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A REVIEW ON ANALYTICAL METHOD DEVELOPMENT AND VALIDATION FOR LOBEGLITAZONE AND GLIMEPIRIDE IN BULK AND PHARMACEUTICAL FORMULATION

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ABSTRACT

Type 2 Diabetes Mellitus (T2DM) is a progressive metabolic disorder characterized by insulin resistance and impaired insulin secretion, requiring effective combination therapy for optimal glycemic control. Lobeglitazone, a thiazolidinedione and potent PPAR-γ agonist, enhances insulin sensitivity in peripheral tissues, while Glimepiride, a third-generation sulfonylurea, stimulates pancreatic β-cells to increase insulin secretion. The fixed-dose combination of these agents provides complementary mechanisms that improve fasting and postprandial glucose levels, reduce HbA1c, and enhance patient compliance. With the growing clinical use of this combination, the development and validation of reliable analytical methods are essential to ensure quality, safety, efficacy, and regulatory compliance. This review comprehensively summarizes physicochemical properties, pharmacokinetics, pharmacodynamics, adverse effects, drug interactions, pharmacovigilance data, regulatory approvals, and marketed formulations of Lobeglitazone and Glimepiride. Emphasis is placed on reported analytical techniques for simultaneous estimation in bulk and dosage forms, including RP-HPLC, HPLC, UPLC, UV–Visible spectrophotometry, and HPTLC, along with validation parameters such as accuracy, precision, linearity, specificity, robustness, LOD, and LOQ in accordance with ICH guidelines. Comparative evaluation indicates that RP-HPLC remains the most widely accepted and reliable method for routine quality control, while emerging green analytical approaches offer sustainable alternatives.

KEYWORDS: Lobeglitazone, Glimepiride, RP-HPLC, UV, ICH Guidelines.

INTRODUCTION

Diabetes Mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia (high blood glucose levels) due to defects in insulin secretion, insulin action, or both. Insulin is a hormone produced by the β-cells of the pancreas that helps glucose enter body cells to be used for energy. The disease is broadly classified into Type 1 diabetes mellitus, Type 2 diabetes mellitus, gestational diabetes mellitus, and other specific types. Type 1 diabetes mellitus results from autoimmune destruction of pancreatic β-cells, causing absolute insulin deficiency and requiring lifelong insulin therapy. It commonly occurs in children and young adults. Type 2 diabetes mellitus is the most prevalent form and is characterized by insulin resistance combined with relative insulin deficiency. It is strongly associated with obesity, physical inactivity, genetic predisposition, and unhealthy dietary habits.[1]

Lobeglitazone is an oral antidiabetic drug belonging to the thiazolidinedione (TZD) class, which is primarily used in the treatment of Type 2 diabetes mellitus. It functions as an insulin sensitizer, helping the body utilize insulin more effectively rather than increasing insulin secretion. Lobeglitazone acts by activating the peroxisome proliferator-activated receptor-gamma (PPAR-γ), a nuclear receptor involved in the regulation of glucose and lipid metabolism. Through this mechanism, it improves insulin sensitivity in peripheral tissues such as muscle, adipose tissue, and liver, leading to better glycemic control in patients with insulin resistance.[2]

Glimepiride is a third-generation sulfonylurea oral hypoglycemic agent widely prescribed for the management of type II diabetes mellitus. It exerts its antidiabetic effect by stimulating insulin secretion from pancreatic β-cells and improving peripheral insulin sensitivity. Glimepiride is characterized by high potency, once-daily dosing, and a comparatively lower risk of hypoglycemia than earlier sulfonylureas. Despite its clinical effectiveness, glimepiride exhibits poor aqueous solubility and high lipophilicity, placing it in Class II of the Biopharmaceutical Classification System, which limits its dissolution rate and oral bioavailability. These physicochemical limitations have prompted extensive research into novel drug delivery systems and formulation strategies to enhance its solubility, dissolution, and therapeutic performance, making glimepiride an important candidate for formulation-based research and pharmaceutical development.[3]

This combination works through complementary mechanisms: lobeglitazone improves insulin sensitivity in peripheral tissues such as muscle and adipose tissue, leading to better glucose utilization, while glimepiride stimulates pancreatic β-cells to release insulin, thereby reducing blood sugar levels, especially after meals. Together, they help effectively control both fasting and post-prandial glucose levels, improve overall glycemic control, and reduce the risk of long-term diabetic complications such as neuropathy, nephropathy, and retinopathy. This fixed-dose combination also enhances patient compliance by providing effective dual therapy in a single tablet.[4]

The lobeglitazone and glimepiride combination tablet is generally available in fixed doses containing lobeglitazone 0.5 mg with glimepiride 1 mg, 2 mg, or 4 mg. It is usually administered once daily, preferably before or with the first main meal of the day, to achieve effective control of blood glucose levels. The exact dose is individualized based on the patient's glycemic status, previous antidiabetic therapy, and risk of hypoglycemia. Dose adjustments are made gradually under medical supervision, and the combination is intended for the treatment of Type 2 Diabetes Mellitus in adults.

