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APPROACHES TO IMPROVE THE PHARMACOKINETIC PROPERTIES OF METFORMIN AND ITS COMBINATION WITH OTHER ANTIDIABETIC DRUGS: A COMPREHENSIVE REVIEW

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ABSTRACT Metformin, a cornerstone therapy for type 2 diabetes mellitus (T2DM), offers broad clinical benefits including glycemic control, cardiovascular protection, and weight neutrality. However, its therapeutic potential is limited by poor pharmacokinetics—low and variable oral bioavailability, short half-life, and dose-dependent gastrointestinal side effects. Recent advances in formulation science and drug delivery technologies have sought to overcome these barriers through nanoparticles, liposomes, nanocochleates, prodrugs, microneedle patches, and gastroretentive systems, each demonstrating improved absorption, sustained release, and reduced adverse effects. In parallel, metformin-based combination therapies with sulfonylureas, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, and thiazolidinediones have become standard practice, though they introduce additional pharmacokinetic and regulatory complexities. This review consolidates current knowledge on metformin's pharmacokinetic limitations, transporter-mediated variability, advanced formulation strategies, and combination regimens. It further highlights regulatory challenges and future directions, emphasizing personalized medicine, targeted delivery, and harmonized approval pathways to optimize metformin therapy for diverse patient populations.

KEYWORDS : Metformin, Pharmacokinetics, Nanoparticles, Liposomes, Prodrugs, Combination Therapy

INTRODUCTION

Metformin, a biguanide derivative originally isolated from French lilac (Galega officinalis), has been the cornerstone of type 2 diabetes mellitus (T2DM) management for decades. Its clinical benefits extend beyond glycemic control, encompassing weight neutrality, cardiovascular protection, and potential reductions in diabetic nephropathy and neuropathy. Despite these advantages, metformin therapy is hampered by significant pharmacokinetic (PK) limitations, including low and variable oral bioavailability, a short half-life, and dose-limiting gastrointestinal (GI) side effects. These challenges often necessitate high and frequent dosing, which can compromise patient adherence and therapeutic outcomes.

Recent advances in pharmaceutical sciences have spurred the development of innovative formulation strategies and drug delivery systems to overcome these limitations. Concurrently, combination therapy—pairing metformin with other antidiabetic agents such as sulfonylureas, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, and thiazolidinediones—has become standard practice to achieve optimal glycemic control. However, combination regimens introduce additional pharmacokinetic and regulatory complexities.

This review provides a comprehensive analysis of the pharmacokinetic barriers associated with metformin, explores advanced formulation and delivery strategies to enhance its bioavailability, examines transporter-mediated absorption and genetic influences, and evaluates the pharmacokinetics and clinical evidence of metformin-based combination therapies. We further discuss novel drug delivery systems for combination regimens, regulatory and translational challenges, and future directions in the field.

Pharmacokinetic Limitations of Metformin

Physicochemical Properties and Absorption

Metformin is a highly hydrophilic, cationic base (pKa ≈ 11.5) with low membrane permeability (logP ≈ -1.43), classifying it as a Biopharmaceutics Classification System (BCS) Class III drug (high solubility, low permeability). At physiological pH, it exists almost entirely in a protonated form, which severely restricts passive diffusion across biological membranes. Consequently, metformin's oral absorption is incomplete and saturable, with an absolute bioavailability of approximately 50–60%. The majority of absorption occurs in the small intestine, particularly the duodenum, jejunum, and ileum, with negligible uptake from the colon.

Transporter-Mediated Uptake and Saturation

Due to its poor passive permeability, metformin relies on a network of transporter proteins for absorption, distribution, and elimination. Key transporters include organic cation transporters (OCT1, OCT2, OCT3), plasma membrane monoamine transporter (PMAT), serotonin transporter (SERT), thiamine transporter 2 (THTR-2), and high-affinity choline transporter (CHT). In the intestine, OCT1, PMAT, and SERT are particularly important, collectively accounting for the majority of metformin's uptake into enterocytes. However, these transporters exhibit saturable kinetics, leading to non-linear absorption at higher doses and contributing to the lack of dose proportionality observed clinically.

Distribution, Metabolism, and Elimination

Metformin is minimally bound to plasma proteins and exhibits a large volume of distribution (Vd ≈ 63–276 L after intravenous administration; ≈ 600 L after oral dosing, adjusted for bioavailability). It preferentially accumulates in the liver, kidneys, and GI tract, with hepatic concentrations several-fold higher than plasma levels. Metformin is not metabolized and is excreted unchanged in the urine via glomerular filtration and active tubular secretion, primarily mediated by OCT2, MATE1, and MATE2-K transporters. The elimination half-life ranges from 1.5 to 6.2 hours for immediate-release formulations, with a terminal half-life of up to 20 hours due to erythrocyte partitioning.

