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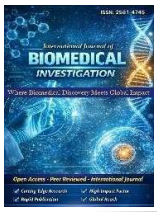

Review Article

GLP-1 Receptor-Targeted Nanomedicine: Emerging Pharmaceutical Strategies for Diabetes Therapy

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ABSTRACT

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have transformed diabetes therapy by improving glycaemic control, body weight and cardiometabolic outcomes. However, peptide instability, gastrointestinal degradation, limited epithelial permeability, variable absorption and frequent administration remain important pharmaceutical challenges. Nanomedicine provides opportunities to protect GLP-1RAs, enhance bioavailability, control drug release and facilitate targeted delivery. This review examines emerging GLP-1 receptor (GLP-1R)-targeted nanomedicine strategies, with emphasis on research published from 2020 to 2026. Polymeric nanoparticles, lipid nanoparticles, liposomes, nanogels, nanoemulsions, nanostructured lipid carriers, biomimetic systems and stimuli-responsive platforms are discussed. Recent advances include FcRn-targeted semaglutide nanoparticles, glycocholic-acid-modified nanoparticles, supramolecular semaglutide nanocomplexes and hydrophobic-ion-paired systems for oral delivery. Particular attention is given to particle size, ligand density, encapsulation efficiency, peptide integrity, release kinetics, receptor-mediated uptake and pharmacokinetic performance. Although direct clinical evidence for GLP-1R-targeted nanoparticles remains limited, emerging preclinical findings indicate considerable potential for improving oral delivery, controlled exposure and therapeutic precision. Future development should prioritize mechanistic targeting validation, scalable manufacturing, long-term safety and clinically meaningful advantages over existing GLP-1RA formulations.

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Introduction

Diabetes mellitus has evolved from a predominantly glycaemic disorder into a complex cardiometabolic disease requiring simultaneous management of glucose, body weight, cardiovascular risk, renal risk and treatment adherence. The expanding use of GLP-1RAs reflects this transition. Oral semaglutide established that a peptide class traditionally associated with injections could be formulated for oral administration, while subsequent clinical programmes demonstrated increasingly broad cardiometabolic effects [1-6]. At the

same time, nanomedicine has progressed from proof-of-concept formulations toward more sophisticated systems incorporating targeting ligands, responsive polymers, lipid assemblies, biomimetic membranes and controlled-release mechanisms [7-12]. The pharmaceutical problem is particularly important for peptide therapeutics. Peptides generally have high molecular weight, hydrophilicity, limited membrane permeability and susceptibility to proteolysis. Their gastrointestinal absorption is therefore poor unless chemical modification, permeation enhancement or protective formulation is used. Even when systemic exposure is achieved, the formulation must preserve the native conformation or active pharmacophore required for receptor recognition. The challenge is consequently multidimensional: the dosage form must protect the peptide, transport it through biological barriers, release it at the correct site and maintain biological activity.

Nanomedicine provides an opportunity to integrate these functions within one dosage form. Polymeric nanoparticles can physically shield peptides from enzymes and provide sustained release; lipid nanoparticles can facilitate membrane interaction and encapsulate biological molecules; nanostructured lipid carriers can combine solid and liquid lipids to modify loading and release; nanogels can respond to pH or enzymes; and biomimetic vesicles can exploit endogenous transport mechanisms. More advanced systems can add surface ligands for receptor-mediated uptake or combine multiple triggers to create sequential delivery. The concept of GLP-1R targeting is particularly interesting because GLP-1R is itself a clinically validated pharmacological target. A GLP-1RA-containing nanoparticle can therefore be designed not only to carry the drug but also to interact with GLP-1R-positive cells. Such a system could theoretically increase cellular association and intracellular delivery, alter tissue distribution and reduce the amount of free agonist required. However, receptor targeting should not be assumed to be beneficial simply because the receptor is pharmacologically important. The targeting ligand must retain affinity after conjugation, remain accessible after protein-corona formation and produce a measurable improvement over a non-targeted carrier [13, 14].

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Recent research has also clarified that "targeted nanomedicine" can mean different things. A nanoparticle may target intestinal epithelial receptors to enhance oral absorption, target L cells to stimulate endogenous GLP-1 secretion, target GLP-1R-expressing tissues after systemic administration, or target a different receptor such as FcRn to promote peptide transcytosis. These mechanisms should be distinguished when interpreting the literature [15-18]. This review therefore examines GLP-1R-targeted nanomedicine as a pharmaceutical technology rather than simply a nanotechnology concept. Particular emphasis is placed on the evidence generated from 2020 through 2026, formulation variables that determine performance, the distinction between oral-absorption targeting and therapeutic-receptor targeting and the translational criteria required for clinical development.