With the expanding clinical use of this FDC, the development of reliable, precise, and stability-indicating analytical methods is essential to ensure pharmaceutical quality, safety, and regulatory compliance. Analytical method development plays a critical role in the quantitative estimation of active pharmaceutical ingredients (APIs) in bulk drugs and finished dosage forms. Techniques such as Reverse Phase High-Performance Liquid Chromatography (RP-HPLC), High-Performance Liquid Chromatography (HPLC), Ultra-Performance Liquid Chromatography (UPLC), UV–Visible spectrophotometry, and High-Performance Thin Layer Chromatography (HPTLC) have been reported for the simultaneous estimation of Lobeglitazone and Glimepiride. Method validation, performed in accordance with International Council for Harmonisation (ICH) guidelines, evaluates parameters including accuracy, precision, specificity, linearity, robustness, limit of detection (LOD), and limit of quantification (LOQ).

In recent years, emphasis has also been placed on green analytical chemistry approaches and impurity profiling to minimize environmental impact while maintaining analytical performance. Considering the therapeutic importance of this combination and the necessity for stringent quality control, a comprehensive review of analytical method development and validation strategies for Lobeglitazone and Glimepiride in pharmaceutical formulations is both timely and scientifically relevant.[5]

ADVERSE DRUG REACTION

Lobeglitazone - adverse drug reactions (ADRs), related to its thiazolidinedione (PPAR-γ agonist) action, include peripheral edema and fluid retention, and also it cause bone fracture (long term use) which are characteristic and dose-related effects and may lead to or worsen congestive heart failure. Weight gain due to increased adipose tissue and fluid retention is also a notable ADR. Lobeglitazone may cause mild to moderate elevation of liver enzymes, requiring periodic liver function monitoring.[6]

Glimepride can cause dizziness, headache, and fatigue. Rare but specific reactions include skin rashes, pruritus, photosensitivity, hematological effects like leukopenia or thrombocytopenia, and cholestatic jaundice or elevated liver enzymes.[7]

Lobeglitazone and Glimepride are given in the combination can cause edema, weight gain also it can cause peripheral fluid retention. Mild elevation of liver enzymes, anemia, and skin reactions like rash or pruritus.

The most common adverse effects of lobeglitazone and glimepiride involve multiple organ systems. Central nervous system (CNS) effects may include dizziness, headache, drowsiness, confusion, tremors, and sweating, often related to neuroglycopenic symptoms. Gastrointestinal disturbances are also observed, such as nausea, vomiting, abdominal discomfort, dyspepsia, diarrhea, and, in the case of glimepiride, increased appetite. Cardiovascular effects include peripheral edema, weight gain, fluid retention, and, in rare cases, worsening of pre-existing heart failure. Metabolic and endocrine effects primarily involve hypoglycemia, increased fat mass, and further weight gain. Hepatic adverse effects can manifest as elevated liver enzymes or mild hepatotoxicity. Musculoskeletal complaints, such as myalgia and a potential increase in fracture risk, have also been reported, particularly with long-term use. Finally, skin and hypersensitivity reactions, including rash, pruritus, and photosensitivity, are rare but noteworthy. Overall, while both drugs are effective in glycemic control, monitoring for these adverse effects is important, especially in patients with comorbidities or long-term therapy.[8]

PHYSICAL AND CHEMICAL PROPERTIES

LOBEGLITAZONE

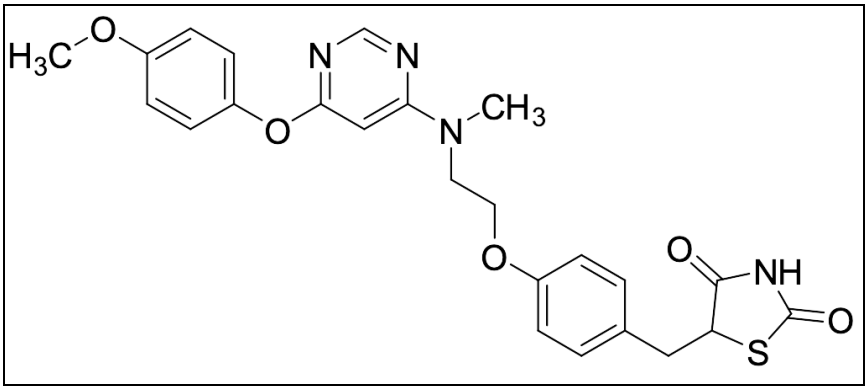

Figure-1: Structure of Lobiglitazone.

The compound, with the IUPAC name **5-(4-[2-(5-ethyl-2-pyridinyl) ethoxy] benzyl)-2,4-thiazolidinedione**, belongs to the thiazolidinedione (TZD) class of antidiabetic agents. It appears as a white to off-white crystalline powder, is odourless, and practically tasteless. The molecular formula is **$C_{24}H_{24}N_3O_4S$**, with a molecular weight of approximately 453.53 g/mol. It is practically insoluble in water, slightly soluble in methanol, and readily soluble in organic solvents such as DMSO. The compound has a melting point of around 137–140 °C, a pKa of approximately 6.8 indicating weak acidity, and a log P of ~4.0, reflecting moderate lipophilicity. It is chemically stable under normal storage conditions but may be sensitive to strong light and moisture. The substance is non-hygroscopic, making it relatively easy to handle and store. It should be stored in a cool, dry place and protected from light and moisture; for finished pharmaceutical products (such as tablets), storage at room temperature typically below 25 °C in the original packaging is recommended.[9]

