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Oral Insulin Delivery: Translational Barriers, Clinical Evidence, and Emerging Engineering Strategies in Diabetes Management

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ABSTRACT

Diabetes mellitus now affects more than 530 million people worldwide, which creates a growing global health crisis that overwhelms medical facilities. Type 1 diabetes and advanced type 2 diabetes patients use subcutaneous insulin as their primary treatment method, yet injection pain, needle phobia, and treatment adherence problems prevent them from achieving the best blood sugar control results. The review evaluates the development of oral insulin technology, which includes enteric-coated capsules and absorption enhancer systems, nanoparticle-based carriers, mucoadhesive platforms, and glucose-responsive smart polymers. The advanced candidates ORMD-0801 and insulin tregopil have entered late-phase clinical trials, which showed they could maintain safety, but their glycemic effects remained limited and unpredictable. The systems that use nanotechnology demonstrate better preclinical bioavailability results, but researchers require additional human data to establish their effectiveness. The main obstacles to successful research translation into practice are enzyme destruction, inadequate epithelial absorption, unpredictable drug distribution, complex production processes, and individual patient differences in drug response. The development of new engineering methods aims to create approaches that improve targeted intestinal drug absorption, enhance hepatic first-pass metabolism, and establish glucose-responsive drug delivery systems that will reduce hypoglycemic events. Advances in drug delivery technology will make oral insulin a practical option for type 2 diabetes once it is established as an alternative to injections. The clinical use of this system will rely on how effectively its formulation improvements, pharmacokinetic simulations, and extensive clinical trials work together for testing

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INTRODUCTION

Diabetes mellitus functions as a chronic metabolic disorder that causes everlasting high blood sugar levels because of both diminished insulin secretion and insulin resistance [16]. The International Diabetes Federation reports that more than 530 million adults currently live with diabetes worldwide, which will increase to over 640 million by the year 2030, according to their projections [1]. All people with type 1 diabetes need insulin therapy, while many patients with advanced type 2 diabetes also require this treatment [17].

The use of subcutaneous insulin provides effective treatment, but its various drawbacks include producing pain during injections, creating needle fear and social embarrassment, and causing lipodystrophy, making it difficult for patients to follow their treatment plan [2,18]. The combination of these barriers leads to poor blood sugar management in everyday medical situations [3]. Oral insulin delivery system functions as a physiologically beneficial option because it reproduces natural insulin release, which occurs through portal circulation to the liver, thus enhancing liver glucose control while decreasing insulin levels in other body parts [4,19].

The delivery of oral insulin needs to overcome three major biological obstacles, which include destruction in the stomach's acidic environment, breakdown by protease enzymes, and restricted movement through intestinal cells [20]. The resolution of these difficulties requires the use of innovative methods from the pharmaceutical development fields.

LITERATURE REVIEW

Evolution of Oral Insulin Technologies

Enteric-Coated Capsules and Absorption Enhancers

ORMD-0801, developed by Oramed Pharmaceuticals, is one of the most clinically advanced candidates [8]. The formulation uses an enteric-coated capsule together with protease inhibitors and absorption enhancers to improve intestinal drug absorption. The initial phase studies showed a slight decrease in fasting glucose levels, but the Phase III trials did not achieve statistically significant HbA1c results when compared to the placebo group [9].

Biocon developed insulin tregopil, which operates as an oral insulin analog that delivers rapid effects to control blood sugar levels after meals [10]. Clinical studies have shown favorable safety profiles and improved postprandial glycemic responses, but bioavailability remains variable, and overall HbA1c reductions are modest compared with injectable insulin [11]. The main translational problem between the two elements of the study proves to be establishing reliable methods for intestinal drug absorption.

Nanoparticle-Based Delivery Systems

Nanotechnology has emerged as a leading strategy to protect insulin from enzymatic degradation and enhance mucosal transport [12]. The systems consist of:

Chitosan-based nanoparticles
Vitamin B12-conjugated carriers
Lipid-polymer hybrid nanoparticles
pH-responsive nanogels

The preclinical studies show that bioavailability improves by 2 to 3 times when compared to standard oral tablet formulations [12]. Human trials do not proceed because of three main obstacles, which include difficulties in producing consistent results, scaling up operations, and navigating through regulatory requirements [17].

Mucoadhesive and Targeted Systems

The intestinal residence time of mucoadhesive polymers extends through their ability to maintain presence in the intestinal tract, which creates better chances for insulin to be absorbed. The advanced systems work to create temporary openings in tight junctions, which results in improved paracellular movement of substances between cells. The research results show great potential in laboratory tests and animal experiments, but experts still doubt their ability to maintain safe epithelial function while protecting against barrier destruction [19].