Global Diabetes Burden and Unmet Pharmaceutical Need

The continuing growth of diabetes creates a strong rationale for pharmaceutical innovations that improve efficacy, adherence and access. Contemporary global estimates place the number of adults living with diabetes in the hundreds of millions, with substantial numbers remaining undiagnosed. The burden is not distributed uniformly: rapid growth is occurring in low- and middle-income regions where treatment affordability, continuity of care and access to specialist services may be constrained. Consequently, a technically sophisticated formulation is only valuable if its manufacturing cost and dosing requirements can ultimately support broad implementation.The unmet need extends beyond glucose control. Many patients require simultaneous management of obesity, hypertension, dyslipidaemia, chronic kidney disease and cardiovascular disease. GLP-1RAs are attractive because they act at several clinically relevant levels. Their glucose-dependent insulinotropic action can lower HbA1c without the same intrinsic hypoglycaemia risk associated with insulin or insulin secretagogues, while appetite reduction and delayed gastric emptying contribute to weight loss. Cardiovascular outcome studies have additionally shown risk reduction for selected populations [19-22].

For nanomedicine, this clinical context changes the development benchmark. A new nanoparticle should not simply reproduce the glucose lowering of an established GLP-1RA. It should solve a clearly defined pharmaceutical limitation, such as oral absorption, dosing frequency, stability, tissue selectivity, dose sparing or tolerability. Development programmes should therefore begin with an explicit target product

profile rather than assuming that nanoscale size itself constitutes therapeutic innovation.

Rationale for GLP-1R-Targeted Nanomedicine

GLP-1R-targeted nanomedicine is based on two complementary concepts: the GLP-1R pathway provides the therapeutic mechanism, while the nanocarrier provides spatial and temporal control over drug exposure. A successful system may protect the agonist from degradation, improve transport across a biological barrier and then increase local interaction with receptor-positive cells. The approach is especially attractive for peptides because receptor-directed internalisation can potentially compensate for poor passive permeability. If a targeting ligand binds the receptor and triggers endocytosis, a nanoparticle can enter the cell through a biological pathway that would be inefficient for a free peptide. The value of this process depends on intracellular trafficking. Endocytosis followed by lysosomal degradation is not useful if the payload must reach the cytosol or extracellular receptor. Conversely, controlled endosomal escape can be beneficial for some payloads but may introduce membrane toxicity. A central research requirement is therefore mechanistic validation. Receptor-positive and receptor-negative cells should be compared; free ligand should be used for competitive blocking; receptor knockdown or knockout should be considered; and nanoparticle uptake should be quantified rather than inferred from microscopy alone. Tissue-level evidence should include biodistribution and pharmacodynamic outcomes. This framework separates genuine molecular targeting from nonspecific nanoparticle accumulation [23-27].

GLP-1 Biology and GLP-1 Receptor Pharmacology

GLP-1 is an incretin hormone derived from proglucagon processing. Nutrient exposure stimulates GLP-1 secretion from intestinal L cells, while central and peripheral GLP-1 systems contribute to appetite regulation and metabolic signalling. The biologically active peptide is rapidly degraded, particularly by dipeptidyl peptidase-4 and is cleared rapidly from the circulation. Therapeutic GLP-1RAs therefore incorporate structural modifications that increase enzymatic stability and/or prolong systemic residence. The GLP-1 receptor is a class B1 G-protein-coupled receptor. Its canonical signalling involves Gs activation, increased adenylyl cyclase activity and cyclic AMP production, followed by downstream protein kinase and exchange-protein signalling. In pancreatic β cells, these pathways amplify glucose-dependent insulin secretion. GLP-1R activation can also reduce glucagon secretion when plasma glucose is elevated, slow gastric emptying and modulate central pathways controlling appetite [28, 29]. The receptor is therefore both a pharmacological target and a potential nanomedicine address. However, the biological distribution of GLP-1R means that targeting can influence multiple tissues. A carrier designed for pancreatic β-cell delivery could have a different safety profile from a carrier designed for intestinal epithelial transport. The ligand should consequently be selected according to the desired tissue rather than merely according to receptor affinity [30].

