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# ADVANCED METFORMIN DELIVERY SYSTEMS AND COMBINATION STRATEGIES FOR OPTIMIZED GLYCEMIC CONTROL: A COMPREHENSIVE REVIEW

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## ABSTRACT

Diabetes mellitus continues to place a significant global health burden, prompting sustained interest in developing safer and more effective therapeutic options. Metformin remains the cornerstone treatment for type 2 diabetes due to its strong glycemic efficacy, favourable safety profile, and affordability; however, its short half-life, poor intestinal absorption, and gastrointestinal intolerance restrict its full therapeutic potential. This review consolidates current evidence from PubMed, Scopus, and Google Scholar to explore the pharmacology of metformin, its limitations, and the evolution of advanced drug-delivery technologies designed to enhance its performance. Contemporary approaches including sustained-release matrices, gastro-retentive systems, nanoparticles, liposomes, microspheres, mucoadhesive films, and fast-dissolving formulations demonstrate meaningful improvements in bioavailability, controlled release, onset of action, and patient adherence. In addition, combination therapies involving DPP-4 inhibitors, SGLT2 inhibitors, sulfonylureas, or GLP-1 analogues provide synergistic glycemic control and reduce the overall therapeutic burden. Evidence further suggests that metformin-loaded nanocarriers may extend its utility beyond diabetes, offering potential benefits in oncology, infectious diseases, and inflammatory disorders. Collectively, these advancements reaffirm metformin's relevance in modern therapy and highlight the growing role of formulation science in optimizing clinical outcomes. Continued innovation in targeted delivery, nanotechnology, and personalized approaches may further strengthen metformin's future applications and improve long-term management of diabetes.



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# INTRODUCTION

In the 21st century diabetes has become a major health concern worldwide(Sha'at *et al*., 2024) .According to survey conducted by International Diabetes Federation (IDF) in 2021 showed that about 537millions worldwide are living with diabetes (Atma Jaya Catholic University of Indonesia *et al*., 2024). The name "diabetes mellitus" comes from two ancient languages: the Greek word 'diabetes', meaning 'to flow through', and the Latin term 'mellitus', which describes something 'sweet as honey' (R *et al*., 2024). Diabetes is a group of metabolic disorder (Kharroubi, 2015)in which insulin function and insulin secretion gets defected and which causes long term harm and dysfunction and organ failures metabolism(Sharma *et al*., 2024)In the diabetes mellitus the body does not create or not respond adequately to insulin, which causes high blood sugar level (hyperglycemia)(R *et al*., 2024). Insulin is produced in pancreas β cells that produced in response to the blood glucose levels, it is associated with chronic long term affect at cardiovascular diseases , retinopathy ,non-alcoholic fatty liver disease, neuropathy, and nephropathy (Barbosa *et al*., 2025). The symptoms of hyper glycemia includes frequent urination, intensify thirst and enhance hunger(Barbosa *et al*., 2025)

**Types of Diabetes mellitus:**

**Diabetes is mainly of four types**

- Type 1 diabetes mellitus(T1DM)
- Type 2 diabetes mellitus (T2DM)
- Gestational diabetes mellitus (GDM)
- Monogenic types diabetes (Banday *et al*., 2020)

**Type 1 diabetes mellitus(T1DM):** It is also known as insulin dependent diabetes mellitus(Wassmuth & Lernmark, 1989) that is occurs dues to the autoimmune conditions also referred as an ketosis prone or juvenile onset diabetes(Jun & Yoon, 2003).

This type of diabetes mainly affects the young adults and children's.

**Type 2 diabetes mellitus (T2DM):** It is also known as non-insulin dependent diabetes mellitus. In individuals with this type of diabetes, the body's cells often do not respond properly to the effects of insulin (Dyck *et al*., 1993)

**Gestational diabetes mellitus (GDM):** Gestational diabetes mellitus (GDM)high blood sugar first detected during pregnancy, sometimes uncovering undiagnosed T2DM or early T1DM. Usually resolves after delivery, but offspring have higher risk of obesity and T2DM due to in-utero hyperglycaemia exposure.

**Monogenic types diabetes:** Monogenic diabetes most commonly due to HNF-1α mutation on chromosome 12, causing beta-cell dysfunction. Presents as early-onset hyperglycaemia (adolescence/young adulthood), sometimes with impaired proinsulin-to-insulin conversion. Inherited autosomal dominantly; <10% of all diabetes cases.

**Pathophysiology:** Type 2 diabetes is marked by reduced insulin sensitivity, stemming from insulin resistance, declining insulin secretion, and gradual loss of pancreatic β-cells. This impairs glucose uptake in the liver, skeletal muscle, and adipose tissue, leading to elevated blood sugar. Normally, insulin regulates glucose by promoting its uptake into cells and inhibiting glycogen breakdown and gluconeogenesis. When insulin is insufficient or ineffective, glucose remains in the bloodstream, causing hyperglycaemia, reduced protein synthesis, and metabolic imbalances. Persistent high blood sugar overwhelms the kidneys, resulting in glucose loss in urine (glycosuria), dehydration, excessive urination (polyuria), and intense thirst (polydipsia (Fujioka, 2007).

**Causes of diabetes mellitus:** Disturbances in β-cell glucose-sensing mechanisms can cause the cells to react only at abnormally high glucose levels, or the β-cells may simply be functionally insufficient. In both circumstances, insulin secretion becomes impaired, increasing the likelihood of progressive β-cell dysfunction and eventual failure. (Alemu *et al*., 2009). Persistent hyper glycemia disrupts normal neuronal metabolism, creating a cascade of biochemical imbalances that impair cellular energy production. Over time, these metabolic disturbances injure the microvasculature supplying neural tissue, ultimately reducing oxygen delivery and leading to progressive neural hypoxia.Reduced insulin sensitivity in peripheral tissues often stems from a decline in the number of insulin receptors as well as receptor down-regulation. Many individuals display a state of hyperinsulinemia despite normal blood glucose levels, reflecting an underlying hypersensitivity to insulin's diminished action. This metabolic profile is frequently accompanied by dyslipidaemia, elevated uric acid levels, and central obesity. Together, these features contribute to a state of relative insulin resistance, particularly in hepatic, muscular, and adipose tissues (Wild *et al*., 2004). chronic hyperglycaemia, excess glucagon, and obesity worsen functional insulin deficit, overworking β-cells and leading to dysfunction. Nitric oxide abnormalities impair perineural blood flow, causing nerve damage; metabolic and vascular disturbances together drive neuropathy progression(Wild *et al*., 2004). Several uncommon forms of diabetes mellitus exist, including maturity-onset diabetes of the young (MODY), endocrine-related diabetes, diabetes following pancreatectomy, and gestational diabetes mellitus (GDM). These conditions often arise from specific genetic defects or disturbances in hormonal regulation. In certain cases, diabetes can also be linked to dysregulation of key metabolic receptors. Receptors such as glucagon-like peptide-1 (GLP-1), peroxisome proliferator–activated receptor-γ (PPAR-γ), and β3-adrenergic receptors, along with enzymes including glycosidases and dipeptidyl peptidase-IV (DPP-IV), have been identified as contributing factors when their normal signalling pathways are altered(Gupta *et al*., 1978)(Wassmuth & Lernmark, 1989).

