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NANO ENABLED ORAL INSULIN DELIVERY SYSTEM FOR IMPROVED GASTROINTESTINAL ABSORPTION

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ABSTRACT

Oral delivery of insulin remains a long-standing challenge due to enzymatic degradation in the gastrointestinal tract, poor epithelial permeability, and rapid first-pass metabolism, resulting in extremely low bioavailability. Nano-enabled drug delivery systems have emerged as promising strategies to overcome these physiological barriers and improve patient compliance compared to subcutaneous injections. This review highlights recent advances in oral insulin nano-systems, including polymeric nanoparticles, liposomes, solid lipid nanoparticles, nano emulsions, micelles, dendrimers, and inorganic nanocarriers. These systems protect insulin from gastric degradation, enhance mucosal adhesion, facilitate transcellular or paracellular transport, and enable controlled release. Surface functionalization with targeting ligands, mucoadhesive polymers, and enzyme inhibitors further improves intestinal absorption and stability. Smart glucose-responsive nanocarriers capable of self-regulated insulin release are also gaining attention for achieving near-physiological glycemic control. Preclinical studies demonstrate improved pharmacokinetics, enhanced bioavailability, and significant hypoglycemic effects; though challenges related to large-scale manufacturing, long-term safety, and regulatory approval remain. Overall, oral insulin nano-delivery platforms represent a transformative approach toward non-invasive diabetes management, offering the potential for better therapeutic outcomes, improved patient adherence, and enhanced quality of life. Continued optimization and clinical translation are essential to realize their full potential in routine diabetes care.

INTRODUCTION

Insulin is a globular protein hormone consisting of 51 amino acids arranged into two polypeptide chains: 21 residues in the A-chain and 30 residues in the B-chain, which are connected through disulfide linkages. This hormone is secreted by the β-cells of the islets of Langerhans in the pancreas and plays a critical role in regulating blood glucose levels. When adequate insulin is not available after food intake, glucose uptake by body cells becomes impaired, leading to elevated blood glucose levels, a condition known as type 1 diabetes mellitus. In type 2 diabetes mellitus, insulin is present but fails to exert its effect due to insulin receptor resistance, resulting in poor glucose utilization.

Subcutaneous injection remains the most commonly used route for insulin administration in the management of hyperglycemia. However, intravenous and injectable insulin therapies are associated with several complications, including hypoglycemia, pain, swelling, skin bulges, and local allergic reactions at the injection site [1]. Repeated injections may further cause physiological hazards such as lipoatrophy lipohypertrophy, erythema, itching, abscess formation, and induration. Additionally, the continuous need for injections creates operational difficulties and imposes a psychological burden on diabetic patients, thereby reducing treatment adherence [2].

Oral administration is considered the safest, most convenient, and most patient-acceptable route for insulin therapy, as it avoids injection-related complications and reduces the risk of localized hypoglycemia. However, the oral bioavailability of insulin remains below 2% because of its high molecular weight, strong hydrophilicity, poor stability, and susceptibility to enzymatic degradation by proteases. Furthermore, insulin must cross multiple physiological barriers within the gastrointestinal tract before

reaching systemic circulation, which poses a major challenge for effective absorption.

Over the past two decades, the integration of nanotechnology with pharmaceutics has created new opportunities for the oral delivery of macromolecular drugs, making nanotechnology a promising research direction for oral insulin therapy [3]. In this review, we summarize the physiological barriers to oral insulin absorption and discuss various nano-drug delivery system constructed from different materials

(A) Materials and nanostructures of oral insulin delivery systems. (B) The physiological absorption barrier of oral administration of insulin. (a) Destruction by gastric acid. (b) Degradation by digestive enzyme. (c) Retention by the mucus layer barrier. (d) Retardation by intestinal epithelial cell layer.

1. PHYSIOLOGICAL ABSORPTION BARRIER OF ORAL INSULIN

Insulin injections impose both psychological stress and several physiological complications in diabetic patients. Therefore, oral insulin delivery is considered a more desirable alternative because it is painless, patient-friendly, and better mimics the natural physiological mechanism of insulin action.

1.1. DESTRUCTION BY GASTRIC ACID

After oral administration, insulin typically remains in the stomach for approximately 2 hours, where it is exposed to gastric fluid with a highly acidic pH of about 1.2–2. This strong acidic environment alters the ionization of amino acids and disrupts the native three-dimensional structure of peptides and proteins, leading to insulin instability and degradation. To protect insulin from acid-induced damage, many delivery systems are designed to remain stable and encapsulate the drug under acidic conditions, while undergoing degradation or swelling at neutral pH to enable controlled insulin release in the intestine [7].

