REVIEW PAPER

Recent advances in nanocarriers and advanced formulation strategies for oral insulin delivery

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ABSTRACT
Diabetes mellitus currently affects an estimated 635 million individuals worldwide. Insulin therapy remains the primary treatment option for patients with type 1 diabetes and those with type 2 diabetes who are unable to achieve adequate glycemic control. However, conventional subcutaneous insulin administration poses challenges to patient compliance and quality of life. In contrast, oral insulin offers a promising alternative by mimicking the physiological pathways of insulin secretion and hepatic metabolism, potentially reducing peripheral hyperinsulinemia and the risk of hypoglycemia. Despite this potential, physiological barriers to oral insulin remain, including enzymatic degradation in the gastrointestinal tract, limited epithelial permeability, and entrapment in the mucus layer. Accordingly, this review aims to synthesize recent advances in oral insulin formulation, with a particular focus on strategies to overcome these barriers, nanotechnology-based delivery systems, and their clinical applications. A comprehensive literature analysis was conducted, emphasizing nanocarrier platforms such as polymeric nanoparticles and metal-organic frameworks. Complementary strategies, such as enteric coatings and absorption enhancers, were also examined for their roles in improving intestinal bioavailability and enabling controlled insulin release. Early-phase preclinical and clinical data suggest that these systems can improve therapeutic outcomes and patient adherence. Various formulation approaches have demonstrated the ability to protect insulin from enzymatic degradation and enhance intestinal transport. Despite promising progress, significant challenges remain in long-term safety, scalable manufacturing, and regulatory approval. Future progress will require interdisciplinary innovations in materials science, biomanufacturing, and data-driven optimization, including artificial intelligence. Overall, nanotechnology-enabled oral insulin delivery represents a next-generation therapeutic strategy with significant potential to transform diabetes management and improve patients' quality of life.

Keywords: *Bioavailability; Diabetes mellitus; Drug delivery systems; Insulin; Nanoparticles*

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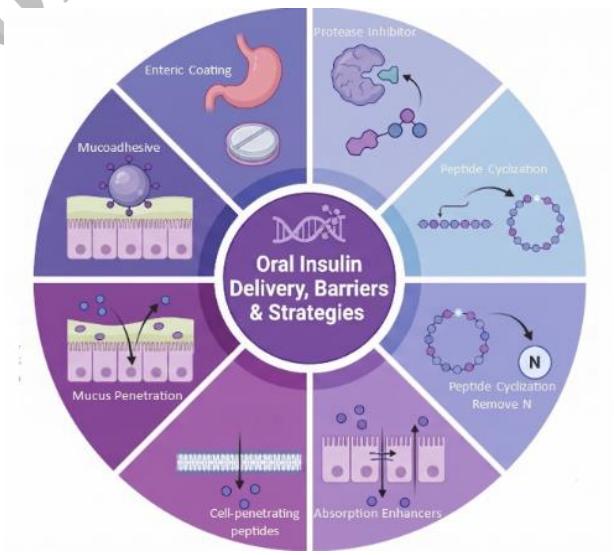
Graphical Abstract



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INTRODUCTION

Diabetes is a long-term metabolic disease that causes high blood sugar levels due to the body does not produce enough insulin, insulin does not function properly, or both [1–3]. Insulin is a hormone produced by beta cells in the pancreas that maintains and facilitates cellular glucose uptake [4–6]. Type 1 diabetes (T1D) arises from the destruction of pancreatic beta cells, leading to insufficient insulin production and hyperglycemia. Type 2 diabetes (T2D), in contrast, occurs when the body becomes insulin-resistant, leading to impaired glycemic control [7,8]. Individuals with T1D require daily insulin therapy, while those with T2D require insulin therapy if other treatments prove ineffective or cause significant side effects [5,9].

It is estimated that 635 million people will have impaired glucose tolerance in 2024, and 488 million will have high fasting blood glucose levels. It is projected that diabetes-related problems will kill more than 3.4 million adults between the ages of 20 and 79 [10]. Insulin is still the main treatment for T1D and severe T2D, even though many other drugs can help with diabetes. Subcutaneous injection is currently the most common method of administering insulin. This method of administering medication can be uncomfortable, compromising patient adherence [11–13].

Oral insulin offers a physiologically advantageous pathway, mimicking endogenous insulin secretion by first passing through the liver via the portal vein [14–16]. This hepatic first-pass effect is critical, as it can reduce peripheral hyperinsulinemia, improve hepatic glucose regulation, enhance cellular insulin sensitivity, and lower the risk of hypoglycemia compared with insulin injection [17–19]. These benefits underscore the potential of oral insulin to provide a more convenient and physiologically appropriate treatment.

The main challenge with oral insulin is that it is a protein degraded by digestive enzymes and stomach acid [20,21]. Furthermore, insulin molecules are large, making them difficult to absorb through the intestinal lining, with less than 2% reaching the bloodstream [11,22]. Researchers have developed formulation strategies to overcome these barriers using polymer- and lipid-based nanoparticles, absorption and permeation enhancers, mucoadhesive systems, and enteric-coated capsules. Each approach targets one or more barriers to oral insulin absorption.

This review summarizes recent advances and remaining challenges in the development of oral insulin formulations, highlighting strategies to achieve enhanced stability, higher bioavailability, and practical clinical applications.

Barriers to Oral Insulin

Recent advances in nanotechnology have presented novel avenues to improve insulin absorption. Encapsulating insulin in nanoparticles protects it from gastric acid and enzymatic degradation. The formulations are designed to prolong residence time in the intestinal lumen, increase epithelial permeability, and facilitate translocation across the intestinal epithelium [23–25].

Gastrointestinal Tract pH and Enzymatic Degradation

The principal limitation of oral insulin delivery stems from its instability in the gastrointestinal tract (GIT). This instability is particularly in the highly acidic gastric environment (pH 1.2–3.0), where insulin undergoes denaturation, aggregation, and structural destabilization driven by acid-catalyzed hydrolysis. Extensive enzymatic degradation further compromises its bioavailability. Proteolytic enzymes such as pepsin in the stomach and trypsin and chymotrypsin in the small intestine rapidly cleave insulin, leading to near-complete degradation within minutes [25–31].

A combination of physicochemical and biological barriers significantly reduces the amount of intact insulin available for absorption after oral administration. To address these challenges, pH modulators to regulate gastric acidity, enzyme inhibitors to limit proteolysis, and permeation-enhancing agents to facilitate intestinal transport have been developed [32,33]. In addition, specialised delivery systems with enteric-coated formulations have been developed to protect insulin from gastric degradation and ensure targeted release within the intestinal lumen, such as Capsulin and ORMD-0801 [28].

Poor Epithelial Permeability

The gastrointestinal tract is lined by a layer of epithelial cells comprising various functional cell types, including enterocytes, goblet cells, and M cells, and is protected by a dynamic mucus layer and glycocalyx, which inhibit the absorption of orally administered insulin. Also, enterocytes make up approximately 90% of the intestinal epithelium and are connected by tight junctions (TJs) that restrict the passage of most molecules larger than 500 Da [20,30,34].

