Original Research Article

Innovations in oral insulin delivery: the role of polymeric carriers in enhancing bioavailability

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Abstract

Insulin therapy remains a cornerstone in the management of diabetes mellitus. However, conventional subcutaneous administration is associated with poor patient compliance, risk of hypoglycemia, and inconsistent pharmacokinetics. Oral insulin delivery, while more convenient and physiologically relevant, poses significant challenges due to enzymatic degradation and poor intestinal absorption. Recent advances in polymeric carriers have shown promise in overcoming these barriers. This review explores the current progress in polymer-based oral insulin delivery systems, emphasizing their design, mechanisms of protection and absorption enhancement, and clinical potential.

Keywords: Oral insulin delivery, Nanoparticles, Micelles, Cyclodextrins

Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both [1]. Effective management of diabetes, particularly type 1 diabetes and advanced type 2 diabetes, relies heavily on exogenous insulin therapy [2]. Traditionally, insulin is administered via subcutaneous injections, a method associated with several limitations including patient discomfort, fear of needles, risk of infection, and poor adherence to long-term treatment regimens [3-4]. Furthermore, subcutaneous delivery bypasses the portal circulation, resulting in non-physiological insulin distribution and an increased risk of peripheral hyperinsulinemia and hypoglycemia [5]. Oral delivery of insulin represents a highly desirable alternative, offering improved patient compliance and the potential to replicate endogenous insulin release patterns by targeting the liver via the hepatic portal system. However, oral insulin delivery poses formidable challenges due to insulin's peptide nature. In the gastrointestinal (GI) tract, insulin is susceptible to degradation by acidic pH in the stomach and proteolytic enzymes such as pepsin, trypsin, and chymotrypsin [6]. Additionally, the large molecular size and hydrophilic nature of insulin hinder its passive absorption across the intestinal epithelium [6]. To overcome these barriers, researchers have developed a variety of innovative drug delivery systems, with polymeric carriers emerging as a particularly promising strategy. Polymeric materials—both natural and synthetic—can encapsulate insulin, protect it from enzymatic degradation, and facilitate its controlled release and absorption in the intestine [7]. These carriers can also be engineered to exhibit mucoadhesive properties, target specific absorption sites, and respond to environmental stimuli such as pH or temperature [8]. This review highlights recent advancements in polymer-based oral insulin delivery systems, focusing on the types of polymers used, their mechanisms of action, design considerations, and performance in preclinical and clinical studies. The goal is to provide a comprehensive understanding of how polymeric carriers can enhance the oral bioavailability of insulin and potentially revolutionize diabetes management [9].

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Delivery systems for insulin oral delivery

The physiological and biological stability of insulin in formulations, the gastrointestinal system, and the cytosol of enterocytes must all be taken into account for effective oral administration of insulin. By adding functional excipients to the dose forms, the obstacles that mostly arise in the oral administration of insulin can be addressed [10]. To preserve insulin stability and improve its paracellular and/or transcellular transport in order to increase its oral bioavailability, the functional excipients work as a stabilizer, a mucoadhesive agent, a protease inhibitor, and/or a permeation enhancer. Numerous dosage forms, including hydrogels, tablets, capsules, microparticles, and nanoparticles, have been produced globally for the oral administration of insulin [11]. When used in vivo, nanoparticles outperform the other delivery techniques owing to their stability and capacity for cellular absorption [12]. Insulin's pharmacokinetic performance after oral delivery is altered by the ability of nanoparticles to pass through and internalize via the intestinal epithelial membrane [13]. A number of factors, including surface charge, particle size, polymer properties, polymer–insulin interaction, insulin loading, insulin release performance, residence time at the absorption site, and body clearance rate, influence how well nanoparticles perform when used for oral insulin delivery [14].