**Diagnosis and screening of diabetes mellitus:** a single abnormal glucose reading in asymptomatic individuals is insufficient. Accurate diagnosis requires multiple tests—urine glucose, blood glucose (capillary/venous), oral or IV glucose tolerance tests, renal glucose threshold, and modified tolerance tests—to distinguish normal, impaired, or diabetic glucose regulation(American Diabetes Association, 2014). In clinical practice, diagnostic tests for diabetes often need to be repeated on a separate day to confirm the findings. The commonly used tests include:

**Random Plasma Glucose Test:** This test measures blood glucose at any time of day and is typically used when a patient presents with classic symptoms of hyper glycemia. A value of ≥ 200 mg/dL is considered diagnostic of diabetes(American Diabetes Association, 2014).

**A1C Test:** The A1C assay reflects average blood glucose levels over the previous two to three months. It has the advantage of not requiring fasting or ingestion of glucose solutions. An **A1C value ≥ 6.5%** confirms the diagnosis of diabetes. (American Diabetes Association, 2014).

**Fasting Plasma Glucose (FPG):** This test measures blood glucose after an overnight fast and is performed before breakfast. A fasting glucose level of ≥ 126 mg/dL is diagnostic. (American Diabetes Association, 2014).

**Oral Glucose Tolerance Test (OGTT):** The OGTT evaluates the body's ability to metabolize a standardized glucose load. Blood glucose is measured when fasting and again two hours after consuming a glucose-rich beverage. A two-hour plasma glucose level of ≥ 200 mg/dL indicates diabetes. (American Diabetes Association, 2014).

**Pharmacological Agents**

**Biguanides:** Metformin, the principal drug in the biguanide class, remains the cornerstone therapy for type 2 diabetes mellitus. Its antihyperglycemic action is primarily achieved by suppressing hepatic gluconeogenesis, enhancing peripheral insulin sensitivity, and promoting glucose uptake through the phosphorylation of glucose transporter–enhancing factors. Additionally, metformin supports increased fatty acid oxidation and reduces intestinal glucose absorption. Compared with sulfonylureas, metformin carries a significantly lower risk of hypoglycemia, making it a safer monotherapy option for many patients(Collier *et al*., 2006). FDA-approved first-line therapy for T2DM, lowers blood glucose by improving hepatic insulin sensitivity. Generally safe and well-tolerated; rare side effects include atypical nightmares and lactic acidosis. Favoured for efficacy, safety, and low cost(Tegegne *et al*., 2024).

**Sulfonylureas:** Second-line therapy for non-obese T2DM patients. First-generation (tolbutamide, acetohexamide, chlorpropamide, tolazamide) and second-generation (glibenclamide, glimepiride, gliclazide, glipizide, gliquidone); second-generation drugs are more potent and require lower doses. Pharmacologically, sulfonylureas act as insulin secretagogues. They stimulate pancreatic β-cells to release greater amounts of insulin, thereby lowering plasma glucose concentrations. This enhancement of endogenous insulin secretion forms the basis of their glucose-lowering action and explains their long-standing role in the treatment of T2DM(Tegegne *et al*., 2024). These agents are typically well tolerated, but their ability to stimulate endogenous insulin release can occasionally lead to hypo glycemia, which remains their most notable adverse effect(Chiniwala & Jabbour, 2011) Patients with diabetes who receive sulfonylurea therapy have been shown to have a significantly higher risk of hypo glycemia, with older individuals experiencing approximately a 36% greater likelihood of developing such episodes compared with younger patients (Van Staa *et al*., 1997).

**Table 1. Different class of drugs used for treatment of diabetes mellitus with their effects and adverse effects**

| Drug Group | Specific Drugs | Effects | Adverse Effects |
|---|---|---|---|
| Biguanides | Metformin | ↓ HbA1c, ↓ body weight↓ | GI disorders ↑, reversible vitamin B12 deficiency ↑, lactic acidosis ↑ |
| Glinides | Repaglinide, Nateglinide | ↓ HbA1c, ↑ body weight↑ | Hypo glycemia ↑, headache ↑, upper respiratory tract infection ↑ |
| Alpha-Glucosidase Inhibitors | Acarbose | ↓ HbA1c, body weight↓ | GI disorders ↑, ↑ AST/ALT |
| SGLT2 Inhibitors | Empagliflozin, Dapagliflozin, Canagliflozin | ↓ HbA1c, ↓ body weight, ↓ BP, ↓ MACE, ↓ HF hospitalization, ↓ renal disease progression | Diabetic ketoacidosis ↑, genital infection ↑, UTI ↑, hypovolemia ↑, AKI ↑ (related to hypovolemia), Canagliflozin: amputation ↑, bone fracture ↑ |
| Thiazolidinediones (TZD) | Pioglitazone | ↓ HbA1c, ↓ BP, ↓ NAFLD, ↓ MACE | ↑ body weight, ↑ peripheral edema, ↑ anemia, ↑ HF hospitalization, ↑ bone fracture (women) |
| DPP-4 Inhibitors | Sitagliptin, Saxagliptin, Alogliptin | ↓ HbA1c | Saxagliptin: hospitalization for HF |
| Sulfonylureas | Glimepiride, Gliclazide, Glibenclamide, Glipizide | ↓ HbA1c | ↑ body weight, ↑ hypoglycemia, lack of durable effect |
| GLP-1 RA | Liraglutide, Dulaglutide, Semaglutide, Orforglipron | ↓ HbA1c, ↓ body weight, ↓ systolic BP, ↓ MACE | GI disorders ↑, Semaglutide: macular edema |
| Combination Therapy | Tirzepatide, Retatrutide | ↑ Quality of life in HF (KCCQ-CSS), ↓ NAFLD | Some intractions(Weinberg Sibony *et al*., 2023) |

**Table 2. Different properties of metformin hydrochloride**

| Sr.no | Parameter | values | references |
|---|---|---|---|
| 1 | Chemical name | N,N-dimethylimidodicarbonimidic diamide | (Sha'at *et al*., 2024) |
| 2 | Molecular formula | $C_4H_{11}N_5 \cdot HCl$. | (Wadher *et al*., 2011) |
| 3 | Molecular weight | 165.62 g/mol | (Sha'at *et al*., 2024) |
| 4 | Melting point | 224.5°C | (Abood *et al*., 2020) |
| 5 | Absolute bioavability | 50-60% | (Wadher *et al*., 2011) |
| 6 | Half life | 1.5-4.5 h | (Wadher *et al*., 2011) |
| 7 | Refractivity | 56.642 | (Wadher *et al*., 2011) |
| 8 | Absorption site | Mainly small intestine | (Wadher *et al*., 2011) |

