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Advances in Oral Nanodelivery Systems for Diabetes Treatment

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Abstract. Long-term control of blood glucose is central to diabetes management, yet two major peptide-based treatments—insulin and glucagon-like peptide-1 receptor agonists (GLP-1RAs)—are still administered mainly by injection. An oral formulation would be easier to use over prolonged treatment, but the gastrointestinal tract is a difficult route for these molecules. Acid and proteases threaten both the drug and the carrier, intestinal mucus can immobilize or remove particles before they reach the epithelial surface, and uptake into epithelial cells does not guarantee release to the bloodstream. Nanodelivery systems are being developed to address these problems, but the relevant barriers occur in sequence and cannot be considered independently. A carrier that survives the stomach may still be trapped in mucus; one that reaches the epithelium may still be retained in endosomal or lysosomal compartments. This review discusses these successive barriers and the nanocarrier strategies used at each stage, including structural stabilization, local protease inhibition, pH-responsive release, regulation of carrier–mucus interactions, and exploitation of endogenous transport and intracellular trafficking pathways. Particular attention is given to approaches that coordinate more than one transport step, because improving a single barrier does not necessarily improve overall oral absorption. The review therefore considers how multistage design may support more effective oral delivery of insulin and GLP-1RAs for diabetes treatment.

Keywords: Oral nanodelivery systems, Insulin, GLP-1 receptor agonists, Gastrointestinal barriers, Diabetes

1. Introduction

Diabetes mellitus is now a major chronic disease worldwide, with population aging and lifestyle changes contributing to its growing prevalence. Its burden extends beyond glucose control itself: patients often require years of medication, regular monitoring, and management of vascular and other complications, while healthcare systems also absorb substantial direct and indirect costs [1, 2]. Type 2 diabetes mellitus (T2DM) represents more than 90% of diabetes cases [3]. The disease is characterized by insulin resistance together with progressive loss of pancreatic β-cell function, so long-term treatment is usually needed to maintain glycemic control and delay complications. Insulin and glucagon-like peptide-1 receptor agonists (GLP-1RAs) are established therapeutic options and

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can provide effective glucose lowering while reducing the risk of diabetes-related complications [4]. Their route of administration, however, remains a practical limitation. Because these drugs are proteins or peptides, they are readily degraded in the gastrointestinal tract and cross the mucus layer and intestinal epithelium poorly. For most available formulations, subcutaneous injection is therefore still required [5].

Repeated injections are clinically effective, but they are not ideal for a disease that may require lifelong treatment. Pain, inconvenience, and needle anxiety can become relevant to adherence, which helps explain the continued interest in oral peptide delivery. The difficulty is that orally administered proteins and peptides do not face a single dominant barrier. They can be degraded before reaching the intestine, retained within mucus, poorly transported across epithelial cells, or eliminated before meaningful systemic exposure is achieved [6]. Improving only one of these steps may therefore leave the overall bioavailability essentially unchanged. Nanomaterials offer a way to combine protection and transport functions within the same formulation, but their value depends on how well these functions are matched to the order in which gastrointestinal barriers are encountered. In this review, we first examine the principal barriers to oral nanodelivery and then discuss strategies for drug protection, mucus transport, and transepithelial absorption, with particular emphasis on the transition from single-barrier solutions to coordinated multistage delivery [7].

2. Gastrointestinal barriers to oral nanodelivery

The gastrointestinal tract presents a moving rather than a static delivery environment. After oral administration, nanocarriers are exposed successively to changes in pH, digestive enzymes, luminal fluids, mucus, and the intestinal epithelium. Each stage can reduce the amount of intact drug that reaches the next one. For this reason, oral bioavailability reflects not only carrier stability but also particle mobility and the efficiency of epithelial transport. The following sections consider these barriers in the order in which an orally administered nanocarrier encounters them.

