



REVIEW ARTICLE

COMPARATIVE REVIEW OF IMMEDIATE-RELEASE AND EXTENDED-RELEASE METFORMIN FORMULATIONS: EFFICACY, SAFETY AND PATIENT ADHERENCE

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Article History

Received: 18 December 2025
Revised: 29 January 2026
Accepted: 21 February 2026
Published: 25 March 2026

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ABSTRACT: Type 2 Diabetes Mellitus (T2DM) is a prevalent metabolic disorder characterized by chronic hyperglycemia and associated with significant morbidity and mortality worldwide. Metformin is the recommended first-line oral antidiabetic agent owing to its efficacy, safety, cost-effectiveness, and favorable metabolic profile. To enhance therapeutic outcomes and patient convenience, metformin is available as Immediate-Release (IR) and Extended-Release (ER) formulations. Although both formulations contain the same active drug, they differ in release characteristics, dosing frequency, gastrointestinal tolerability, and adherence patterns. This review critically compares IR and ER metformin formulations with respect to pharmacokinetic properties, clinical efficacy, safety, and patient adherence. Evidence from clinical studies demonstrates that both formulations provide comparable glycemic control, including reductions in glycated hemoglobin (HbA1c) and fasting plasma glucose levels. However, ER metformin offers a controlled drug-release profile that minimizes peak plasma concentrations and improves gastrointestinal tolerability. Consequently, ER formulations are associated with fewer adverse gastrointestinal events such as nausea, diarrhea, and abdominal discomfort. The reduced dosing frequency of ER metformin also contributes to improved patient adherence, treatment satisfaction, and long-term persistence with therapy. Despite its higher cost, ER metformin may be particularly beneficial for patients experiencing intolerance or poor compliance with IR formulations. Future research should focus on personalized treatment approaches, innovative delivery technologies, real-world studies evaluating long-term adherence and clinical outcomes, and optimization of formulation selection strategies. Overall, both IR and ER metformin remain effective therapeutic options, with formulation selection depending on individual patient requirements and treatment goals.

Keywords: Metformin, Immediate-release, Extended-release, Type 2 Diabetes Mellitus, Patient Adherence, Safety

1. INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic condition that is defined by the presence of a high blood glucose level for a long time, due to insulin resistance and gradual decline in the function of the pancreatic β -cells [1]. One of the most rapidly increasing non-communicable diseases in the world, and a significant burden on the health systems, economies and patient quality of life. The global epidemiological reports show that the prevalence of T2DM has skyrocketed in the past few decades because of the rapid urbanisation, sedentary lifestyle, unhealthy eating habits, obesity and ageing population. It has been linked to many complications which contribute to morbidity and mortality, such as diabetic nephropathy, diabetic retinopathy, neuropathy, cardiovascular disease and stroke. Thus, this is a key diabetes management objective to achieve and sustain optimal glycemic control [2]. For decades, metformin has been the mainstay of the treatment of T2DM and is widely recommended as the first-line pharmacological treatment of T2DM by the major diabetes organizations. It has a beneficial effect on lowering blood glucose through reducing hepatic gluconeogenesis, increasing insulin sensitivity, and stimulating

glucose uptake in the periphery. Besides its ability to lower blood glucose levels, metformin has a number of clinical benefits such as being weight neutral, not having a high risk of hypoglycemia, being cardioprotective, and being cost-effective. The advantages of these have made metformin the most commonly prescribed oral antidiabetic drug in the world [3].

The drug has traditionally been available as Immediate-Release (IR) formulations that dissolve quickly and release the drug after it is taken by mouth. IR metformin is very effective in controlling blood sugar, but it can also cause some side effects in the gut, including nausea, diarrhea, abdominal pain and bloating. Moreover, the need for 2 or 3 doses a day could decrease compliance with treatment, especially in older age groups and those taking more than one medication [4].

In addressing these limitations, new controlled-release technologies have been used to formulate extended-Release (ER) metformin products. These formulations slowly release the drug through the gastrointestinal tract, leading to steady plasma concentrations over time, enhanced gastrointestinal tolerability and the benefit of once-daily administration. This

has led to the growing acceptance of ER metformin as an alternative to standard IR formulations in the clinic [5].

The decision between IR and ER metformin formulations is clinically relevant, as variations in drug release, tolerability, dosing interval, patient preference and adherence may impact the therapeutic results. A full awareness of these formulations is therefore necessary to tailor treatment plan at an individual level [6]. This review is aimed to make a comprehensive comparison of the Immediate-Release and Extended-Release metformin formulations with their pharmacokinetic properties, clinical efficacy, safety profile, gastrointestinal tolerability, patient adherence and overall therapeutic value in the management of Type 2 Diabetes Mellitus [7].