Nanoparticles and micelles

Particles between 1 and 100 nm in size are frequently referred to as nanocarriers. Numerous nanocarriers, including solid lipid nanoparticles, liposomes, polymeric nanoparticles, and micelles, have been described for the delivery of insulin [15]. The polymeric micelles and nanoparticles Methods for Insulin-Loaded Nanoparticles and Micelles shown in table 1. The fundamental conformations of these are shown in Figure. 1. Nanospheres and nanocapsules are examples of nanoparticles. While nanocapsules are vesicles with a polymeric film enclosing the drug core, nanospheres are matrix-type particles where the drug is evenly dissolved or spread in the polymer matrix [16]. Amphiphilic copolymers self-assemble into nanoscale aggregates above the critical micellar concentration to create micelles. While the

hydrophilic moiety creates the corona in the micelle shell, the hydrophobic moiety forms the micelle core. Micelles have a dynamic structure in which the amphiphilic copolymer's unimers may be switched out. Insulin-loaded nanoparticles and micelles are made using a broad range of polymers and production techniques (Table 1). Endocytosis, which is influenced by the surface characteristics of the nanocarriers, is the primary mechanism of insulin delivery by nanoparticles and micelles [17].

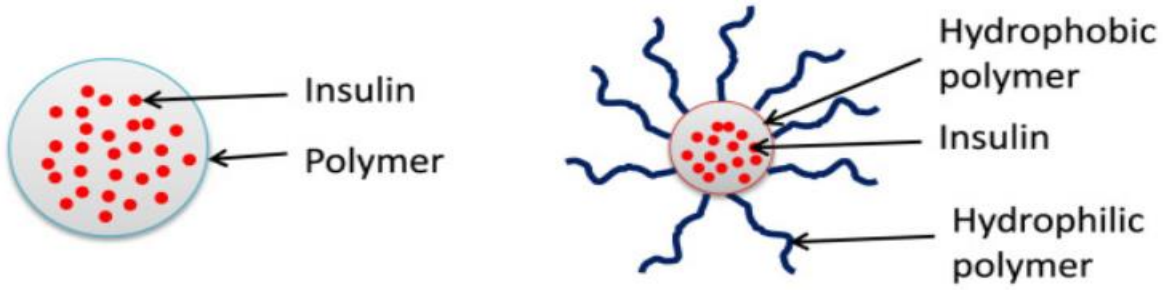

Fig 1. polymeric nanoparticle and polymeric micelles

Table1. Polymers and Methods for Insulin-Loaded Nanoparticles and Micelles

Polymer Type	Polymer/System	Properties	Preparation Methods	Advantages/Features
Natural	Chitosan	Cationic, mucoadhesive, biodegradable	Ionic gelation, polyelectrolyte complexation	Opens tight junctions, enhances absorption
	Alginate	Anionic, pH-sensitive, forms hydrogels	Emulsion cross-linking, ionotropic gelation	Protects insulin in gastric pH, biocompatible
	Dextran	Hydrophilic, non-toxic	Self-assembly, emulsification	Biodegradable and versatile
	Gelatin	Amphiphilic, protein-based	Desolvation, coacervation	Biocompatible, suitable for protein drugs
	Cellulose derivatives / Starch	Biodegradable, plant-derived	Solvent evaporation, nanoprecipitation	Safe, natural polymer source
Synthetic	PLGA (Poly(lactic-co-glycolic acid))	Biodegradable, FDA-approved	Double emulsion (W/O/W), solvent evaporation	Sustained release, enzyme protection
	PEG (Polyethylene glycol)	Hydrophilic, "stealth" polymer	PEGylation, self-assembly	Reduces immunogenicity, prolongs circulation
	Eudragit	pH-sensitive, enteric polymer	Solvent casting, nanoprecipitation	Targeted intestinal release
	PCL (Polycaprolactone)	Hydrophobic, slow-degrading	Solvent diffusion, nanoprecipitation	Sustained drug release
	Poloxamer (Pluronics)	Amphiphilic block copolymer	Self-assembly into micelles	Temperature-responsive, good solubilizer
Copolymer/Hybrid	PEG-PLA	Amphiphilic block copolymer	Self-assembly into micelles	Core–shell structure, high loading efficiency
	Chitosan-PEG	Modified biopolymer	Ionic gelation, nanoprecipitation	Improved solubility, stability
	Alginate–Chitosan	Polyelectrolyte complex	Layer-by-layer deposition	Combines pH sensitivity and mucoadhesion
	Cyclodextrin-based polymers	Host–guest interaction	Self-assembly	Protects insulin via molecular encapsulation
Applicable to All	—	—	**General Methods:** - Ionic Gelation - Double Emulsion - Nanoprecipitation - Self-Assembly - Spray Drying - Coacervation - Layer-by-Layer Assembly	Selection depends on insulin stability, release profile, and target site