Insulin, a water-soluble peptide with a molecular weight of approximately 5.8 kDa, faces

substantial impediments to crossing this epithelial barrier [12, 26]. Its hydrophilic nature prevents substantial passive diffusion through the lipophilic epithelial cell membrane. Concurrently, its size exceeds the typical threshold for effective paracellular transport through the limited TJs [31, 32, 34–36]. Although transcellular transport mechanisms, such as endocytosis (endocytosis is the process by which cells engulf molecules by wrapping their membranes around them to form internal vesicles) and receptor-mediated transport (Insulin binds to the Insulin Receptor (IR), causing a conformational change that triggers intracellular autophosphorylation) play a role in the absorption of protein drugs, the intrinsic properties of insulin and the protective function of the intestinal barrier limit the natural absorption of insulin [12,26,34–36].

The intestinal lining is a delicate structure with small pores, and insulin molecules tend to clump together and are zwitterionic at normal body pH, reducing their ability to penetrate the epithelial barrier. Therefore, compounds that increase tight junction permeability in the intestinal epithelium are required. Examples include bile salts, trisodium citrate, EDTA, Labrasol, and polymeric substances such as chitosan. Chemical modifications of insulin, such as the synthesis of diacyl insulin derivatives, have been studied to improve its absorption while maintaining biological activity. However, the complex protein structure renders this approach technically challenging to scale up [37]. Cell-penetrating peptides (CPPs) derived from the human immunodeficiency virus have been successfully used to enhance the transcellular transport of oral insulin formulations [20].

First-pass hepatic metabolism

The pharmacokinetics of oral insulin are less predictable than traditional methods of insulin administration via subcutaneous injection, primarily due to at least half of the insulin undergoes hepatic metabolism [38,39]. Most studies show that a combination of metabolic degradation and limited intestinal absorption results in oral bioavailability of less than 2% [26,40–42]. However, given that insulin does not readily enter the bloodstream, the clinical application of oral insulin is challenging.

Mucosal clearance and variability in absorption

Researchers have developed various strategies to improve absorption and overcome the physical and chemical barriers associated with oral insulin delivery. A significant biological challenge arises from the rapid turnover of the mucosal layer, a process maintained by constant mucus secretion and intestinal motility. As a result, insulin remains at the site of absorption for a limited period. Moreover, individual physiological differences, including gastric emptying rate, intestinal acidity, and gut microbiome composition, further complicate predictions of insulin absorption [26].

Insulin Delivery Strategies

Researchers have developed alternatives to subcutaneous insulin injections, including infusion, pen, inhalation, oral, and transdermal delivery methods [43–45]. Among these, continuous subcutaneous insulin infusion is commonly used for type 1 diabetes, particularly in the pediatric population, despite its higher cost and the need for comprehensive patient education [43]. Exubera is the first inhaled human insulin preparation approved for the treatment of type 1 and type 2 diabetes in adults. However, this product was removed from the market because both patients and healthcare providers reported it demonstrated suboptimal efficacy [43,44].

Oral insulin therapy more effectively stabilizes glycemic levels by passing through the liver via the portal vein before entering systemic circulation. This reduces hyperinsulinemia, increases cellular insulin sensitivity, and prevents hypoglycemia. These findings indicate that oral insulin can induce rapid effects and sustain stable blood glucose levels over time [46,47].

Researchers have been investigating oral insulin since its discovery in 1923 to determine whether it could mitigate hypoglycemia and to observe the immune response to its injection [48–51]. Current efforts focus on developing innovative methods to deliver oral insulin that make it more stable and easier to absorb. Nanotechnology prevents insulin from degradation and facilitates its penetration into the mucous membrane. In addition, oral insulin formulations using ionic liquids significantly improve absorption, enabling the development of superior oral insulin preparations [46,52–54].

Nanoparticles

Oral insulin in tablet and capsule form does not effectively permeate the epithelial barrier. To address this difficulty, subsequent studies have concentrated on nanoparticle-based carriers [55,56]. Nanoparticles (NPs) are delivery systems that are between 1 and 100 nm in size and exhibit colloidal properties in water. NPs enhance stability, possess adaptable morphology, and facilitate the controlled release of large macromolecules in a regulated manner [57,58].

Nanoparticles used to deliver insulin orally are often made from natural polymers such as chitosan (CS), alginate, starch, dextran, hyaluronic acid (HA), gelatin, zein, keratin, and transferrin; synthetic polymers such as polylactic acid (PLA), polylactic acid-co-glycolic acid (PLGA), polyalkyl cyanoacrylate (PACA), polycaprolactone (PCL), polyamide ester (PEA), polyvinyl alcohol (PVA), polyamino acids, and pluronics; and a number of synthetic porous polymers are used [23,59–62]. Natural polymers are desirable because they are biocompatible, adhere to mucus, and degrade naturally. On the other hand, synthetic polymer carriers have structures and physicochemical properties that enable precise control. This makes it easier to modify drug release and how the drug behaves in the body. These synthetic porous polymers enable precise control of particle size, surface chemistry, and drug release rate [23].

Chitosan (CS), derived from chitin, forms nanoparticles that prevent insulin from breaking down in the stomach and help it reach the gastrointestinal tract (GIT) [41]. Chitosan and sodium tripolyphosphate (CS/STPP) in a microemulsion delivery system help stabilise insulin and make it more readily usable by the body. Stability testing showed that this formulation retained 53.076% of insulin in a pepsin environment and 62.982% in a trypsin environment after 60 minutes. In vivo investigations showed that CS/STPP accelerated the onset of action and sustained the hypoglycemic effect in diabetic rats. The insulin/chitosan/sodium tripolyphosphate microemulsion (Ins/CS/STPP-ME) crossed the intestinal epithelium and entered the bloodstream via lymphatic transport [63]. CS has significant promise in the biomedical sector because it can degrade, is safe for living organisms, and can bind and release a variety of medicinal substances. Recent studies suggest that chitosan has the potential to revolutionize therapies across fields such as tissue engineering, cancer therapy, drug delivery, and diabetes management [11].

Alginate is a polysaccharide derived from brown algae and can be used to make an oral insulin delivery system. Because it is biocompatible and biodegradable, it offers enhanced biocompatibility by reducing the risk of immune reactions and toxicity. Alginate-based systems release insulin in a controlled way, as the body usually does, and prevent it from being broken down. Recent studies on the structural properties of alginate have enhanced the oral delivery of insulin [11]. Nonionic surfactants Labrasol ALF and Labrafil M 2125 CS were incorporated into alginate nanoparticles at 0.10% (v/v) in various combinations to improve their oral absorption. For each composition, the encapsulation effectiveness was over 80%. The in vitro dissolution and enzymatic stability investigations showed that insulin was released at a higher pH. Simulated intestinal fluid (SIF) had broken down after 120 minutes; therefore, 66% of the insulin remained. These results indicate that this formulation may improve the oral bioavailability of insulin [64]. Researchers have recently been working on alginate-based insulin delivery systems to make alginate hydrogels stronger, make insulin release faster, and make systems that respond to glucose. The goal of these changes is to make insulin delivery more personalized and effective. Alginate is biocompatible and forms a hydrogel, enabling controlled insulin delivery. Although challenges remain in controlling release and stability, current research is making significant progress in addressing these issues. If successful, alginate-based systems could revolutionise diabetes treatment, making it simpler, more effective, and less invasive [11].