2.1. Gastric acid and digestive enzyme barrier

The first challenge is exposure to the acidic and enzyme-rich gastrointestinal environment. In the fasted stomach, pH may fall to 1.0–2.0 [8], a range in which many proteins and peptides lose activity through conformational change, denaturation, or hydrolysis. Proteolysis adds a second source of damage: pepsin acts in the stomach, whereas trypsin and chymotrypsin continue peptide cleavage in the intestine. The formulation itself may also be affected. Acidic conditions and digestive components can promote aggregation, disassembly, or premature leakage from nanocarriers before they reach the principal sites of intestinal absorption [9].

Exposure time is also variable. Gastric emptying depends on feeding state, food composition, and individual physiology, so identical formulations may experience different durations of acid and enzyme exposure. At the same time, gastrointestinal motility and continuous fluid turnover dilute the formulation and impose mechanical stress on carrier structures. These factors make the early gastrointestinal phase more than a simple acid-stability problem: the carrier has to remain intact under changing chemical and physical conditions long enough to deliver an active payload to the intestine. Gastric acidity, proteolysis, and gastrointestinal dynamics therefore act together to reduce the amount of drug available for subsequent absorption [10].

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2.2. Mucus barrier

Once a carrier leaves the stomach, the mucus covering the intestinal epithelium becomes an important transport barrier. This layer is formed mainly by highly glycosylated mucins together with water, electrolytes, lipids, and other biological components. Mucins assemble into a hydrated three-dimensional network that is essential for lubrication and epithelial protection, but the same structure restricts the movement of exogenous particles. For an oral nanocarrier, reaching the intestine is therefore not equivalent to reaching the epithelial cell surface [11].

How strongly a nanoparticle interacts with mucin largely determines its behavior in this layer. Cationic or hydrophobic surfaces can associate with mucins through electrostatic attraction, hydrophobic interactions, and hydrogen bonding, which slows diffusion and can immobilize particles within the mucus network [12]. Retention is not necessarily beneficial, because intestinal mucus is continuously secreted and renewed. Particles that remain trapped may be swept away before they contact the epithelium, shortening the time available for absorption. The mucus barrier thus combines two related effects: it limits forward diffusion and, through turnover, removes particles that fail to progress toward the epithelial surface [13].

2.3. Intestinal epithelial barrier

Crossing the mucus layer still leaves the epithelial barrier. The intestinal epithelium is a single layer of columnar cells joined by tight junctions, which strongly restrict paracellular passage of most hydrophilic macromolecules and nanoparticles. As a result, many nanocarriers depend primarily on transcellular transport. This route, however, involves more than entry into the cell; internalization, intracellular sorting, and release from the basolateral side all influence whether a carrier actually contributes to systemic absorption [14].

Nanoparticles can enter intestinal epithelial cells through several endocytic routes, including clathrin- and caveolae-mediated pathways, macropinocytosis, and other non-classical mechanisms [15]. Internalization alone is not sufficient. After uptake, particles commonly move through early and late endosomes and may ultimately reach lysosomes, where acidic and hydrolytic conditions can damage the carrier or its protein cargo. Some nanoparticles remain sequestered in intracellular vesicles instead of being transported across the cell. In that case, a formulation may show strong cellular uptake in vitro while still delivering only a small fraction of drug to the systemic circulation [16].

Efflux transport further complicates epithelial transport. Intestinal cells express several ATP-binding cassette (ABC) transporters, including P-glycoprotein (P-gp), multidrug resistance-associated proteins (MRPs), and breast cancer resistance protein (BCRP). These ATP-dependent systems can return intracellular substrates to the intestinal lumen and thereby reduce net transepithelial transport [17]. Taken together, the epithelial barrier is therefore a sequence of restrictions rather than a single membrane-crossing event: paracellular passage is limited, cellular entry may be inefficient, intracellular vesicles can retain or degrade cargo, and basolateral delivery may remain incomplete.

3. Nanodelivery strategies to overcome gastrointestinal barriers

Because these gastrointestinal barriers occur one after another, successful oral nanodelivery requires a formulation to retain function across several stages. The design problem can be viewed as three linked tasks: keeping the drug and carrier intact during gastrointestinal transit, allowing sufficient

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movement through mucus, and ensuring that epithelial uptake leads to productive transcellular transport rather than intracellular retention. The strategies discussed below are organized around these three tasks.