**Table 3. GRDDS systems of metformin**

| Sr. no | Year | Delivery system | Ingredients | Inference | Refernces |
|---|---|---|---|---|---|
| 1 | 2024 | Sodium alginate–starch capsules prepared by extrusion and crosslinking with $CaCl_2$ | Metformin HCl (100 mg), sodium alginate (1500–2500 mg), wheat starch (500–1500 mg), calcium chloride (5% solution) | Metformin capsules (~104–116 µm; alginate:starch 1:1) showed high encapsulation (9.5%), balanced swelling, and sustained release up to 8 h. Resistant to gastric fluid and soluble in intestinal fluid, they are suitable for low-dose initiation to minimize GI side effects. | (Gheorghita *et al*., 2024) |
| 2 | 2022 | Gastro retentive in situ oral gel (floating system) prepared via factorial design (DoE) | Metformin HCl; sodium alginate (Sod ALG); calcium carbonate (crosslinker); sodium bicarbonate; hydroxy ethyl cellulose (HEC, thickener); water | Formulation E2 (ALG + $CaCO_3$ + HEC) achieved USP extended-release criteria with 12 h floating lag time and no drug–excipient interactions. The optimized gastro-retentive gel provides sustained release and improved patient compliance compared to large tablets. | (Kim *et al*., 2022) |
| 3 | 2021 | Immediate-release tablet using direct compression | Metformin HCl, crospovidone, sodium starch glycolate, croscarmellose sodium (superdisintegrants), HPMC, AOT, MCC | Focused on rapid disintegration and dissolution using superdisintegrants; intended for fast onset of action; no specific formulation batch or release profile reported | (Tyagi *et al*., n.d.) |
| 4 | 2016 | Gastroretentive floating sustained-release tablet using effervescence ($NaHCO_3$) and swelling (HPMC:PEO 1:4 | Metformin HCl (500 mg), HPMC K100M, PEO WSR 301, sodium bicarbonate (40–60 mg), sodium starch glycolate (40–60 mg), PVP K30, DCP, talc, Mg stearate | Optimized formulation showed 24 h buoyancy, and 12 h sustained release (97.56%); release followed Korsmeyer-Peppas kinetics; stable under accelerated conditions for 3 months | (Senjoti *et al*., 2016) |

**Table 4. Sustained-release (SR) delivery systems of metformin**

| Sr. no | Year | Delivery system | Ingredients | Inference | References |
|---|---|---|---|---|---|
| 1 | 2025 | Sustained-release floating matrix tablet (gastroretentive drug delivery system) via direct compression | Metformin HCl (750 mg), HPMC K15M (120 mg), kappa-carrageenan, sodium alginate, xanthan gum, sodium bicarbonate (gas-generating agent), MCC, magnesium stearate | Formulation F2 (HPMC K15M + kappa-carrageenan) achieved 99.6% drug release over 24 h, excellent buoyancy (>8 h), and a swelling index of 3.864. Release followed Higuchi and Korsmeyer-Peppas kinetics ($R^2 = 0.9938$), indicating non-Fickian diffusion, and the formulation remained stable under accelerated conditions. | |
| 2 | 2025 | Sustained-release oral capsule formulated via wet granulation | Metformin HCl (500 mg), HPMC K100, PVP K30, sodium CMC, MCC, starch, magnesium stearate | F7 formulation showed sustained release up to 13 hours (vs. 11 hours for marketed tablet); release followed Korsmeyer-Peppas model ($n > 0.89$), indicating super case-II transport; stable over 3 months under ICH conditions | (Vijetha R *et al*., 2025) |
| 3 | 2025 | Mucoadhesive buccal film using solvent casting technique for sustained systemic delivery | Metformin HCl, HPMC K4M, PVA, PVP K30, glycerin, PEG 400 | Films showed uniform thickness, drug content (97.6–98.5%), and strong mucoadhesion (up to 335 min); sustained release over 8 h; Higuchi model best fit; bypassed first-pass metabolism and improved bioavailability | (Department of Pharmaceutics, Sree Sastha Pharmacy College, Chembarambakkam, Chennai-123, India *et al*., 2025) |
| 4 | 2025 | Sustained-release tablets prepared by wet granulation using hydrophilic polymers | Metformin HCl (500 mg), HPMC K15M, Xanthan gum, Eudragit RSPO, lactose, MCC, Mg stearate | Formulation F1 (high polymer content) showed 90% release at 12 h, following Korsmeyer-Peppas kinetics (diffusion + erosion). In vivo, Tmax 4 h, t½ 8 h, AUC0–12 78 µg·h/mL vs 42 µg·h/mL for IR, providing prolonged glycemic control in diabetic rats. | (Mausami *et al*., 2025) |
| 5 | 2025 | Sustained-release matrix tablets prepared by direct compression | Metformin HCl (500 mg), Benecel™ K100M (HPMC), Carbopol G71, binders (MCC, Povidone K-29/32, DCP), magnesium stearate, colloidal silica | Formulations T3 (10% HPMC + 5% MCC) and T7 (15% HPMC + 5% MCC) closely matched the marketed SR product ($f2 > 50$, $f1 < 15$). MCC was key in optimizing release, while Carbopol-based tablets failed friability or showed dissimilar release. HPMC + MCC matrices best mimic commercial SR metformin. | (Abdulkarim *et al*., 2025) |
| 6 | 2025 | Fast-dissolving sublingual films prepared by solvent casting | Metformin HCl (40 mg per film), Polymer A (20–180 mg), Plasticizer B (20–40 mg), citric acid (10 mg), crosspovidone (10 mg), distilled water | P1 formulation was optimal: thickness 221 µm, folding endurance 195, disintegration 28 s, drug release 89% in 5 min, content uniformity ~100%; rapid onset, improved bioavailability, reduced GI side effects compared to oral tablets | (Isla *et al*., 2025) |
| 7 | 2024 | Mucoadhesive sustained-release tablet using wet granulation | Metformin HCl (250 mg), xanthan gum (100–350 mg), pectin (100–350 mg), MCC, talc, Mg stearate | F7 (xanthan:pectin 150:150 mg) showed optimal 12 h release (101.16%) with Fickian diffusion; tablets passed all physicochemical tests; DSC, TGA, and XRD confirmed stability and compatibility | (Abid Mustafa *et al*., 2024) |
| 8 | 2024 | Sustained-release matrix tablet via wet granulation | Metformin HCl (500 mg), guar gum (100–150 mg in MT1–MT3), HPMC K100M (100–150 mg in MT4–MT6), PVP K30, MCC, talc, Mg stearate | MT5 (HPMC K100M 125 mg) showed >99% release at 12 h and high similarity ($f2 = 75.33$) to Glyciphage SR 500; release followed zero-order and Higuchi kinetics with anomalous diffusion | (Bishal *et al*., 2024) |
| 9 | 2021 | Sustained-release matrix tablet via wet granulation | Metformin HCl (500 mg), HPMC K4M (100–200 mg), xanthan gum (0–110 mg), MCC PH101, PVP K30, talc, magnesium stearate | Formulation F7 (HPMC K4M + xanthan gum) achieved 101.08% release over 12 h with minimal burst. Release followed first-order and Higuchi kinetics (Fickian diffusion) and was comparable to Bigomet SR 500. Xanthan gum improved gel strength and controlled drug release. | (Alam *et al*., 2021) |
| 10 | 2019 | Sustained-release matrix tablet using direct compression | Metformin HCl (500 mg), xanthan gum (250–350 mg), HPMC K4M or K15M (0–350 mg), dicalcium phosphate, talc, magnesium stearate | F5 (xanthan gum + HPMC K4M) showed optimal 12 h release (99.86%), following first-order kinetics and Fickian diffusion; xanthan alone caused burst release; HPMC blends formed stronger gel matrix | (Jaya & Chinnaeswaraiah, 2020) |
| 11 | 2018 | Sustained-release matrix tablet via direct compression | Metformin HCl (300 mg), HPMC (10–20 mg), sodium alginate (10–20 mg), MCC (50 mg), talc, Mg stearate | F3 (HPMC:sodium alginate 1:2) showed optimal 10 h release (93.86%) with diffusion-controlled kinetics; formulation followed first-order and zero-order models with $R^2 > 0.99$ | (Singh *et al*., 2018) |
| 12 | 2017 | Floating sustained-release tablet using wet granulation | Metformin HCl (500 mg), HPC (400 mg in F1), HPMC K100M (400 mg in F2), combination (200 mg each in F3), PVP K30, lactose, talc, Mg stearate | F2 (HPMC K100M) showed best performance: floating lag time 5.27 min, floating duration >48 h, and 84.68% drug release over 8 h; HPC alone (F1) dissolved in | (Fitriani *et al*., 2017) |
| 13 | 2017 | Sustained-release matrix tablet using wet granulation | Metformin HCl (250 mg), HPMC E5 or K100 (125–375 mg), Eudragit (125–375 mg), lactose, MCC, Mg stearate | F9 (Eudragit 375 mg) showed optimal 24 h release (99.2%); increasing polymer concentration slowed release; HPMC formed gel matrix, Eudragit delayed release further; release followed zero/first-order and Higuchi kinetics | (Adimulka & Devandla, n.d.) |
| 11 | 2017 | Sustained-release matrix tablet using continuous melt granulation (MG) with high drug loading (up to 75%) | Metformin HCl (75%), HPC Nisso-H (15%), stearic acid (10%) | MG enabled compact 670 mg tablets with 500 mg dose strength; F6 (75% drug load) showed 10 h sustained release within USP limits; release followed non-Fickian diffusion; stearic acid improved flow, compressibility, and release control; superior to wet and dry granulation in tablet quality and release profile | (Vaingankar & Amin, 2017) |
| 14 | 2012 | Sustained-release oral matrix tablet formulated via wet granulation | Metformin HCl (500 mg), HPMC (K4M, K15M, K100M), PVP K30, magnesium stearate, talc, isopropyl alcohol | Formulation F3 (HPMC K100M, drug:polymer 5:2) achieved 93.44% release over 8 h with minimal burst. Release followed Higuchi and Korsmeyer-Peppas kinetics ($n = 0.465$), indicating anomalous diffusion. HPMC viscosity directly affected the release rate. | (Diwedi *et al*., 2012) |
| 15 | 2011 | Extended-release oral matrix tablet using melt granulation and direct compression techniques | Metformin HCl (500 mg), Polyethylene oxide (hydrophilic), Stearic acid (hydrophobic) | Melt granulation with 30% PEO and 8% SA (Formulation M6) achieved sustained release comparable to commercial SR tablet ($f_2 = 81.08$), following Korsmeyer-Peppas kinetics ($n \approx 0.5$) Melt granulation provided better control of drug release due to uniform hydrophobic coating; increasing PEO and SA slowed release effectively. | (Nanjwade *et al*., 2011) |
| 16 | 2010 | Extended-release oral matrix tablet formulated via wet granulation | Metformin HCl (500 mg), HPMC K100M CR (240–300 mg), Carbopol 71G (142–190 mg), PVP K-30, magnesium stearate, water/IPA (as granulating fluid | Formulation F10 (280 mg HPMC + 142 mg Carbopol) showed sustained release up to 10 h, closely matching the innovator profile in both 0.1N HCl and pH 4.5 buffer; release followed Higuchi and Korsmeyer-Peppas kinetics (non-Fickian diffusion); stable under ICH conditions for 3 month | (Chandira *et al*., 2010) |