Starch is a biopolymer containing amylose and amylopectin. Its low toxicity and biocompatibility make it safe for use in oral insulin preparations. Oral insulin preparations containing added flour form a hydrogel that allows insulin to adhere to the intestinal environment and be released in a controlled manner. The pH-sensitivity of modified carboxymethyl starch (CMS) demonstrated potential for oral insulin delivery, supported by equilibrium swelling studies in simulated gastric and intestinal fluids. Insulin was successfully entrapped, and its release profiles were assessed in both simulated environments [23,65].

Dextran is a branched homopolysaccharide consisting of glucose molecules linked by α-1,6 glycosidic bonds. It is mainly produced by *Lactobacillus* sp. from sucrose using the enzyme β-glucan sucrase. Ordinary amylase enzymes cannot break down dextran; only a specific enzyme, dextranase, can do so, and it is found in the large intestine, liver, spleen, and kidneys. The use of dextran in oral insulin preparations protects insulin from chemical and enzymatic degradation in the digestive tract and enhances absorption by the intestinal epithelium, thereby increasing oral bioavailability. Commonly used dextran derivatives include dextran esters, dextran ethers, and dextran dialdehydes [23].

HA is a biocompatible, biodegradable material, making it suitable for oral insulin delivery. HA is abundant in biological tissues, which facilitates insulin distribution. The use of HA effectively controls insulin delivery; facilitates sustained and

pH-responsive insulin release throughout the gastrointestinal tract; improves insulin retention, absorption, and bioavailability; promotes cellular uptake through interaction with the CD44 receptor expressed on intestinal epithelial cells; enhances protective capacity against enzymatic degradation; improves physicochemical stability, and optimizes mucosal adhesion during gastrointestinal transit. However, HA-based nanoparticles face challenges due to limited understanding of the complexity of CD44 and its off-target effects. HA-based delivery platforms, including HA-coated chitosan nanoparticles, have been shown to improve the efficiency of insulin delivery [11].

Gelatin is a natural biopolymer that can be used as a carrier for oral insulin formulations because it is safe for the body and degrades naturally. Gelatin is a biopolymer that can be used in oral insulin formulations because it is safe for the body and biodegradable. Compared with other materials, gelatin can form nanoparticles or hydrogels that control insulin release and prevent its breakdown [11].

Zein is a natural protein derived from corn that is harmless and can be broken down naturally. That is why zein is a popular choice for both polymer nanoparticles and drugs. Research indicates that zein nanoparticles can facilitate oral insulin delivery, with a bioavailability of 4.2% to 10.2%. In type 1 diabetic mice, these zein nanoparticles demonstrated an insulin-loading efficacy of 74.6% [23].

Keratin is a structural protein found in mammals and birds. Studies show that keratin nanoparticles improve the efficiency of insulin coating and release. Further research is needed to confirm the effectiveness of keratin [23].

Transferrin (Tf) is an important protein that regulates iron absorption and transport. NPs modified with Tf have been reported to improve oral insulin delivery. However, Tf-coated polymeric nanoparticles often exhibit poor insulin release and low therapeutic bioavailability [23].

PLA is a synthetic polymer made of amphiphilic polymers. Its hydrophilic shell and hydrophobic core allow it to hold both hydrophilic and hydrophobic drugs. PLA-F127-PLA vesicles containing insulin markedly decreased blood glucose levels in diabetic mice within 4.5 hours after an oral administration of 50 IU/kg, with the effect lasting for up to 18.5 hours. Additionally, insulin-loaded PLA-P85-PLA vesicles given at 200 IU/kg lowered glucose levels to a minimum after 2.5 hours and kept them low for more than 14 hours [61].

PLGA is a synthetic biodegradable polymer that forms a film. The US Food and Drug Administration (FDA) has approved PLGA for use because it is non-toxic, non-irritating, and non-immunogenic, and allowing drugs to be released over time. PLGA also shows good cellular uptake and maintains drug stability when combined with insulin nanoparticles [45]. PLGA nanoparticles with a slight negative surface charge exhibit weaker bioadhesive abilities than positively charged nanoparticles. Cationic modifications, such as chitosan coating, enhance the bioavailability of insulin-loaded PLGA nanoparticles by reducing initial burst release and improving mucosal adhesion, thereby increasing insulin bioavailability. Additionally, Concanavalin A was used as a targeting ligand for oral insulin formulations, significantly reducing blood glucose levels from about 260.17 to 196.33 mg/dL within 3 hours, with sustained hypoglycemic effects lasting 24 hours, unlike the effect of PLGA nanoparticles without the ligand [61].

PACA is a synthetic polymer utilized as a biocompatible and biodegradable nanoparticle for the oral administration of proteins and peptides. The success of PACA systems relies heavily on the type of microemulsion used in the formulation, as this directly affects how well the drug is trapped and released. When the structure changes, it becomes more difficult to formulate effectively because the nanoparticles lose stability, and it becomes harder to control drug release [59].

Polycaprolactone (PCL) is a biodegradable polyester that can be used to create nanoparticles for delivering insulin orally. For example, aspart-insulin in PCL/Eudragit RS nanoparticles can reduce plasma glucose levels by up to 52% in diabetic rats. The duration of action is 12 to 24 hours, significantly longer than the 6 to 8 hours observed with standard insulin. This enhancement is presumably attributable to improved absorption [61].

L-Lysine/L-Leucine based poly(ester amide) with bound COOH groups was synthesized for the preparation of oral insulin. This copolymer is made by solution polycondensation of three monomers. This allows insulin to be trapped in PEA microspheres via a solid-in-oil-in-oil technique with DMF and maize oil. Insulin release depends on pH, and hydrophobicity can be altered by adding leucine, thereby making the drug more stable and easier to absorb. In trials in diabetic rats, administering these microspheres orally lowered plasma glucose levels by 49.4% within 5 hours and maintained the reduction for 8 hours. Later, Arg-PEA was added to produce blended microspheres, resulting in much better hypoglycemic effects [61].

PVA is a polymer that is biodegradable and biocompatible. It is noted for its safety and stability at high temperatures. It has high mechanical strength and is easy to make, enabling it to be mixed with natural polymers to create new drug delivery systems (DDS) with improved properties. Crosslinked CS–PVA polymers have been used to develop nano-insulin-loaded hydrogels for noninvasive transdermal delivery, which exhibit robust thermal and physical properties. Additionally, the preparation of PVA nanoparticles (NPs) through solid o/w emulsion optimized for surfactants demonstrated good properties for insulin stabilization and protection, retaining insulin bioactivity and producing hypoglycemic effects in animal studies. PVA also serves as a stabilizing surfactant in the creation of NPs for oral insulin delivery [62]. Amino acids play a key role in shaping biological systems, and synthetic amino acid side-chain polymers are now being used in biomedical fields due to their ease of production. In recent studies, researchers created different types of nanoparticles to improve oral insulin delivery. For example, CS/poly-g-glutamic acid nanoparticles, made by heating PGA acid with CS, lowered blood glucose for up to 10 hours and achieved 15.1% insulin bioavailability. TMC/gPGA nanoparticles have shown potential to help insulin move across the intestinal lining. Another approach used a gelatin enteric coating on CS-poly(g-glutamic acid) nanoparticles to prevent insulin from being degraded and to allow it to reach the small intestine. This caused blood sugar levels to drop slowly. In China, researchers developed multifunctional CS-based nanoparticles that were safe and effective for oral insulin delivery. In animal trials, they showed great effects in decreasing blood glucose levels [62].