2. Literature Search Methodology

A thorough literature review was performed to gather and analyze published research concerning the IR and ER formulation of metformin and their effectiveness, safety, gastrointestinal tolerability, pharmacokinetic properties, and adherence in the treatment of Type 2 Diabetes Mellitus (T2DM). The purpose of the literature search was to locate clinical, pharmacological and review studies which would yield evidence of the comparative performance of both formulations [8]. Systematically all the electronic databases were searched that included PubMed, Scopus, ScienceDirect, SpringerLink and Google Scholar. The choice of these databases was made because they provide a wide range of resources on biomedical, pharmaceutical and clinical research publications. Studies published in the English language between 2000 and 2025 were searched for to ensure that both foundational and recent studies were included [9].

Combination of keywords and Boolean operators (AND, OR) were used to identify relevant articles. The most relevant search terms were “Metformin,” “Immediate-Release Metformin,” “Extended-Release Metformin,” “Type 2 Diabetes Mellitus,” “Glycemic Control,” “HbA1c,” “Pharmacokinetics,” “Patient Adherence,” “Medication Compliance,” “Safety,” “Gastrointestinal Tolerability,” and “Controlled-Release Formulations.” A second-hand search of the reference lists of the selected articles was also carried out to search for other relevant studies [10].

To include IR and ER metformin studies, the inclusion criteria were original research articles, randomized controlled trials, observational studies, comparative clinical studies, meta-analyses, systematic reviews, and pharmacokinetic studies. The studies that reported efficacy, safety, tolerability, adherence, and patient satisfaction were included in the criteria for eligibility [11].

The following criteria were used for excluding the articles: Duplicate publications, conference abstracts not available in full text, non-English publications, animal studies not related to formulation comparison, case reports, editorials, and insufficient methodological details or relevant outcome measures [12].

Study selection was conducted by screening of titles and abstracts, and then by reading of the full text of articles that might be relevant. Eligible studies were critically reviewed, analyzed, and categorized based on the purpose of this review, to get a clear idea about the differences between the Immediate-Release (IR) and Extended-Release (ER) of metformin [13].

3. Metformin: Pharmacological Overview

Metformin is a synthetic biguanide, and is the most commonly used oral antidiabetic medication for Type 2 Diabetes Mellitus (T2DM). It is widely regarded as one of the pillars of diabetes care due to its effectiveness, safety, minimal risk of hypoglycemia and positive impact on weight and cardiovascular well-being. Metformin is different from many other antidiabetic medications, because it does not directly stimulate insulin secretion in the body but rather it lowers production of glucose by the liver and increases insulin sensitivity. Both Immediate-Release (IR) and Extended-Release (ER) formulations have been developed to enhance therapeutic/clinical outcomes and patient convenience and are commonly encountered in clinical practice [14].

3.1 History and Development

Metformin is derived from the medicinal plant *Galega officinalis* (French lilac), which has been used to treat the symptoms of diabetes. The drug was first synthesized in the 1920s, but its clinical relevance was first realized in the 1950s when studies demonstrated that it lowered glucose levels. Metformin was first used in Europe in 1957 and approved by the U.S. Food and Drug Administration (FDA) in 1995 [15].

The original formulation of the conventional IR was as a tablet which was taken orally two to three times a day. It was effective, but was often correlated with gastrointestinal side effects and poor compliance. To overcome these drawbacks, ER formulations with controlled-release technologies have been developed, which deliver a slow or controlled release of the drug, maintain serum concentrations, enhance gastrointestinal tolerability, and offer once-a-day dosing [16].

3.2 Mechanism of Action

Metformin lowers blood glucose levels through multiple mechanisms without causing significant hypoglycemia.

Reduction of Hepatic Glucose Production

The primary action of metformin is the inhibition of hepatic gluconeogenesis, which reduces the production of glucose by the liver and lowers fasting blood glucose levels.

Increased Insulin Sensitivity

Metformin enhances insulin sensitivity in skeletal muscle and adipose tissue, promoting glucose uptake and utilization while reducing insulin resistance [17].

AMPK Activation

A major mechanism involves activation of adenosine monophosphate-activated protein kinase (AMPK), an important cellular energy regulator. AMPK activation suppresses glucose production, promotes fatty acid oxidation, and improves overall metabolic function.