Approaches for insulin oral delivery

Nanocarriers have great promise for the efficient oral administration of insulin. By altering the surface property of the polymer or nanoparticle and covering the nanoparticles with an enteric coating, it is possible to design nanocarriers that enhance the gastrointestinal absorption of insulin. As was already indicated, they can be used in conjunction with absorption enhancers or enzyme inhibitors [18]. A combination of protective encapsulation, mucoadhesion, targeted delivery, and stimuli-responsive release makes nanocarrier systems a powerful tool for oral insulin delivery. Future research should focus on optimizing multi-functional nanocarriers that integrate several of these mechanisms while maintaining safety, scalability, and clinical efficacy. These methods for improving insulin absorption through the use of nanoparticle delivery systems are compiled in Table 2 [19,20,21,22].

Approach	Nanocarrier System	Mechanism of Enhancement	Examples	Advantages
Enzyme Protection	Polymeric nanoparticles (e.g., PLGA, chitosan) - Liposomes	Encapsulation protects insulin from proteolytic enzymes in GI tract	Chitosan–TPP nanoparticles, PLGA microspheres	Enhances insulin stability during GI transit
pH-Responsive Release	Enteric-coated nanoparticles (Eudragit, alginate) - pH-sensitive hydrogels	Releases insulin in neutral/basic pH (intestine), avoids gastric degradation	Eudragit-coated chitosan particles	Site-specific release in the small intestine
Mucoadhesion	Chitosan-based systems - Thiolated polymers	Prolongs residence time on mucosal surfaces, improves	Chitosan–alginate beads	Enhances localized absorption window

		drug retention and absorption		
Permeation Enhancement	Surface-modified nanoparticles - Surfactant- or bile salt-coated particles	Opens tight junctions or interacts with membrane to increase paracellular transport	Chitosan nanoparticles with EDTA or bile salts	Improves epithelial transport across gut wall
Receptor-Mediated Transport	Ligand-conjugated nanoparticles - Vitamin B12, folate, transferrin-decorated systems	Targets epithelial transporters to facilitate endocytosis	Vitamin B12–insulin conjugates, lectin-modified nanoparticles	Promotes active uptake across gut epithelium
Nanomicelles and Self-Assembled Systems	PEG-PLA micelles - Cyclodextrin-based nanocarriers	Encapsulates insulin in hydrophobic core, improves solubility and stability	PEG-PLA micelles, β-cyclodextrin complexes	Enhances solubilization and controlled release
Lipid-Based Systems	Solid lipid nanoparticles (SLNs) - Nanostructured lipid carriers (NLCs)	Facilitates lymphatic transport and avoids first-pass metabolism	SLNs with stearic acid or glyceryl monostearate	High encapsulation efficiency, reduced enzymatic attack
Use of Absorption Enhancers	Nanoparticles co-loaded with absorption enhancers (e.g., bile salts, chitosan derivatives)	Increases epithelial permeability via chemical modulation	Insulin nanoparticles with sodium caprate or Zonula occludens toxin	Transient, reversible tight junction opening
Smart Responsive Systems	Glucose-responsive nanoparticles - pH/enzymatically triggered systems	Releases insulin in response to physiological stimuli (e.g., glucose levels)	Glucose oxidase-modified micelles	Mimics endogenous insulin regulation, reduces hypoglycemia

