (25:75) **FR:** 1.2 mL/min **IV:** 20 µl	**RT:** 2.009 mins (MFH), 2.956 mins (EGT) respevtively **W:** 205nm	[21]
12.	Development and validation of RP-HPLC method for simultaneous estimation of **metformin and evogliptin** in dosage form.	RP- HPLC	Octadecylsilane (ODS) (4.6 x 150mm, 5µ, Hypersil**)**	**MP:** methanol:water (70:30) (pH adjusted to 3.0 with orthophosphoric acid) **FR:** 0.8 mL/min **IV:** 20 µl	**RT:** 2.548 mins (MFH), 2.107 mins (EGT) respecvtively. **W:** 254 nm	[22]

13.	Development and validation of RP-HPLC method for determination of **metformin and evogliptin** in bulk and pharmaceutical dosage form.	RP-HPLC	Waters XTerra RP-18 (150 x 4.6mm, 3.5µ Column**)**	**MP:** Acetonitrile:KH_2PO_4:Methanol (50:40:10% v/v) **FR:** 1 mL/min	**RT:** 2.730 mins (MFH), 4.468 mins (EGT) respecvtively. **W:** 228nm	[23]
14.	RP-HPLC Based Stability Indicating Assay of **Evogliptin and Metformin**: Development and Validation of the Analytical Method	RP-HPLC	symmetry C-18 (4.6×150mm, 5µ Kromasil column)	**MP:** phosphate buffer (pH 4.5) and acetonitrile in the ratio of 30:70 v/v **FR:** 0.8mL/min	**RT:** 7.03 min (EGT) and 9.50 min (MFH) respectively.	[24]

2. Spectroscopic Estimation

UV spectroscopy plays a crucial role in quantitatively estimating substances such as evogliptin and metformin hydrochloride, which are antidiabetic drugs. Researchers have extensively utilized UV spectroscopy to analyze these drugs in both their dosage forms and bulk states. By examining their absorbance, transmittance, and reflectance properties across varying concentrations, UV spectroscopy enables the establishment of linearity, providing valuable insights into the characteristics of these drugs.

Table 2: UV Spectroscopic method for estimation of Evogliptin and Metformin Hydrochloride.

S. No	Title	Method	Materials & Description	Ref. no
15.	Eco-friendly UV spectrophotometric method for simultaneous estimation of **evogliptin and metformin hydrochloride** in bulk and combined tablet dosage form.	UV- Vis method (UV-1800, Shimadzu)	**Software:** UV probe software **Wavelength:** Scanned individually entire UV range (400-200nm) and 233.1 nm (MFH) and 267.0 nm (EGT) respectively. **Solvet:** Deionized water **Concentration Range:** 10- 100 µg/ml^{-1} **Linearity (R^2):** 0.9986 (EGT) & 0.9983 (MFH)	[25]
16.	Development and Validation of Novel UV Spectrophotometric Method for the Determination of **Evogliptin Tartarate** in Pharmaceutical Dosage Form	UV- Vis method (UV-1800, Shimadzu)	**Wavelength:** 267 nm **Solvet:** Deionized water **Concentration Range:** 10- 100 µg/ml^{-1} **Linearity (R^2):** 0.992 (EGT)	[26]
17.	Derivative Spectrophotometric Method Development and Validation for the Estimation of Evogliptin Tartrate in Pharmaceutical Dosage Form	Shimadzu 2600 UV-visible double beam spectrophotometer	**Wavelength:** 267 nm **Solvet:** Deionized water **Concentration Range:** 20-120 µg/ml^{-1}	[27]
18.	Solvent effect on the UV absorption spectra of evogliptin Tartrate	effect of solvents on the UV Absorption spectra	**Wavelength:** 258.60 nm (water), 264nm (n-butyl alcohol), 264 nm (Ethanol), 259 nm (Ethanol). **Solvet:** Water, n-butyl alcohol, DMSO, Ethanol **Concentration Range:** 50 µg/ml^{-1}	[28]
19.	Development and Validation of UV-Spectrophotometric Method for Estimation of **Metformin** in Bulk and Tablet Dosage Form	A Shimadzu UV-1800 240V UV/VIS Spectro-photometer	**Wavelength:** 234 nm **Solvet:** Water **Concentration Range:** 10- 50 µg/ml^{-1} **Linearity (R^2):** 0.9998 (MFH)	[29]
20.	Method Development and Validation of **Metformin Hydrochloride** in Tablet Dosage Form.	UV spectroscopy (Shimadzu UV-1700)	**Wavelength:** 233 nm **Solvet:** Methanol **Concentration Range:** 8-13 µg/ml^{-1} **Linearity (R^2):** 0.99996 (MFH)	[30]
21.	Development and validation of UV spectroscopic method for the determination of **Metformin**	Shimadzu (Kyoto, Japan) UV Visible	**Wavelength:** 233 nm **Solvet:** Sodium hydroxide **Concentration Range:** 1-25 µg/ml^{-1} **Linearity (R^2):** 0.9998 (MFH)	[31]

	Hydrochloride in tablet dosage form	spectro-Photometer, Model UV mini1700		

CONCLUTION

Metformin is an age-old but widely employed medication for managing diabetes, while evogliptin is a recently sanctioned drug in India. The combination of both drugs is also utilized for diabetes treatment. This review exclusively focuses on the analytical methods used to assess both the combined and individual effects of evogliptin and metformin. Current literature predominantly discusses metformin, with limited attention given to evogliptin and its combination. Notably, there is a dearth of studies on the analysis of evogliptin and its combination, especially in bulk form. Existing research often concentrates on dosage forms rather than bulk substances. The hope is that this article proves beneficial for future researchers by shedding light on this unexplored aspect. It's worth mentioning that only RP-HPLC and UV methods have been reported for studies involving dosage forms. Among these, only one method has been employed with bulk substances, while others have primarily focused on dosage forms.

ABBREVIATION

RP-HPLC: Reversed-Phase High-Performance Liquid Chromatography, **UV:** Ultraviolet, **HPLC:** High-Performance Liquid Chromatography, **HPTLC:** High-Performance Thin-Layer Chromatography, **GLP-1**: Glucagon-Like Peptide 1, **DPP-4:** Dipeptidyl Peptidase-4, **$C_{19}H_{26}F_3N_3O_3$:** Evogliptin, **$C_4H_{12}ClN_5$:** Metformin Hydrochloride, **BDS:** Base Deactivated Silica column, **ODS:** Octadecyl-silica column, **pH:** Potential of Hydrogen, **HILIC-1:** Hydrophilic interaction liquid chromatography column, **TFA:** Trifluoroacetic Acid, **µl:** microliter, **mL:** milliliter, **KH_2PO_4:** Potassium Dihydrogenphosphate, **MP:** Mobile Phase, **RT:** Retention Time, **IV:** Injection Volume, **MFH:** Metformin, **EGT:** Evogliptin.

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