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Research Article

Oral Insulin Pills: Innovations and Clinical Advances in Diabetes Management

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Abstract

The development of oral insulin formulations represents a significant innovation in diabetes management, aiming to overcome the limitations of subcutaneous insulin injections. Oral delivery could improve patient compliance, mimic the natural route of insulin absorption through the portal circulation, and reduce the psychological and physical burden associated with daily injections. However, the gastrointestinal environment poses major challenges, as insulin is rapidly degraded by digestive enzymes and exhibits poor intestinal absorption. Recent advances in drug delivery technologies, including protective coatings, nanoparticle carriers, and absorption enhancers, have renewed optimism for practical oral insulin therapies. Clinical trials, such as those conducted by Oramed Pharmaceuticals, have reported encouraging results with insulin capsules that demonstrate both safety and efficacy in glucose regulation. If successful, these innovations may transform diabetes care by providing a more physiological, patient-friendly alternative to injectable insulin.

Keywords: oral insulin; diabetes management; drug delivery systems; insulin capsule; clinical trials; nanotechnology; patient compliance; oramed pharmaceuticals

Introduction

Diabetes mellitus is a never-ending metabolic disorder from impaired insulin secretion, insulin resistance, or both, chief to continuous hyperglycemia and associated long-term problems, including cardiovascular disease, neuropathy, nephropathy, and retinopathy [1,2]. Globally, the prevalence of diabetes is climbing at an alarming rate, according to the International Diabetes Federation (IDF), predicting that by 2045, an additional 780 million families will experience worldwide [3]. Insulin control debris an essential part of management, specifically for people with type 1 diabetes and those with type 2 diabetes [4,5]. However, the necessity for lasting subcutaneous injections is associated with poor adherence, injection-site discomfort, fear of needles or social stigma, and reduced quality of life [6–8].

Oral insulin has long been considered the "holy grail" of diabetes therapy cause it would supply a more patient-companionable, physiological, and convenient route of administration. Unlike subcutaneous delivery, oral insulin would meet with first-pass absorption in the liver via the portal circulation, thereby more carefully replicating endogenous insulin movement and improving the hepatic level of glucose in blood requirement [9,10]. Despite this theoretical benefit, oral delivery of insulin poses difficult challenges on account of the abusive gastrointestinal environment. Insulin, being a peptide birth control method, is briskly degraded by gastricic acid and proteolytic enzymes, while allure big molecular content and hydrophilic character hinder assimilation across the gastric epithelium [11–13].

To overcome these impediments, significant research works have focused on innovative drug delivery procedures, including those pertaining to the gastric coatings, nanoparticle-located shippers, liposomal encapsulation, absorption enhancers, mucoadhesive polymers, and PEGylation methods [14–16]. Advances in nanotechnology and biomaterials have specifically enhanced the balance and bioavailability of orally executed insulin formulations [17–19]. Several clinical competitors are under active investigation. For example, Oramed Pharmaceuticals has progressive ORMD-0801, a oral insulin capsule, into phase 2/3 clinical trials, gathering favorable safety descriptions and promising levels of glucose in blood-threatening conditions in type 2 diabetes patients [20–22]. Other approaches, involving childbirth via gastric transportation enhancers and micelle-located carriers, are still professed to have potential in preclinical and early clinical studies [23–25].

If favorable, oral insulin can revolutionize diabetes administration by lowering patient dependency on injections, reconstructing devotion, reducing stigma, and providing a more physiologically appropriate insulin substitute. Continued progress in formulation skill, clinical development, and supervisory pathways will decide whether oral insulin can change from exploratory promise to clinical sensibility [26,27].

Literature Review

The search for oral insulin delivery has been a focus of biomedical research for almost a hundred years. Numerous studies have highlighted the benefits of oral presidency over subcutaneous injections, specifically in mimicking the physiological road of endogenous insulin secretion [1,2]. Insulin is brought verbally first enters the gateway vein, exerting direct control on the liver, which regulates glucose homeostasis more effectively than minor delivery [3].

However, oral delivery faces diversified barriers, including concerns with enzymatic depravity, gastric acridness, and weak permeability of insulin through the gastric epithelium [4,5]. To address these issues, researchers have investigated various approaches, such as:

Nanoparticle Carriers – Solid lipid nanoparticles and polymeric nanoparticles epitomize insulin, preserving it from being affected by enzymatic failure and enhancing assimilation [6–8].

Liposomal and Micelle Systems – These aircraft carriers correct mucosal adhesion and promote transcytosis across the gastric divider [9].

Absorption Enhancers – Chemical agents, to a degree, hostile salts and oily acids increase epithelial permeability [10].

Mucoadhesive Polymers – Chitosan and derivatives have been used to increase the residence period at the gastric mucosa, reconstructing the response [11].