A further consideration is receptor pharmacology. GLP-1R ligands can act as agonists, partial agonists, antagonists or biased ligands. An agonistic targeting ligand could itself produce biological activity before the payload is released. An antagonist-derived ligand may provide binding without excessive receptor stimulation, but it must maintain sufficient affinity after surface conjugation. The linker chemistry is equally important because steric hindrance can reduce receptor access. Receptor internalisation is another determinant. Some GLP-1R ligands induce receptor trafficking and recycling. A nanoparticle may exploit this process for intracellular transport, but excessive receptor engagement could alter receptor availability and potentially attenuate signalling. Thus, targeting density should be optimised experimentally rather than maximised [31, 32].

Molecular Engineering of GLP-1R Agonists

The clinical development of GLP-1RAs demonstrates how molecular engineering can overcome peptide instability. Semaglutide incorporates amino-acid substitutions and a fatty-acid side chain that increase albumin binding and prolong systemic exposure. Liraglutide and dulaglutide employ different strategies to extend pharmacokinetics. These modifications provide a useful design framework for nanomedicine: molecular half-life extension and formulation-based protection are complementary rather than mutually exclusive [33-36]. A nanocarrier can also change the apparent pharmacokinetics of a peptide without modifying its sequence. Encapsulation may reduce proteolysis, while controlled release may decrease peak-to-trough fluctuation. However, the carrier can introduce new barriers, including incomplete release and adsorption of peptide to internal surfaces. Therefore, intact active peptide rather than total peptide mass should be quantified during development. The molecular and formulation strategies can be combined. A long-acting analogue can be incorporated into a biodegradable depot, while an oral analogue can be paired with a permeation-enhancing nanoparticle. The optimal combination depends on the desired clinical profile.

Clinical Pharmacology of Semaglutide and Other GLP-1RAs

The clinical development of oral semaglutide is central to the nanomedicine discussion because it demonstrates that an orally administered GLP-1RA can achieve meaningful systemic exposure. The PIONEER programme included more than 9500 patients across multiple trials and evaluated oral semaglutide across different background therapies [19]. PIONEER 9 and PIONEER 10 showed clinically relevant HbA1c and body-weight responses in Japanese populations, while other PIONEER studies established efficacy against placebo and selected active comparators [37-41]. Dose escalation has been important because higher semaglutide exposure generally increases pharmacodynamic effects. SUSTAIN FORTE compared 2.0 mg with 1.0 mg once weekly in type 2 diabetes and demonstrated greater glycaemic efficacy with the higher dose [22]. This illustrates the relationship between exposure and response but also highlights why a delivery system should control dose efficiently rather than simply increase dose.

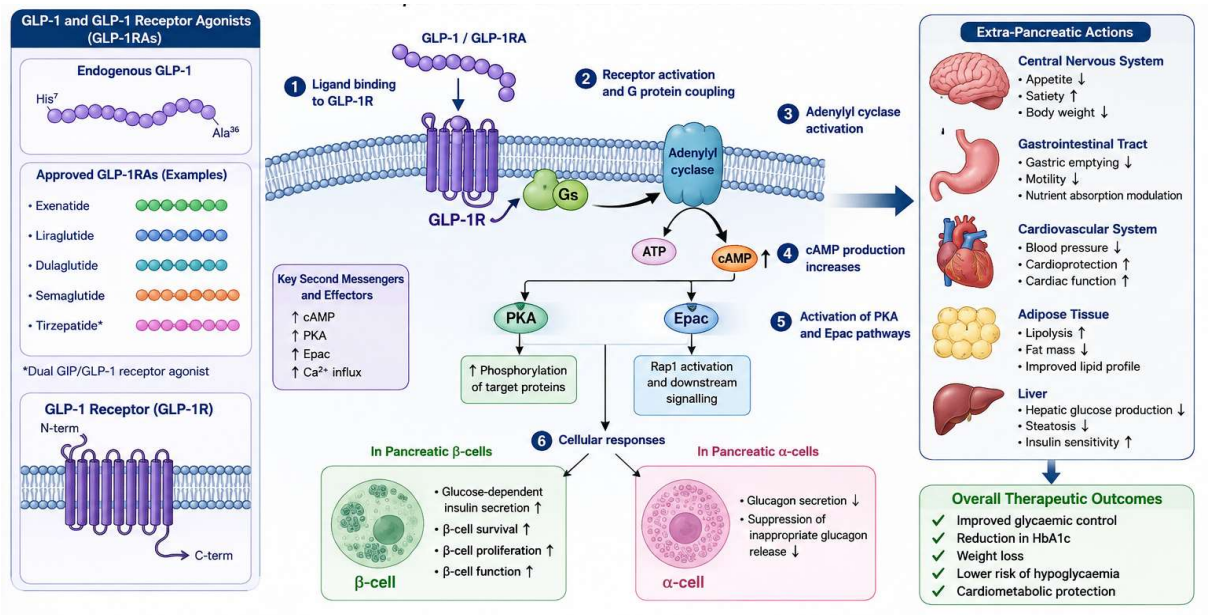

Figure 1: Molecular Pharmacology and Therapeutic Signalling of GLP-1 Receptor Agonists.