Barriers to Oral Insulin Delivery

A protein and peptide medication taken orally must pass through the gastrointestinal system, stick to and penetrate the mucus layer, pass through the intestinal epithelium, enter the portal vein, and then enter the peripheral circulation in order to be effective [23]. However, the GI tract presents a number of physiological hurdles to insulin taken orally, which may be categorized as chemical, enzymatic, and physical barriers. The GI tract serves as the body's first line of defense against external toxins and infections [24]. The formulation may become unstable and the insulin may denature or degrade due to the enzymatic (proteolytic enzymes in the GI tract) and chemical (ultra-acidic pH in the stomach) barriers [25]. Furthermore, the intestinal epithelium and mucus layers are examples of physical barriers that may hinder the entry and absorption of insulin taken orally [26]. Because of this, insulin and other protein and peptide medications have a very low oral bioavailability of less than 1% in clinical settings [27]. A thorough understanding of the properties of these barriers is necessary to create an oral insulin system that works well. There are already several thorough studies that go into great detail on these obstacles [28,29]; in this case, we provide a quick synopsis and illustrate them in Figure 2.

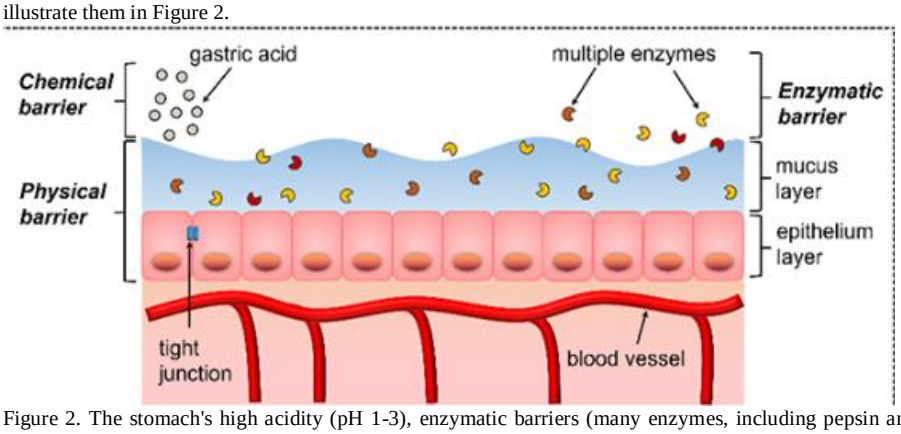

Figure 2. The stomach's high acidity (pH 1-3), enzymatic barriers (many enzymes, including pepsin and cathepsin in the stomach and trypsin, chymotrypsin, and carboxypeptidase in the small intestine), and physical barriers (mucus layer, epithelial layer, and their tight junction) are the three primary obstacles to oral delivery.

Recent innovations in oral insulin delivery

The development of oral insulin has the potential to greatly enhance the quality of life for diabetic patients who require frequent injections of this medication, since the disease is becoming more widespread worldwide [30]. Even though finding a trustworthy and efficient oral insulin delivery system has been a difficult task for many years, attempts to find the holy grail have never slowed and are even picking up speed [31]. In the sections that follow, we describe key and exemplary innovations that have emerged in this field in recent years, with a focus on those that show great potential for clinical assessment shown in table 3 [32,33,34,35].

Table3. Recent Innovations in Oral Insulin Delivery

Innovation Type	Nanocarrier/System	Mechanism/Technology	Key Examples	Advantages
Polymeric Nanoparticles	Chitosan, PLGA, Eudragit, Alginate	pH-sensitive release, mucoadhesion, enzyme protection	Eudragit-coated chitosan nanoparticles	Protects insulin from GI degradation, targeted intestinal release
Self-Assembling Nanostructures	PEG-PLA, PCL-PEG micelles	Amphiphilic block copolymer self-assembly	PEG-PLA micelles	Improves insulin solubility, stability, controlled release
Solid Lipid Nanoparticles (SLNs)	Lipid matrices (e.g., stearic acid)	Lipid encapsulation and lymphatic uptake	SLNs with insulin–phospholipid complex	Bypasses first-pass metabolism, high encapsulation
Nanostructured Lipid Carriers (NLCs)	Solid-liquid lipid blends	Improved lipid matrix for better drug loading	Insulin-loaded NLCs with glyceryl monostearate	Enhanced stability and permeability