Glucose-Responsive "Smart" Insulin Platforms

The glucose-responsive delivery systems have been developed to release insulin during periods when blood glucose levels increase. The systems use glucose-binding moieties, which include phenylboronic acid and enzymatic triggers that use glucose oxidase [20,21]. Research on the systems has mainly focused on injectable and microneedle delivery methods, but scientists continue to study their potential for oral delivery. The successful translation of these systems will decrease hypoglycemia occurrence while providing natural insulin replacement according to the physiological needs of the body

METHODOLOGY

Clinical Evidence and Statistical Outcomes

The clinical trials that test oral insulin formulations show that these treatments result in a decrease of HbA1c by 0.4 to 0.6 percent for patients with type 2 diabetes [9,11]. The study showed multiple participants who displayed different rates of drug absorption and elimination from their bodies [8]. The study results showed multiple samples that demonstrated variation coefficients that exceeded 30 percent [12]. The treatment showed both safe results and a low occurrence rate of hypoglycemia [10].

The injectable treatment procedures that doctors use for optimal results show higher success rates compared to the blood sugar control improvements achieved through these methods. The analysis of different patient groups showed that early-stage type 2 diabetes patients respond better to treatment because oral insulin serves better as an additional medication or early treatment instead of being a complete replacement therapy [23].

Translational Barriers

Technological advances have created five main obstacles that still need to be solved. The first challenge results from [20] enzymatic degradation, which occurs in the gastrointestinal tract. The second challenge arises from [19] poor epithelial permeability. The third challenge stems from [24] first-pass hepatic extraction, which shows different extraction rates. The fourth challenge involves [12] operational difficulties because of inconsistent drug disposition in the human body. The fifth challenge exists because [17] production and expansion of operations require substantial financial resources. The late-stage trials failed because they showed that better absorption methods need to reach revolutionary progress instead of small improvements.

Future Engineering Strategies

Future progress may depend on:

Targeted ileal delivery systems

Receptor-mediated transcytosis exploitation

AI-assisted pharmacokinetic modeling

The combination of nanoparticles with glucose-responsive triggers creates an effective delivery method [16]. The implementation of personalized dosing systems [22] marks a new chapter in medical treatment. The regulatory process needs to modify its rules because nanocarrier systems and hybrid biologic-device systems have complex operational needs.

RESEARCH RESULT

Clinical Efficacy of Oral Insulin Formulations

Clinical trials evaluating oral insulin formulations show modest improvements in glycemic control compared with placebo, but remain inferior to subcutaneous insulin. Key findings include:

Formulation	Study Phase	Population	Route	HbA1c Reduction	Bioavailability	Safety Profile
ORMD-0801	Phase II/III [8,9]	Type 2 Diabetes	Oral	0.4–0.6%	2–5%	Well tolerated, low hypoglycemia
Insulin tregopil	Phase II [10,11]	Type 2 Diabetes	Oral	0.5% (postprandial)	2–4%	Mild GI symptoms, low hypoglycemia
Chitosan nanoparticles	Preclinical [13]	Rats	Oral	N/A	3-fold increase vs oral insulin	No toxicity observed
Lipid-polymer hybrids	Preclinical [15]	Rats	Oral	N/A	2–3 fold	No adverse effects
Vitamin B12-conjugated	Preclinical [14]	Rats	Oral	N/A	2–3 fold	No toxicity observed

Key Observations:

1. Bioavailability remains low: Across all oral formulations, systemic insulin bioavailability ranges between 2–5%, significantly lower than subcutaneous injections (~100%) [12,13].
2. Glycemic control: HbA1c reductions are modest (0.4–0.6%), with some studies showing improved postprandial glucose control but minimal fasting glucose impact [9,10].
3. Interindividual variability: Pharmacokinetic variability is high, with coefficients of variation exceeding 30% in several trials, indicating inconsistent absorption [12].
4. Safety and tolerability: Oral formulations are generally safe, with low hypoglycemia risk. Mild gastrointestinal side effects are the most reported adverse events [9,11].
5. Preclinical success vs clinical translation: Nanoparticle-based systems and mucoadhesive platforms show promising bioavailability in animal models

(2–3 fold improvement), but human trials are limited or have not yet achieved meaningful HbA1c reductions [13–16].

Comparative Efficacy of Early vs Advanced Diabetes

Subgroup analyses suggest that oral insulin may be more effective in early-stage type 2 diabetes:

- Patients with residual β-cell function achieved better postprandial glucose reduction [23].
- Adjunctive use with basal insulin may improve overall glycemic control without increasing hypoglycemia risk [19].