Clinical Implications and Variability

The combination of low permeability, saturable transporter-mediated absorption, and rapid renal elimination necessitates high and frequent dosing (500–2000 mg/day,

divided) to maintain therapeutic plasma concentrations. However, high doses are associated with increased GI side effects (nausea, diarrhea, bloating), which affect up to 30% of patients and are a leading cause of treatment discontinuation. Furthermore, approximately 35% of patients experience inadequate glycemic control with standard metformin therapy, highlighting substantial interindividual variability.

Formulation Strategies to Enhance Metformin Bioavailability

Given the pharmacokinetic challenges of metformin, numerous formulation approaches have been developed to improve its absorption, prolong its action, and mitigate side effects. Table 1 summarizes key strategies and their outcomes.

Table 1. Comparative Overview of Formulation Strategies for Metformin

Strategy	Carrier/Excipient	Key Outcomes
Polymeric nanoparticles	PLGA, chitosan	Increased Bioavailability (2.6–5.5×), sustained release, decreased GI side effects
Liposomes, elastic liposomes	Soya lecithin, cholesterol, HDCA	Increased Encapsulation (60–83%), sustained release, increased hepatic targeting, decreased fasting glucose
Nanocochleates	DCP, phospholipids	Increased Permeation (4–5.5×), controlled release, increased AUC, prolonged Tmax
Solid lipid microparticles	Stearic acid, GMS	Sustained release, stability, improved absorption
Prodrugs	Sulfenamide, PEG conjugates	Increased Lipophilicity, increased oral absorption (43–65%), decreased GI side effects
Microneedle patches	PEGDA, PLGA, HA	Transdermal delivery, rapid onset, sustained effect, decreased GI irritation
Permeation enhancers	-cyclodextrin, Pluronic F127	Increased Permeability (2–3×), Increased Cmax,
Gastroretentive floating tablets	HPMC, xanthan gum	Prolonged gastric retention, sustained release, improved adherence

Polymeric Nanoparticles

Poly(lactic-co-glycolic acid) (PLGA) nanoparticles have emerged as a leading platform for metformin delivery due to their biocompatibility, tunable degradation, and regulatory approval. Metformin-loaded PLGA nanoparticles, prepared via solvent evaporation or nanoprecipitation, exhibit high drug entrapment (65–85%), mean particle sizes of 150–450 nm, and negative zeta potentials for colloidal stability. In vivo, these formulations demonstrate 2.6–5.5-fold increases in oral bioavailability, sustained plasma concentrations, and enhanced antidiabetic efficacy compared to conventional metformin. Notably, PLGA nanoparticles can be engineered for targeted delivery, controlled release, and co-encapsulation of multiple drugs for combination therapy.

Liposomes and Elastic Liposomes

Liposomes, composed of phospholipid bilayers, can encapsulate hydrophilic drugs like metformin and facilitate their transport across biological membranes. Modifications with bile acids (e.g., hyodeoxycholic acid, HDCA) or surfactants yield elastic liposomes with enhanced deformability and tissue penetration. These systems achieve encapsulation efficiencies of 60–83%, sustained drug release over 8–24 hours, and improved hepatic targeting, resulting in superior glycemic control and reduced oxidative stress in diabetic models.

Nanocochleates

Nanocochleates are spiral, cigar-shaped lipid assemblies stabilized by interactions between anionic phospholipids and cationic drugs or metal ions. Metformin-bridged nanocochleates exhibit high entrapment efficiency (>75%), controlled biphasic release, and markedly enhanced intestinal permeation (up to 5.5-fold higher than free metformin). In vivo, these formulations prolong Tmax, increase Cmax and AUC, and sustain plasma concentrations, offering a promising oral delivery platform.

Solid Lipid Microparticles (SLMs) and Nanostructured Lipid Carriers (NLCs)

SLMs and NLCs utilize biocompatible lipids (e.g., stearic acid, glyceryl monostearate) to encapsulate metformin, providing controlled drug release, improved stability, and protection from gastric degradation. These systems can be tailored for dual-drug loading, enabling combination therapy in a single formulation.

Prodrug Approaches

Chemical modification of metformin to generate prodrugs (e.g., sulfenamide, PEG conjugates) increases its lipophilicity, facilitating passive diffusion and enhancing oral absorption. Sulfenamide prodrugs have demonstrated 43–65% bioavailability in animal models, with rapid in vivo conversion to active metformin and reduced GI side effects. However, safety profiles depend on the specific promoiety used.