Effects on Gut Microbiota

Recent studies suggest that metformin also alters gut microbiota composition and enhances intestinal glucose metabolism, contributing to improved glycemic control and metabolic health [18].

3.3 Pharmacokinetic Properties

Absorption

Metformin is absorbed mainly from the small intestine. IR metformin reaches peak plasma concentrations within 2–3 hours, whereas ER formulations delay peak concentrations to approximately 4–8 hours because of their sustained-release characteristics.

Distribution

Following absorption, metformin is widely distributed throughout body tissues, particularly the liver, kidneys, and gastrointestinal tract. The drug exhibits minimal plasma protein binding [19].

Metabolism

Metformin undergoes negligible hepatic metabolism and circulates largely unchanged in the body, reducing the likelihood of metabolic drug interactions.

Elimination

The drug is primarily eliminated through renal excretion via glomerular filtration and tubular secretion. Its elimination half-life ranges from 4 to 8 hours. Since kidney function plays a major role in drug clearance, careful monitoring is recommended in patients with renal impairment to prevent drug accumulation and adverse effects (Fig. 1) [20].

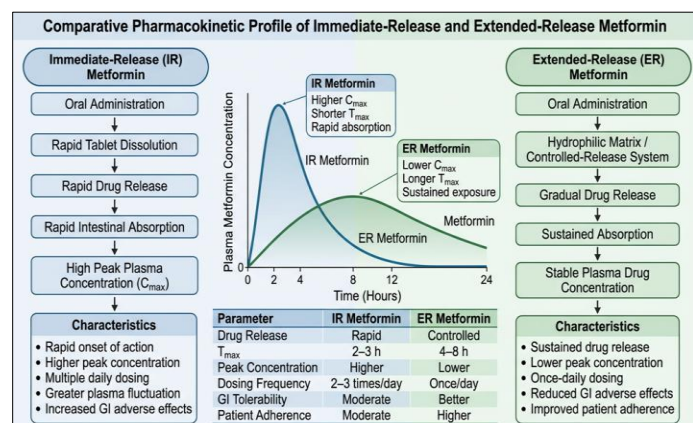


Figure 1: Comparative Pharmacokinetic Profile of Immediate-Release and Extended-Release Metformin [21]

4. Immediate-Release Metformin Formulation

Immediate-Release (IR) metformin is the conventional and most extensively prescribed formulation of metformin for the treatment of Type 2 Diabetes Mellitus (T2DM). Since its introduction into clinical practice, IR metformin has served as the standard formulation for achieving glycemic control in patients with T2DM. The formulation is designed to release the active drug rapidly after oral administration, resulting in prompt absorption and therapeutic action. Due to its proven efficacy, affordability, and widespread availability, IR metformin remains a preferred treatment option in many healthcare settings worldwide [22].

4.1 Formulation Characteristics

Tablet Composition

Immediate-Release metformin tablets contain metformin hydrochloride as the active pharmaceutical ingredient along with various excipients such as microcrystalline cellulose, povidone, magnesium stearate, and starch-based binders. These excipients provide tablet integrity, stability, and uniform drug distribution while facilitating rapid disintegration after administration. IR metformin is commonly available in strengths of 500 mg, 850 mg, and 1000 mg, allowing dose adjustments according to individual patient requirements [23].

Drug Release Profile

The IR formulation is specifically designed for rapid disintegration and dissolution in the gastrointestinal tract. Following oral administration, the tablet quickly releases metformin, leading to absorption primarily in the small intestine. Peak plasma concentrations are generally achieved within 2–3 hours after dosing. Because of its relatively short duration of action, IR metformin usually requires administration two or three times daily to maintain effective glycemic control [24].

4.2 Clinical Efficacy

Glycemic Control

Numerous clinical studies have demonstrated the effectiveness of IR metformin in improving glycemic control among patients with T2DM. The drug significantly reduces fasting plasma glucose levels and improves overall glucose regulation by suppressing hepatic glucose production and enhancing insulin sensitivity. Long-term treatment with IR metformin has consistently shown beneficial effects on metabolic control and disease progression [25].

HbA1c Reduction

Reduction in glycated hemoglobin (HbA1c) is a key indicator of long-term glycemic management. Clinical evidence indicates that IR metformin can lower HbA1c levels by approximately 1–2%, depending on baseline glycemic status, dosage, and treatment duration. These improvements contribute to a reduced risk of diabetes-related complications and support its role as a first-line therapeutic agent [26].