Semaglutide has also demonstrated cardiovascular relevance. Analyses of SUSTAIN and PIONEER data showed cardiovascular risk reduction across different baseline risk categories [23]. The SELECT programme subsequently established a cardiovascular benefit for semaglutide 2.4 mg in adults with overweight or obesity and established cardiovascular disease without diabetes. Prespecified analyses in heart failure and according to baseline HbA1c have further expanded the evidence base [24,25]. For nanomedicine, these data establish a demanding clinical benchmark. A GLP-1R-targeted nanoparticle should ideally maintain the known glucose, weight and cardiovascular pharmacology while improving a specific delivery characteristic. If it merely reproduces the effect of an approved injection at greater manufacturing complexity, the translational rationale will be weak.

Pharmaceutical Limitations of Conventional GLP-1RA Delivery

The first limitation is peptide instability. Although engineered GLP-1RAs are more stable than native GLP-1, oral formulations remain vulnerable to gastrointestinal proteolysis. The second limitation is permeability. Semaglutide and related peptides are hydrophilic macromolecules and do not readily diffuse across the intestinal epithelium. The third limitation is dosing convenience. Weekly injection is already a substantial improvement over daily injection, but a tablet or less frequent depot may further improve adherence for selected patients. The fourth limitation is

tolerability. Gastrointestinal adverse events are common during dose escalation and a delivery system that produces uncontrolled bursts could theoretically worsen symptoms [42-45]. The fifth limitation is variability in exposure. Oral absorption is influenced by gastric emptying, intestinal physiology, food, administration conditions and formulation performance. This is important because a nanocarrier can reduce variability only if its interaction with the gastrointestinal environment is itself reproducible. The sixth limitation is access and manufacturing. Advanced GLP-1 medicines can be expensive and adding a complex nanoparticle may increase production costs. The formulation must therefore generate a meaningful benefit in dose efficiency, dosing interval or patient usability. These limitations define the pharmaceutical objectives of nanomedicine: protect the peptide, increase useful exposure, reduce unnecessary systemic exposure, control release and improve patient convenience.

Table 1: Pharmaceutical Limitations of Conventional GLP-1 Receptor Agonist Delivery and Potential Nanomedicine-Based Solutions [33-41].

Pharmaceutical limitation	Underlying problem	Consequence for GLP-1RA therapy	Potential nanomedicine strategy	Expected pharmaceutical advantage
Peptide instability	Susceptibility to gastrointestinal and enzymatic degradation	Loss of intact biologically active peptide	Polymeric nanoparticles, liposomes, lipid nanoparticles, nanogels and protective coatings	Protection of peptide structure and increased intact-payload availability
Poor intestinal permeability	High molecular weight and hydrophilicity restrict epithelial transport	Low and variable oral absorption	Permeation-enhancing nanoparticles, lipid systems, bile-acid-modified carriers and transporter-targeted systems	Enhanced epithelial interaction and systemic exposure
Gastrointestinal degradation	Gastric acid, pepsin and intestinal proteases can degrade peptide cargo	Reduced oral bioavailability	Enteric-protected and enzyme-responsive nanocarriers	Site-specific protection and release
Mucus barrier	Mucus can trap or retard nanoparticle movement	Reduced access to intestinal epithelium	Mucus-penetrating surface modification or optimized bile-acid-derived ligands	Improved transport toward epithelial cells
Tight epithelial barrier	Tight junctions and limited transcellular transport restrict macromolecule uptake	Poor systemic delivery	Receptor-mediated transport, lipid nanoparticles and permeation-enhancing systems	Increased epithelial uptake and transcytosis
Variable oral exposure	Gastric emptying, food, intestinal physiology and administration conditions affect absorption	Inter-individual variability in therapeutic response	Controlled-release and barrier-specific nanocarriers	More reproducible exposure
Frequent administration	Injectable therapy may impose adherence burden despite long-acting formulations	Reduced convenience for some patients	Long-acting nanoparticles, nanodepots and controlled-release systems	Prolonged therapeutic exposure and reduced dosing frequency
Peak-related tolerability	Rapid increases in systemic exposure may contribute to adverse effects	Gastrointestinal intolerance during dose escalation	Sustained-release nanoparticles and controlled-release depots	Reduced peak-to-trough fluctuation
Limited tissue selectivity	Conventional formulations distribute according to systemic pharmacokinetics	Unnecessary exposure of non-target tissues	Ligand-decorated nanoparticles and receptor-targeted systems	Potentially improved spatial selectivity
Manufacturing complexity	Advanced formulations may increase production and quality-control requirements	Higher cost and translational difficulty	Scalable lipid/polymeric platforms and simplified multifunctional systems	Improved manufacturability and reproducibility
Limited reversibility of long-acting depots	Drug cannot be rapidly removed after administration	Potential concern during adverse events	Predictable release kinetics and dose-flexible depot systems	Improved control of therapeutic exposure
Need to preserve peptide activity	Processing and encapsulation can affect peptide conformation	Reduced receptor activity despite adequate drug loading	Stabilizing excipients, optimized encapsulation and analytical assessment of intact active peptide	Maintenance of biological activity