1.2. DEGRADATION BY DIGESTIVE ENZYMES

Numerous proteolytic enzymes present in the gastrointestinal tract contribute to the degradation of proteins and peptides (Figure 1b). The stomach is particularly rich in pepsin, while the intestine, which maintains a neutral to slightly alkaline pH, contains enzymes such as trypsin, chymotrypsin, elastase, and carboxypeptidase. When unprotected insulin is incubated in simulated gastric and small intestinal fluids containing these digestive enzymes at 37 °C for 2–3 h, less than 10% of the insulin retains its biological activity, and in some cases, the activity is completely lost[8].

1.3. RETENTION BY THE MUCUS LAYER BARRIERS

The intestinal epithelial surface is coated with an electronegative mucus layer secreted by goblet cells (Figure 1c). This mucus primarily consists of water and contains smaller amounts of glycoproteins, proteins, electrolytes, and lipids. Due to its negative charge, the mucus layer tends to attract and retain electroneutral or positively charged substances, which can limit their diffusion across the intestinal barrier. Moreover, highly interactive or strongly electroneutral materials may become electrostatically trapped within the mucus network, resulting in reduced permeability.

1.4. RETARDATION BY INTESTINAL EPITHELIAL CELL LAYER

The intestinal epithelial cell layer serves as a critical physiological barrier that regulates the passage of substances from the gastrointestinal tract into the blood or lymphatic circulation (Figure 1d). This layer is composed of various specialized cells, including absorptive enterocytes, mucus-secreting goblet (cup) cells, microfold (M) cells, enteroendocrine cells, and lysozyme-secreting Paneth cells. These cells are tightly connected, forming a protective barrier that restricts the transport of protein and peptide drugs while simultaneously defending against harmful agents [9].

2. DRUG RELEASE STRATEGY

2.1. NANOCARRIER SYSTEM

A nanocarrier is an advanced drug delivery platform designed to release therapeutic agents at the target site through controlled nanoparticle degradation or diffusion mechanisms. Typically, nano-based targeted delivery systems consist of three fundamental components: (a) a physiologically inert nanocarrier matrix, (b) a pharmaceutically active drug molecule, and (c) a surface-attached targeting ligand or moiety that directs the system toward specific tissues or cells [12]. These nanocarrier systems have demonstrated significant in vivo potential by enhancing drug stability and improving targeting specificity, while simultaneously reducing systemic toxicity and minimizing adverse side effects.

2.2. STRATEGIES FOR TARGETED DRUG RELEASE

The drug-loading capacity of a nanomaterial refers to the quantity of drug incorporated per unit mass of nanoparticles. Drug incorporation into nanoparticles generally occurs through two approaches: (i) encapsulation or integration of the drug during nanoparticle fabrication, and (ii) adsorption or attachment of the drug onto preformed nanoparticles after synthesis. The efficiency of drug loading is largely influenced by the physical and chemical characteristics of the nanomaterial. Therefore, maintaining the structural integrity of the nanoparticles is essential to ensure optimal loading performance and effective targeted drug delivery [10].

2.3. PH-RESPONSIVE INSULIN RELEASE

Ionizable polymers, such as polyacids and polybases, are frequently utilized in the fabrication of nanosystems. These polymers respond to environmental pH variations, and changes in pH can trigger conformational or solubility alterations in the polymer chains, leading to the decomposition or destabilization of the nanocarriers and subsequent release of the encapsulated drug. Because the pH of the gastrointestinal tract ranges from highly acidic in the stomach (1.2–3.0) to slightly alkaline in the intestine (7.5–8.0), insulin is susceptible to pH-induced oxidation and deamination [11].

2.4. PH AND GLUCOSE DUAL RESPONSIVE INSULIN RELEASE

When designing oral insulin delivery systems for individuals with T1DM, it is essential to account for both the variations in gastrointestinal pH and the effect of blood glucose levels on insulin release from nanoparticles. Considering these physiological fluctuations, delivery platforms that exhibit dual responsiveness to both pH and glucose are particularly advantageous and reliable for achieving controlled and on-demand insulin release.

3. NANOSTRUCTURED LIPID CARRIERS

Nanostructured lipid carriers (NLCs) are advanced lipid-based delivery systems formulated by combining solid and liquid lipids to enhance the oral therapeutic bioavailability of drugs. These carriers are typically prepared using a mixture of lipids along with surfactants, co-surfactants, and lipophilic counter-ions to achieve improved stability and efficient drug incorporation. NLCs offer several advantages for oral drug delivery, including high drug entrapment efficiency and loading capacity, controlled and sustained release profiles, and protection of the encapsulated drug against pH variations and enzymatic degradation. They also provide extended shelf life, reduce P-glycoprotein–mediated efflux, and help mask unpleasant sensory properties. Furthermore, NLCs facilitate effective gastrointestinal absorption and promote lymphatic uptake via chylomicrons, thereby improving systemic bioavailability [12].