Pluronics, or poloxamers, are amphiphilic triblock polymers made up of blocks of polypropylene oxide on either side of blocks of polyethylene oxide. These granules break down naturally and change with temperature. They can gel and are grouped by their physical condition and molecular weight. The use of Pluronics has been shown to improve insulin absorption and maintain stable blood glucose levels. Pluronics' ability to gel under normal conditions allows for the formation of injectable gels for controlled drug release. This suggests that Pluronics could be used as a nanocarrier to improve insulin delivery [62].

Synthetic porous polymers (SPPs) are flexible materials that can be tailored to meet each patient's needs. Silica, porous coordination polymers (PCPs), metal-organic frameworks (MOFs), and porous organic polymers (POPs) are the four main forms of SPPs. One interesting use of POPs is to make anionic silica nanoparticles, which are intended to help the body absorb insulin more effectively in the gut. These nanoparticles have negatively charged surfaces, which make it harder for molecules to interact with one another. This increases intestinal permeability, allowing insulin to enter the body more quickly. Formulations containing the ionic liquids choline and geranylate have shown improved oral insulin delivery, resulting in a 45% drop in blood glucose levels and improved insulin absorption [23]. Figure 1 presents a review of the nanoparticles typically utilized in oral insulin formulations.

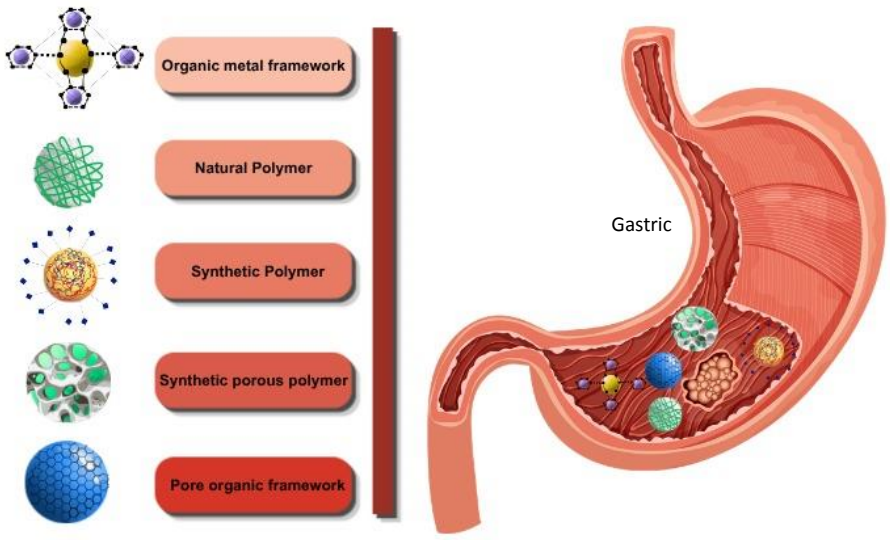

Fig. 1. Overview of nanoparticle-based systems for oral insulin

Organic metal polymers, particularly coordination polymer carriers (PCPs), are promising nanomaterials because they degrade in the environment, thereby reducing their environmental impact. In nanomedicine, polymer carriers (PCPs) have been used for photodynamic therapy and oral insulin delivery. There are now around 20,000 metal-organic frameworks (MOFs). Different methods are used to make these frameworks, which have different structures, including IRMOFs, ZIFs, CPLs, MILs, and UiOs [23].

Metal-organic frameworks (MOFs) may be useful as nanoparticles for oral insulin delivery, as they are highly porous, biocompatible, water-soluble, and readily degradable. MOFs can transport pharmaceuticals in ways that differ from those of other materials, either chemically or physically. MOF nanoparticles can shield proteins from the extreme environments of the stomach and intestines, hence enhancing their use in oral macromolecule delivery systems. Multiple investigations have demonstrated reductions in glucose levels and in the duration required to attain peak plasma insulin concentration. Also, glucose-responsive MOF microfluidics may hold up to 77% and 88% of insulin per unit weight. MOFs linked to transferrin had an oral hypoglycemic impact and an oral bioavailability of 29.6% [23].

Pore-organic frameworks (POFs) are microporous and mesoporous materials with high specific surface areas and well-defined pore structures, making them suitable for oral insulin formulations. Sodium N-[8-(2-hydroxybenzoyl)aminocaprylate (SNAC) can enhance absorption, facilitating insulin transport across biological membranes. POFs comprise various classes of materials, including hypercrosslinked polymers (HCPs), polymers with intrinsic microporosity (PIMs), conjugated microporous polymers (CMPs), porous aromatic frameworks (PAFs), and covalent organic frameworks (COFs). Covalent organic frameworks (COFs) are crystalline, have adjustable pore dimensions, exhibit inherent regularity, and offer unlimited configurations, making them ideal carriers for controlled insulin loading and release [23].

Covalent organic frameworks (COFs), such as imines, imides, hydrazones, and triazines, have potential as oral insulin delivery systems. In 2016, two nanoscale porous COFs loaded with anticancer drugs demonstrated high dispersion and effective drug release in laboratory tests. In 2018, a polymer-COF nanocomposite facilitated doxorubicin delivery and inhibited tumour growth. In 2021, a safe imine COF (TTA-DFP-nCOF) was developed for oral insulin delivery and demonstrated improved insulin loading, favourable biocompatibility, and enhanced bioavailability [23].

Nanotechnology-based drug delivery methods, including chitosan-polylactic-co-glycolic acid (PLGA) polymer nanoparticles, protect insulin from enzymatic degradation, promote better adherence to mucosal surfaces, and facilitate intercellular insulin movement [36,66,67]. Cells typically take up these nanocarriers via endocytosis, which is influenced by particle size, surface charge, and the balance between hydrophobic and hydrophilic properties. In general, these nanocarriers improve drug efficacy, reduce side effects, and make it easier for patients to adhere to their insulin therapy [56,68]. Figure 1 shows a list of nanoparticle materials that can be used to make oral insulin. A comparative analysis of nanoparticle-based oral insulin delivery systems is presented in Table 1.

Absorption Enhancer and Mucoadhesive

Absorption enhancers increase intestinal permeability, thereby facilitating the absorption of oral peptides. Common absorption enhancers include fatty acids, salts, bioadhesive polymers, and surfactants [36,69].

Fatty acids produced from triglyceride digestion increase intestinal permeability. Fatty acids produced from triglyceride digestion increase intestinal permeability. Capric acid was one of the first fatty acids used to enhance absorption, and the FDA has approved its use in oral insulin. A concentration of 1.5-2% is safe and can increase insulin bioavailability. The mechanism of action of fatty acids is the activation of phospholipase C and the release of calcium with calmodulin-dependent actin filament contraction. These changes cause damage to the plasma membrane, facilitating insulin penetration [69].

SNAC, or Sodium N-[8-(2-hydroxybenzoyl) amino]-caprylate, is an additive that enhances the oral absorption of large molecules. SNAC was used in Semaglutide tablets to help control blood sugar in 2019. SNAC forms noncovalent complexes with peptides, increasing their fat solubility and helping them penetrate cell membranes, and forms stable complexes with insulin [69].