Liposomes	Phospholipid bilayers, bile salt or PEG-modified	Membrane fusion, enzyme shielding	Bile salt liposomes, PEGylated liposomes	High biocompatibility, improved intestinal uptake
Mucoadhesive Systems	Thiolated chitosan, carbopol, polycarbophil	Prolonged mucosal adhesion	Thiomer-insulin complexes	Increases intestinal residence time, absorption window
Glucose-Responsive Systems	Glucose oxidase, phenylboronic acid-modified nanoparticles	Smart release in response to high glucose	Glucose-sensitive micelles	On-demand insulin release, reduces hypoglycemia
Ligand-Targeted Delivery	Transferrin, folate, vitamin B12-modified carriers	Receptor-mediated endocytosis in the intestine	Vitamin B12–insulin conjugates	Active transport, improved uptake in ileum
Mechanical/Smart Capsules	Ingestible devices with microneedles or sensors	Physical injection into stomach lining, triggered release	SOMA microneedle capsule (MIT), Oramed capsule	Needle-free systemic delivery, responsive dosing
Hybrid Multifunctional Systems	Combinations of mucoadhesive, pH-sensitive, targeted systems	Integrative nanocarriers for multiple barriers	Transferrin–chitosan–alginate nanoparticles	Synergistic enhancement of stability, release, and uptake
Clinical Formulations	Oral capsules with enzyme inhibitors and enhancers	Controlled release and protection	ORMD-0801 (Oramed), OG217SC (Novo Nordisk)	First-generation human trials show safety and modest efficacy

Polymer approaches for solubility and bioavailability enhancement

Poor solubility and limited bioavailability of insulin in the gastrointestinal (GI) tract are major barriers to its oral delivery [36]. Polymers play a crucial role in addressing these issues by modifying drug solubility, protecting insulin from degradation, and facilitating its absorption. The following approaches leverage the unique physicochemical properties of natural, synthetic, and modified polymers to enhance the oral bioavailability of insulin [37].

Cyclodextrins (CDs)

Cyclodextrins (CDs) are cyclic oligosaccharides composed of glucose monomers linked by α-1,4-glycosidic bonds. They possess a unique structure: a) Hydrophilic outer surface and b) Hydrophobic central cavity [38]. This amphiphilic architecture allows them to form inclusion complexes with various drugs—including peptides like insulin—by encapsulating hydrophobic or labile regions within their cavity [39].

Table 4. Types of Cyclodextrins

Type	Number of Glucose Units	Cavity Size	Examples of Modified Forms
α-CD	6	~4.7–5.3 Å	Methylated α-CD, hydroxypropyl-α-CD
β-CD	7	~6.0–6.5 Å	HP-β-CD, RM-β-CD (Randomly Methylated)
γ-CD	8	~7.5–8.3 Å	Sulfobutyl ether-γ-CD

Mechanism of Complexation

Cyclodextrins interact with insulin primarily through:

- Hydrophobic interactions with amino acid residues (e.g., phenylalanine, tyrosine)
- Hydrogen bonding
- Van der Waals forces [40]

The insulin molecule (or a fragment) enters the cavity of the cyclodextrin, forming a reversible non-covalent inclusion complex.

Applications in Formulations

- Inclusion Complex + Polymeric Carrier: CDs can be loaded into chitosan or PLGA nanoparticles to combine the benefits of protection and controlled delivery.
- Mucoadhesive Complexes: Cyclodextrins are sometimes modified with thiol or amino groups to enhance mucoadhesion and interaction with epithelial cells [41].
- Transcellular Transport Enhancement: Some CD derivatives modulate membrane fluidity or open tight junctions transiently.

