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REVIEW OF ANALYTICAL TECHNIQUES FOR SIMULTANEOUS ESTIMATION OF PIOGLITAZONE HYDROCHLORIDE AND VILDAGLIPTIN IN PHARMACEUTICAL FORMULATIONS

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ABSTRACT

Diabetes mellitus is a chronic metabolic disorder characterized by persistently elevated blood glucose levels due to defects in insulin secretion, insulin action, or both. Based on etiology and pathophysiology, diabetes mellitus is broadly classified into Type 1 and Type 2 diabetes mellitus. Type 1 diabetes results from autoimmune destruction of pancreatic β-cells, leading to absolute insulin deficiency and requiring lifelong insulin therapy. In contrast, Type 2 diabetes mellitus is primarily associated with insulin resistance and relative insulin deficiency and is commonly managed using oral antidiabetic agents, with or without insulin. Pioglitazone hydrochloride and vildagliptin are widely prescribed oral antidiabetic drugs used either alone or in combination for the management of Type 2 diabetes mellitus. The present work focuses on the development and validation of a robust, accurate, and precise HPLC method for the simultaneous estimation of pioglitazone hydrochloride and vildagliptin in pharmaceutical dosage forms using a Quality by Design (QbD) approach.

KEYWORDS: Pioglitazone hydrochloride, Vildagliptin, Diabetes mellitus, HPLC, Method development and validation, QbD.

INTRODUCTION

Introduction of diabetes mellitus

Diabetes mellitus (DM) is a complex metabolic disorder marked by chronic hyperglycemia resulting from abnormalities in insulin secretion, insulin action, or a combination of both. Several forms of diabetes have been identified, including Type 1 diabetes mellitus (T1DM), Type 2 diabetes mellitus (T2DM), maturity-onset diabetes of the young (MODY), gestational diabetes, neonatal diabetes, and diabetes secondary to endocrinopathies or prolonged steroid therapy.

Type 1 diabetes mellitus typically manifests during childhood or adolescence and is caused by autoimmune-mediated destruction of pancreatic β-cells, resulting in absolute insulin deficiency. Conversely, Type 2 diabetes mellitus usually develops in adults and is associated with insulin resistance combined with an inadequate compensatory insulin secretory response. Lifestyle factors such as unhealthy diet, physical inactivity, and obesity play a major role in the development of T2DM.[1-2]

Introduction of Pioglitazone hydrochloride

Pioglitazone hydrochloride is an oral hypoglycemic agent belonging to the thiazolidinedione class and is commonly used in the treatment of Type 2 diabetes mellitus. It is a weakly basic compound (pKa ≈ 12.06) and exhibits poor aqueous solubility. According to the Biopharmaceutical Classification System (BCS), pioglitazone is categorized as a Class II drug, indicating low solubility and high permeability.

Following oral administration, pioglitazone is rapidly and extensively absorbed, exhibiting nearly complete bioavailability. The drug has an elimination half-life ranging from 3 to 7 hours, making it suitable for once-daily dosing.[3]

Mechanism of Action

Pioglitazone acts primarily by activating the peroxisome proliferator-activated receptor gamma (PPAR-γ) and, to a lesser extent, PPAR-α. Activation of these nuclear receptors regulates the transcription of genes involved in glucose and lipid metabolism in adipose tissue, skeletal muscle, and liver. This results in enhanced insulin sensitivity, reduced hepatic gluconeogenesis, and decreased circulating glucose and glycated hemoglobin levels.[4]

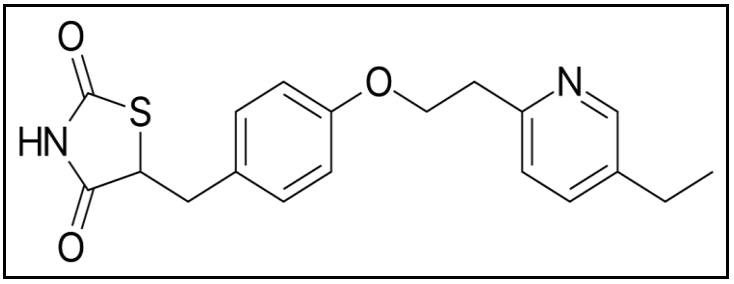

Figure 1: Structure of Pioglitazone Hydrochloride.