4.3 Advantages

Rapid Onset

Due to its immediate drug-release characteristics, IR metformin achieves therapeutic plasma concentrations relatively quickly after administration. This rapid absorption contributes to effective glucose-lowering activity and prompt therapeutic response.

Lower Cost

One of the major advantages of IR metformin is its affordability. As a widely available generic medication, it is considerably less expensive than many newer antidiabetic therapies and extended-release formulations, making it accessible to a large patient population [27].

Wide Availability

IR metformin is available globally through hospitals, pharmacies, and healthcare centers. Its extensive availability and long history of clinical use have contributed to its widespread acceptance among healthcare professionals and patients [28].

4.4 Limitations

Gastrointestinal Adverse Effects

Despite its clinical effectiveness, IR metformin is commonly associated with gastrointestinal adverse effects, particularly during treatment initiation. Frequently reported symptoms include nausea, diarrhea, abdominal discomfort, bloating, and gastrointestinal irritation [29]. These adverse effects may negatively affect patient comfort and treatment continuation.

Multiple Daily Doses

The relatively short duration of drug release necessitates administration two or three times daily. Frequent dosing may increase treatment burden and complicate medication schedules, especially in elderly patients and individuals receiving multiple medications [30].

Lower Adherence

The combination of gastrointestinal intolerance and multiple daily dosing can reduce patient adherence to therapy. Poor adherence may compromise glycemic control, increase the risk of treatment failure, and negatively affect long-term clinical outcomes. Consequently, alternative formulations such as Extended-Release metformin have been developed to address these limitations and improve overall patient satisfaction [31].

5. Extended-Release Metformin Formulation

Extended-Release (ER) metformin was developed to overcome the limitations associated with conventional Immediate-Release (IR) metformin, particularly gastrointestinal intolerance and the need for multiple daily dosing. By utilizing advanced drug-delivery technologies, ER formulations provide gradual and sustained release of

metformin throughout the gastrointestinal tract, resulting in prolonged therapeutic activity and improved patient compliance. Since its introduction, ER metformin has gained considerable clinical acceptance and is widely prescribed for patients who experience intolerance to IR formulations or require a more convenient dosing regimen (Table 1) [32].

5.1 Formulation Technologies

Hydrophilic Matrix Systems

Hydrophilic matrix systems are among the most commonly employed technologies in ER metformin formulations. These systems utilize polymers such as hydroxypropyl methylcellulose (HPMC), which swell upon contact with gastrointestinal fluids and form a hydrated matrix around the tablet. The drug is gradually released through diffusion and matrix erosion, ensuring sustained plasma concentrations over an extended period [33].

Gel-Forming Systems

Gel-forming technologies play an important role in controlling the release of metformin. Upon hydration, the tablet develops a gel barrier that regulates the penetration of gastrointestinal fluids and the diffusion of the drug. This mechanism slows drug release and helps maintain consistent therapeutic concentrations while reducing fluctuations in plasma levels [34].

Controlled-Release Technologies

Modern ER formulations incorporate sophisticated controlled-release systems designed to optimize drug delivery. These technologies enable gradual release of metformin over several hours, extending its therapeutic effect and reducing the frequency of administration. Controlled-release mechanisms also contribute to improved gastrointestinal tolerability by minimizing high local concentrations of the drug within the gastrointestinal tract [35].

5.2 Clinical Efficacy

HbA1c Reduction

Clinical studies have consistently demonstrated that ER metformin provides glycemic control comparable to that achieved with IR formulations. Significant reductions in glycated hemoglobin (HbA1c), typically ranging from 1–2%, have been reported following long-term treatment. These findings indicate that the slower drug-release profile does not compromise therapeutic efficacy.

Fasting Blood Glucose Control

ER metformin effectively lowers fasting blood glucose levels by suppressing hepatic glucose production and improving insulin sensitivity. Sustained drug exposure throughout the day contributes to stable glycemic control and supports long-term diabetes management. Several comparative studies have shown similar improvements in fasting plasma glucose levels between ER and IR formulations [36].

5.3 Advantages

Improved Tolerability

One of the most significant advantages of ER metformin is its superior gastrointestinal tolerability. The gradual release of the drug reduces peak concentrations within the gastrointestinal tract, thereby decreasing the incidence and severity of adverse effects such as nausea, diarrhea, abdominal pain, and bloating [37].

Once-Daily Administration

ER formulations are generally administered once daily, providing a simpler dosing regimen compared with the two or three daily doses often required for IR metformin. This reduced dosing frequency enhances treatment convenience and minimizes medication burden [38].