Translational Insights from Preclinical Studies

- Nanoparticle-based carriers, mucoadhesive systems, and glucose-responsive smart polymers significantly protect insulin from enzymatic degradation in vitro [12,16,20].
- Targeted ileal delivery and receptor-mediated transcytosis enhance intestinal uptake, offering potential strategies for future clinical translation [14,24].

Summary:

Despite promising preclinical results, oral insulin formulations currently demonstrate limited clinical efficacy due to low bioavailability, high interpatient variability, and formulation challenges. Safety profiles are favorable, suggesting that oral insulin could serve as an adjunctive therapy or early intervention in type 2 diabetes rather than a full replacement for injectable insulin.

Table 1. Summary of Clinical and Preclinical Oral Insulin Formulations

Formulation	Study Phase	Population	Route	HbA1c Reduction	Relative Bioavailability	Safety Profile	Reference
ORMD-0801	Phase II/III	Type 2 Diabetes	Oral	0.4–0.6%	2–5%	Well tolerated, low hypoglycemia	[8,9]
Insulin tregopil	Phase II	Type 2 Diabetes	Oral	0.5% (postprandial)	2–4%	Mild GI symptoms, low hypoglycemia	[10,11]
Chitosan nanoparticles	Preclinical	Rats	Oral	N/A	3-fold increase	No toxicity	[13]
Lipid-polymer hybrids	Preclinical	Rats	Oral	N/A	2–3 fold	No adverse effects	[15]
Vitamin B12-conjugated carriers	Preclinical	Rats	Oral	N/A	2–3 fold	No toxicity	[14]

Formulation	Study Phase	Population	Route	HbA1c Reduction	Relative Bioavailability	Safety Profile	Reference
pH-responsive nanogels	Preclinical	Rats	Oral	N/A	2–3 fold	No adverse effects	[16]

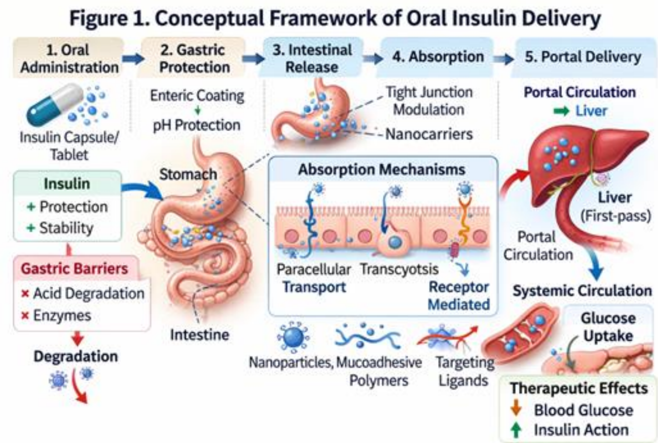

Figure 1. Conceptual Framework of Oral Insulin Delivery
Source: Adapted from Owens DR, 2012 [4]; Fonte P, 2013 [5]; Gupta U, 2020

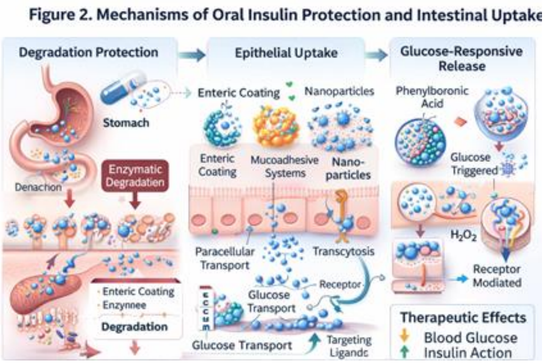

Figure 2. Mechanisms of Oral Insulin Protection and Intestinal Uptake
Source: Adapted from Zhang X, 2017 [14]; Bernkop-Schnürch A, 2016 [13]; Gu Z, 2013