GLIMEPRIDE

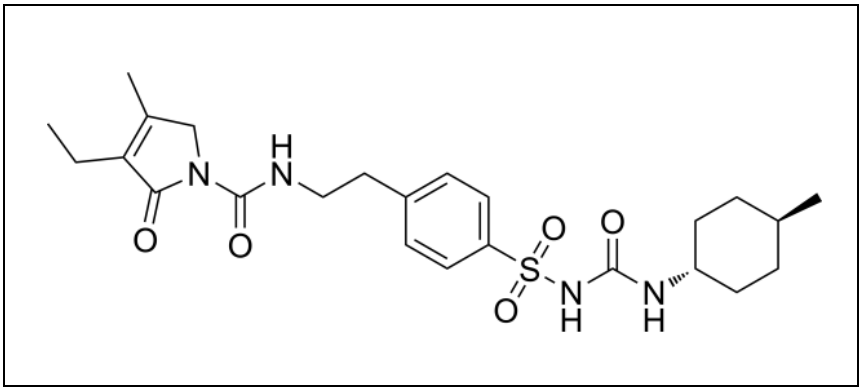

Figure-2: Structure of Glimepride.

Glimepiride has the IUPAC name **3-ethyl-2,5-dihydro-4-methyl-N- [2- [4- [[[(trans-4-methyl cyclohexyl) amino] carbonyl] amino] sulfonyl] phenyl] ethyl]-2-oxo-1H-pyrrole-1-carboxamide.** It appears as a white to pale yellow crystalline powder that is odourless and practically tasteless. Its molecular formula is **$C_{24}H_{34}N_4O_5S$,** with a molecular weight of approximately 490.62 g/mol. Glimepiride has a melting point of about 207–209 °C and is non-hygroscopic, although it is sensitive to light and should be stored accordingly. The compound is practically insoluble in water, slightly soluble in methanol, and soluble in organic solvents such as acetone and chloroform. It has a pKa of

approximately 6.2 and a log P value of around 3.2, reflecting moderate lipophilicity that facilitates oral absorption. Pharmacologically, Glimepiride acts by stimulating pancreatic β-cells to enhance insulin secretion, helping to lower blood glucose levels in patients with type 2 diabetes. It should be stored at room temperature, generally below 25–30 °C, in a cool, dry place, protected from moisture, heat, and direct light.[10]

DRUG APPROVAL DETAILS

LOBEGLITAZONE:

The development of lobeglitazone began in May 2000, with a structured research program aimed at treating type 2 diabetes mellitus (T2DM). The drug received its first regulatory approval from the Ministry of Food and Drug Safety (MFDS), South Korea, in July 2013, after which post-marketing surveillance was conducted from 2013 to 2019 to further assess its safety. In India, lobeglitazone was approved by the Drug Controller General of India (DCGI) based on Phase III clinical trial data and was first launched by Glenmark Pharmaceuticals Limited under the brand name LOBG. Early Phase I clinical trials conducted during 2004–2005 demonstrated that lobeglitazone was safe and well tolerated up to a dose of 4 mg in healthy male volunteers. A major Phase III trial in India, the 16-week randomized, double-blind SENSITIZE INDIA study published in 2024, confirmed that lobeglitazone 0.5 mg was effective, safe, and non-inferior to pioglitazone in Indian patients with T2DM. Clinically, lobeglitazone is used either as monotherapy or in combination with metformin and has shown significant reductions in HbA1c compared to placebo. Structurally, it is a modified derivative of rosiglitazone and exhibits nearly 12-fold higher affinity for PPAR-γ than pioglitazone and rosiglitazone. The approved therapeutic dose is 0.5 mg once daily, and studies suggest a comparatively favorable safety profile with lower or tolerable risks of weight gain, peripheral edema, and bone mineral density loss relative to other thiazolidinediones. As of late 2023, lobeglitazone is primarily approved for use in South Korea and India and has not received approval from the U.S. FDA, Health Canada, or the European Medicines Agency.[11]

GLIMEPRIDE

Glimepiride was approved in the United States in 1995, although it was originally patented in 1979. It is indicated for improving glycemic control in adults with type 2 diabetes mellitus, either as monotherapy or in combination with metformin or insulin. A key historical distinction of glimepiride is that it was the first sulfonylurea approved by the U.S. FDA for use in combination with insulin in patients who did not respond adequately to oral therapy alone. After its approval, glimepiride gained widespread clinical use because of its comparatively better safety profile, particularly a lower risk of hypoglycemia and weight gain when compared with older sulfonylureas. The U.S. patent for glimepiride expired in 2005, which led to extensive generic competition, and by around 2010, several manufacturers such as Teva, Mylan, and Sandoz were marketing generic versions. Clinically, glimepiride is recognized for its unique mechanism of action, as it binds to a specific 65-kD protein on pancreatic β-cells, resulting in less inhibition of cardiac ischemic preconditioning than older agents like glyburide. Despite the availability of newer antidiabetic drug classes, glimepiride remains a cost-effective, widely used option and continues to be recommended in clinical practice guidelines.[12]

LOBEGLITAZONE AND GLIMEPRIDE COMBINATION:

The fixed-dose combination of lobeglitazone sulfate (0.5 mg) and glimepiride (1 mg or 2 mg) was initially developed in South Korea and later introduced in India, with key regulatory approvals occurring between 2022 and 2024. Lobeglitazone was originally developed by CKD Pharmaceutical and received approval from the Ministry of Food and Drug Safety (MFDS), South Korea, in 2013 as a monotherapy under the brand name Duvie Tablet. In India, Glenmark