**Table 5. liposomal system of metformin**

| Sr. no | Year | Delivery system | Ingredients | Inference | References |
|---|---|---|---|---|---|
| 1 | 2025 | Nanostructured lipid carriers (NLCs) prepared by solvent injection for topical delivery | Metformin HCl (50 mg), beeswax (75 mg), oleic acid (25 mg), Span 60 (1% w/w), Tween 80 (1% w/w, aqueous phase, pH 12.5) | Optimized NLCs: entrapment efficiency 53.7%, particle size 333 nm, negative zeta potential (stable); DSC and docking confirmed MTF–oleic acid salt formation; sustained release and enhanced skin permeation; promising for inflammatory skin conditions (psoriasis, acne, dermatitis, etc.) | (Mahran *et al*., 2025) |
| 2 | 2021 | Liposomal vesicles for topical delivery via thin-film hydration | Metformin HCl (varied), Phospholipon® 90G (40–80 mM), cholesterol (10–60% molar), chloroform, ethanol | F2 (80 mM lipid, 4:1 drug/lipid, 70:30 lipid:cholesterol) showed best performance: EE 80%, permeation 53%, vesicle size 10.9 µm, zeta potential −53.4 mV; stable over 90 days with 10% drug leakage | (Magdy *et al*., 2021) |