Microneedle and Transdermal Systems

Microneedle (MN) patches, fabricated from PEGDA, PLGA, or hyaluronic acid, enable minimally invasive transdermal delivery of metformin. These systems bypass GI absorption barriers, provide rapid and sustained drug release, and reduce GI irritation. In animal models, MN patches achieve glycemic control comparable to subcutaneous injection, with improved safety and patient convenience.

Permeation and Absorption Enhancers

Inclusion complexes with -cyclodextrin, surfactants (e.g., Pluronic F127), and spray-drying techniques have been employed to enhance metformin's intestinal permeability and absorption. These approaches increase the free drug concentration at the absorptive surface, improve Cmax and AUC, and may allow for dose reduction.

Gastroretentive and Controlled-Release Formulations

Gastroretentive floating tablets, formulated with hydrophilic polymers (e.g., HPMC, xanthan gum), prolong gastric residence time and provide sustained metformin release, reducing dosing frequency and improving adherence. These systems maintain therapeutic plasma concentrations and may mitigate GI side effects by avoiding high local concentrations in the intestine.

Transporter Modulation and Absorption Enhancement

Role of Transporters in Metformin Pharmacokinetics

Metformin's absorption, distribution, and elimination are governed by a network of solute carrier (SLC) and ATP-binding cassette (ABC) transporters. In the intestine, OCT1 (SLC22A1), OCT3 (SLC22A3), PMAT (SLC29A4), SERT (SLC6A4), and CHT (SLC5A7) are key mediators of apical uptake. In the liver, OCT1 and OCT3 facilitate hepatic uptake, while MATE1 (SLC47A1) mediates biliary excretion. Renal elimination is primarily via OCT2 (SLC22A2), MATE1, and MATE2-K (SLC47A2).

Transporter Saturation and Drug–Drug Interactions

Transporter-mediated uptake is saturable, leading to non-linear absorption at higher doses. Co-administration of drugs that inhibit or compete for these transporters (e.g., cimetidine, trimethoprim, dolutegravir) can increase metformin plasma concentrations and the risk of lactic acidosis. Conversely, inducers (e.g., rifampin) may enhance absorption and efficacy.

Genetic Polymorphisms and Interindividual Variability

Genetic variants in transporter genes, particularly SLC22A1 (OCT1), contribute to interindividual differences in metformin response and tolerance. Reduced-function alleles (e.g., R61C, G401S, M420del) are associated with impaired hepatic uptake, higher plasma concentrations, reduced glycemic efficacy, and increased risk of GI side effects. The prevalence and impact of these variants vary across populations, with notable interethnic differences.

Strategies to Modulate Transporter Activity

Formulation approaches that enhance transporter-mediated uptake (e.g., targeting OCT1/PMAT with specific excipients) or bypass saturable pathways (e.g., prodrugs, nanocarriers) can improve metformin absorption and reduce variability. Additionally, personalized dosing based on transporter genotype may optimize therapeutic outcomes.

Combination Therapy with Other Antidiabetic Drugs

Combination therapy is often required to achieve and maintain glycemic targets in T2DM, especially as -cell function declines over time. Metformin is commonly combined with agents from different classes, each with distinct mechanisms of action and pharmacokinetic profiles.

Metformin + Sulfonylureas

Sulfonylureas stimulate insulin secretion but are associated with increased risks of hypoglycemia, weight gain, and, in some studies, higher all-cause mortality and cardiovascular events compared to newer agents. While the combination with metformin provides robust glycemic control, the safety profile is less favorable, particularly in older adults and those with renal impairment.

Metformin + DPP-4 Inhibitors

DPP-4 inhibitors enhance endogenous incretin activity, increasing insulin secretion and suppressing glucagon release in a glucose-dependent manner. The combination with metformin is effective, weight-neutral, and carries a low risk of hypoglycemia. Pharmacokinetic studies indicate no significant drug–drug interactions, supporting the feasibility of fixed-dose combinations.

Metformin + SGLT2 Inhibitors

SGLT2 inhibitors promote urinary glucose excretion, leading to improved glycemic control, weight loss, and reductions in blood pressure. When combined with metformin, these agents confer additional cardiovascular and renal protection. The risk of hypoglycemia is low, but genital tract infections are more common.

Metformin + GLP-1 Receptor Agonists

GLP-1 RAs stimulate insulin secretion, inhibit glucagon, slow gastric emptying, and promote weight loss. Combination therapy with metformin yields superior HbA1c reductions and weight loss compared to other regimens, with a low risk of hypoglycemia. However, GI side effects (nausea, vomiting) are more frequent.