PNPs FOR ORAL INSULIN DELIVERY

Polymeric nanoparticles (PNPs) are oral drug delivery systems characterized by their nanoscale dimensions, typically below 100 nm, although their size can often extend up to 100–500 nm depending on the formulation. Based on the type of material used, PNPs are broadly categorized into two groups: those derived from natural polymers and those composed of synthetic porous polymers.

3.1. NATURAL POLYMERS

Natural polymers, including polysaccharides, proteins, peptides, and nucleic acids, provide numerous advantages for drug encapsulation and delivery, such as biodegradability, biocompatibility, low toxicity, and minimal immunogenicity. These favorable properties make them suitable and safe carriers for transporting active pharmaceutical agents. Owing to their excellent compatibility with biological systems and their ability to degrade naturally within the body, natural polymer–based nanocarriers are considered highly promising materials for the development of advanced oral insulin delivery systems [13].

3.2. NATURAL POLYSACCHARIDE

Starch is a versatile, economical, and naturally renewable biopolymer composed of two main constituents: amylose and amylopectin, which make it suitable for a wide range of biomedical applications. Amylose consists of α-D-(1→4)-linked glucose units arranged in linear chains, whereas amylopectin contains a similar α-D-(1→4) glucose backbone with additional α-D-(1→6) branched linkages that create a highly branched structure.

3.3. NATURAL PROTEINS

Proteins are among the most important natural biomaterials used in the fabrication of advanced nanovehicles due to their distinctive properties, including biodiversity, biodegradability, low immunogenicity, minimal toxicity, and excellent biocompatibility. Protein-based nanocarriers possess well-defined primary structures, which allow for easy modification through pre- or post-functionalization. This structural adaptability enables the incorporation of various drugs, functional components, or auxiliary carriers through interactions with the hydrophobic or hydrophilic domains of the protein using appropriate reagents [14].

3.4. SYNTHETIC POROUS POLYMERS

Synthetic porous polymers (SPPs) offer several advantages over natural polymers and other material classes, primarily due to their design flexibility and the ability to tailor their composition and properties to meet specific pathological conditions and individual patient needs. These materials can be engineered with precise structural and functional characteristics, making them highly suitable for advanced drug delivery applications.

3.5. ACTIVATED CHARCOAL

Several studies have indicated that activated charcoal may help reduce obesity, metabolic syndrome, and related metabolic disorders. It has been reported that supplementation with acidic activated charcoal in combination with a high-fat diet (HFD) decreased obesity in insulin-resistant mice in a dose-dependent manner. Despite these potential benefits, activated charcoal presents certain limitations for oral insulin delivery.

3.6. SILICA

Silica nanoparticles (SNs), particularly mesoporous silica nanoparticles (MSNs), have emerged as promising carriers for oral insulin delivery because of their excellent biocompatibility, high drug encapsulation efficiency, controlled release behaviour, and favorable loading characteristics. Using the sol–gel method, researchers synthesized silica nanoparticles and polyethylene glycol-modified silica nanoparticles (PEG-SiNPs) and evaluated their potential as insulin delivery vehicles. Subsequently, developed dendritic mesoporous dendritic mesoporous silica nanoparticles that enabled efficient insulin encapsulation [15].

3.7. POROUS COORDINATION POLYMERS (PCPs)

Porous coordination polymers (PCPs) are crystalline materials characterized by infinite network structures formed through coordination bonds between metal nodes (metal ions or clusters) and organic linkers. Unlike many conventional inorganic nanostructures that exhibit poor biodegradability, numerous PCPs possess inherent biodegradable properties and can be cleared from the body through renal excretion, thereby minimizing the risk of long-term accumulation

and toxicity. Owing to these favorable characteristics, PCPs have emerged as a promising class of nanomaterials in nanomedicine, with increasing application in oral insulin delivery systems [16].

4. ORAL INSULIN DELIVERY NANOSYSTEMS

To overcome the previously described barriers to oral insulin absorption, nanotechnology-based delivery strategies have been developed using suitable carrier materials to encapsulate bioactive insulin and enhance its oral bioavailability. These oral drug delivery nanosystems are formed by dissolving, dispersing, embedding, adsorbing, or chemically coupling insulin into various carrier matrices, resulting in a wide range of nanoparticulate formulations such as nanoliposomes, nanosolid dispersions, polymeric micelles, nanocapsules, nanospheres, microemulsions, and inorganic–organic hybrid systems [17].

Materials for Oral Insulin Delivery Nanosystems

Carrier materials play a crucial role in formulating oral insulin delivery nanosystems by encapsulating and protecting insulin while facilitating its transport across the gastrointestinal tract. Ideally, these materials should exhibit pH responsiveness, strong bioadhesion, biocompatibility, biodegradability, ease of modification, and simple processability to preserve drug stability and enhance overall bioavailability. A wide range of polymers has therefore been employed in the development of oral nanoscale delivery platforms [18].