**Table 6. Microspheres and other various delivery systems formulations of metformin**

| Sr. no | Year | Delivery system | Ingredients | Inference | References |
|---|---|---|---|---|---|
| 1 | 2025 | Self-Micro-emulsifying Drug Delivery System (SMEDDS) | Metformin HCl (100 mg), castor oil (1.11–3.12 mL), Tween 20 (4.59–5.93 mL), propylene glycol (2.29–2.96 mL) | F1 (castor oil 1.11 mL) showed optimal performance: droplet size 81.3 nm, PDI 0.232, zeta potential +61.9 mV, transmittance 98.7%, viscosity 111 cP; rapid emulsification (35 s), excellent stability and bioavailability enhancement | (Nagaveni *et al*., 2025) |
| 2 | 2025 | Chitosan-based mucoadhesive nanoparticles (CS-MNPs) incorporated into HPMC buccal films | Metformin HCl, chitosan (MW ~85% deacetylation), sodium TPP (crosslinker), glycerol (plasticizer), HPMC | Optimized CS-MNPs: particle size 182 nm, PDI 0.21, zeta potential +32.6 mV, EE 87.3%, drug loading 14.5%; sustained release 91% over 12 h; ex vivo flux 4.7 µg/cm²/h, mucoadhesive strength 0.42 N; stable at 25 °C/60%RH but sensitive to high humidity/temperature; release followed diffusion + polymer relaxation mechanism | (Kamble *et al*., 2025) |
| 3 | 2023 | Mucoadhesive microspheres (solvent evaporation) and nanoparticles (nanoprecipitation) using factorial design | Metformin HCl, Eudragit RSPO; solvents: acetone, liquid paraffin + Span 80 (microspheres), PVA solution (nanoparticles), n-hexane, methanol | **Microspheres (2.2–5.5 µm) and nanoparticles (160–360 nm)** showed sustained 12 h release and high entrapment. A4 and B3 had optimal performance. Nanoparticles also showed anticancer activity against HeLa cells. | (Kotha *et al*., 2023) |
| 4 | 2022 | Silver-metformin nanostructure (Ag-MET-Ns) for anti-virulence therapy against S. aureus | Metformin HCl (100 mg/mL), silver nitrate (1 mM), PVP (50 mg/mL), Tween 80 (10%), isopropyl alcohol (0.02%) | **Ag-MET-Ns (66 nm, ±30 mV)** showed strongest biofilm inhibition (87%) and staphyloxanthin reduction (64%), modulated key genes (down: crtM, sigB, sarA, fnbA; up: agrA, icaR), and was the most effective agent in vitro and in vivo. | (Abbas *et al*., 2022) |
| 5 | 2020 | Alginate microspheres prepared by ionotropic gelation–aerosolization, freeze-dried with maltodextrin (lyoprotectant) | Metformin HCl; sodium alginate (1.25–1.75%); $CaCl_2$ (3–5%); maltodextrin (stabilizer); solvents: deionized water, sodium citrate buffe | **Microspheres (1.8–2.8 µm)**: optimal (1.75% alginate + 3% $CaCl_2$) showed 40% entrapment, 15% loading, 75% yield; release 22–28% (pH 1.2) then 67–95% (pH 7.4, 10 h), Higuchi kinetics; spherical, smooth, crosslinked particles. | (Hariyadi *et al*., 2020) |
| 6 | 2018 | Controlled-release microspheres prepared by ionotropic gelation (chitosan–TPP crosslinking) | Metformin HCl, chitosan (1–2%), sodium tripolyphosphate (0.5–3%), acetic acid (solvent) | **F7 (chitosan:drug 1:2.5)**: 580 µm, 26.5% yield, 95% drug content, 94% EE; spherical porous microspheres, 10 h controlled release (first-order/Higuchi/Korsmeyer–Peppas); stable 6 months. | (Kalpna *et al*., 2018) |
| 7 | 2015 | Ion-sensitive biopolymeric beads using gellan gum (GG) via ionotropic gelation | Metformin HCl (1–3% w/v), gellan gum (1–3% w/v), calcium chloride (4% w/v) as crosslinker | F5 (2% GG, 2% drug) showed optimal performance: 990 µm diameter, 94.5% yield, 88.5% EE, sustained release up to 8 h, Higuchi diffusion kinetics, bioequivalent to marketed XR tablet | (Allam & Mehanna, 2015) |
| 8 | 2015 | Floating microspheres prepared by oil-in-oil emulsion solvent evaporation | Metformin HCl; polymers: ethyl cellulose, Eudragit RS100, RSPO, RLPO; solvents: ethanol, dichloromethane; external phase: liquid paraffin + Span 80 | **Floating microspheres (MF5)**: spherical, porous; 75–91% yield, 68–96% EE, buoyancy 94% (>12 h); 8 h sustained release, Korsmeyer–Peppas kinetics; improved gastric retention and bioavailability. | (Ansary *et al*., 2016) |

**Table 7. Herbal Drug-Loaded Nanocarriers and Their Formulation Strategies in Rheumatoid Arthritis Management**

| Sr. no | Year | Delivery system | Ingredients | Inference | Refernces |
|---|---|---|---|---|---|
| 1 | 2025 | Systemic oral combination therapy: Metformin + DPP-4 inhibitor + SGLT2 inhibitor | Metformin (biguanide), DPP-4 inhibitors (e.g., sitagliptin), SGLT2 inhibitors (e.g., empagliflozin); often in fixed-dose combinations (FDCs) | Triple therapy in T2DM: recommended for patients uncontrolled on dual therapy or with high HbA1c; provides durable glycemic control, weight loss, low hypoglycemia, and cardiorenal benefits; supported by RCTs and real-world evidence. | (Yu *et al*., 2025) |
| 2 | 2024 | Combined tablets (VD 50 mg + MET 500 mg) prepared by wet granulation to overcome poor compressibility of metformin | Metformin HCl, Vildagliptin; binders: Kollidon K30 or K90; diluent: Avicel PH101; disintegrant: Explotab; lubricant: Mg stearate; solvents: ethanol + water | F7 (Kollidon K90): good flow (Carr 13–25%, angle 25–28°), hardness 5–13 kg/cm², friability acceptable; >95% drug release in 30 min vs 80% for Galvus Met; HPLC accurate (99.8–99.9%), precise; rapid disintegration and superior dissolution. | (Mohamed *et al*., 2024) |
| 3 | 2021 | Immediate-release fixed-dose combination tablet (FDC) of linagliptin and metformin HCl | Metformin HCl (500–1000 mg), linagliptin (2.5 mg), co-povidone, meglumine (stabilizer), corn starch, colloidal silicon dioxide, Mg stearate, Opadry pink | >90% drug release within 15–20 min for all strengths; meglumine stabilized the formulation; dissolution 10–25% faster than reference (Jentadueto); assay and uniformity within limits | (Jat & Chatterjee, 2021) |
| 4 | 2022 | Bilayer tablet: Gliclazide immediate release + Metformin HCl sustained-release matrix | Gliclazide (60 mg), DCP, HPMC K4M/K15M/K100M (20–40 mg), PVP K30, SA, Mg stearate (IR); Metformin HCl (100 mg), HPMC K100M or Polyox WSR (160–240 mg), MCC, mannitol, PVP K30 (SR) | M7 (Polyox WSR 25%) showed optimal 24 h release (90% at 12 h); G4 (HPMC K15M 20 mg) showed 99.8% release at 40 min; bilayer design achieved rapid gliclazide release and sustained metformin delivery | (K.Manga *et al*., 2022) |
| 5 | 2018 | Bilayer tablet: Gliclazide solid dispersion (immediate release) + Metformin HCl sustained-release matrix | Gliclazide (240 mg) + PEG 6000 (1:5 SD), croscarmellose Na, MCC (IR); Metformin HCl (500 mg), HPMC K4M/K15M/K100M (110–150 mg), MCC, starch (SR) | B3 (G3 + M9) was optimal: gliclazide showed rapid release via anomalous diffusion; metformin followed zero- or first-order kinetics; bilayer design enabled effective postprandial and sustained glycemic control | (Gangane *et al*., 2018) |

**Meglitinides:** Individuals with type 2 diabetes can achieve better glycemic control by combining lifestyle measures such as a balanced diet and regular physical activity with insulin secretagogues like repaglinide and nateglinide, collectively known as "glinides." These meglitinide derivatives act rapidly to stimulate insulin release, making them particularly effective for controlling postprandial glucose excursions. Used either as monotherapy or alongside metformin, glinides provide an additional means of improving blood sugar regulation in adults with T2DM when lifestyle interventions alone are insufficient(Tegegne *et al*., 2024). Repaglinide and nateglinide are non-sulfonylurea insulin secretagogues that promote insulin release by targeting the ATP-dependent potassium channels on pancreatic β-cells. Although their mechanism resembles that of sulfonylureas, they bind to a distinct site on the channel, giving them a faster onset and shorter duration of action(Fuhlendorff *et al*., 1998). Because meglitinides have a rapid onset and a short duration of action (approximately 4–6 hours), they are associated with a lower risk of hypo glycemia compared with longer-acting secretagogues. Their primary role is to control postprandial blood glucose levels, and their pre-meal dosing schedule offers flexibility—if a meal is skipped, the dose can be omitted without significantly increasing the risk of hypo glycemic episodes. Repaglinide, in particular, undergoes extensive hepatic metabolism and is eliminated only minimally through the kidneys. As a result, dose adjustments are generally unnecessary in patients with renal impairment, except in those with end-stage renal disease(Shorr *et al*., 1997).