3.1. Strategies to overcome the gastric acid and digestive enzyme barrier

Acid and digestive enzymes threaten both the biological drug and the carrier that contains it. Strategies used to limit this damage generally fall into three categories: strengthening the carrier structure, reducing local proteolytic activity, and designing release that responds to gastrointestinal pH [18, 19]. These approaches differ in mechanism, but all aim to preserve an active dose until the formulation reaches a more favorable site for absorption.

One approach is to make the carrier itself less susceptible to disruption. Polymeric networks can reduce penetration of acid and enzymes and can also slow premature leakage of the encapsulated drug. For instance, hyaluronic acid-modified lysine-based poly(ester amide) (Lys-aaPEA) nanocarriers retained structural stability under gastrointestinal conditions and reduced insulin degradation [20]. Chitosan-coated porous PLGA particles provided a related form of protection and produced a sustained hypoglycemic effect lasting more than 8 h [21]. These examples show that carrier integrity is not simply a formulation property; it determines how much intact drug remains available for all downstream transport steps.

Protease inhibition addresses the same problem from the surrounding intestinal environment rather than from the carrier structure. In CS/γPGA-DTPA nanoparticles, diethylenetriaminepentaacetic acid (DTPA) chelated intestinal divalent metal ions and thereby reduced the activity of metal-dependent proteases. The component also contributed to pH-responsive disassembly and increased paracellular permeability. This combination of local enzyme inhibition with other delivery functions increased intestinal insulin absorption and produced a relative oral bioavailability of approximately 20% [22].

A third option is to use gastrointestinal pH as a trigger rather than merely treating acidity as a threat. An alginate coating, for example, improved the acid stability of ZIF-8 and restricted premature release, whereas the higher intestinal pH promoted pore exposure and drug release. A formulation containing metformin and a GLP-1 receptor agonist released its payload more rapidly at pH 8.0 than at pH 1.5 [23]. P(MMA-co-MAA)-b-PAEMA micelles showed a similar principle: they remained stable at pH 1.2 but rearranged as pH increased, which triggered insulin release [24]. Such systems link protection and release in time, so the property that is useful in the stomach does not have to remain unchanged in the intestine.

3.2. Strategies to overcome the mucus barrier

Mucus presents a different design conflict. Weak interaction with mucin favors diffusion toward the epithelium, whereas stronger interaction can prolong residence in the intestine. Neither extreme is necessarily optimal: highly adhesive particles may never reach the epithelial surface, but completely non-adhesive particles may be cleared too quickly [25]. Current work therefore includes not only low-fouling surfaces but also coatings that change after mucus penetration and formulations that deliberately separate retention from later penetration. The key issue is to control when, and for how long, a carrier interacts with mucus.

Reducing nonspecific mucin binding is the most direct way to increase movement through mucus. Because electrostatic, hydrophobic, and hydrogen-bonding interactions can retain particles, hydrophilic and weakly charged surfaces are often favored. Zwitterionic coatings are particularly

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useful because their strongly hydrated interfaces reduce direct contact with mucin. Rao et al. applied the zwitterionic polyphosphoester P(PyEP-g-SB) to porous silicon nanoparticles and observed improved particle diffusion, a 1.4–1.7-fold increase in insulin transport across Caco-2/HT-29-MTX monolayers, and an approximate doubling of oral insulin bioavailability [26]. Anionic coatings can achieve a similar reduction in mucus interaction. Alginate-coated chitosan–insulin nanocomplexes, for example, showed approximately 1.6–2.5-fold greater mucus penetration, with lower-G-content and lower-molecular-weight alginate performing particularly well [27].