Gastrointestinal Barriers to Oral Peptide Delivery

The gastrointestinal tract presents sequential barriers. Gastric acid can destabilize sensitive components, while pepsin and intestinal proteases can cleave peptide bonds. Mucus can trap particles through hydrophobic and electrostatic interactions and epithelial tight junctions limit paracellular transport. After cellular uptake, endosomal trafficking can direct macromolecules toward degradation. The oral nanoparticle therefore needs a sequence of functions rather than a single property. It may require enteric protection in the stomach, mucus penetration in the intestine, epithelial interaction, receptor-mediated uptake and controlled intracellular or extracellular release. This sequential-barrier concept is now a central theme in peptide nanomedicine [46]. Research in semaglutide nanoparticles has shown that surface chemistry matters. Glycocholic-acid density can influence mucus penetration, cellular uptake, apparent permeability and oral bioavailability, indicating that the optimum ligand density is not necessarily the highest possible density [26]. This provides a strong example of why formulation variables must be optimized quantitatively.

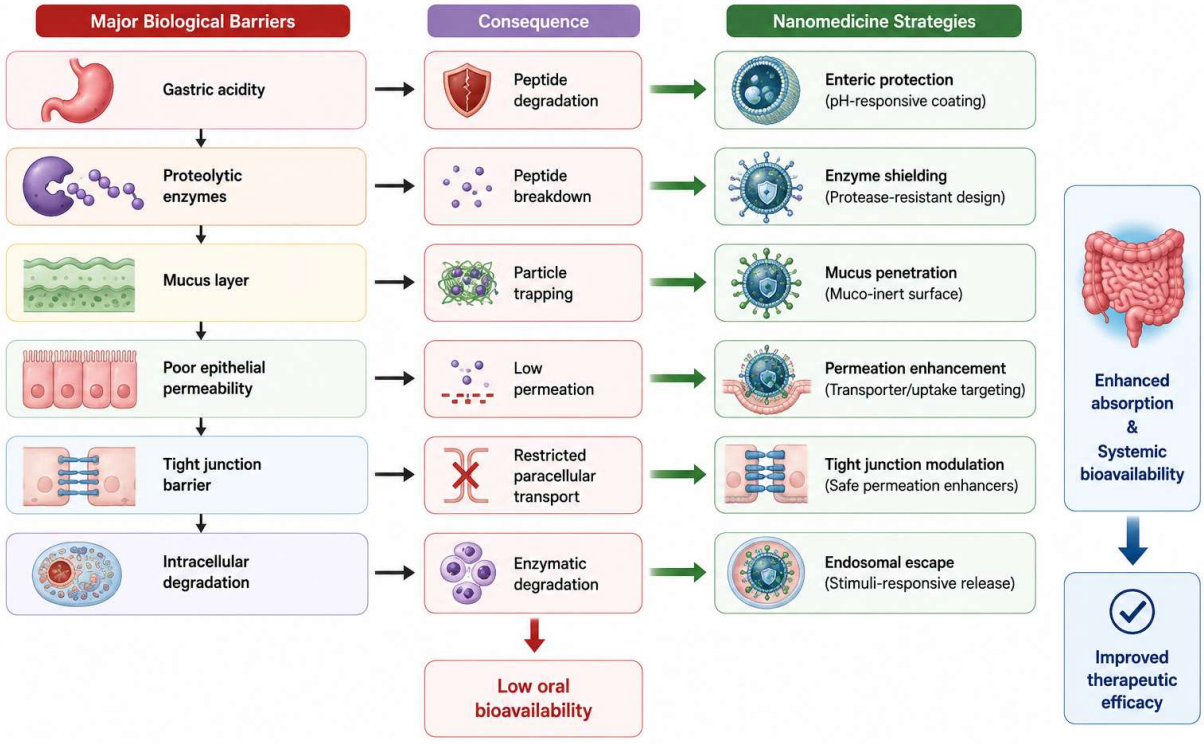

Figure 2: Pharmacological and Physiological Barriers to Oral GLP-1RA Delivery.

Injection-Site and Long-Acting Delivery Challenges

Injectable nanomedicines avoid the gastrointestinal barrier but introduce local depot and systemic clearance considerations. A biodegradable polymeric carrier can create a local reservoir, but polymer degradation may change pH and affect peptide stability. Excessive burst release can produce high early exposure, while excessively slow release can result in subtherapeutic concentrations. For chronic diabetes therapy, reversibility is important. A patient who receives a long-acting depot cannot simply remove the dose if an adverse event occurs. Consequently, release kinetics must be highly predictable. Injectable systems should be evaluated for burst release, cumulative release, depot persistence, tissue histology and systemic exposure [47-49].

Nanocarrier Platforms for GLP-1-Based Delivery

Nanocarrier selection determines loading, release, stability, biological interaction and manufacturability. The principal platforms include polymeric nanoparticles, lipid nanoparticles, liposomes, solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions, micelles, nanogels and biomimetic vesicles. Polymeric systems are attractive because

polymer composition can be adjusted to control degradation and release. PLGA is widely studied because its degradation products are metabolically compatible and its properties can be tuned by lactide:glycolide ratio and molecular weight. However, acidic degradation products may destabilize peptide cargo [50-53].