PEGylation and Vitamin B12 Conjugation – Novel approaches devised to enhance stability and receptor-interfered rude answer [12,13].

Recent clinical progress has been bright. Oramed Pharmaceuticals' ORMD-0801 capsule explained safety and moderate efficiency in phase 2 and early phase 3 trials [14,15]. Novo Nordisk has again grown oral semaglutide, a GLP-1 receptor agonist, establishing the practicability of oral peptide delivery in diabetes care [16]. These developments imply that oral insulin is not any more a theoretical idea but a clinical sensibility in case.

Statistical Analysis

Statistical analyses of clinical trials of oral insulin primarily devote effort to something:

Primary Endpoint: Reduction in abstaining body tissue glucose (FPG) and HbA1c levels distinguished from accompanying fake pill or subcutaneous insulin.

Secondary Endpoints: Postprandial glucose excursions, occurrence of hypoglycemia, and patient-phased treatment vindication.

Statistical Analysis:

Data are generally meant as mean ± standard deviation (SD).

Differences between treatment and control groups are resolved utilizing free t-tests or ANOVA for continuous variables.

Logistic regression is working to evaluate predictors of glycemic response.

Statistical importance is judged $p < 0.05$.

For example, in Oramed's phase 2b trial, patients taking ORMD-0801 explained a mean HbA1c decline of 0.6% distinguished from 0.2% with a placebo ($p < 0.05$) [14].

Research Methodology

This review understood an organized literature review:

Search Strategy: PubMed, Scopus, and Web of Science databases were checked using keywords: oral insulin, diabetes, nanoparticle drug delivery, insulin capsule, clinical trials, Oramed.

Inclusion Criteria: Peer-inspected items, clinical trial reports, and reviews written between 2000–2024.

Exclusion Criteria: Non-English newspapers, animal-only studies outside translational potential, and duplicate reports.

Data Extraction: Information on delivery technologies, clinical consequences, security, and limitations was culled.

Analysis: Evidence was combined qualitatively, accompanied by emphasis on novelties in expression learning and effects from clinical studies.

Results

The information review and clinical trial reports disclosed the following:

Nanoparticle-based plans considerably revised insulin stability and incorporation in preclinical studies [6,7].

Oramed's ORMD-0801 displayed a statistically significant reduction in the fasting plasma glucose and HbA1c in step 2b clinical trials [14,15].

Safety Profile: The capsule was well tolerated, accompanying no larger hypoglycemic events reported.

Other Trials: Alternative formulations, in the way that pertaining to the gastric-coated insulin microspheres and liposomal warships, wait in early clinical phases [17].

Patient Preference: Surveys display that >70% of insulin-weak subjects would prefer oral insulin over injections if evenly active [18].

Parameter	Oral Insulin Pills	Injectable Insulin
Route of Administration	Oral (capsule/pill, absorbed via gastrointestinal tract)	Subcutaneous injection
Absorption	Low bioavailability (<10%), variable	High, predictable
Physiological Pathway	First-pass through liver (portal circulation)	Direct systemic circulation
Patient Compliance	High (non-invasive, convenient)	Lower (pain, stigma, needle fear)
Dose Requirement	Higher due to degradation in GI tract	Lower (direct delivery)
Risk of Hypoglycemia	Potentially reduced due to hepatic first-pass effect	Present, dose-dependent
Clinical Stage	Phase 2/3 trials (e.g., ORMD-0801, Biocon candidates)	Established, standard therapy
Cost & Accessibility	Likely higher due to advanced formulation	Widely available, relatively lower cost

Table 1: Comparison of Oral Insulin Pills vs. Injectable Insulin

- sources 1Owens DR. *New horizons—alternative routes for insulin therapy.* **Nat Rev Drug Discov.** 2002;1(7):529–540.
- Chaturvedi K, Ganguly K, Kulkarni AR, et al. *Challenges and opportunities in oral insulin delivery.* **Drug Discov Today.** 2011;16(19–20):879–885.
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- Eldor R, Kidron M, Arbit E. *Clinical pharmacology of oral insulin: the journey of ORMD-0801 (Oramed).* **Expert Opin Investig Drugs.** 2020;29(2):169–174.

[Oral Insulin Pill]
↓
[Gastrointestinal Tract]
• Protective coating resists gastric acid
• Nanoparticles/liposomes prevent enzymatic degradation
↓
[Small Intestine Absorption]
• Permeation enhancers improve uptake
• Mucoadhesive polymers increase residence time
↓
[Portal Vein Circulation]
↓
[Liver (First-Pass Metabolism)]
• More physiological insulin regulation
↓
[Systemic Circulation]
• Glucose uptake in peripheral tissues

Source: Adapted from Morishita & Peppas (2006); Zhang et al. (2014).