Introduction of Vildagliptin

Vildagliptin is a potent, selective, and reversible dipeptidyl peptidase-4 (DPP-4) inhibitor approved for the treatment of Type 2 diabetes mellitus, either as monotherapy or in combination with other antidiabetic agents. Since its clinical development began in the early 2000s, vildagliptin has been approved in more than 110 countries worldwide.

Extensive clinical studies involving thousands of patients have demonstrated that vildagliptin is both effective and well tolerated, with significant improvement in glycaemic control and a favourable safety profile.[5]

Mechanism of Action

Vildagliptin lowers blood glucose levels by inhibiting the DPP-4 enzyme responsible for the rapid degradation of incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). By prolonging the activity of these hormones, vildagliptin enhances glucose-dependent insulin secretion, suppresses glucagon release, and improves both fasting and postprandial glucose levels. Additionally, it contributes to improved lipid metabolism and β-cell responsiveness.[6]

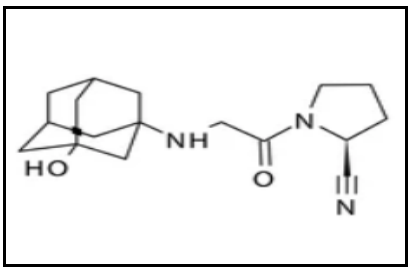

Figure 2: Structure of Vildagliptin.

REVIEW OF LITERATURE

A comprehensive review of official pharmacopeial methods and reported analytical techniques reveals that pioglitazone hydrochloride and vildagliptin have been analyzed

individually and in combination using various analytical approaches. These include UV-visible spectrophotometry, RP-HPLC, and HPTLC methods.[7]

Pharmacopeial monographs from the Indian Pharmacopoeia and United States Pharmacopoeia describe validated liquid chromatographic methods for the assay of pioglitazone hydrochloride and vildagliptin as active pharmaceutical ingredients. Several researchers have also reported stability-indicating and QbD-based RP-HPLC methods for individual drugs and their combined dosage forms.

OFFICIAL REPORTED METHODS

Table 2.1 Official methods for assessment of Pioglitazone Hydrochloride and Vildagliptin.

Sr.No.	Official	Method	Description
PIOGLITAZONE HYDROCHLORIDE [8-9]			
1	**Indian Pharmacopoeia (2022)**	**Liquid Chromatography (API)**	**Stationary phase:** A stainless-steel column (250 x 4.6 mm, 5 µm), packed with octadecylsilane bonded to porous silica **Mobile phase:** Acetonitrile: 0.01M Potassium Dihydrogen Phosphate (50: 50 %v/v) **Flow rate:** 1 mL/min Wavelength: **225nm** **Injection volume:**20 µL
2	United states Pharmacopoeia (2013)	**Liquid Chromatography (API)**	**Stationary phase:** Packing L1 (150 x 4.6 mm, 5 µm) **Mobile phase:** Acetonitrile: 0.1 M Ammonium acetate: Glacial acetic acid (25: 25: 1 %v/v) **Flow rate:** 0.7 mL/min **Wavelength:** 269 nm **Injection volume:** 20 µL
VILDAGLIPTIN [10]			
2	**Indian Pharmacopoeia (2022)**	**Liquid Chromatography (API)**	**Stationary phase:** Column C_{18} (150 x 4.6 mm, 5 µm) **Mobile phase:** N-Hexane: Ethanol: Methanol: Trifluoroacetic acid (90: 5: 5: 0.1 % v/v/v) **Flow rate:** 10 mL/min **Wavelength:** 215 nm **Injection volume:** 20 µL

Non official reported methods

Table 2.2: Methods for assessment of Pioglitazone hydrochloride.