Lipid systems provide high biocompatibility and can facilitate membrane interaction. Liposomes offer an aqueous core for hydrophilic molecules, while lipid nanoparticles can incorporate ionizable lipids and surface ligands. Their principal challenges include oxidation, hydrolysis, leakage and storage stability. Nanogels are water-rich polymer networks with tunable responsiveness. They can be designed to swell or degrade under specific pH, ionic or enzymatic conditions. Nanoemulsions and self-emulsifying systems can increase interfacial area and are particularly relevant to oral delivery [54]. Recent 2025 and 2026 reviews emphasize that nanoformulation is moving toward multifunctional systems rather than simple encapsulation [27-31]. For GLP-1 delivery, the most useful carrier is therefore the one that solves a defined pharmacokinetic problem with the minimum necessary structural complexity.

Table 2: Comparative Characteristics of Nanocarrier Platforms for GLP-1-Based Delivery [50-54].

Nanocarrier platform	Structural characteristics	Major role in GLP-1 delivery	Key advantages	Major limitations	Suitable delivery strategy	Important formulation parameters
Polymeric nanoparticles	Biodegradable polymeric matrix or shell	Peptide protection and controlled release	Tunable degradation, sustained release and surface functionalization	Possible peptide instability within polymer matrix and acidic degradation products	Oral or injectable controlled delivery	Polymer composition, molecular weight, particle size, PDI, loading and release rate
PLGA nanoparticles	Poly(lactic-co-glycolic acid) matrix	Sustained peptide release	Established biodegradable polymer and adjustable degradation	Acidic microenvironment during degradation may affect peptide integrity	Long-acting and controlled delivery	Lactide:glycolide ratio, molecular weight, particle size and stabilizer
Chitosan nanoparticles	Cationic polysaccharide-based particles	Oral delivery and mucosal interaction	Mucoadhesion and potential permeability enhancement	Excessive positive charge may increase nonspecific interactions and membrane disruption	Oral peptide delivery	Degree of deacetylation, charge, particle size and polymer concentration
Lipid nanoparticles	Lipid-based self-assembled nanostructures	Protection and membrane interaction	High biocompatibility and efficient biological-macromolecule delivery	Oxidation, hydrolysis, leakage and storage stability	Oral or systemic delivery	Lipid composition, particle size, surface charge and ligand density
Liposomes	Phospholipid bilayer surrounding aqueous core	Encapsulation of hydrophilic peptide cargo	Flexible surface modification and high biocompatibility	Leakage, oxidation and physical instability	Oral, injectable or targeted delivery	Lipid composition, cholesterol, size, encapsulation efficiency and surface ligand
Solid lipid nanoparticles	Solid lipid matrix	Protection and sustained release	Biocompatibility and controlled release potential	Limited loading for some hydrophilic cargos	Oral or systemic delivery	Lipid type, crystallinity, particle size and drug loading
Nanostructured lipid carriers	Mixture of solid and liquid lipids	Improved loading and modified release	Less ordered lipid matrix and greater loading flexibility	Physical stability and formulation complexity	Oral delivery and sustained release	Solid/liquid lipid ratio, particle size and surface modification
Nanoemulsions	Fine oil/water dispersions	Increase interfacial area and facilitate oral delivery	High surface area and formulation flexibility	Physical instability and limited suitability for some peptide cargos	Oral delivery	Droplet size, surfactant concentration and phase composition