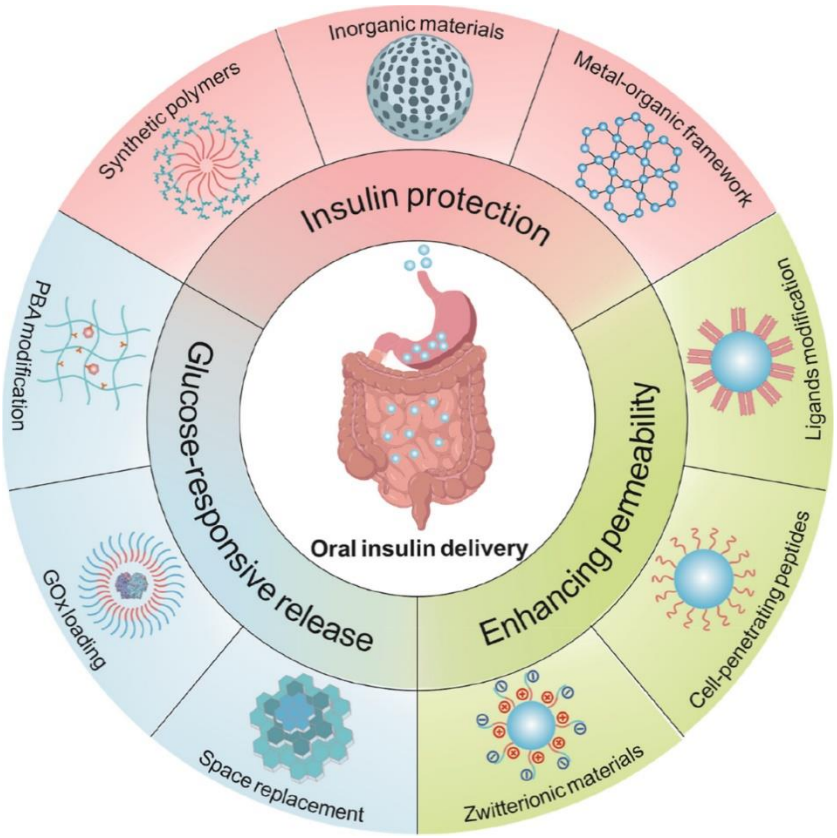
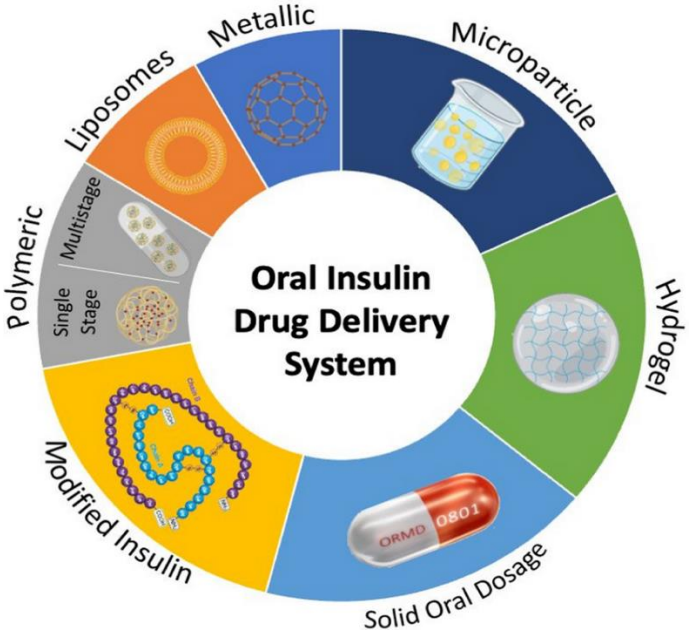


Figure 1: Conceptual Framework of Oral Insulin Pill Delivery

Material design for oral insulin delivery



Source: Critical updates on oral insulin drug delivery systems for type 2 diabetes mellitus | Journal of Nanobiotechnology

Discussion

The evidence suggests that oral insulin is a hopeful novelty, accompanying the potential to transform diabetes administration. Oral childbirth addresses diversified unmet needs, including needle-connected distress, weak adherence, and shortened condition of life [19]. From a pharmacological belief, oral insulin likewise offers benefits by replacing physiologic insulin gradients, enhancing hepatic glucose metabolism, and potentially reducing minor hyperinsulinemia [3,20].

However, various challenges await. First, the bioavailability of oral insulin remains is intensely reduced, frequently <10%, necessitating larger doses distinguished accompanying injections [21]. Second, inter-patient instability in assimilation on account of gastrointestinal differences poses an obstacle to patterned drug. Third, the cost of advanced expression sciences can limit approachability in low-system scenes.