Pharmaceuticals became the first company to launch lobeglitazone in 2022 after receiving approval from the Drug Controller General of India (DCGI). Subsequently, in 2023, the Subject Expert Committee (SEC) under the Central Drugs Standard Control Organization (CDSCO) approved Akums Drugs and Pharmaceuticals Ltd to manufacture and market the fixed-dose combination of lobeglitazone and glimepiride, and the combination was formally added to the list of approved drugs, with Glenmark also receiving approval to launch the product. Further strengthening its regulatory profile, in March 2024 the SEC approved Glenmark's proposal to conduct Phase IV clinical trials for the combination, with specific conditions related to HbA1c levels, highlighting continued post-marketing evaluation. Pharmacologically, lobeglitazone acts as a thiazolidinedione and PPAR-γ agonist to enhance insulin sensitivity, while glimepiride, a sulfonylurea, stimulates pancreatic insulin secretion. The combination is indicated for adult patients with type 2 diabetes who are inadequately controlled on glimepiride or a thiazolidinedione alone. In India, it is marketed under brand names such as "Lobg G" by Glenmark, and clinical evaluations have demonstrated the combination to be safe and effective, with commonly reported adverse effects including hypoglycemia, weight gain, and dizziness.[13]

Table-1: Pharmaceutical Manufacturing Companies and Associated Brand Information.[14,15,16]

Brand Name	Strength (Per Tablet)	Pack Size	Manufacturer	Marketing / Distributor	Approx. Price (India)
LOBG G1	Lobeglitazone 0.5 mg + Glimepiride 1 mg	Strip of 10 Tablets	Glenmark Pharmaceuticals Ltd.	Glenmark Pharmaceuticals Ltd.	₹110 – ₹135
LOBG G2	Lobeglitazone 0.5 mg + Glimepiride 2 mg	Strip of 10 Tablets	Glenmark Pharmaceuticals Ltd.	Glenmark Pharmaceuticals Ltd.	₹140 – ₹160
Generic Salt (Zeelab)	Lobeglitazone 0.5 mg + Glimepiride 1 mg	Strip of 10 Tablets	Zeelab Pharmacy	Zeelab Pharmacy (Generic)	₹35 – ₹55
Akums FDC	Lobeglitazone 0.5 mg + Glimepiride 1 mg	Strip of 10 Tablets	Akums Drugs & Pharmaceuticals	Multi-brand Supply (Contract)	*Varies by brand*

Table 2: Official Method of Lobeglitazone and Glimepride.

S. No.	Drug and Pharmacopoeia	Method	Description (Chromatographic Conditions)	Reference No.
1	Lobeglitazone Sulphate (Literature – IP format)	RP-HPLC	**Column:** C18 (250 × 4.6 mm, 5 µm) **Mobile Phase:** 0.02 M KH_2PO_4 buffer (pH 2.3 adjusted with OPA) : Methanol (27:73 v/v) **Flow Rate:** 1.0 mL/min **Detector:** UV at 230–285 nm **Injection Volume:** 20 µL **Retention Time:** ~9 min **System Suitability:** Tailing factor ≤ 2.0; Theoretical plates ≥ 2000; %RSD ≤ 2%	[17]
2	Glimepiride (Indian Pharmacopoeia)	HPLC (Chromatographic System)	**Column:** Octadecylsilane bonded silica gel (C18), 250 × 4.6 mm, 5 µm **Mobile Phase:** Phosphate buffer (pH adjusted as per monograph) : Acetonitrile (specified ratio in IP) **Flow Rate:** 1.0 mL/min **Detector:** UV at 228 nm **Injection Volume:** 10–20 µL **System Suitability:** Tailing factor ≤ 2.0; %RSD for replicate injections ≤ 2.0%; Resolution between impurity peaks as per IP requirement	[18]

Table 3: Analytical Method Development and Validation of Lobiglitazone and Glimepiride.