Self-microemulsifying systems	Spontaneously emulsifying lipid systems	Improve apparent solubility and intestinal delivery	Useful for hydrophobic or chemically modified peptide forms	Requires compatible molecular and formulation properties	Oral delivery	Oil/surfactant ratio, hydrophobic ion pairing and droplet size
Nanogels	Water-rich cross-linked polymer networks	Protection and stimuli-responsive release	High water content and tunable responsiveness	Complex synthesis and characterization	Oral or intracellular delivery	Cross-linking density, swelling, particle size and stimulus sensitivity
Biomimetic/extracellular-vesicle systems	Biological membranes or vesicular structures	Biological transport and receptor interactions	Potential biocompatibility and endogenous transport mechanisms	Source variability, cargo heterogeneity and difficult standardization	Experimental oral or systemic delivery	Vesicle size, cargo loading, surface markers and purification
Stimuli-responsive nanoparticles	Nanocarriers engineered to respond to pH, enzymes, glucose or redox conditions	On-demand or site-specific release	Programmable release and sequential delivery	Increased formulation and manufacturing complexity	Oral, intracellular or controlled delivery	Trigger threshold, response kinetics, stability and release profile

Polymeric Nanoparticles

Polymeric nanoparticles can be prepared by nanoprecipitation, emulsion-solvent evaporation, ionic gelation or related methods. Particle sizes commonly fall within approximately 50-300 nm depending on formulation and route. A polydispersity index below about 0.2 is often desirable for relatively uniform colloidal systems, although the acceptance range must be product-specific. Peptide loading can occur by encapsulation, adsorption or chemical conjugation. Encapsulation protects the peptide but exposes it to manufacturing stresses. Adsorption is simpler but may provide weaker retention. Covalent attachment can stabilize the payload but may interfere with receptor activity. Chitosan-based systems are attractive for oral delivery because of mucoadhesion and potential permeability enhancement. However, excessive positive charge can increase nonspecific protein adsorption and membrane disruption. Surface modification is therefore often necessary to balance intestinal interaction with tolerability. PLGA nanoparticles provide controlled release but require attention to peptide stability within the polymer matrix. Stabilizing excipients, buffering agents and hydrophilic additives may reduce denaturation. Analytical characterization should include both chemical integrity and receptor activity [34-43].

Lipid Nanoparticles and Liposomes

Lipid nanoparticles have become a major pharmaceutical platform because of their scalable self-assembly and ability to deliver biological macromolecules. For GLP-1 delivery, lipid systems can protect the peptide from enzymatic attack and facilitate interaction with biological membranes. Liposomes can be surface-decorated with targeting ligands, while solid lipid nanoparticles and nanostructured lipid carriers can provide sustained release [55-57]. A 2025 review specifically examined nanoliposome-based systems for diabetes and highlighted their potential for improving stability and delivery of antidiabetic agents [32]. The lipid composition is critical because chain length, saturation, phase transition and cholesterol content influence membrane rigidity and leakage. PEGylation can reduce aggregation and nonspecific protein adsorption but may also decrease cellular uptake. Ligand attachment must therefore be balanced against the stealth requirement. The “PEG dilemma” is particularly relevant when a targeting ligand must remain accessible after exposure to serum proteins.