Better Patient Convenience

The combination of improved tolerability and once-daily administration contributes to greater patient satisfaction and adherence. Better compliance may ultimately improve long-term glycemic control and reduce the risk of diabetes-related complications [39].

Table 1: Comparative Formulation Characteristics of IR and ER Metformin [42]

S. No.	Parameter	Immediate-Release (IR) Metformin	Extended-Release (ER) Metformin
1	Formulation type	Conventional oral tablet	Controlled-release oral tablet
2	Drug release pattern	Rapid drug release	Gradual and sustained drug release
3	Release technology	Immediate dissolution system	Hydrophilic matrix/gel-forming system
4	Time to peak plasma concentration (T _{max})	Approximately 2–3 hours	Approximately 4–8 hours
5	Plasma concentration profile	Higher peak concentration	Lower and more stable concentration
6	Dosing frequency	Two to three times daily	Once daily
7	Duration of drug release	Short duration	Prolonged duration
8	Gastrointestinal exposure	Higher local drug concentration	Reduced local drug concentration
9	Gastrointestinal tolerability	Lower tolerability	Improved tolerability
10	Tablet manipulation	Can be split in some formulations as prescribed	Should not be crushed, chewed, or split
11	Patient convenience	Moderate	High
12	Cost and availability	Lower cost and widely available	Higher cost with increasing availability

5.4 Limitations

Higher Cost

Despite its clinical benefits, ER metformin is generally more expensive than conventional IR formulations due to the advanced technologies used in its manufacture. The increased cost may limit accessibility for some patients, particularly in resource-constrained settings [40].

Limited Dose Flexibility

ER formulations offer fewer dosing adjustment options compared with IR metformin. Because the tablet is designed for controlled drug release, splitting or crushing the tablet is not recommended, which may restrict dose customization in certain clinical situations. Consequently, healthcare providers must carefully consider patient-specific requirements when selecting the most appropriate metformin formulation [41].

6. Comparative Clinical Efficacy

The clinical efficacy of metformin in the management of Type 2 Diabetes Mellitus (T2DM) is well established. Both Immediate-Release (IR) and Extended-Release (ER) formulations contain the same active drug and provide effective glycemic control. Although differences exist in drug-release characteristics and dosing schedules, numerous clinical studies have demonstrated comparable therapeutic efficacy between the two formulations [43].

6.1 HbA1c Reduction

Glycated hemoglobin (HbA1c) is an important indicator of long-term glycemic control. Clinical studies have shown that both IR and ER metformin significantly reduce HbA1c levels, typically by 1–2%. Comparative trials have reported no significant differences between the two formulations, indicating equivalent glucose-lowering efficacy when administered at appropriate doses [44].

6.2 Fasting Plasma Glucose Control

Both IR and ER metformin effectively lower fasting plasma glucose levels by reducing hepatic glucose production and improving insulin sensitivity. ER metformin provides similar fasting glucose control while maintaining more stable plasma drug concentrations due to its sustained-release properties [45].

6.3 Postprandial Glucose Control

Postprandial hyperglycemia contributes significantly to overall glycemic burden and the development of diabetic complications. Both formulations effectively reduce postprandial glucose excursions. While IR metformin acts more rapidly following administration, ER metformin provides prolonged glucose-lowering activity throughout the day, resulting in comparable overall efficacy [46].

6.4 Long-Term Glycemic Outcomes

Long-term glycemic control is essential for reducing the risk of microvascular and macrovascular complications. Several studies have demonstrated sustained reductions in HbA1c and fasting plasma glucose with both IR and ER formulations. The improved tolerability and simplified dosing regimen of ER metformin may contribute to better treatment persistence and long-term therapeutic success [47].

6.5 Impact on Weight Management

Metformin is generally considered weight-neutral and may produce modest weight reduction in some patients. Both IR and ER formulations have shown beneficial effects on body weight and body mass index (BMI), particularly among overweight and obese individuals. No clinically significant differences have been reported between the two formulations regarding weight management outcomes [48].

6.6 Cardiometabolic Benefits

In addition to glycemic control, metformin provides several cardiometabolic benefits, including improved insulin sensitivity and favorable effects on lipid metabolism. Both formulations have been associated with reductions in serum triglycerides, low-density lipoprotein cholesterol (LDL-C), and cardiovascular risk factors. Since both contain the same active drug, their cardiometabolic benefits are largely comparable, although improved adherence with ER metformin may enhance long-term treatment outcomes. Overall, available evidence suggests that IR and ER metformin formulations provide similar efficacy in reducing HbA1c, fasting plasma glucose, and postprandial glucose levels while offering comparable benefits in weight management and cardiometabolic health. The primary advantage of ER metformin lies in its improved tolerability and convenience, which may positively influence adherence and long-term treatment success [49].