Sr.No.	Title	Description	Ref no.
UV-VISIBLE SPECTROSCOPY			
1	Methods Development and Validation for the Estimation of Pioglitazone HCL in Bulk and Formulations by **UV Spectroscopy and FTIR**	**Solvent:** Phosphate buffer (pH 7.4) and Methanol **Wavelength:** 268 nm **Linearity**: 1–20 µg/mL	[11]
2	**UV and visible Spectrophotometric** analysis of Pioglitazone hydrochloride in bulk and tablets	**Solvent:** 0.2 N Sulphuric acid solution **Wavelength:** 269 nm **Linearity:** 10-60 µg/mL	[12]
3	Determination of Pioglitazone hydrochloride in bulk and pharmaceutical formulations by **UV Spectrophotometric method**	**Solvent:** Phosphate buffer (pH 7.4) **Wavelength:** 238 nm **Linearity:** 10-50 µg/mL	[13]
4	Analytical Method Development and Validation of a **UV-Spectrophotometric** Technique for Pioglitazone HCL Estimation in Bulk and Polymeric Nanoparticles	**Solvent:** Phosphate buffer (pH 7.4) **Wavelength:** 269 nm **Linearity:** 5–60 µg/mL	[14]
5	**UV-Spectrophotometric** determination of Pioglitazone in pharmaceutical dosage forms	**Solvent:** Ethanol **Wavelength:** 224.4 nm **Linearity**: 5-25 µg/mL	[15]
HIGH PERFORMANCE LIQUID CHROMATOGRAPHY			
6	A validated stability indicating **RP-HPLC** method of estimation of pioglitazone HCL in dosage form	**Stationary phase:** Reverse-phase Hypersil BDS, C_8 (250 × 4.6 mm, 5 µm) **Mobile phase:** 0.01M Potassium Phosphate buffer (pH 7.4): Acetonitrile (40: 60 % v/v) **Flow rate:** 1 mL/min **Wavelength:** 225 nm	[16]
7	**RP-HPLC** Method Development and Validation for Pioglitazone in Bulk and Marketed Formulation	**Stationary phase**: C_{18} Column (300 × 3.9 mm, 5 µm) **Mobile phase:** Acetonitrile: Phosphate buffer (pH 7.4) (50: 50 %v/v) **Flow rate:** 1 mL/min **Wavelength:** 267 nm	[17]
8	Analytical method development and validation of Pioglitazone hydrochloride by **RP-HPLC**	**Stationary phase:** Intersil ODS C_{18} (150 × 4.6 mm, 5 µm) **Mobile phase:** Ammonium acetate buffer (pH 7.4): Acetonitrile: Glacial acetic acid (50: 50: 1 %v/v)	[18]

		Flow rate: 0.7 mL/min **Wavelength:** 269 nm	
9	Determination of Pioglitazone Hydrochloride in Tablets by **High-Performance Liquid Chromatography**	**Stationary phase:** C_{18} Column (3.9 x 150 mm, 5 µm) **Mobile phase**: Formic acid (pH 3): Acetonitrile (75: 25 %v/v) **Flow rate:** 1 mL/min **Wavelength:** 225 nm	[19]
HIGH PERFORMANCE THIN LAYER CHROMATOGRAPHY			
10	Development and Validation of A **HPTLC** Method For Estimation of Pioglitazone in Bulk and Tablet Dosage Form	**Stationary phase:** TLC aluminium plates precoated with silica gel 60 F_{254} **Mobile phase:** Toluene: Ethyl acetate: Formic acid (10: 3: 1 % v/v) **Wavelength:** 254 nm	[20]

Table 2.3 Methods for assessment of Vildagliptin.

Sr.No	Title	Description	Ref No.
UV-VISIBLE SPECTROSCOPY			
1	**UV Spectroscopy** method development and validation for determination of Vildagliptin in bulk and formulation**.**	**Solvent:** Distilled water **Wavelength:** 210 nm **Linearity:** 10-50 µg/mL	[21]
2	Analytical method development and validation for the estimation of Vildagliptin in bulk and its dosage form using **UV Spectrophotometer.**	**Solvent:** 0.1 N NaOH **Wavelength:** 216 nm **Linearity:** 10-100 µg/mL	[22]
HIGH PERFORMANCE LIQUID CHROMATOGRAPHY			
3	Development and validation of **HPLC** method for the estimation of Vildagliptin in pharmaceutical dosage form	**Stationary phase:** Kromosil C_{18} Column (150 x 4.6 mm, 5 µm) **Mobile phase:** Orthophosphoric acid: Acetonitrile (pH-2.6 ± 0.5) (72: 28 %v/v) **Flow rate:** 1 mL/min **Wavelength:** 266 nm	[23]
4	Development and validation of **RP-HPLC** assay method for Vildagliptin using **QbD** approach and its application to forced degradation studies	**Stationary phase:** Jasco Crest Pack RP C_{18} Column (250 x 4.6 mm, 5 µm) **Mobile phase:** Buffer (pH-6) : Acetonitrile : Methanol (70: 10: 20 % v/v/v) **Flow rate:** 1 mL/min **Wavelength:** 210 nm	[24]
5	Efficient **RP-HPLC** method for the detection and quantification of Vildagliptin in bulk and pharmaceutical formulation	**Stationary phase:** C_{18} Column (150 x 4.6 mm, 5 µm) **Mobile phase:** Acetonitrile : Ammonium dihydrogen phosphate (10: 90 % v/v) **Flow rate:** 1.5 mL/min	[25]