A surface optimized only for mucus diffusion may perform poorly at the next step. Near-neutral or highly hydrated particles can traverse mucus efficiently but may interact only weakly with epithelial cells. This trade-off has encouraged the development of surfaces that change during transit. In one example, a detachable pHPMA layer temporarily masked the positive charge of insulin-loaded N-trimethyl chitosan (TMC) nanoparticles. The shield reduced interaction with mucus; after removal near the epithelial surface, the TMC core was exposed and epithelial interaction increased. This sequence of mucus penetration, deshielding, and epithelial permeation increased relative oral bioavailability 2.8-fold compared with uncoated TMC nanoparticles [28]. A related design used enzyme-triggered charge conversion. In P-R8-Pho nanoparticles, phosphate groups initially masked the cationic R8 peptide and produced a near-neutral surface (−2.39 mV). Intestinal alkaline phosphatase removed these groups, exposing R8 and shifting the potential to +7.37 mV. The change promoted epithelial uptake and transepithelial transport and increased oral insulin bioavailability by approximately 1.9-fold compared with R8-modified nanoparticles without responsive shielding [29].

Retention and penetration can also be assigned to different components of the same formulation. Sheng et al. combined mucoadhesive TMC-coated PLGA nanoparticles with low-molecular-weight protamine (LMWP)–insulin complexes. TMC prolonged residence at the mucosal surface, whereas released LMWP subsequently promoted insulin penetration. The resulting retention–release–penetration sequence produced an oral pharmacological bioavailability of 17.98 ± 5.61%, approximately twice that of the corresponding mucoadhesive formulation containing native insulin [30]. The comparison by Cheng et al. is especially informative because it shows why mucus penetration should not be treated as an isolated endpoint. About 70% of mucoadhesive Ins/PBCA/CS particles accumulated in mucus within 10 min, whereas roughly 80% of alginate-coated Ins/PBCA/CS/Alg particles crossed the mucus layer. The mucus-penetrating formulation produced a faster hypoglycemic response, while the mucoadhesive formulation gave a more sustained effect; nevertheless, pharmacological bioavailability was similar (8.80% versus 8.44%). Faster passage through mucus, therefore, did not automatically yield greater total absorption. A useful formulation must balance access to the epithelium with sufficient local residence [7].

3.3. Strategies to overcome the intestinal epithelial barrier

At the epithelial stage, the useful endpoint is not cellular uptake itself but net transport to the basolateral side. A carrier may enter cells efficiently and still fail because it is routed to lysosomes, retained in intracellular vesicles, or poorly released. For this reason, epithelial delivery strategies increasingly address the full sequence from apical uptake to intracellular sorting and basolateral exocytosis. Two broad approaches have emerged: using endogenous transport pathways that naturally support transcytosis and deliberately redirecting intracellular trafficking away from degradative compartments [31].

Endogenous nutrient-transport systems provide one way to couple uptake with movement across the epithelium. Zhang et al. developed glucose-modified PLGA–lipid hybrid nanoparticles intended

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to engage glucose transport-related mechanisms. The modified particles showed improved epithelial uptake and transepithelial transport and produced a sustained glucose-lowering effect in mice with type 1 diabetes. Bile acid transport offers another example. Because bile acids are normally reabsorbed through the apical sodium-dependent bile acid transporter (ASBT), bile acid-functionalized nanoparticles can make use of this physiological pathway [32]. Such modification improved epithelial transport, intestinal insulin absorption, and the in vivo glucose-lowering response [33].

Receptor-mediated transcytosis can be particularly useful when intracellular routing and basolateral release need to be coordinated. The neonatal Fc receptor (FcRn) illustrates this principle: it binds IgG in acidic endosomes and releases it at near-neutral extracellular pH, thereby supporting directional transport. Site-adaptive milk-derived nanovesicles (MiNVs) used the natural IgG–FcRn interaction to promote intestinal transcytosis. After apical uptake, the vesicles entered FcRn-associated trafficking pathways and were released from the basolateral side. The system improved transepithelial insulin delivery, oral bioavailability, and sustained glucose-lowering activity in vivo [34]. The important point is that the gain came from directing what happened after uptake, not simply from increasing the number of particles entering cells.

Intracellular routing can also be altered without relying on a classical transcytosis receptor. L-cysteine (Cys) modification, for example, promoted Golgi-associated trafficking of nanoparticles. Compared with unmodified particles, Cys-modified carriers showed less lysosomal sorting and greater entry into Golgi-associated secretory pathways after uptake. This redistribution increased extracellular release and transepithelial transport of protein therapeutics [35]. The example reinforces a broader design principle: once a carrier is inside an epithelial cell, directing it toward a secretory route may be as important as improving its initial internalization.