Cyclodextrins offer a powerful approach to enhance the oral delivery of insulin through complexation-based stabilization, solubilization, and absorption enhancement [42]. Their biocompatibility, versatile chemistry, and ability to form non-covalent complexes make them ideal excipients in modern insulin nanodelivery systems, especially when integrated with other polymeric or lipid-based platforms.

Nanosizing in Oral Insulin Delivery

Nanosizing refers to the process of reducing the particle size of drugs or drug carriers to the nanometer scale (typically 1–1000 nm) [43]. This technique significantly increases the surface area-to-volume ratio, which can drastically improve drug solubility, dissolution rate, absorption, and bioavailability—particularly important for hydrophilic macromolecules like insulin [44]. Nanosizing, by significantly increasing the surface area of insulin carriers, offers remarkable advantages in improving insulin solubility, protection, and absorption [45]. Nanoscale delivery systems are central to overcoming the barriers of oral insulin therapy, especially when combined with mucoadhesive, targeting, and stimuli-responsive strategies [46].

Lipid-Based Delivery Systems for Oral Insulin

Lipid-based delivery systems are a promising approach for **oral insulin delivery,** designed to overcome the major barriers in the gastrointestinal (GI) tract such as enzymatic degradation, acidic pH, and limited permeability [47]. These systems **encapsulate insulin within lipid matrices or emulsions,** offering protection and enhanced absorption through both **lymphatic uptake** and **membrane permeability enhancement [48]**.

Amorphous Solid Dispersions (ASDs) in Oral Insulin Delivery

Amorphous solid dispersions (ASDs) are pharmaceutical formulations in which an active pharmaceutical ingredient (API), such as insulin, is molecularly dispersed in a polymer matrix in the amorphous (non-crystalline) state [49]. This approach is widely used to enhance the solubility, dissolution rate, and oral bioavailability of poorly soluble drugs.Although insulin is a hydrophilic peptide, ASDs have been explored to stabilize insulin, protect it from degradation, and modulate its release in oral formulations [50].

Table 5. Polymers Used in ASDs for Insulin

Polymer	Role	Properties
Hydroxypropyl methylcellulose (HPMC)	Matrix former, pH-responsive	Soluble in basic pH, protective in acidic pH
Polyvinylpyrrolidone (PVP, PVP-VA)	Carrier, solubilizer	High glass transition temperature (Tg), enhances stability
Eudragit (L100/S100)	Enteric coating	Dissolves in intestinal pH, allows site-specific release
PEG (Polyethylene glycol)	Plasticizer, solubilizer	Improves drug wettability and matrix flexibility

Amorphous solid dispersions offer a promising strategy for oral insulin delivery by enhancing solubility, protecting the drug, and enabling pH-triggered site-specific release [51]. When combined with enteric coatings or nanocarrier systems, ASDs can play a pivotal role in the development of stable, effective oral insulin formulations.

Conclusion

Oral insulin delivery has long been considered the “holy grail” in diabetes therapy due to its potential to improve patient compliance, quality of life, and physiological insulin action by mimicking endogenous secretion pathways. However, the harsh gastrointestinal environment and the structural fragility of insulin pose significant obstacles to its successful oral administration. Polymeric carriers have emerged as a transformative platform in overcoming these challenges. By offering protection against enzymatic degradation, enhancing mucosal adhesion, promoting intestinal permeability, and enabling controlled or targeted release, these systems have demonstrated great potential in improving insulin bioavailability. Natural polymers such as chitosan and alginate, and synthetic polymers like PLGA and Eudragit, have been extensively explored, each bringing unique advantages to formulation strategies. Despite promising results from in vitro and preclinical studies, the clinical translation of these technologies remains limited. Challenges related to scalability, batch-to-batch consistency, long-term safety, and regulatory approval must be addressed. Continued interdisciplinary research combining materials science, pharmaceutical technology, and clinical medicine will be key to bringing effective oral insulin formulations from the laboratory to the patient. In conclusion, polymeric carriers are at the forefront of innovation in oral insulin delivery. With sustained research and strategic development, they have the potential to redefine the landscape of diabetes care and reduce dependence on injectable insulin therapies.

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