S.no.	Title/Method	Method description	Ref.no	Year of published
RP-HPLC METHODS				
1.	Development and Validation of Stability Indicating RP-HPLC Method for Simultaneous Estimation of Lobeglitazone and Glimepiride in Tablet Dosage Form	**Colum:** Intersil Octadecyl silyl (ODS) 250 x 4.6 mm, **Partical size:** 5µ **Mobile phase:** 50:50(v/v) mixture of 0.1%formic acid and acetonitrile. **Wavelength;**260nm **Concentration:**12.5 -75 g/ml LOB and 25-150 g/ml GLM **Flow rate:** 1ml/min	(19)	April 2024
2.	Reverse phase HPLC method development and validation for simultaneous estimation of Lobeglitazone sulphate and Glimepride in pharmaceutical dosage form	**Column:** shim pack solar C18 (250mm X 4.6mm, 5µm) **Mobile phase:** Acetonitrile: Water (pH 3.0 adjusted with 1% (OPA) orthophosphoric acid. **Flow rate:** 1.0 ml/min **Wavelength:** 224nm **Retention time:**4.472min for Lobeglitazone and 6,089min for Glimepride.	(20)	August 2024
3.	Greenness analysis of stability indicating RP-HPLC method for determination of lobeglitazone sulphate and glimepiride in tablets	**Column:** Intersil C-18 column (150mm× 4.6mm, 5µm) **Mobile phase:** Potassium Dihydrogen Phosphate Buffer (pH 2.3) : Methanol (27:73V/V). **Flow rate:** 1.2mL/min. **Wavelength:** 228nm **Concentration:**2.50-7.50µg/ml for LOB and 5-15µg-/ml.for GMP	(21)	September 2025
4.	A Quality by Design Driven RP-HPLC Method for the Assay of Lobeglitazone & Glimepiride and In-silico Admet Studies	**Column:** Acetonitrile C-18 Column **Mobile Phase:** 10µm ammonium acetate buffer **Flow Rate:** 1.0ml/min **Column Temperature:** 40^{o}C **Retention Time:** 8.923 for glimepiride and 10.529 for lobeglitazone **RSD Value:** Below 2%	**(22)**	June 2025
5.	A Study of Development and validation of a method for simultaneous estimation of lobeglitazone sulfate and glimepiride using reversed-phase high-performance liquid chromatography in dosage form and characterization of degradants using liquid chromatography-mass spectrometry	**Column:** octadecyl silyl (ODS) 250 x 4.6mm **Mobile Phase:** 50:50 (v/v) mixture of 0.1% formic acid and acetonitrile **Wave Length:**260nm **Flow Rate:** 1ml/min **Concentration:** 12.5µ/ml to 75µ/ml **Run Time:** 5min **Injection Volume:** 10µl	**(23)**	October 2025
6.	Analytical Quality by Design-Based RP-HPLC Method for Simultaneous Estimation of Lobeglitazone sulfate and Glimeperide in Pharmaceutical Formulations	**Column:** Phenomenex C18(250mm, 4.6mm, 5µm) column **Mobile Phase:** Acetonitrile: Water [% Orthophosphoric acid (OPA)] (80:20% v/v). **PH : 2.5** **Wave Length:**243nm **Flow Rate:** 1ml/min **Concentration:** 5-25µg/ml for LOB and 10-50µg-/ml for GMP	(24)	January 2026
7.	Development and Validation of QBD-Assisted Using Central Composite Design RP-HPLC Method for Lobeglitazone Sulfate and Glimipiride in Bulk and Its Combined Dosage Form	**Column:** Zorbax SB 618 column (5 µm, 46 × 150 mm) **Mobile Phase:** ACN:KH_2PO_4 buffer (pH 3.5, 50:50 v/v) **PH:** 3.5 **Wave Length:** 227nm	(25)	April 2025

		Flow Rate: 1ml/min **Retention times:** 5.6 min for LBZ and 8.6 min for GPR.		
8.	A Quality by Design Driven RP-HPLC Method for the Assay of Lobeglitazone & Glimepiride and In-silico Admet Studies.	**Column:** C18 column **Mobile Phase:** acetonitrile and 10 mM ammonium acetate buffer. **Colum temperature:** 40 °C **Flow Rate:** 1ml/min **Retention times:** Glimepiride 8.923 minutes and Lobeglitazone 10.529 minutes.	(26)	2025
UV SPECTROSCOPY METHODS				
1.	Development and Validation of UV Spectrophotometric methods for simultaneous estimation of Lobeglitazone Sulfate and Glimepiride in combined dosage form	**Wavelength:** 250nm for LOB and 227nm for GLM **Solvent:** Methanol **Concentration:** 3-13µg/mL for LOB and 6-26µg/mL for GLM. **RSD Value:** Below 2%	**(27)**	July 2024
2.	Development and validation of UV-spectroscopy simultaneous estimation of lobeglitazone sulphate and glimepride in bulk and pharmaceutical dosage form.	**Wavelength:**248nm for LOB and 228nm for GLM **Solvent:** Acetonitrile : water (80:20V/V) **Concentration:**1-5µg/ml for LOB 2-10µg/ml for GLM **RSD value** -less than 1% **R^2value**-0.996(LOB) 0.998(GLM) **Isobestic point**:250nm	**(28)**	September 2025
3.	Quantitative Spectrophotometric Estimation of Lobeglitazone and Glimepride from the Combined Formulation by Vierordt's and Q Absorption Technique	**Wavelength:**251nm for LOB and 228nm for GLM **Solvent:** 0.1N NaoH **Concentration:** 2-30µg/mL for LBG and 1-24µg/mL for GLM **Run Time**: 10min	**(29)**	March 2025
4.	Novel Validated Approach for the Simultaneous Determination of Lobeglitazone Sulfate and Glimepiride in its Pure and Combined Dosage Form Using Tandem Quantification Methods by UV-Vis Spectroscopy	**Linearity range:** 4 to 10.4 µg/mL for LOB and from 8 20.8 µg/mL for GLM. **Wavelength:** LOB and GLM both shows at 250 nm and 226 nm. **R^2 Value:** R^2 = 0.9987 for lobeglitazone sulfate at two wavelengths and R^2 = 0.9987 for glimepiride.	**(30)**	**May 2025**
UPLC METHODS				
1.	Design of experiments-assisted UPLC method for quantification of nitrosamine impurities in glimepiride and lobeglitazone sulfate: A green chemistry approach	**Wavelength:**237.3nm for LOB and 241.3nm for GLM **Concentration:**10-200µg/ml for LOB 5-25µg/ml for Nitrosamine 200µg/mL GLM **RSD value** -less than 1% **Column: (**2.1mm X 50mm, 1.7µm) **Flow Rate:** 0.2mL/Min	**(31)**	June 2025
2.	Exploration on UPLC method for the analysis of lobeglitazone Sulphate and glimepiride with their stree degradation studies	**Wavelength:** UV detector set between 220 to 250 nm. **Mobile phase:** Acetonitrile and phosphate buffer, with the pH adjusted to about 3.0 using orthophosphoric acid. **Column:** C18 column **Retention time:** 3 to 5 minutes. **Temperature:** 25°C to 40°C. **Flow Rate:** 0.3-0.5 mL/Min	**(32)**	September 2025
RP-UPLC METHOD				
1.	Box-behnken assisted validation and optimization of an RP-UPLC method for	**Wavelength:**248nm. **Mobile phase**: 0.1N Potassium dihydrogen Ortho	**(33)**	November 2024