Mucosal adhesive (MA) formulations are designed to enhance adhesion and binding to the mucosal layer throughout the gastrointestinal tract, thereby improving insulin absorption. MA formulations exhibit positive charges that interact electrostatically with the negative charges of mucin glycoproteins. Factors affecting mucosal adhesion include particle size, surface charge distribution, and surface modification. PLA, PLGA, poly(sebacic acid) (PSA), and poly(acrylic acid) (PAA) facilitate interpenetration of polymer chains. This interpenetration improves stability. This review examines several methods for making MA formulations [70].

Table 1. Comparison of nanoparticle-based systems for oral insulin

Nanoparticle Material	Modification/Formulation	Stability (Acidic pH)	Rationale for Modification	Insulin Bioavailability	Blood Glucose Reduction	Ref.
Chitosan/Sodium Tripolyphosphate (CS/STPP)	Nanoparticle	53.08% insulin retained in pepsin (60 min)	Protection from enzymatic degradation; enhanced mucoadhesion via positive charge	Not explicitly reported	Accelerated onset; sustained hypoglycemic effect	[63]
Alginate + Labrasol ALF/Labrafil M 2125 CS	Nonionic surfactant incorporation	Excellent (enteric protection)	Improved absorption; controlled release	>80% encapsulation efficiency	N/A	[64]
Carboxymethyl Starch (CMS)	pH-sensitive hydrogels	Good (equilibrium swelling studies)	pH-responsive release; mucoadhesion	Not explicitly reported	N/A	[23,65]
Zein nanoparticles	Unmodified zein NPs	Moderate	Biocompatible protein carrier; hydrophobic core for insulin loading	4.2–10.2% bioavailability		[23]
PLA-F127-PLA vesicles	Amphiphilic block copolymer	Good (controlled release)	Hydrophilic shell/hydrophobic core for dual drug loading	Not explicitly reported	Decreased blood glucose within 4.5 h (50 IU/kg); effect lasted 18.5 h	[61]
PLGA nanoparticles (chitosan-coated)	Cationic modification with chitosan	Excellent	Reduced burst release; enhanced mucosal adhesion; improved bioavailability	Not explicitly reported	Improved glucose control	[61]
PCL/Eudragit RS	Polymer blend	Good (enteric coating)	Prolonged insulin release; enhanced absorption	Not explicitly reported	52% reduction in plasma glucose; 12–24 h duration	[61]
Poly(ester amide) (PEA-COOH)	L-Lysine/L-Leucine-based; Arg-PEA blend	pH-dependent release	Tunable hydrophobicity; improved stability and absorption	Not explicitly reported	49.4% reduction within 5 h; 8 h duration	[61]
Zwitterionic micelles (PCB/DSPE)	Zwitterionic surface coating	Good	Mucus penetration without tight junction opening	42.6% oral bioavailability; 43.4% pharmacological activity	Superior to polysorbate 80 (8.4% bioavailability)	[69,70]
Transferrin-MOF nanoparticles	MOFs with transferrin ligand	Good (MOF structure)	Receptor-mediated transcytosis via transferrin receptors	29.6% oral bioavailability	Hypoglycemic effect confirmed	[23,71]
Thiolated Eudragit nanoparticles	Thiomer modification	Good	Disulfide bond formation with mucin; prolonged mucosal retention	7.33% vs. 2.65% (unmodified Eudragit)	28% reduction over 12 h	[69]

Chitosan (CS) forms nanoparticles that enhance peptide absorption upon oral administration. Due to its intrinsic charge, CS exhibits increased adhesion to mucus and facilitates its interaction with proteins in cell membranes. Studies have shown that chitosan nanoparticles facilitate cell motility. These actions make it easier for orally administered peptides to be absorbed. Using these sticky properties, a mucoadhesive platform has been made. It increases the time insulin remains in the intestinal lining and enhances its absorption [69,70]. Several preclinical studies have shown promising results, but further work is needed to improve the bioavailability and controlled-release profiles of oral insulin formulations using chitosan-based carriers [19].

Thiolated polymers, also known as thiomers, are mucoadhesive polymers with thiol-bearing side chains. Through thiol/disulfide exchange reactions and/or simple oxidation processes, disulfide bonds are formed between these polymers and the cysteine-rich subdomains of mucus glycoproteins that form the mucus gel layer. In contrast, lectin-bound carriers interact with carbohydrate moieties on epithelial cells to promote transcytosis. Thiol polymers also impede mucociliary clearance. This, in turn, increases insulin bioavailability. Nevertheless, the long-term immunogenicity of

Table 2. Comparison of absorption enhancers for oral insulin

Absorption Enhancer	Class	Mechanism of Action	Reported Bioavailability Enhancement	Clinical Status	Ref.
Sodium caprate (C10)	Medium-chain fatty acid	Increased permeation by opening epithelial tight junctions and increasing membrane fluidity in the intestine	Significant improvement	Approved for exipient; clinical trials ongoing	[78]
Sodium N-(4-chlorosalicyloyl)-4-aminobutyrate (4-CNAB)	Salicylate derivative	facilitate insulin absorption through the transcellular pathway	Promising preclinical enhancement	Eligen® technology; phase II/III	[26]
Chitosan	Polymeric bioadhesive	Electrostatic interaction between the positive charge of chitosan and the negative charge on the cell surface, which causes the opening of tight junctions between cells	~10%	Preclinical to early clinical	[72]
Thiolated polymers (thiomers)	Polymeric mucoadhesive	Opening tight junctions (connections between cells) in the epithelium	Up to 7.33% bioavailability	Preclinical	[69]
Labrasol (caprylocaproyl macrogol-8 glyceride)	Surfactant	opening tight junctions between epithelial cells	>80% encapsulation efficiency in alginate systems	Preclinical	[64]

lectins remains a significant concern. It requires further investigation [71–73]. Oral administration of insulin-loaded thiolated Eudragit nanoparticles in diabetic rats achieved a 7.33% insulin bioavailability, surpassing that of Eudragit nanoparticles at 2.65%. This method also resulted in a 28% decrease in blood glucose levels over 12 hours [74]. A comparative analysis of absorption enhancers for oral insulin delivery is presented in Table 2.

Permeation enhancers

A primary challenge with oral insulin formulations is the inherent difficulty of insulin in penetrating mucus and the intestinal epithelium. The viscosity, negative charge, and hydrophobic properties of the mucus layer limit the entry of cationic and hydrophobic agents. Particle size also affects the ability to penetrate mucus. New studies aim to improve insulin absorption by using zwitterionic compounds, cell-penetrating peptides, and intestinal receptor ligands [75].

Penetrating compounds are intended to penetrate mucosal surfaces, and permeability enhancers can increase intestinal absorption by modulating the epithelial barrier. The most widely studied permeability enhancers include surfactants and bile salts, which disrupt tight junctions or alter membrane flexibility. Although effective in preclinical trials, their clinical usefulness is limited by side effects leading to intestinal irritation and cellular toxicity [76–78].