**Thiazolidinediones (TZDs):** Thiazolidinediones (TZDs), commonly referred to as glitazones, include troglitazone, pioglitazone, and rosiglitazone, and act primarily by enhancing insulin sensitivity in individuals with type 2 diabetes mellitus. Since their introduction in the late 1990s, TZDs have been widely used due to their effectiveness in improving insulin resistance and supporting long-term glycemic control. Troglitazone was the first agent in this class to receive FDA approval; however, it was withdrawn from the market within three years after reports of severe hepatotoxicity emerged. Currently, pioglitazone and rosiglitazone remain the only TZDs approved for clinical use. Beyond their glucose-lowering effects, TZDs have been shown to exhibit anti-inflammatory properties and potential anti-cancer benefits, highlighting their broader physiological influence (Tegegne *et al*., 2024). It functions as an insulin sensitizer by binding to the peroxisome proliferator–activated receptor-γ (PPAR-γ), a nuclear transcription factor that regulates genes involved in glucose and lipid metabolism(Blicklé, 2006). Pioglitazone does not induce hypoglycaemia when used as monotherapy and can be safely administered in patients with renal impairment, which makes it a suitable and well-tolerated option for older adults (Yki-Järvinen, 2004). However, its use in women may be limited due to concerns such as peripheral edema, fluid retention, and an increased risk of fractures. Pioglitazone should be used with caution in older adults with a history of congestive heart failure and is contraindicated in individuals with class III–IV heart failure, where the risk of worsening fluid overload is significant(Jun & Yoon, 2003).

**α-glucosidase inhibitors (AGIs):** The primary oral α-glucosidase inhibitors (AGIs) used in the management of diabetes include voglibose, miglitol, and acarbose. These agents act within the small intestine to delay the absorption of carbohydrates by competitively inhibiting enzymes responsible for breaking down complex, non-absorbable carbohydrates into simple, absorbable monosaccharides. The targeted enzymes include isomaltase, maltase, sucrase, and glucoamylase. By slowing carbohydrate digestion, AGIs help blunt the postprandial rise in blood glucose, typically reducing post-meal glucose excursions by approximately 3 mmol/L(Tegegne *et al*., 2024). Acarbose is the most widely studied drug in this class. It inhibits α-amylase, sucrase, maltase, and dextranase, though its strongest inhibitory effect is on glucoamylase. Notably, it does not affect lactase β-glucosidase. AGIs have minimal systemic absorption, limited bioavailability, and are predominantly excreted unchanged in the feces. Miglitol differs slightly from acarbose in that it is completely absorbed and eliminated via the kidneys, bypassing gastric absorption. Additionally, miglitol and voglibose do not undergo metabolism within the intestine, whereas acarbose does(Tegegne *et al*., 2024). Because of their ability to reduce postprandial hyperglycaemia without causing significant hypoglycemia, AGIs are particularly beneficial for individuals with impaired glucose tolerance or early-stage type 2 diabetes(Tegegne *et al*., 2024).

**Incretin-Based Therapies:** The core of incretin-based therapeutics is glucagon-like peptide-1 (GLP-1) analogues, which specifically target this previously under-recognized component of diabetes mellitus pathophysiology. By enhancing the endogenous incretin response, these agents contribute to sustained improvements in glycaemic regulation as well as effective body-weight control(Kawamori *et al*., 2009). GLP-1 receptor agonists like liraglutide and exenatide can be used alone, with diet/exercise, or alongside other oral antidiabetics. They enhance insulin secretion in a glucose-dependent manner, minimizing hypoglycemia risk when not combined with insulin secretagogues(Chiniwala & Jabbour, 2011). Furthermore, emerging research indicates that incretin-based therapies may exert beneficial effects beyond glycaemic control, including improvements in inflammatory pathways, cardiovascular and hepatic health, sleep regulation, and central nervous system function(Martin *et al*., 2011).

**Dipeptidyl peptidase-4 (DPP-4) inhibitors:** Dipeptidyl peptidase-4 (DPP-4) inhibitors, also known as "gliptins," such as sitagliptin, saxagliptin, linagliptin, and alogliptin, are increasingly replacing sulfonylureas for the management of type 2 diabetes mellitus in many countries(Tegegne *et al*., 2024).These agents offer several key advantages:

- they are not associated with hypoglycaemia or weight gain;
- they possess a favourable safety and tolerability profile; and
- they serve as effective alternatives when first-line therapies such as metformin or sulfonylureas fail to achieve adequate glycaemic control(Tegegne *et al*., 2024).

DPP-IV inhibitors act by blocking dipeptidyl peptidase-4 (DPP-4), a widely distributed enzyme responsible for the rapid degradation of incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). By inhibiting DPP-4, these agents increase the circulating levels of active incretins, thereby enhancing pancreatic islet function and improving overall glycaemic control in patients with type 2 diabetes mellitus. DPP-4 inhibitors represent a relatively newer class of antidiabetic drugs, demonstrating efficacy comparable to existing therapeutic options. They may be used as monotherapy in individuals inadequately controlled with diet and exercise, or as add-on therapy in combination with metformin, thiazolidinediones, or insulin. These medications are generally well tolerated, associated with a low risk of hypoglycaemia, and are weight-neutral. However, their clinical utility may be limited in some settings due to their comparatively high cost(Pratley & Salsali, 2007).

**Insulin therapy:** Insulin therapy is employed either as monotherapy or in combination with oral hypoglycaemic agents to achieve optimal glycaemic control. In individuals with residual β-cell function, basal insulin supplementation can provide effective augmentation therapy. However, when β-cell exhaustion occurs, a basal–bolus insulin regimen becomes necessary to mimic physiological insulin secretion patterns. In situations of glucotoxicity, full insulin replacement is required to restore metabolic balance and replicate the natural secretion profile of pancreatic β-cells. Clinically, insulin preparations are classified into four major types—rapid-acting, short-acting, intermediate-acting, and long-acting formulations. Compared with short-acting insulin, long-acting preparations carry a lower risk of hypoglycaemia due to their stable and prolonged pharmacodynamic profile(Mayfield & White, 2004).