	simultaneous determination of lobeglitazone sulfate and glimepiride	phosphate (pH 4.8) (61 v/v) and Acetonitrile (39 v/v). **Concentration:**10-200µg/ml for LOB 5-25µg/ml for Nitrosamine 200µg/mL GLM **Flow rate:** 0.3ml/min. **Column:** UPLC HSS C18 column with diameter of 1.8 µm, 2.1 mm X 100 mm. **Run time:** 3 minutes. **Injection volume:** 1 µl.		
HPLC				
1.	Method Development and Validation for the Simultaneous Estimation of Lobeglitazone Sulphate and Glimepiride by HPLC Method	**Wavelength:**254nm **Column:** Shimpack C_{18} (250 X 4.6mm;5µm) **Mobile Phase:** 40 volumes of phosphate buffer pH 3 and 60 volumes of acetonitrile with methanol as diluent. **RSD Value**: $\leq$ 2.0 **Flow Rate**: 1mL/Min **R2 Value:** 0.9972% for pioglitazone **Run Time**: 10min	(34)	August 2024
HPTLC METHOD				
1.	HPTLC-Based Stability Indicating Mehod Development and Validation for Lobeglitazone Sulphate Analysis Followed by Green Assessment	**Wavelength:**248nm **Column:** Precoated silica gel 60 F254TLC plates Mobile Phase: Chloroform methanol (10:02 V/V). **RSD Value**: <2% **Flow Rate**: 1000-6000ng/band **Rf Value**: 0.36±0.02 **Run Time**: 10min	(35)	December 2025
2.	Quantitative determination of lobeglitazone sulfate and glimepiride in combined tablet by robust high-performance thin layer chromatographic method	**Wavelength:**238nm **Stationary phase:** aluminium plates layered with silica gel $60F_{254.}$ **Mobile phase:** solvent system consisted of ethyl acetate, benzene, and hexane (4:3:1 v/v/v). **R_f value:** 0.68 ± 0.001 for LBZ and 0.48 ± 0.002 for GLM. **linearity range:** 100–2000 ng/band for LBZ and 200–4000 ng/band for GLM. **LOD:** 23.86 ng/band for LBZ and 58.26 ng/band for GLM **LOQ:** 72.32 ng/band for LBZ and 176.55 ng/band for GLM.	(36)	**May 2024**

PHARMACOLOGICAL ACTION

LOBEGLITAZONE

PHARMACOKINETIC (ADME) PROPERTIES

Lobeglitazone is efficiently absorbed following oral administration, reaching peak plasma concentrations within 1–3 hours. Food may slightly delay absorption, but it does not significantly alter overall bioavailability. The drug is highly bound to plasma proteins (>99%, primarily albumin) and distributes moderately into tissues, with minimal penetration into the central nervous system. Hepatic metabolism is the primary route of biotransformation, predominantly via CYP3A4 and to a lesser extent CYP2C19, producing pharmacologically inactive metabolites. Excretion occurs mainly through the bile into feces, while renal elimination is minimal. The elimination half-life is approximately 7–10 hours, supporting a convenient once-daily dosing regimen.

PHARMACODYNAMICS PROPERTIES

Lobeglitazone acts as a selective agonist of the peroxisome proliferator-activated receptor gamma (PPAR-γ), primarily expressed in adipose tissue, skeletal muscle, and the liver. Activation of PPAR-γ modulates transcription of genes involved in glucose and lipid metabolism, resulting in enhanced insulin sensitivity, increased peripheral glucose uptake, and reduced hepatic gluconeogenesis. Additionally, the drug elevates adiponectin levels, decreases pro-inflammatory cytokines, and improves lipid handling. These pharmacodynamic effects collectively contribute to lower fasting and postprandial blood glucose levels, improved glycemic control, and potential beneficial effects on metabolic and inflammatory markers in patients with type 2 diabetes mellitus.[37]

GLIMEPRIDE

PHARMACOKINETICS PROPERTIES

Glimepiride is rapidly and almost completely absorbed after oral administration, with peak plasma concentrations occurring within 2–3 hours, and food may slightly delay absorption without affecting overall bioavailability. It is highly protein-bound (>99%, mainly to albumin) and has a low volume of distribution, with negligible penetration into the central nervous system, though it can cross the placenta, so caution is advised during pregnancy. The drug is extensively metabolized in the liver via CYP2C9, producing two main metabolites: M1 (hydroxy-glimepiride), which retains weak activity, and M2 (carboxy-glimepiride), which is inactive. Excretion occurs through both urine (approximately 60%, primarily as metabolites) and feces (around 40%). Glimepiride has an elimination half-life of 5–9 hours and a duration of action of about 24 hours, allowing for convenient once-daily dosing. Its pharmacokinetic profile may be influenced by age, renal or hepatic impairment, and concomitant medications, which can affect plasma levels, efficacy, and the risk of hypoglycemia.