A new method using zwitterionic materials such as 1,2-Distearoyl-sn-glycero-3-phosphoethanolamine (DSPE) and zwitterionic polycarboxybetaine (PCB). The use of these materials facilitates the efficient penetration of insulin across the mucosal barrier. The use of PCB has been shown to provide insulin bioavailability of 27.0%. Changes in the surface charge of nanoparticles are employed to enhance oral insulin delivery [74,75]. In vivo testing in diabetic rats showed that orally delivered insulin via zwitterionic micelles achieved a bioavailability of 42.6% and pharmacological activity of 43.4%. In contrast, polysorbate 80 insulin capsules demonstrated significantly lower bioavailability (8.4%) and pharmacological activity (8.6%) [74,79].

Cell-penetrating peptides (CPPs), or protein transduction domains (PTDs), are short sequences of 4–30 amino acids that can traverse cell membranes with minimal toxicity. They facilitate the intracellular delivery of bioactive substances, including nucleic acids and small drugs, through various mechanisms. Modification of the formulation with cell-penetrating peptides (CPPs) significantly enhances insulin internalization and transport across the intestinal epithelium. Arginine, a critical residue in CPPs, has also been modified to increase permeability. Core-shell structured nanoparticles have been developed to enhance mucus penetration and cellular internalization. When coated with a layer of the hydrophilic copolymer N-(2-hydroxypropyl) methacrylamide, these nanoparticles exhibit 20 times higher absorption than free insulin. Advancements in CPP technology have been shown to enhance insulin absorption and delivery [80].

A common strategy in antibody engineering is to modify the Fc region, which facilitates enhanced binding of immunoglobulin G (IgG) across different pH environments and enhances its circulation

within the body. Modifications to material properties can enhance absorption. Albumin and transferrin can also function as ligands, binding to FcRs and aiding transport through the epithelium. Other ligands, such as folate, biotin, vitamin B12, and peptides, are used to functionalize materials and increase permeability through passive mechanisms by binding to specific transporters. In the presence of a carrier, insulin is facilitated into intestinal epithelial cells [74].

Hydrophilic-coated carriers are not only smaller in size but also have less contact with the mucosa. The presence of carriers allows insulin to penetrate more easily and then be transported across the epithelium. Among these materials, the hydrophilic properties, neutrality, and strong affinity for epithelial cells in PCBs position them as optimal candidates for enhancing insulin absorption [75].

The adverse effects of permeation enhancers that modulate tight junctions via paracellular transport include disruption of barrier integrity and a transient increase in the risk of autoimmune disorders. Conversely, cell-penetrating peptides with nonspecific mechanisms may facilitate the uptake of coexisting compounds. Consequently, safety evaluations of permeation enhancers must consider not only acute effects but also the consequences of chronic administration, as diabetes management requires lifelong therapy [81].

Permeation enhancers (PEs) such as sodium deoxycholate (SDC) and sodium caprate (C10) modulate the intestinal epithelial barrier and facilitate macromolecular absorption. SDC and C10 induce increased claudin-2 expression in the intestinal epithelium. Increased claudin-2 expression is associated with impaired epithelial barrier integrity and inflammatory processes in the gastrointestinal tract. In conditions such as inflammatory bowel disease, increased claudin-2 levels contribute to increased paracellular permeability, which can exacerbate inflammation and facilitate luminal antigen translocation. Therefore, the PE-induced increase in claudin-2 can, in principle, be interpreted as an indicator of epithelial damage or an inflammatory response. Although SDC and C10 can transiently increase claudin-2 levels, studies of long-term administration of these agents show that changes in tight junction protein gene expression often return to normal after drug withdrawal. Furthermore, this suggests that SDC and C10-induced epithelial disruption is transient and reversible. This reversibility is an important factor in assessing the overall safety profile of SDC and C10 in oral drug administration, distinguishing transient functional changes from ongoing pathological damage [82].

Table 3. Barriers and strategies to overcome them for oral insulin

Barriers	Strategies	Examples of agent	Ref.
Biochemical pH	Enteric coating	CODES, Capsulin, and ORMD-0801	[28]
Enzymes	Protease inhibitors	Soyabean trypsin inhibitor, camostat mesylate, duck and chicken ovomucoid, aprotinin, bacitracin, na-glycocholate, N-acetylcysteine, sodium cholate, and chelating agent	[20,26,28]
Physiological Mucus	Mucoadhesive systems	Chitosan, alginate, polyacrylic acid	[28]
	Mucus penetration systems	Virus-mimetic zwitterionic surface, hydrophilic polymers like PEG chains, pHPMA derivatives, and self-nanoemulsifying drug delivery systems	[20,28,84]
Cellular	Permeable enhancers Cell-penetrating peptides (CPPs)	Sodium caprate (C10), labrasol, salcaprozate sodium, acyl carnitine, penetratin, oligoarginine, transportan, and TAT	[28,84]
	Absorption enhancers	EDTA, surfactants, fatty acids, ZOT, bile salts, surfactants, polyethylene glycol, trisodium citrate, labrasol, polymeric compounds, silica nanoparticles and FITC–DX4	[9,28,29,32]
Physicochemical of insulin	Peptide cyclization removes N and C termini from peptides	Peptide cyclization using a disulfide bridge, the two cysteine residues form a disulfide bridge between their side chains, forming a cyclic peptide	[33]

Oral capsules with enteric coating

Enteric-coated oral capsules aim to prevent the release of active compounds in the digestive tract and dissolve in the small intestine. There are three main approaches in targeting oral drugs in the colon, namely: (1) utilizing the microflora in the colon environment and/or enzymes, with this anaerobic nature, which is a characteristic of the microflora, requiring enzymatic degradation of biodegradable polymers such as polysaccharides; (2) pH-dependent with a target pH of 5-8 using pH-sensitive polymers; and (3) time-dependent preparations (3-4 hours) that delay drug release [83]. The insulin release profile is further modulated by gastrointestinal transit time, luminal pH, and fluid composition, all of which influence nanoparticle stability and insulin release. Researchers have enhanced the pharmacokinetic characteristics of oral insulin by using enteric-coated nanoparticles, suggesting that oral insulin could be a viable option [84]. Table 3 presents the main problems with delivering insulin orally and the plans to address them.

Preclinical and clinical advances

Preclinical studies

Preclinical research indicates the feasibility of oral insulin. In diabetic mouse models and non-human primates (NHPs), it has been consistently shown that the bioavailability of orally administered insulin is significantly improved when combined with nanoparticle carriers, mucoadhesive polymers, and permeability enhancers. For example, sustained glucose-lowering effects were achieved with chitosan-coated nanoparticles in streptozotocin-induced diabetic mice, and marked increases in intestinal absorption and improved glycemic control were observed in a canine model using lipid-based nanocarriers. While there is variability in pharmacokinetics across platforms, these findings support enhanced oral insulin absorption by reducing enzymatic degradation and increasing systemic exposure [85–87].

Clinical candidates

This section details studies on various oral insulin formulations. Biocon's clinical trials involve IN-105, a modified insulin analog with improved solubility and stability. In contrast, the Emisphere formulation uses monosodium N-aminobutyrate to enhance absorption [26,28,33]. In a study of 20 patients with type 2 diabetes, IN-105 reduced blood glucose levels across all tested doses. Higher doses resulted in six cases of hypoglycemia in five individuals, and increased triglyceride levels were a side effect. Preliminary studies have examined the effect of IN-105 on the absorption of metformin and sodium caprate, showing increased absorption of both. Additionally, IN-105 can be combined with metformin to maintain elevated postprandial insulin levels [26].