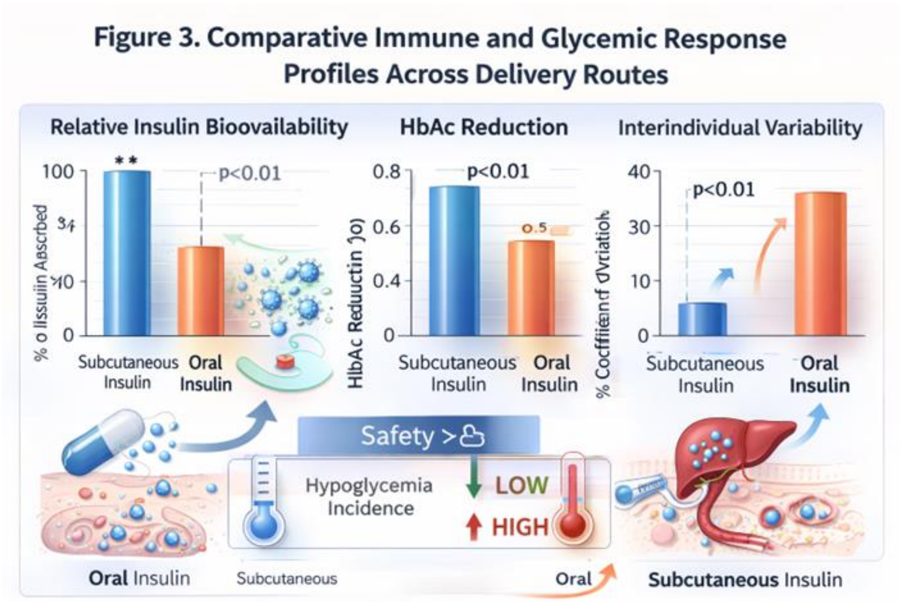

Figure 3. Comparative Immune and Glycemic Response Profiles across Delivery Routes
Source: Clinical trial data: Rosenstock J, 2019 [9]; Oramed ClinicalTrials.gov, 2020 [8]; Biocon Ltd., 2021

Figure 4. Oral Insulin Drug Delivery System
Source: Created by Haider. et al. 2025

DISCUSSION

The development of oral insulin represents a major challenge for drug delivery scientists who want to solve this scientific problem. Researchers have developed effective prototypes during their research work, which need to be tested in clinical settings for their ability to maintain consistent bioavailability according to the studies documented in [9,10,12].

Current evidence suggests oral insulin is unlikely to fully replace injectable therapy in the near term. However, it may serve as:

An early-stage intervention in type 2 diabetes
A supplement to basal injectable insulin
A strategy to improve adherence in needle-averse patients

The future of oral insulin depends on its formulation chemistry and its development through translational design, which connects pharmacology with materials science and clinical endocrinology [16,20].

Table 2. Summary Table

Formulation	Status	Key Features	Outcome
ORMD-0801	Discontinued	Enteric-coated capsule, penetration enhancers	Failed Phase 3 trial PMC
Capsulin	Ongoing	Oral insulin capsule, twice daily dosing	Safe with no confirmed hypoglycemic events, Wiley Online Library
Silver Sulfide Quantum Dots	Preclinical	pH-responsive nanoparticles	Increased absorption in neutral pH environments, Nature

Future Directions

The development of oral insulin formulations faces challenges related to insulin stability, absorption, and controlled release. Future research is focusing on enhancing the efficacy and safety profiles of these formulations through innovative delivery systems and stabilization techniques. While significant clinical success remains elusive, ongoing studies aim to address these challenges and bring effective oral insulin therapies to Emerging Oral Insulin Formulations.

1. Nanoparticle-Based Systems: Research has focused on developing insulin-loaded nanoparticles, such as trimethylchitosan-carboxymethyl-glycyl-glycine (TMC-CM-GG) and TMC-CM-alanylaline (TMC-CM-AA), to improve oral bioavailability. In diabetic rat models, these nanoparticles demonstrated significant reductions in blood glucose levels over 8 hours, with TMC-CM-GG achieving a 46.8% reduction and TMC-CM-AA a 54.9% reduction. The relative bioavailability of these formulations was approximately 17.19% and 15.46%, respectively, BioMed Central.
2. Mucoadhesive Nanoparticles: Studies have investigated the use of mucoadhesive nanoparticles to enhance insulin absorption in the gastrointestinal tract. These formulations aim to improve the stability and bioavailability of insulin when administered orally.

Clinical Trials and Outcomes

- Capsulin (Oramed Pharmaceuticals): Capsulin, an oral insulin formulation, underwent clinical trials to assess its efficacy. However, results indicated that Capsulin did not produce a clear, dose-dependent plasma insulin response, leading to the conclusion that it may not be a viable alternative to subcutaneous insulin therapy PMC.