Metformin + Thiazolidinediones (TZDs)

TZDs improve insulin sensitivity but are associated with weight gain, edema, and potential cardiovascular risks. The combination with metformin is effective for glycemic control but may not be preferred in patients at risk for heart failure.

Triple and Quadruple Combinations

Recent studies have evaluated triple fixed-dose combinations (e.g., metformin + DPP-4 inhibitor + SGLT2 inhibitor), demonstrating superior glycemic efficacy, weight loss, and blood pressure reduction compared to dual therapy, with minimal hypoglycemia risk. However, the risk of genital tract infections is increased with SGLT2 inhibitor-containing regimens.

Novel Drug Delivery Systems for Combination Therapy

Advanced drug delivery systems are being developed to co-deliver metformin with other antidiabetic agents, aiming to optimize pharmacokinetics, enhance efficacy, and improve patient adherence.

Polymeric and Lipid-Based Nanocarriers

PLGA nanoparticles, liposomes, and nanostructured lipid carriers can encapsulate multiple drugs, providing controlled and sustained release, improved stability, and targeted delivery. Dual-drug loading strategies enable combination therapy in a single formulation, reducing pill burden and enhancing compliance.

Prodrug and Bioconjugate Approaches

Prodrugs and drug–polymer conjugates (e.g., PEGylated metformin, dendrimer–metformin conjugates) can be engineered to release multiple active agents sequentially or simultaneously, achieving synergistic effects and tissue-specific targeting.

Microneedle and Transdermal Systems

Microneedle patches and transdermal systems offer non-invasive, sustained delivery of metformin and co-administered drugs, bypassing GI absorption barriers and minimizing systemic side effects.

Smart and Responsive Systems

Emerging technologies include glucose-responsive nanoparticles and stimuli-sensitive carriers that release drugs in response to physiological cues, enabling personalized and adaptive therapy.

Regulatory and Translational Challenges

Manufacturing and Scale-Up

The translation of advanced metformin formulations from bench to bedside is hindered by challenges in large-scale, reproducible manufacturing, particularly for nanomedicines. Batch-to-batch variability, control of particle size and distribution, and maintenance of physicochemical stability are critical issues. Continuous manufacturing and microfluidic technologies offer potential solutions but require further validation.

Quality, Safety, and Efficacy

Regulatory agencies (FDA, EMA) require comprehensive characterization of nanomedicines, including critical quality attributes (CQAs), process parameters, and robust analytical methods. Demonstrating bioequivalence to existing products, long-term stability, and absence of nanotoxicity are essential for approval.

Clinical Translation

Despite promising preclinical data, few advanced metformin formulations have reached clinical trials or market approval. Challenges include high production costs, complex formulation processes, and stringent regulatory requirements for safety and efficacy. Intellectual property considerations and the need for standardized testing protocols further complicate commercialization.

Future Directions

Personalized and Precision Medicine

Integration of pharmacogenomics, transporter genotyping, and real-time biomarker monitoring can enable individualized metformin dosing and selection of optimal combination regimens. Machine learning and computational modeling may facilitate prediction of drug–drug interactions and personalized therapy.

Targeted and Responsive Delivery

Development of targeted delivery systems (e.g., liver-specific, gut-restricted, or adipose-targeted nanocarriers) and glucose-responsive formulations holds promise for maximizing efficacy while minimizing systemic exposure and side effects.

Expanded Therapeutic Applications

Metformin's pleiotropic effects in oncology, neurodegeneration, and inflammatory diseases are being explored, with advanced delivery systems potentially extending its utility beyond diabetes.

Regulatory Harmonization and Commercialization

Efforts to harmonize regulatory requirements for nanomedicines and establish standardized protocols for characterization, safety assessment, and bioequivalence are critical for accelerating clinical translation and commercialization.

CONCLUSION

Metformin remains a foundational therapy for T2DM, but its clinical utility is constrained by significant pharmacokinetic limitations and interindividual variability. Advances in formulation science—including nanoparticles, liposomes, prodrugs, and transdermal systems—have demonstrated substantial improvements in bioavailability, sustained release, and tolerability. Combination therapy with other antidiabetic agents is essential for optimal glycemic control, and novel drug delivery systems are poised to further enhance efficacy and patient adherence. However, regulatory, manufacturing, and translational challenges must be addressed to realize the full potential of these innovations. Future research should prioritize personalized approaches, targeted delivery, and harmonized regulatory pathways to optimize metformin therapy for diverse patient populations.

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