5. POLYLACTIC ACID (PLA)

Poly lactic acid (PLA) is a biodegradable, biocompatible, and bioadhesive polyester synthesized through the polymerization of lactide (Figure 5A). Owing to these favorable properties, PLA has been widely applied in pharmaceutical formulations. PLA-b-Pluronic-b-PLA (PLA–F127–PLA) aggregates have been developed as nanocarriers for oral insulin delivery, demonstrating a sustained hypoglycemic effect in diabetic rats for up to 18.5 hours [27]. The negatively charged hydroxyl and carboxyl groups of PLA enhance adhesion to the intestinal wall and prolong nanoparticle residence time, which may hinder effective transport.

5.1.1. POLY LACTIC-CO-GLYCOLIC (PLGA)

Poly lactic-co-glycolic acid (PLGA) is a biodegradable functional polymer synthesized through the random copolymerization of lactic acid and glycolic acid monomers (Figure 5B). It exhibits excellent biocompatibility, low toxicity, and favorable film-forming properties, making it widely used in oral delivery systems for macromolecular drugs [19].

5.1.2. CHITOSAN AND ITS DERIVATIVES

Chitosan is a natural polysaccharide polymer composed of deacetylated glucosamine and N-acetylglucosamine units (Figure 5C). It exhibits favorable biological properties, including biocompatibility, biodegradability, mucoadhesion, and enhanced permeability, making it suitable for oral drug delivery applications. Owing to its positive charge, chitosan can interact with silicate groups in mucin through hydrogen bonding and electrostatic interactions, thereby improving adhesion to the gastrointestinal mucosa [20].

5.1.3. METAL ORGANIC FRAMEWORKS (MOFs)

Metal–organic frameworks (MOFs), also referred to as porous coordination polymers, are three-dimensional crystalline materials formed by inorganic metal clusters interconnected with organic ligands. They possess well-defined porous architectures and stable, tunable structures (Figure 5D), enabling purposeful modification of their chemical and functional properties for applications in drug delivery. In one study, iron-based metal–organic frameworks were synthesized to encapsulate insulin through physical adsorption, and the resulting insulin-loaded particles were coated with the amphiphilic polymer poly (ethylene glycol-b-lactide) to enhance stability in the acidic gastric environment [21].

6. FUTURE DIRECTIONS TO ENHANCE DELIVERY OF ORAL INSULIN

Future research on oral insulin delivery is focused on overcoming the major physiological and biochemical barriers of the gastrointestinal tract, such as enzymatic degradation, poor epithelial permeability, and low bioavailability. Several promising strategies are being explored to enhance the effectiveness and reliability of oral insulin formulations. One important direction involves the development of advanced nanocarrier systems, including polymeric nanoparticles, liposomes, solid lipid nanoparticles, and micelles, which can protect insulin from acidic gastric conditions and enzymatic degradation while promoting controlled and targeted release in the intestine. These carriers may also improve mucoadhesion and prolong intestinal residence time, thereby enhancing absorption.

7. DISCUSSION

Researchers in the medical and pharmaceutical fields are increasingly focused on developing noninvasive strategies for insulin delivery, with the primary goals of improving patient compliance and reducing the pain and serious adverse effects associated with injectable therapies. In this systematic review, relevant findings have been consolidated to support the design and optimization of novel nano- and micro-based insulin formulations. The collected evidence highlights percentage entrapment efficiency (%EE) as a crucial parameter in achieving effective reductions in serum glucose levels. In addition, formulations with an optimal particle size in the range of 200–400 nm and a favorable polydispersity index (PDI) between 0.086 and 0.3 were consistently associated with improved glycemic control. The choice of excipients used in carrier systems also plays an important role in blood glucose reduction, as reflected by the variability in outcomes among the reviewed studies; however, no direct correlation was observed between specific

excipient types and the most pronounced therapeutic effects [22].

8. CONCLUSION

Oral insulin delivery nanosystems represent a promising and patient-friendly alternative to conventional subcutaneous insulin injections. By employing nanocarriers such as nanoparticles, liposomes, polymeric systems, and nanoemulsions, insulin can be protected from enzymatic degradation and the harsh acidic environment of the gastrointestinal tract while improving its stability, permeability, and intestinal absorption. These nanoscale formulations enhance mucoadhesion, facilitate transcellular and paracellular transport, and promote targeted delivery, thereby increasing bioavailability and therapeutic efficacy.

AUTHOR CONTRIBUTIONS

All authors are contributed equally.

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The authors have no conflicts of interest to declare.

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