7. Safety and Tolerability Assessment

Metformin is widely recognized as one of the safest and most effective oral antidiabetic agents for the management of Type 2 Diabetes Mellitus (T2DM). Its favorable safety profile, low risk of hypoglycemia, and extensive clinical experience have established it as the first-line pharmacological therapy worldwide. Both Immediate-Release (IR) and Extended-Release (ER) formulations demonstrate comparable safety and efficacy; however, differences in drug-release characteristics may influence tolerability and patient acceptance [50].

7.1 Gastrointestinal Adverse Effects

Gastrointestinal (GI) disturbances are the most frequently reported adverse effects of metformin therapy and often occur during treatment initiation or dose escalation. These effects are generally more pronounced with IR formulations due to rapid drug release [51].

Nausea

Nausea is one of the most common adverse effects associated with metformin therapy. It is believed to result from local gastrointestinal irritation and altered intestinal motility. Studies have shown that ER metformin is associated with a lower incidence of nausea because of its gradual drug-release pattern.

Vomiting

Vomiting may occur in some patients, particularly at higher doses. Although less common than nausea, persistent vomiting

can affect treatment adherence and quality of life. ER formulations generally demonstrate improved tolerability and fewer vomiting episodes [52].

Diarrhea

Diarrhea is among the most prevalent gastrointestinal side effects of metformin. The rapid release of drug from IR tablets may increase gastrointestinal exposure, leading to a higher incidence of diarrhea. ER metformin has been shown to significantly reduce both the frequency and severity of this adverse effect.

Abdominal Discomfort

Abdominal pain, bloating, cramping, and gastrointestinal discomfort are frequently reported during metformin therapy. These symptoms are usually transient but may negatively influence patient compliance. Clinical studies consistently indicate superior gastrointestinal tolerability with ER formulations [53].

7.2 Hypoglycemia Risk

Metformin does not stimulate pancreatic insulin secretion and therefore carries a very low risk of hypoglycemia when used as monotherapy. Both IR and ER formulations exhibit a similar safety profile in this regard. Hypoglycemic episodes are uncommon and are generally associated with combination therapy involving insulin or insulin secretagogues [54].

7.3 Vitamin B12 Deficiency

Long-term metformin therapy has been linked to reduced intestinal absorption of vitamin B12. Prolonged treatment may result in vitamin B12 deficiency, potentially leading to anemia, fatigue, peripheral neuropathy, and neurological complications. Regular monitoring of vitamin B12 levels is therefore recommended, particularly in patients receiving long-term treatment [55].

7.4 Lactic Acidosis

Lactic acidosis is a rare but serious adverse effect associated with metformin accumulation. Although its incidence is extremely low, the risk increases in patients with severe renal impairment, advanced hepatic disease, congestive heart failure, or conditions causing tissue hypoxia. Both IR and ER formulations possess a similar risk profile because lactic acidosis is related to systemic drug accumulation rather than formulation type [56].

7.5 Renal Considerations

Since metformin is primarily eliminated through renal excretion, kidney function is a critical factor in its safe use. Impaired renal function may reduce drug clearance and increase the risk of accumulation. Current guidelines recommend assessment of estimated glomerular filtration rate (eGFR) before initiating therapy and periodic monitoring

during treatment. Dose adjustments may be necessary in patients with moderate renal impairment [57].

7.6 Hepatic Considerations

Although metformin undergoes minimal hepatic metabolism, caution is advised in patients with significant liver disease. Hepatic impairment may reduce lactate clearance and increase susceptibility to lactic acidosis. Therefore, careful clinical evaluation and monitoring are recommended when metformin is prescribed to patients with hepatic dysfunction.

Overall, both IR and ER metformin formulations exhibit excellent safety profiles and comparable therapeutic effectiveness. However, ER metformin generally offers superior gastrointestinal tolerability, which may enhance patient satisfaction, treatment adherence, and long-term persistence with therapy while maintaining the established safety benefits of metformin (Fig. 2) [58].