**Insulin Analogues:** The ability of conventional insulin therapy to mimic normal physiological insulin secretion has historically been limited. Traditional intermediate-acting and long-acting insulin formulations demonstrate variable absorption rates and pronounced activity peaks, which can increase the risk of hypoglycaemia. In

contrast, modern insulin analogues were developed to overcome these limitations by modifying the pharmacokinetic and pharmacodynamic profiles of endogenous insulin. These structural alterations result in more predictable absorption, more consistent glucose-lowering activity, and onset and duration of action ranging from rapid to prolonged (Burge & Schade, 1997),(Cameron & Bennett, 2009). Currently, two rapid-acting insulin analogues—insulin lispro and insulin aspart—are widely used due to their rapid onset and short duration, making them effective for controlling postprandial glucose excursions. Additionally, the long-acting insulin analogue insulin glargine provides a sustained, peakless basal insulin supply, thereby reducing the likelihood of hypoglycaemia and improving overall glycaemic stability. Newer drugs for diabetes are still being developed. SGLT2 inhibitors help remove extra glucose through urine. Drugs that block 11β-HSD1 reduce the effect of glucocorticoids in the liver and fat. Researchers are also studying glucokinase activators, fatty-acid receptor agonists, glucagon-receptor blockers, and medicines that slow down the liver's glucose production. These agents may offer better control of blood sugar in the future (Tahrani *et al*., 2011).

**Metformin Hydrochloride:** Metformin, along with the older drug phenformin, traces its origin to galegine, a compound found in the herb *Galega officinalis*, which was used in medieval European medicine. Although galegine was tested for lowering blood sugar in the 1920s, it proved too toxic. During the same period, scientists created safer synthetic derivatives—metformin and phenformin, both belonging to the biguanide class. Unlike modern medicines that are designed to target specific pathways, metformin evolved from a natural remedy and was used clinically long before its exact mechanisms were understood. Even after more than 60 years of medical use, researchers continue to study how it works, and current evidence suggests that its benefits come from multiple molecular actions rather than a single pathway (Rena *et al*., 2017). Metformin is considered the core therapy for type 2 diabetes because it reliably controls blood sugar, doesn't cause weight gain, is safe, and is inexpensive(Rojas & Gomes, 2013). Metformin hydrochloride is an Biguanide hydrochloride is a white, crystalline, hygroscopic powder that dissolves easily in water. It is used as a hypoglycemic agent and has the molecular formula $C_4H_{11}N_5 \cdot HCl$ (Wadher *et al*., 2011). Metformin is valued for its strong glucose-lowering effect, its ability to pair easily with most other diabetes medications, and its affordability. It is generally well tolerated, causes only mild side effects, carries minimal risk of hypo glycemia, and can help with modest weight reduction(Weinberg Sibony *et al*., 2023). It is absorbed poorly in the lower gastrointestinal tract and has a relatively short elimination half-life (Yadav & Jain, 2011). Metformin, widely used as the first-line treatment for type 2 diabetes, is now drawing interest for reasons beyond blood-sugar control. Growing evidence shows that it may also influence how the body responds to both viral and bacterial infections, suggesting benefits that extend well past its original purpose (Halabitska *et al*., 2024)

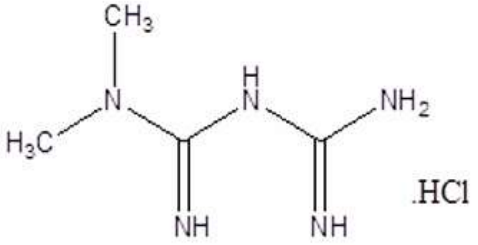


**Figure 1. Chemical structure of metformin hydrochloride.**

**Metabolism:** Metformin undergoes very little metabolism in the body. It is not significantly broken down and is eliminated mainly through the kidneys (R *et al*., 2024).

**Elimination:** Metformin is primarily eliminated through active tubular secretion in the kidneys. Its transport in the body relies on specific proteins, such as OCT1 and OCT3 in the liver for uptake, and MATE1 for excretion from the liver and kidneys. In the kidneys, OCT2, MATE1, and MATE2-K move metformin from the blood into urine. Although metformin is not metabolized in the liver, other drugs that affect these transporters can influence its effectiveness and safety. Recent studies suggest that tyrosine kinase inhibitors, including imatinib, nilotinib, gefitinib, and erlotinib, may interact with metformin and alter its clinical outcomes (R *et al*., 2024).

**Mechanism of action:** The organic cation transporter-1 (OCT1) facilitates the uptake of metformin into hepatocytes. Its positive charge, influenced by cellular pH and pKa, causes it to accumulate within cells, reaching concentrations up to 1000 times higher in mitochondria than outside. The mitochondrial membrane potential also affects its entry. Inside mitochondria, metformin inhibits complex I of the respiratory chain, reducing ATP production and increasing AMP and ADP levels. This shift in the ADP/ATP ratio impairs gluconeogenesis, as the energy-intensive process cannot proceed efficiently. Metformin also alters the $NAD^+$/NADH ratio, further contributing to the inhibition of glucose production in the liver(R *et al*., 2024).

**Dosage:** The typical starting dose of metformin is 500 mg taken with the evening meal. If needed, an additional 500 mg can be taken with breakfast. The dose is gradually increased based on tolerance and clinical response, with a maximum daily dose of 2000 mg. Individual factors, such as body mass index, may influence the final dose (Sutkowska *et al*., 2021).

**Advantages of metformin hydrochloride:** Metformin offers benefits beyond its role in managing diabetes. It can support weight loss and reduce abdominal fat, and it has been shown to improve fertility in some individuals. Evidence also suggests that metformin may enhance longevity in people with certain medical conditions. Additionally, it can help manage obesity and related disorders, such as metabolic syndrome, and there is emerging research indicating that it may slow the growth of some tumors and prevent the formation of others(R *et al*., 2024).

**Disadvantages of metformin hydrochloride:** Metformin can cause some gastrointestinal side effects, including nausea, vomiting, diarrhea, and general stomach discomfort. To help manage these symptoms, patients are often advised to take small, frequent sips of water or diluted drinks to prevent dehydration (R *et al*., 2024).

**Side effect of metformin:** Metformin is generally well tolerated, but it can cause some side effects. Commonly reported adverse effects include a metallic taste in the mouth, gastrointestinal symptoms such as diarrhea, nausea, or vomiting, and occasional swelling. Some patients may experience increased appetite, rapid heart rate, or headaches. Long-term use of metformin can reduce the absorption of vitamin B12, potentially leading to anemia. Rarely, metformin may cause a serious condition known as lactic acidosis(Abood *et al*., 2020).

**Advanced Delivery Systems for Metformin:** Traditional metformin therapy requires frequent dosing due to its short half-life and limited absorption, which can cause gastrointestinal side effects and reduce patient compliance. To overcome these issues, advanced delivery systems such as sustained-release (SR) tablets, microspheres, nanoparticles, and floating drug delivery systems have been developed. These systems improve drug bioavailability, provide a more controlled and prolonged release, reduce dosing frequency, minimize side effects, and enhance overall patient adherence and therapeutic efficacy. Metformin is often combined with other antidiabetic agents, such as sulfonylureas, DPP-4 inhibitors, or SGLT2 inhibitors, to achieve better blood sugar control. Combination therapy can improve efficacy, reduce individual drug doses, and minimize side effects.