RMD-0801, developed by Oramed Pharmaceuticals, is a nanoparticle capsule encapsulating insulin. ORMD-0801 failed to meet its primary efficacy endpoint in a 26-week Phase 3 clinical trial, despite positive results from Phase 1 and Phase 2 trials. The Phase III trial of ORMD-0801 failed to meet its primary efficacy endpoint, although the study results have not been published. In this double-blind study, participants were randomly assigned to three groups, each receiving ORMD-0801 8 mg once daily, twice daily, or a placebo for 26 weeks. Participants were expected to undergo a 26-week extension period, but the study was stopped based on the primary results at week 26. The primary efficacy endpoint was the mean change in A1C from baseline at week 26, while the secondary endpoint was the mean change in fasting glucose levels. ORMD-0801 8 was no better than the placebo at improving glycemic control. Consequently, the failure of the Phase 3 clinical trial hampered the development and commercialization of oral insulin therapy [14,26]. Currently, ORMD-0801 is the most advanced oral insulin in clinical development and successfully reduced fasting plasma glucose and HbA1c levels (i.e., glycemic control) by a moderate but statistically significant amount in individuals with type 2 diabetes (T2D) [26,88–90].

In a Phase I clinical study, NN1952 was shown to be safe in healthy volunteers with type 2 diabetes (T2D). Four treatments were administered: NN1952 at a non-hypoglycemic dose, insulin aspart with glucose clamp, NN1952 15 minutes before meals, and oral placebo 15 minutes before meals. The 14,400 nmol dose resulted in greater insulin exposure, with Cmax at 1.5 hours. Its bioefficacy was 0.7%. Meanwhile, no significant differences in postprandial blood glucose levels were observed between treatment groups in the prandial study [26].

I-338, a new oral basal insulin, has been tested in Phase I and Phase II clinical trials. The Phase I trial, sponsored by Novo Nordisk A/S, measured adverse events, and the Phase II trial examined the effect of I-338 on fasting plasma glucose concentration compared to SC insulin glargine. The study found no significant difference in mean glucose concentrations, except for a significant reduction in HbA1c [26].

A study examined the PK/PD profile of Capsulin using an isoglycemic glucose clamp technique. Participants were divided into two groups: one received 150 U Capsulin twice daily, followed by 12 U SC Actrapid, and the other received Actrapid at the same dose twice daily. To explore the in vivo pharmacodynamics of Capsulin, researchers varied the glucose infusion rate (GIR) and dextrose infusion rate. Actrapid showed increases in the maximum concentration (Cmax) and the area under the GIR curve (AUC), which correlate with Capsulin's cellular activity [26].

Nobex Corporation evaluated the effectiveness of HIM-2 for postprandial glycemia in patients with T2D. Three dose levels were tested, and analysis revealed no statistically significant differences in glucose levels between groups [26].

Rani Therapeutics developed RaniPill™, a biocompatible, enteric-coated capsule that enables the insertion of sucrose-based microneedles into the small intestine for direct mucosal drug delivery. This results in approximately 70% bioavailability of octreotide. MIT and Novo Nordisk have developed a microneedle-based capsule device for GI insulin delivery with up to 80% bioavailability [91].

HDV is composed of natural phospholipids and vitamins, which are generally recognized as safe. HDV-I is a nanoparticle with very low toxicity, specifically targets hepatocytes, and is effective in animal models of diabetes. The results showed that HDV injected peripherally into hyperglycemic diabetic dogs efficiently delivered insulin to the liver and increased hepatic glucose uptake with a potency 100 times greater than that of the same dose of recombinant insulin [92].

NOD Pharmaceuticals developed Nodlin™, an oral insulin consisting of insulin nanoparticles in a bioadhesive enteric capsule. Results of a Phase I study in 12 healthy volunteers reported a glucose reduction similar to that of subcutaneous Hagedorn neutral protamine insulin, with a bioavailability of 37%, although with substantial variability (standard deviation [SD] of 90%) [20].

HIM-2 (hexyl-insulin monoconjugate 2) is an experimental oral insulin formulation studied in phase I/II clinical trials for the treatment of type 1 and type 2 diabetes. HIM-2, a treatment studied in a three-way, randomised, single-blind, placebo-controlled crossover dose-escalation study by Nobex Corporation, aimed to assess its efficacy and safety in managing postprandial glucose levels in patients with T2DM. Subjects were divided into 0.375, 0.5, and 1.0 mg/kg dose groups and received HIM-2, insulin, or placebo for three days. Results showed no significant differences in glucose parameters between the 0.375 mg/kg HIM-2 and placebo groups. However, HIM-2 at 0.5 and 1.0 mg/kg demonstrated better control of plasma glucose than placebo. No serious adverse events occurred, and common side effects included headache and anemia [26,93].

The biotech company Oshadi Drug Administration Ltd. advanced its Oshadi-Icp formulation into Phase II clinical trials (NCT01973920) for patients with Type 1 Diabetes (T1D). The formulation comprises enteric capsules containing insulin, proinsulin, and C-peptide, each associated with a silica nanoparticle core. Initial results indicate an effective reduction in plasma glucose levels and a good safety profile after multiple oral doses. Nevertheless, development has stalled pending evaluation of the clearance of silica nanoparticles from the body to prevent long-term accumulation. Additionally, the low bioavailability of oral insulin formulations necessitates high dosing, impacting the commercial viability of the treatment [74]. A summary of several oral insulin preparations currently under development is shown in Table 4.

Semaglutide for Peptide Oral Delivery

The FDA authorized Novo Nordisk's oral semaglutide (Rybelsus®) as the first oral peptide treatment. It also contains sodium N-[8-(2-hydroxybenzoyl) amino]caprylate (SNAC), a permeability enhancer that facilitates the drug's absorption in the stomach and its attainment of therapeutic plasma levels. The positive outcomes from clinical trials and worldwide approval of oral semaglutide demonstrate the feasibility of oral administration for peptide medications. This supports the further development of oral insulin [94,95].

In general, the pharmacokinetics of oral vs. subcutaneous semaglutide are as follows: oral semaglutide is absorbed considerably more rapidly (Tmax ~1–1.75 hours) than subcutaneous injection (Tmax ~24–77 hours); oral bioavailability is very low (~0.8%), resulting in greater variability. However, once-daily dosing and a long half-life help maintain stable drug levels. Despite its low bioavailability, oral semaglutide improves blood glucose control and promotes weight loss, but it requires higher doses than injections. Renal and hepatic impairment, as well as gastrointestinal disease, do not significantly affect drug exposure. Body weight affects pharmacokinetics but does not require dose adjustment; unlike most oral medications, semaglutide is absorbed in the stomach, aided by SNAC, which increases permeability. Food reduces absorption; consequently, it is recommended to administer on an empty stomach. Semaglutide has