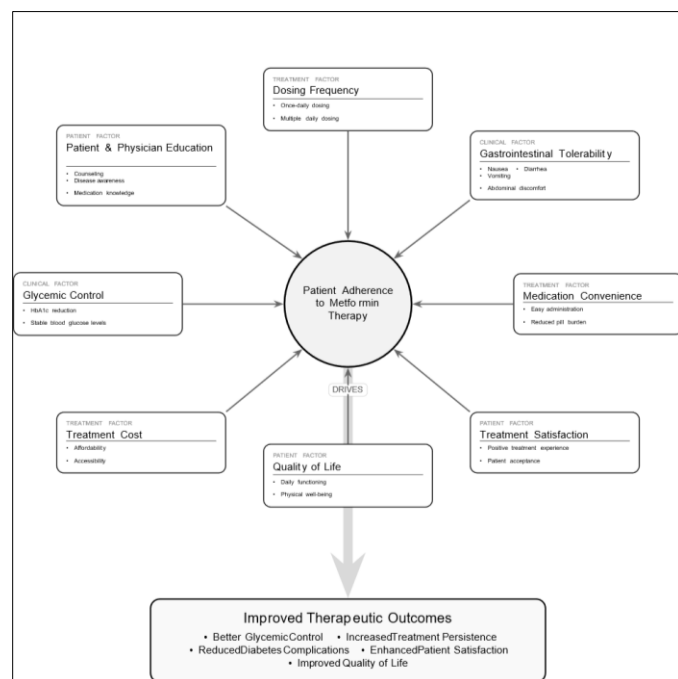


Figure 2: Factors Influencing Patient Adherence to Metformin Therapy [59]

8. Patient Adherence and Quality of Life

Patient adherence is a key factor in achieving successful glycemic control and preventing long-term complications in individuals with Type 2 Diabetes Mellitus (T2DM). Effective diabetes management requires consistent medication use, lifestyle modifications, and regular monitoring of blood glucose levels. Although Immediate-Release (IR) and Extended-Release (ER) metformin formulations demonstrate comparable clinical efficacy, differences in dosing frequency, tolerability, and convenience can significantly influence patient adherence and overall quality of life. Therefore, understanding these factors is essential when selecting the most appropriate metformin formulation [60].

8.1 Importance of Medication Adherence

Medication adherence refers to the extent to which patients follow prescribed treatment regimens. Poor adherence is a common challenge in diabetes management and is associated with inadequate glycemic control, increased healthcare utilization, and a higher risk of diabetes-related complications. Studies have shown that patients who consistently adhere to metformin therapy achieve better HbA1c reduction and improved metabolic outcomes. Consequently, improving adherence remains an important goal in diabetes care [61].

8.2 Effect of Dosing Frequency

Dosing frequency is one of the most influential factors affecting treatment compliance. IR metformin generally requires administration two or three times daily because of its shorter duration of action, whereas ER metformin is usually administered once daily. Simplified dosing schedules reduce treatment burden, improve convenience, and increase the likelihood of patients following their prescribed regimen. Several studies have reported higher adherence rates among patients receiving ER formulations compared with IR metformin [62].

8.3 Influence of Adverse Effects

Adverse effects can significantly impact patient willingness to continue therapy. Gastrointestinal symptoms such as nausea, diarrhea, abdominal discomfort, bloating, and vomiting are among the most common reasons for treatment discontinuation. Since ER metformin releases the drug gradually, it is generally associated with fewer gastrointestinal adverse effects than IR formulations. Improved tolerability enhances patient comfort and supports long-term treatment persistence [63].

8.4 Patient Preference Studies

Patient preference plays an important role in treatment success. Clinical and observational studies have consistently shown that many patients prefer ER metformin because of its once-daily dosing schedule and improved gastrointestinal tolerability. Patients who switch from IR to ER formulations often report greater treatment satisfaction, which may contribute to better adherence and persistence with therapy [64].

8.5 Quality-of-Life Outcomes

Quality of life is an important aspect of diabetes management and includes physical health, emotional well-being, treatment satisfaction, and daily functioning. Effective glycemic control combined with convenient treatment regimens can positively influence overall well-being. ER metformin may improve quality of life by reducing medication burden and minimizing gastrointestinal discomfort, allowing patients to manage their condition more comfortably and effectively [65].

8.6 Real-World Adherence Evidence

Evidence from real-world studies, prescription databases, and patient surveys consistently demonstrates improved adherence and treatment persistence among individuals receiving ER metformin. Higher adherence rates are often associated with better glycemic control, reduced healthcare costs, and improved long-term clinical outcomes. While both formulations remain effective, the convenience and tolerability advantages of ER metformin may contribute to greater therapeutic success in routine clinical practice.