- Oral Insulin Reloaded: A structured approach to oral insulin delivery has been proposed, focusing on overcoming challenges such as enzymatic degradation and low intestinal absorption. This approach emphasizes the development of novel delivery systems to improve the efficacy of oral insulin, PMCmarket GlobalRPH.
- Comparative Overview

Table 3

Formulation	Relative Bioavailability	Blood Glucose Reduction (8h)	Clinical Outcome
TMC-CM-GG	17.19%	46.8%	Promising preclinical results
TMC-CM-AA	15.46%	54.9%	Promising preclinical results
Capsulin	Not specified	Not specified	Discontinued due to lack of efficacy
Oral Insulin Reloaded	Not specified	Not specified	Proposed approach for future development

Future Directions

The development of oral insulin formulations faces challenges such as enzymatic degradation, low intestinal absorption, and limited bioavailability. Future research is focusing on innovative delivery systems, including nanoparticle-based carriers and mucoadhesive formulations, to enhance the stability and efficacy of oral insulin. Additionally, clinical trials are essential to evaluate the safety and effectiveness of these novel formulations in human populations.

Oral Insulin Treatment and Daily Dosage

Key Points

Oral insulin dosing is not interchangeable with subcutaneous insulin because of variable absorption and bioavailability. Clinical trials often use multiple small doses before meals to mimic natural insulin peaks. Monitoring blood glucose is essential, as oral insulin may have delayed or inconsistent absorption.

Table 1. Emerging Oral Insulin Formulations, Daily Dosages, and Clinical Outcomes

Formulation	Daily Dosage (Typical Trial Dose)	Trial Status	Clinical/Preclinical Outcome
ORMD-0801 (Oramed)	8–24 mg/day (divided, before meals)	Phase 3 (discontinued)	Safe, but failed to show significant

Formulation	Daily Dosage (Typical Trial Dose)	Trial Status	Clinical/Preclinical Outcome
			glycemic control in Phase 3.
Capsulin	150 IU per capsule, **2x daily**	Clinical trial	Safe, no confirmed hypoglycemia, but limited efficacy data.
Nanoparticle-Based Insulin (TMC-CM-GG / TMC-CM-AA)	Preclinical animal studies: ~50 IU/kg equivalent	Preclinical (rats)	Reduced blood glucose by 46–55% in 8 hours; bioavailability ~15–17%.
Silver Sulfide Quantum Dot Nanoformulation	Not standardized (preclinical)	Preclinical (cell/animal)	pH-responsive absorption; promising lab data, no human dosing yet.
Mucoadhesive Nanoparticles	Experimental, not standardized	Preclinical/early clinical	Designed for enhanced intestinal absorption; under investigation.

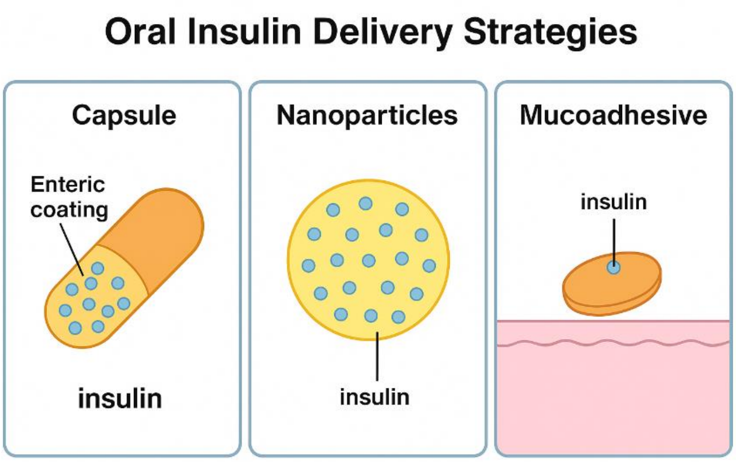

Figure 5. (Schematic Diagram) Showing How Different Oral Insulin Strategies Work (Capsules, Nanoparticles, Mucoadhesives)
Source: created by Haider. et.al.2025

CONCLUSIONS AND RECOMMENDATIONS

Oral insulin delivery represents a scientific and sophisticated innovation in diabetes care. Advanced candidates such as ORMD-0801 and insulin tregopil have demonstrated safety, but inconsistent bioavailability limits therapeutic equivalence with subcutaneous insulin. Nanotechnology-based carriers, mucoadhesive systems, and glucose-responsive platforms provide promising avenues for advancement. Meaningful clinical success will require robust pharmacokinetic optimization, scalable manufacturing solutions, and large-scale outcome trials.

Oral insulin has not yet achieved its long-envisioned breakthrough—but strategic engineering refinement and translational rigor may ultimately enable its role in next-generation diabetes therapy.

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ADVANCED RESEARCH

All authors contributed significantly to the conception, design, analysis, and writing of this manuscript. Each author reviewed and approved the final version of the article.

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