4. Conclusions and future perspectives

Oral nanodelivery remains attractive for insulin and GLP-1RAs because it could reduce dependence on repeated injections, but the major translational problem is the cumulative loss that occurs across gastrointestinal transport. A carrier must arrive intact, avoid excessive mucus retention, enter the epithelium, survive intracellular processing, and finally be released toward the systemic circulation. Failure at any one of these stages can offset improvements made earlier. This argues against evaluating formulations by a single favorable property, such as high mucus penetration or high cellular uptake. More informative designs and experiments should consider how performance is coupled across successive delivery steps. At the same time, any increase in transport efficiency must remain compatible with long-term safety, patient-to-patient variability, reproducible manufacture, and practical formulation complexity.

4.1. Current challenges

Low and variable oral bioavailability is still the main obstacle to clinical translation. Part of this variability is biological: gastric emptying, intestinal transit, mucus properties, and other aspects of gastrointestinal physiology differ among individuals and can alter nanocarrier performance. Part is methodological. Formulation composition, dose, animal model, and the way bioavailability is calculated vary considerably among studies, making apparently similar systems difficult to compare. Encouraging animal results should therefore be interpreted with this heterogeneity in mind. Another unresolved issue is the fate of carriers after they reach the epithelial surface. High mucus penetration or cellular uptake does not necessarily predict systemic absorption [36], because intracellular

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degradation, recycling, or retention can interrupt productive transport. Future evaluation should include intracellular sorting, transcytosis, and basolateral release rather than relying on uptake alone. Safety is equally important for a chronic disease. Materials that transiently enhance permeability or disturb epithelial barriers may behave differently under repeated administration, so long-term dosing studies are needed. Finally, complex multilayer coatings and extensive functionalization can create manufacturing and quality-control problems. Translational design must therefore balance delivery performance with structural simplicity and manufacturability [37].

4.2. Future directions

Future oral nanocarriers are likely to benefit from changing their behavior as they move through the gastrointestinal tract rather than maintaining one fixed surface or structure. Protection is most useful in the stomach, release becomes desirable in the intestine, and epithelial interaction should increase only after mucus has been crossed. pH-, enzyme-, and surface-responsive materials provide possible ways to impose this temporal order. Glucose-responsive designs extend the concept further by linking release to physiological need. Phenylboronic acid and glucose oxidase are representative components used for such systems, with the aim of increasing insulin release during hyperglycemia while limiting unnecessary release at lower glucose concentrations. Their response threshold, kinetics, and stability in the gastrointestinal environment, however, still require optimization. At the epithelial stage, greater attention should be paid to productive transport. Manipulating endogenous transcytosis pathways, intracellular sorting, and basolateral exocytosis may provide a more useful route to higher systemic exposure than simply maximizing uptake.

4.3. AI/ML-assisted design

The number of variables that can be adjusted in an oral nanocarrier is increasing rapidly. Composition, particle properties, ligand density, and processing conditions can influence one another, which makes formulation optimization difficult to handle by changing one factor at a time. Artificial intelligence (AI) and machine learning (ML) could help identify combinations of variables associated with useful transport or pharmacokinetic outcomes and could be used to prioritize formulations for experimental testing [38]. Their value, however, will depend less on model complexity than on the quality of the underlying data. Comparable datasets should record formulation characteristics together with relevant transport and in vivo outcomes, and they should include unsuccessful formulations as well as positive results. With such data, iterative workflows that combine prediction, experimental screening, validation, and model updating may reduce the experimental search space and make formulation development more systematic.

Adding more functional layers is unlikely, by itself, to resolve the translational limitations of oral nanodelivery. A more practical strategy is to identify the dominant loss at each stage of transport and introduce only the function needed to address it. This requires quantitative links between formulation properties, barrier-specific behavior, and in vivo exposure. Data-driven design may help establish those links, but it does not remove the need to consider safety and manufacturing. For oral nanocarriers intended for long-term diabetes treatment, the most successful formulation may therefore be not the most complex one, but the simplest system that preserves adequate performance across the full delivery pathway.

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