Overall, patient adherence and quality of life are important considerations when selecting a metformin formulation. Although IR and ER metformin provide similar glucose-lowering efficacy, ER formulations generally offer superior convenience, improved tolerability, and greater patient satisfaction, which may ultimately enhance long-term diabetes management and treatment outcomes (Table 2) [66].

Table 2: Comparative Impact of IR and ER Metformin on Patient Adherence [67]

S. No.	Adherence Parameter	Immediate-Release (IR) Metformin	Extended-Release (ER) Metformin
1	Dosing frequency	Two to three times daily	Once daily
2	Medication burden	Higher	Lower
3	Treatment convenience	Moderate	High
4	Gastrointestinal tolerability	Lower	Higher
5	Incidence of nausea	More frequent	Less frequent
6	Incidence of diarrhea	More common	Reduced occurrence
7	Missed dose probability	Higher	Lower
8	Patient satisfaction	Moderate	High
9	Treatment persistence	Lower	Higher
10	Long-term adherence	Moderate	Improved
11	Quality-of-life impact	May be affected by adverse effects and frequent dosing	Enhanced due to convenience and better tolerability
12	Overall adherence outcome	Good, but limited by dosing frequency and GI effects	Superior adherence and greater treatment acceptance

9. Future Perspectives

Although metformin remains the cornerstone of Type 2 Diabetes Mellitus (T2DM) management, ongoing advances in pharmaceutical and digital health technologies continue to create opportunities for improving its therapeutic performance. Future research is expected to focus on enhancing drug delivery, optimizing treatment adherence, and supporting personalized diabetes care [68].

9.1 Novel Metformin Delivery Systems

Advanced delivery technologies such as gastro-retentive systems, nanoparticles, microspheres, and controlled-release formulations are being explored to improve bioavailability, prolong drug release, and reduce gastrointestinal adverse effects [69].

9.2 Personalized Diabetes Therapy

Personalized treatment approaches based on patient characteristics, genetic factors, renal function, and disease severity may help optimize metformin dosing and formulation selection, leading to improved therapeutic outcomes [70].

9.3 Fixed-Dose Combinations

The development of fixed-dose combinations containing metformin and other antidiabetic agents can simplify treatment regimens, reduce pill burden, and enhance patient adherence while maintaining effective glycemic control [71].

9.4 Digital Adherence Monitoring

Digital health tools such as mobile applications, electronic reminders, wearable devices, and telemedicine platforms may improve medication adherence and support better diabetes management through continuous monitoring and patient engagement [72].

9.5 Real-World Evidence Studies

Future real-world studies involving patient registries, healthcare databases, and observational research are needed to evaluate long-term effectiveness, safety, adherence, and treatment outcomes across diverse patient populations [73].

Overall, future advancements in metformin therapy are likely to emphasize innovative drug-delivery systems, personalized treatment strategies, digital healthcare integration, and real-world clinical evidence to further improve diabetes management and patient outcomes [74].

10. CONCLUSION

Metformin remains the first-line pharmacological therapy for Type 2 Diabetes Mellitus (T2DM) because of its proven efficacy, safety, affordability, and favorable metabolic effects. This review compared Immediate-Release (IR) and Extended-Release (ER) metformin formulations in terms of efficacy, safety, gastrointestinal tolerability, and patient adherence. Available evidence indicates that both IR and ER formulations provide comparable glycemic control, including significant reductions in HbA1c, fasting plasma glucose, and postprandial glucose levels. However, ER metformin offers improved gastrointestinal tolerability due to its controlled drug-release profile, resulting in fewer adverse effects such as nausea, diarrhea, vomiting, and abdominal discomfort. The once-daily dosing regimen of ER metformin also enhances patient convenience and treatment adherence compared with the multiple daily doses often required for IR formulations. Improved adherence and persistence with therapy may contribute to better long-term glycemic outcomes and patient satisfaction.

Overall, both formulations remain effective treatment options, and the choice between IR and ER metformin should be based on individual patient needs, tolerability, adherence patterns,

and economic considerations. Future advancements in diabetes management are expected to focus on personalized treatment approaches, innovative metformin delivery systems, digital adherence monitoring, and real-world clinical evidence to further optimize therapeutic outcomes in patients with T2DM.

ACKNOWLEDGEMENT: Nil

CONFLICT OF INTEREST: Nil

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How to cite this article:

Dubey S, Choudhary JS, Tomar V, Verma R. Comparative review of immediate-release and extended-release metformin formulations: efficacy, safety and patient adherence. *International Journal of Pharmaceutical Science and Medicine* 2026; 4(1): 36-46.