PHARMACODYNAMIC PROPERTIES

Glimepiride's pharmacodynamic properties are primarily focused on its ability to stimulate insulin release from pancreatic beta cells and its extrapancreatic effects. It works by blocking ATP-sensitive potassium channels (K ATP channels) in the beta cells, leading to depolarization and increased insulin release. Glimepiride also improves the sensitivity of peripheral tissues to insulin, enhancing peripheral glucose uptake. Additionally, it inhibits glucose production in the liver by increasing the intracellular concentration of fructose-2,6-bisphosphate, which inhibits gluconeogenesis. The minimum effective oral dose is approximately 0.6 mg, and the effect is dose-dependent and reproducible.[38]

COMBINATION OF LOBIGLIPTAZONE SULFATE AND GLIMEPIRIDE:

Pharmacokinetics of the Combination

The fixed-dose combination of Lobeglitazone sulfate and Glimepiride exhibits complementary pharmacokinetic properties. Both drugs are well absorbed after oral administration, with Lobeglitazone reaching peak plasma concentrations in approximately 1–3 hours and Glimepiride in 2–3 hours. Food may slightly delay absorption of either agent but does not significantly affect overall bioavailability. Both drugs are highly protein-bound (>99%), primarily to albumin, and no clinically significant protein-binding interactions have been reported. Metabolic pathways differ between the two drugs: Lobeglitazone is predominantly metabolized in the liver via CYP3A4, whereas Glimepiride is mainly metabolized by CYP2C9. This difference in enzymatic pathways minimizes the risk of metabolic drug–drug interactions. Elimination also differs: Lobeglitazone is primarily excreted via bile and feces, while Glimepiride is

eliminated as metabolites through urine and feces. The combination's pharmacokinetic profile supports once-daily dosing with predictable plasma levels.

Pharmacodynamics of the Combination

The pharmacodynamic actions of the combination provide complementary antidiabetic effects. Lobeglitazone, a PPAR-γ agonist, enhances insulin sensitivity in adipose tissue, skeletal muscle, and liver, leading to increased peripheral glucose uptake and reduced hepatic gluconeogenesis. Glimepiride, a sulfonylurea, stimulates pancreatic β-cells by blocking ATP-sensitive potassium channels, thereby increasing insulin secretion. Together, the combination addresses both insulin resistance and impaired insulin secretion, resulting in improved fasting and postprandial glucose control, significant reductions in HbA1c, and enhanced overall glycemic management. Careful monitoring is recommended due to potential adverse effects such as hypoglycemia, weight gain, and fluid retention.[39]

PHARMACOVIGILANCE

LOBEGLITAZONE

The drug is generally well tolerated, but several adverse effects have been reported. Peripheral edema occurs at a low to moderate incidence, commonly presenting as lower limb swelling, while weight gain is a frequent adverse effect that may complicate diabetes management. Hypoglycemia is uncommon and is mainly seen with combination therapy, particularly with insulin or sulfonylureas. Elevated liver enzymes (AST, ALT, and alkaline phosphatase) may occur, so regular liver function monitoring is recommended. Rare but serious effects include congestive heart failure, especially in patients with pre-existing cardiac disease, and an increased risk of bone fractures with long-term use, particularly in post-menopausal women. Other rare adverse events include mild gastrointestinal disturbances, skin reactions, fluid retention (notably in cardiac or renal disease), hematological changes such as anemia or thrombocytopenia, hypersensitivity reactions, and possible worsening of pre-existing renal impairment, warranting routine clinical monitoring.

GLIMEPRIDE

Hypoglycemia is one of the most frequently reported adverse effects of glimepiride, especially in elderly patients, those with renal impairment, or when higher doses are used, and the risk increases if the medication is not taken with meals. Weight gain is also commonly seen, particularly with prolonged therapy in certain individuals.

Occasionally, patients may experience gastrointestinal symptoms such as nausea, vomiting, or dyspepsia, although these effects are usually mild. Skin reactions, including rashes, pruritus, and photosensitivity, as well as hematological abnormalities like leukopenia, thrombocytopenia, and hemolytic anemia, have been rarely reported. Liver function abnormalities, such as elevated ALT and AST levels, hepatitis, or jaundice, may develop in some cases. Very rare but serious reactions include cardiovascular complications, hypersensitivity reactions, hyponatremia, peripheral neuropathy with long-term use, and isolated reports of pancreatitis, highlighting the need for careful monitoring during treatment.[40]

Table 4: PHARMACOVIGILANCE OF LOBEGLITAZONE AND GLIMEPRIDE COMBINATION.[41]