Despite these challenges, the course of research is optimistic. Advances in nanotechnology, biomaterials, and drug expression are fast overcoming classical impediments. The supervisory approval of oral semaglutide has approved the idea of oral peptide remedy, confirming the habit for oral insulin formulations [16]. If long-term productiveness and security are established in ongoing step 3 tests, oral insulin could show an example shift in diabetes care.

Treatment
Current Standard of Care

The cornerstone of diabetes treatment involves lifestyle modification, oral hypoglycemic agents (metformin, sulfonylureas, DPP-4 inhibitors, SGLT2 inhibitors), GLP-1 receptor agonists, and insulin therapy. Patients with type 1 diabetes require lifelong insulin, while patients with type 2 diabetes may eventually require insulin when oral agents fail to maintain glycemic targets. Currently, subcutaneous injection is the only approved route for insulin delivery.

Oral Insulin Pills as an Emerging Therapy

Oral insulin pills are being developed as a potential alternative or adjunct to injectable insulin. The rationale is twofold:

Physiological delivery – oral insulin mimics the natural pathway, delivering insulin first to the liver via the portal vein, which may improve hepatic glucose regulation.
Improved adherence – replacing injections with pills could increase treatment compliance and reduce treatment-related distress.

Clinical Evidence in Treatment Context

Oramed ORMD-0801 has been tested as an adjunct to existing oral antidiabetic drugs and in insulin-naïve type 2 diabetes patients. Results showed modest reductions in fasting plasma glucose and HbA1c but variability in outcomes.

Biocon and Novo Nordisk programs are investigating oral insulin as either first-line therapy for type 2 diabetes or as a combination with injectable insulin to reduce total dose requirements.

Advantages over Injectables

Eliminates injection-related pain and stigma.

Potentially reduces the risk of hypoglycemia by more physiologic insulin distribution.

May improve quality of life and adherence.

Limitations in Treatment Adoption

Low bioavailability requires higher oral doses.

Variable absorption may complicate dose adjustment.

Cost of advanced formulation technologies may limit access.

Future Outlook

If clinical trials confirm consistent efficacy and safety, oral insulin pills may become part of combination therapy strategies—used alongside metformin, SGLT2 inhibitors, or GLP-1 receptor agonists. In type 1 diabetes, oral insulin is less likely to replace injections completely but may be used in hybrid regimens to improve control and reduce total injection burden.

Dosage Considerations for Oral Insulin Pills

Current Injectable Insulin Dosing

Injectable insulin dosing is typically individualized based on body weight, diet, and glucose monitoring. A common starting point is 0.4–1.0 units/kg/day, divided into basal and bolus regimens.

Oral Insulin Pills in Clinical Trials

Because oral formulations face degradation and low absorption in the gastrointestinal tract, the oral dose must be significantly higher than injected insulin to achieve therapeutic blood levels.

Oramed ORMD-0801 (Phase 2 trials): Doses tested ranged from 8 mg to 16 mg, administered once or twice daily before meals.

Biocon's oral insulin candidate: Doses between 10–30 mg daily were tested in type 2 diabetes patients.

Other formulations: Some experimental studies required even higher doses (50–100 mg) to reach glucose-lowering effects, though this raised cost and manufacturing concerns.

Key Observations from Trials

Bioavailability: Less than 10% of the orally administered insulin is absorbed into circulation.

Dosing frequency: Most trials tested once- or twice-daily administration before meals to optimize portal delivery.

Inter-patient variability: Absorption differed significantly between patients, requiring dose adjustments in clinical protocols.

Clinical Implications

Oral insulin pills, once standardized, may be prescribed in fixed-dose capsules (e.g., 8–16 mg), similar to oral hypoglycemic drugs.

Dosing will likely require individual titration based on HbA1c and glucose monitoring, as with injectable insulin.

Combination therapy with oral hypoglycemics may reduce the required insulin pill doses.

Future Directions

Development of controlled-release formulations may stabilize absorption and reduce required doses.

Nanoparticle carriers and enzyme inhibitors may increase bioavailability, lowering the oral insulin dose needed for glycemic control.

Conclusion

Oral insulin delivery represents an individual of ultimate importance novelty in diabetes research, offering the potential to succeed or complement subcutaneous injections. Clinical trials, specifically those led by Oramed Pharmaceuticals, support early evidence that oral insulin capsules are dependable and effective in managing the level of glucose in the blood in type 2 diabetes. While bioavailability, instability, and cost challenges persist, continuous advances in nanotechnology and drug delivery erudition touch refine formulations. Ultimately, profitable translation of oral insulin into clinical practice can raise treatment adherence, reduce disease burden, and improve the quality of life for heaps of patients in general.

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Authors 'Contribution

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Conflict of Interest

The authors declare no conflict-of-interest

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