**GRDDS:** GRDDS are designed to keep drugs in the stomach for an extended period, improving bioavailability and enhancing the solubility of drugs that are poorly soluble at high pH. By prolonging gastric retention, these systems reduce drug waste, maintain therapeutic levels, and may extend the drug's half-life, allowing less

frequent dosing. Common GRDDS formulations include floating, high-density, expandable, raft-forming, and effervescent systems. However, drugs that irritate the stomach or are unstable in gastric pH are not suitable for this approach. Overall, gastro retentive systems enable better targeting of the

**Sustained-release (SR) delivery systems:** Sustained-release metformin tablets are designed to release the drug gradually over an extended period, reducing the frequency of dosing and minimizing gastrointestinal side effects. These formulations improve patient compliance, maintain steadier blood glucose levels, and enhance overall therapeutic efficacy compared to conventional immediate-release metformin.(Wadher *et al*., 2011). Metformin is an oral anti-hyperglycemic drug with incomplete gastrointestinal absorption, a bioavailability of 50–60%, and a short plasma half-life of 1.5–4.5 hours. Gastrointestinal side effects, such as nausea, diarrhea, and abdominal discomfort—especially during the first weeks—can reduce patient compliance. Frequent dosing also affects adherence. Sustained-release (SR) formulations that maintain therapeutic plasma levels for 10–16 hours could allow once-daily dosing, prolong the drug's action, and improve patient compliance(Wadher *et al*., 2011).

**Liposome:** Liposomes are tiny, spherical vesicles made of one or more phospholipid bilayers surrounding aqueous compartments. They can be formed from natural, non-toxic phospholipids and cholesterol. Their unique structure allows them to carry both hydrophilic and hydrophobic drugs, including peptides, proteins, hormones, enzymes, antibiotics, antifungals, and anticancer agents. Their biocompatibility and versatility make liposomes attractive carriers for targeted drug delivery(Kumar *et al*., 2022). Metformin HCl has been successfully incorporated into liposomal drug delivery systems using methods such as the physical dispersion technique and the ether injection method, enhancing its potential for targeted and controlled release (Kumar *et al*., 2022).

**Microsphere and Nanoparticles:** Microspheres provide controlled drug release, improved bioavailability, and reduced dosing frequency, enhancing patient compliance and therapeutic outcomes. To reduce gastric irritation from metformin HCl, microspheres have been formulated with Hydroxypropyl Methylcellulose (HPMC) via spray drying. Encapsulation allows controlled release, limiting direct contact with the gastric mucosa while improving absorption in the proximal small intestine, where metformin HCl is primarily absorbed. Compared to conventional dosage forms, microspheres and other particulate systems offer higher local drug concentrations, reduced gastrointestinal variability, lower risk of dose dumping, and the flexibility to deliver both hydrophilic and hydrophobic drugs. Additionally, metformin-loaded nanoparticles have shown potential in novel applications, including cancer treatment, making them a promising approach for diabetic patients with comorbid conditions (Kotha *et al*., 2023). Nanoparticles, with their small size, high surface area, and ability to be functionalized, are well-suited for targeted therapies, including cancer treatment. Metformin-loaded nanoparticles have gained attention for their potential anticancer effects, such as inhibiting cell proliferation, inducing apoptosis, and blocking angiogenesis. Formulating metformin as microspheres or nanoparticles can enhance bioavailability, reduce side effects, and provide controlled drug release, offering benefits in both hyperglycemia management and potential anticancer applications(Kotha *et al*., 2023).

**Metfromin combination:** Metformin has been a cornerstone in the management of type 2 diabetes (T2D) for over 60 years. T2D is a chronic, progressive disease, and treatment decisions are increasingly patient-centered, considering cardiovascular comorbidities, side-effect risk, and patient preferences. While new drug classes like DPP-4 inhibitors, SGLT2 inhibitors, and GLP-1 receptor agonists have expanded treatment options, metformin remains the preferred initial therapy. As beta-cell function declines, most patients eventually require metformin-based combination therapy(Schnaars *et al*., 2022).
Fixed-dose combinations (FDCs) of metformin with other antidiabetic agents simplify therapy, reduce pill burden, improve adherence, and enhance glycemic control. Vildagliptin, a DPP-4 inhibitor, is commonly added to metformin due to complementary mechanisms: metformin decreases hepatic glucose production and enhances insulin-mediated glucose uptake, while vildagliptin prolongs incretin hormone action, stimulating insulin secretion and suppressing glucagon. The combination further reduces HbA1c and fasting plasma glucose, is weight neutral, has a low risk of hypoglycemia, and is generally cardiovascular safe. Generic versions provide a cost-effective treatment option(Schnaars *et al*., 2022). Patients who cannot tolerate metformin or experience side effects from monotherapy may be prescribed fixed-dose combinations (FDCs) of other oral antidiabetic agents, such as SGLT2 inhibitors, DPP-4 inhibitors, thiazolidinediones, sulfonylureas, GLP-1 analogues, or basal insulin. In some cases, a third agent may be added to further improve blood glucose control and treatment efficacy (Kalra *et al*., 2020). Metformin, alone or combined with other glucose-lowering agents, effectively reduces blood glucose in type 2 diabetes. Combinations with non-insulin drugs produce similar reductions in HbA1c but differ in effects on weight gain and risk of hypoglycemia. Beyond glucose control, metformin also offers benefits for diabetes-related comorbidities(Dutta *et al*., 2022).

**Merits and demerits of fixed-dose combinations:** Many clinicians recommend fixed-dose combinations (FDCs**)** for newly diagnosed T2DM patients due to their multiple benefits. FDCs reduce pill burden, lower side effects, decrease costs, and improve patient compliance, all of which contribute to better treatment outcomes. Advantages include simpler dosing, improved adherence, reduced medication errors, synergistic drug effects, and lower manufacturing costs (Kalra *et al*., 2020). However, FDCs also have drawbacks, such as limited dosing flexibility, potential drug interactions, incompatible pharmacokinetics if the combination is irrational, the need to stop treatment if a patient is allergic to any component, and in some cases, higher costs compared to single-drug tablets (Kalra *et al*., 2020).

**Future aspects:** Future research should focus on developing smarter, more personalized metformin delivery systems that integrate nanotechnology, targeted delivery, and real-time therapeutic monitoring. Novel carriers like ligand-decorated nanoparticles, responsive hydrogels, and bio-engineered liposomes offer potential for organ-specific or receptor-specific delivery, reducing side effects while maximizing efficacy. Combination systems with GLP-1 analogues, SGLT2 inhibitors, or dual-acting peptides may provide superior glycemic control and cardiometabolic benefits. Additionally, exploring metformin's anticancer, antiviral, and anti-inflammatory potential could expand its therapeutic applications. Advancements in 3D-printed dosage forms, artificial intelligence-aided formulation design, and precision medicine will further revolutionize metformin therapy.

# CONCLUSION

Diabetes mellitus remains a major global health challenge, requiring continuous advancement in therapeutic and drug-delivery approaches. Metformin, despite being an old drug, continues to be the backbone of type 2 diabetes management due to its safety, affordability, and multi-targeted mechanism. However, its limitations in absorption, gastrointestinal tolerance, and short half-life have encouraged the development of innovative formulations. Advanced systems such as sustained-release tablets, microspheres, nanoparticles, liposomes, gastro-retentive systems, and combination therapies significantly enhance metformin's bioavailability, therapeutic performance, and patient adherence. Overall, these modern strategies provide safer, more effective, and patient-friendly options for long-term diabetes management.

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