Adverse Event	Incidence/Details	Management
Hypoglycemia	**Increased risk**, especially with Glimepiride. The combination may lead to a higher risk of hypoglycemia due to the insulin secretion stimulation from Glimepiride and increased insulin sensitivity from Lobeglitazone.	Monitor blood glucose regularly, adjust doses as needed, especially during meal changes or exercise.
Weight Gain	**Common**, especially in combination therapy. Lobeglitazone can contribute to weight gain, and Glimepiride can also cause weight increase through increased insulin levels.	Regular monitoring of weight. Consider alternative therapies if weight gain becomes a concern.
Peripheral Edema	**Possible**, particularly in patients at risk (e.g., elderly, or those with existing heart or kidney disease). Lobeglitazone can cause fluid retention, and Glimepiride may exacerbate edema in some cases.	Monitor for signs of edema, especially in the legs or ankles. Discontinue if severe or worsening.
Gastrointestinal Issues	**Rare** in combination, but can occur. Includes nausea, diarrhea, or discomfort, often related to gastrointestinal irritation.	Discontinue or adjust dose if symptoms persist. Usually self-limiting.
ElevatedLiver Enzymes	**Possible**, particularly with Lobeglitazone. Mild to moderate elevations in ALT, AST, and alkaline phosphatase can occur.	Monitor liver function regularly, especially in patients with pre-existing liver conditions.
Congestive Heart Failure (CHF)	**Rare** but still a concern. Lobeglitazone's risk for CHF is amplified when combined with drugs like Glimepiride, which may cause fluid retention and exacerbate heart failure in susceptible patients.	Use caution in patients with a history of heart disease. Regular monitoring for signs of heart failure is recommended.
Bone Fracture	**Low**, but there is a slight increased risk, particularly with long-term use. Lobeglitazone can contribute to bone density changes, and Glimepiride's effect on insulin could indirectly affect bone metabolism.	Regular monitoring for bone health, particularly in post-menopausal women or those with osteoporosis.
Hematological Issues	**Rare**, but may include conditions like anemia, leukopenia, or thrombocytopenia. Both drugs can affect blood cell production to some degree.	Monitor complete blood count (CBC) periodically, especially if fatigue or infection signs occur.
Fluid Retention	**Moderate**, especially in patients with pre-existing cardiovascular or kidney problems. Both medications can cause or exacerbate fluid retention.	Monitor renal and cardiac function regularly. Discontinue therapy if edema becomes severe.
Hypersensitivity Reactions	**Very Rare**, but includes anaphylaxis, angioedema, and other severe allergic reactions to either drug.	Discontinue medication immediately and treat allergic reactions as necessary.
Renal Impairment	Both drugs are affected by renal function, and dose adjustments may be required. Glimepiride can accumulate in renal impairment, and Lobeglitazone is also primarily eliminated via the kidneys.	Regular monitoring of renal function, adjust doses as needed, and avoid in severe renal impairment.

DRUG INTERACTIONS OF LOBEGLITAZONE AND GLIMEPRIDE COMBINATION

When Lobeglitazone is administered in combination with Glimepiride, several clinically important drug interactions may occur that can alter efficacy or increase adverse effects. Concomitant use with other antidiabetic agents such as insulin or additional sulfonylureas may produce additive glucose-lowering effects and significantly increase the risk of hypoglycemia, necessitating close blood glucose monitoring and dose adjustments. Since lobeglitazone is primarily metabolized by CYP3A4 enzymes, co-administration with CYP3A4 inhibitors like Ketoconazole may elevate its plasma concentration, increasing the likelihood of edema, weight gain, and hypoglycemia, whereas CYP3A4 inducers such as Rifampin may reduce its therapeutic effect by lowering plasma levels. Additionally, beta-blockers such as Metoprolol can mask typical symptoms of hypoglycemia, delaying its recognition, particularly in elderly or cardiovascular patients. Glucocorticoids like Prednisone may elevate blood glucose levels and counteract the antidiabetic action of the combination. Therefore, individualized dosing and careful clinical monitoring are essential to ensure safe and effective therapy.[42]

CONCLUSION

In conclusion, the fixed-dose combination of Lobeglitazone and Glimepiride represents a rational and synergistic therapeutic approach for the management of Type 2 Diabetes Mellitus (T2DM). Lobeglitazone improves insulin

sensitivity in peripheral tissues such as skeletal muscle, adipose tissue, and liver, thereby enhancing glucose utilization and reducing hepatic gluconeogenesis. In contrast, glimepiride primarily stimulates pancreatic β-cells to increase insulin secretion, effectively controlling postprandial hyperglycemia. The complementary mechanisms of action provide improved glycemic control, significant reduction in HbA1c levels, and better management of both fasting and postprandial blood glucose. The availability of this combination as a once-daily fixed-dose formulation enhances patient compliance and simplifies therapy. From a pharmaceutical perspective, the development and validation of reliable analytical methods such as RP-HPLC, UPLC, UV spectrophotometry, and HPTLC are essential to ensure quality, safety, efficacy, and regulatory compliance of the formulation. Although the combination demonstrates favorable efficacy and tolerability, careful monitoring is required due to potential adverse effects such as hypoglycemia, weight gain, edema, and hepatic enzyme alterations, particularly in patients with cardiovascular, hepatic, or renal comorbidities. Overall, the lobeglitazone and glimepiride combination offers an effective, clinically valuable, and economically feasible option for T2DM management, supported by validated analytical methodologies and ongoing pharmacovigilance to ensure long-term therapeutic safety and effectiveness.

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