		Wavelength: 210 nm	
HIGH PERFORMANCE THIN LAYER CHROMATOGRAPHY			
6	Validated stability indicating **HPTLC** method development for determination of Vildagliptin as bulk drug and its tablet dosage form	**Stationary phase:** Silica gel aluminum plate $60F_{254}$ **Mobile phase:** Ethyl acetate: Methanol (8.5: 1.5 %v/v) **Wavelength:** 217 nm	[26]

Table 2.4: Methods for combination of Pioglitazone hydrochloride and Vildagliptin.

Sr.No.	Title	Description	Ref No.
UV-VISIBLE SPECTROSCOPY			
1	Simultaneous estimation of Vildagliptin and Pioglitazone in bulk and pharmaceutical dosage form by **UV**	**Solvent:** Water, Acetonitrile **Wavelength:** Pioglitazone: 226 nm Vildagliptin: 210 nm **Linearity:** Pioglitazone: 12-18 µg/mL Vildagliptin: 40-60 µg/mL	[27]
HIGH PERFORMANCE LIQUID CHROMATOGRAPHY			
2	Stability indicating **RP-HPLC method** development and validation for quantitative estimation of Pioglitazone and Vildagliptin in synthetic mixture	**Stationary phase:** Hypersil ODS C_{18} (250 x 4.6 mm, 5 µm) **Mobile phase:** Acetonitrile: Methanol: Water (20: 40: 40 % v/v) **Flow rate:** 1 mL/min **Wavelength:** 210 nm	[28]
3	Concurrent Estimation of Pioglitazone HCL and Vildagliptin in their Bulk and Pharmaceutical dosage form using **RP-HPLC**	**Stationary phase:** Sunfire C_{18} Column (250 x 4.6 mm, 5 µm) **Mobile phase:** ACN: Water (70: 30 %v/v) **Flow rate:** 1 mL/min **Wavelength:** 210 nm	[29]
4	A Revised **RP-HPLC** Method for Simultaneous determination of Vildagliptin and Pioglitazone HCL – application to commercially available drug products	**Stationary phase:** ACE 3 C_{18} (150 × 4.6 mm, 3.5 µm) **Mobile phase:** Water: ACN (70: 30 %v/v) **Flow rate:** 1.5 mL/min **Wavelength:** 210 nm	[30]
HIGH PERFORMANCE THIN LAYER CHROMATOGRAPHY			
5	Stability-indicating **High-Performance thin-layer chromatography** method development and validation for pioglitazone hydrochloride and vildagliptin in active pharmaceutical ingredient and tablet dosage form	**Stationary phase:** Silica gel 60 F_{254} HPTLC plates **Mobile phase**: Methanol: Toluene: Ethyl acetate: Triethylamine (2: 6: 2: 0.1 %v/v) **Wavelength:** 210 nm	[31]

CONCLUSION

This review critically summarizes and compares the analytical techniques reported for the simultaneous estimation of pioglitazone hydrochloride and vildagliptin in pharmaceutical formulations. The literature reveals that a wide range of methods—primarily UV–visible spectrophotometry, RP-HPLC, HPTLC, and stability-indicating chromatographic approaches—have been successfully developed and validated in accordance with ICH guidelines. Among these, UV spectrophotometric methods offer simplicity, cost-effectiveness, and suitability for routine quality control where high sensitivity is not critical, whereas chromatographic techniques, particularly RP-HPLC and HPTLC, provide superior specificity, precision, and robustness, making them more appropriate for complex formulations and stability studies. Overall, the compiled analytical strategies provide a valuable reference for researchers and analysts in selecting appropriate methods for routine quality control, method development, and regulatory compliance of combined pioglitazone hydrochloride and vildagliptin pharmaceutical dosage forms.

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