Table 4. Various oral insulin currently under development

Name	Form	Company	Ref
IN-105 (Tregopil)	Modified insulin, a recombinant human insulin with a short-chain amphiphilic oligomer, enhances oral hydrophobicity, protein stability, and enzymatic degradation resistance by reacting with methoxy tri-ethylene glycol	Biocon	[26,28]
ORMD-0801	The capsule utilized bile salts as a permeation enhancer and aprotinin as a protease inhibitor	Oramed Pharmaceutics	[28,34]
NN1952	The formulation uses an oily suspension with a transient permeation enhancer to encapsulate insulin, facilitating its delivery through the gastrointestinal tract and lowering blood glucose levels.	Novo Nordisk	[26,34]
I-338	Oral insulin 338 (I338) is a long-acting, basal insulin analogue formulated in a tablet with sodium caprate for enhanced absorption	Novo Nordisk	[26]
Eligen®	Eligen® insulin formulations use monosodium N-(4-chlorosalicyloyl)-4-aminobutyrate (4-CNAB) as a permeation enhancer, along with sodium N-[8-(2-hydroxybenzoyl)amino] caprylate (SNAC) and other similar agents, to protect against degradation and facilitate hormone absorption through the intestinal wall.	Emisphere Technologies, Inc	[26]
Capsulin	The capsule is an enteric-coated form that contains a blend of solubilizer and permeation enhancer, specifically aromatic alcohols	Diabetology	[34]
RaniPill™	RaniPill™, a biocompatible, enteric-coated capsule designed to insert sucrose-based microneedles into the small intestine, facilitating direct mucosal drug delivery.	Rani Therapeutics	[91]
HDV-1	HDV-1, a formulation of liposomes with a diameter of less than 150 nm, is designed to selectively target the liver	Diasome	[20,34,69]
Nodlin	The bioadhesive enteric-coated capsule contains insulin nanoparticles to enhance retention and absorption in the GIT	NOD technology	[28]
HIM-2	An insulin-oligomer conjugate formed by the covalent attachment of a low- molecular-weight amphiphilic polymer to the lysine moiety at position 29 of the β chain.	Nobex Corporation	[26]
Oshadi-Icp	Silica Nanoparticles: Enteric capsules containing insulin, proinsulin, and C-peptide non-covalently associated with a silica nanoparticle core and embedded in an oil phase	Oshadi Drug Administration Ltd. Rehovot, Israel	[69]

minimal clinically relevant drug interactions, although it may slightly alter the absorption of some drugs due to delayed gastric emptying [96].

The pooled analysis revealed that subcutaneous semaglutide achieved significantly greater reductions in HbA1c than oral semaglutide. For weight reduction, subcutaneous semaglutide was more effective, though the difference was not statistically significant. Patients receiving oral semaglutide had a significantly higher risk of discontinuing treatment due to adverse events. Both formulations demonstrated clinical benefit, but subcutaneous semaglutide provided superior glycemic control with fewer adverse events [97].

Challenges and Future Perspectives

Research on oral insulin is progressing rapidly, but many obstacles remain before clinical implementation. Early research suggests that individuals respond differently to oral insulin, making it difficult to ensure the effectiveness of a universal treatmenty [11,98]. Gastrointestinal pH, enzyme levels, and gut bacterial composition collectively influence insulin absorption kinetics, thus impairing glycemic control [99]. Continued research and innovation are essential to provide more effective and convenient treatment options for patients with diabetes.

Large-scale production and storage of oral insulin are also challenging, as variations in temperature, pH, and storage duration can compromise insulin stability. New approaches, such as the use of nanoparticles and encapsulation, add complexity to the manufacturing process and increase production costs [32,85]. Further research should simplify production techniques to improve scalability and consistency. Cost-effective nanoparticle-based technologies should be

optimized to reduce production costs. In addition, process optimization should focus on reducing material usage, processing time, and production steps to maintain therapeutic efficacy and ensure the commercial viability of nanoparticle-based delivery systems [30].

Although oral insulin delivery systems have advanced, scaling up production for clinical use remains a challenge, limiting their real-world impact. To address this, researchers are turning to biomanufacturing technologies that can make production more efficient and cost-effective. For example, microfluidic devices allow for precise synthesis of nanoparticles and hydrogels, supporting large-scale, high-quality manufacturing. Automation in encapsulation processes also improves consistency and facilitates adherence to clinical standards. Using green chemistry principles in manufacturing can further reduce environmental impact and costs, thereby enhancing the sustainability and practical applicability of these systems. While challenges to scaling production and long-term safety remain, ongoing research suggests that these barriers can be overcome, thereby enabling more efficient and accessible diabetes care. Continued innovation in materials science and biomanufacturing could transform diabetes management, improving treatment effectiveness and quality of life [11]. To be successful, oral insulin must be high-quality and affordable, but high production costs continue to restrict its availability, especially in low- and middle-income countries [66,100].

The Role of Artificial Intelligence (AI) in contributing to the enhancement of oral insulin development by accelerating and optimizing research precision. AI's role includes: AI can facilitate the design of optimized insulin molecules and nanoparticles by predicting stability, absorption, and biological activity, minimizing empirical experimentation; AI with machine learning assists in identifying optimal combination of ingredients and processing conditions, improving efficiency and scalability; AI-based models can simulate the in vivo pharmacokinetics and pharmacodynamics of oral insulin, contributing to the optimization of dosing and reducing experimental work; AI can personalize insulin doses using patient data (e.g., glucose levels), but this is more complex for oral insulin due to slower and more variable absorption; AI can optimize clinical trial design and execution, and identify optimal responders; however, challenges remain, including data quality, model transparency, and regulatory approval [81].

CONCLUSION

Oral insulin administration is an alternative to conventional injectable insulin, offering physiological advantages such as reduced peripheral hyperinsulinemia, and potentially improved patient compliance. Major barriers to oral insulin are enzymatic degradation, poor epithelial permeability, mucus entrapment, and high variability in absorption.

Recent advances in nanotechnology demonstrate enhanced insulin stability and facilitate its transport across biological barriers. However, no single platform has yet emerged as universally optimal. Polymeric systems such as chitosan and PLGA offer robust mucoadhesion and safety profiles,while more advanced materials, such as MOFs and zwitterionic systems, demonstrate higher bioavailability but still face concerns about biocompatibility and long-term scalability. The hybrid systems, by integrating the advantages of different nanocarriers—such as providing an enteric coating to protect insulin.

Despite promising preclinical results, translation into clinical success remains limited. The failure of ORMD-0801 in late-stage testing highlighted challenges associated with insufficient and variable bioavailability, high dose requirements, and inconsistent pharmacokinetics.

Future progress will be based on mechanism-based rational design and direct comparative evaluation of delivery systems. Standardized pharmacokinetic and pharmacodynamic data, along with well-designed clinical trials, are essential for identifying effective nanoparticles for oral insulin formulations. In this context, artificial intelligence and data-driven modeling offer potent tools for optimizing formulation design, predicting in vivo outcomes, and personalizing therapy, thereby reducing development time and failure rates.

Although oral insulin is not yet in clinical use, advances in nanotechnology and computational approaches provide a realistic pathway to its clinical use.

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CONFLICTS OF INTEREST

The authors declare there are no competing interests to declare.

DECLARATION OF GENERATIVE AI TOOLS

During the preparation of this work, the authors did not utilize any AI-assisted technologies.

DATA AVAILABILITY

All data are included in the published article and will also be available after publication.

AUTHORS CONTRIBUTION

MM and JIR wrote the initial manuscript; EM, LN, and RM edited the manuscript. DH created the design and illustrations and finalized the manuscript. All authors approved the final version.

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