Nanostructured Lipid Carriers and Nanoemulsions

Nanostructured lipid carriers contain mixtures of solid and liquid lipids, producing a less ordered matrix than solid lipid nanoparticles. This can increase loading capacity and modify release. Surface decoration can alter mucus interaction and intestinal uptake. Self-emulsifying formulations provide a different approach. In 2026, hydrophobic-ion-pairing of semaglutide was investigated for incorporation into a self-microemulsifying system intended to improve oral delivery [33]. The significance of this strategy is that peptide chemistry and nanostructure are optimized together. Rather than attempting to force a highly hydrophilic peptide into a conventional lipid core, hydrophobic ion pairing changes the apparent physicochemical properties before formulation. The development principle is transferable: when a molecule has intrinsic biopharmaceutical limitations, molecular

engineering may be combined with nanotechnology to reduce the burden placed on the carrier.

Nanogels and Stimuli-Responsive Systems

Nanogels can respond to pH, temperature, redox conditions, enzymes or glucose. In diabetes, glucose responsiveness is conceptually attractive because glucose is the central disease biomarker. However, GLP-1RAs already exhibit glucose-dependent insulinotropic activity, so a glucose-triggered release system must demonstrate a benefit beyond the intrinsic pharmacology. pH-responsive systems are more immediately applicable to oral delivery. A formulation may remain stable in the stomach and release the peptide in the small intestine. Enzyme-responsive systems can provide another layer of protection. Redox-responsive carriers may be useful after cellular uptake, where intracellular glutathione concentrations differ from the extracellular environment [58-60]. Recent reviews published in 2024-2025 describe glucose-responsive nanoparticles, hydrogels, microneedles and related systems [34,35]. The challenge is achieving a response window that corresponds to clinically relevant glucose fluctuations without creating oscillatory or unpredictable exposure.

Biomimetic and Extracellular-Vesicle-Based Systems

Biomimetic carriers use cell membranes, extracellular vesicles or protein-based structures to exploit endogenous biological transport. Their potential advantages include biocompatibility and receptor-specific interactions. Milk exosome-based liraglutide delivery has been explored as an oral peptide strategy, illustrating the increasing interest in biologically derived carriers [36]. However, extracellular vesicles create substantial manufacturing and characterization challenges. Source variability, cargo heterogeneity, purification and storage can complicate quality control. For chronic diabetes therapy, batch reproducibility must be comparable to conventional pharmaceutical products. Biomimetic systems may therefore be particularly useful as research platforms for understanding transport mechanisms before a more standardized synthetic carrier is developed.

5. GLP-1R-Targeting Ligands and Receptor-Mediated Delivery

Targeting is the defining feature that differentiates GLP-1R-targeted nanomedicine from conventional GLP-1-loaded nanoparticles. The targeting ligand can be an agonist-derived peptide, antagonist-derived sequence, antibody fragment, affibody, aptamer or other receptor-binding motif. Each class has different affinity, size, immunogenicity and manufacturing implications.

A targeting ligand should ideally show selective binding, preserved affinity after conjugation, adequate accessibility on the nanoparticle surface and receptor-dependent internalisation. Ligand density should be optimized experimentally. Too little ligand may produce weak targeting, while excessive density can cause steric crowding, alter surface charge and increase aggregation [61-63].

Recent work on engineered GLP-1R-targeting nanoplatforms has highlighted lipid, polymeric, inorganic and biomimetic architectures **[37]**. Importantly, the review literature indicates that the field is still predominantly preclinical. The clinical maturity of GLP-1RAs should therefore not be mistaken for clinical validation of GLP-1R-targeted nanoparticles. Targeting can also be indirect. For oral semaglutide, FcRn-targeted nanoparticles have been investigated to promote epithelial transcytosis **[38].** Glycocholic-acid modification has been used to influence intestinal mucus penetration and uptake **[26].** These systems target the delivery barrier rather than GLP-1R itself. Such approaches may be more practical for oral delivery because epithelial transport is the immediate limiting step.

Targeting Density, Affinity and Internalization

A quantitative targeting strategy should characterize ligand density, receptor affinity and uptake kinetics. Surface density can be estimated from ligand input and post-conjugation analysis, while affinity can be evaluated by surface plasmon resonance, biolayer interferometry or cellular binding assays. Cellular uptake should be compared between receptor-positive and receptor-negative cells. Competitive inhibition with excess free ligand provides additional evidence. Receptor knockdown is stronger evidence still. These experiments are essential because nanoparticles can enter cells through nonspecific endocytosis and fluorescence associated with a cell does not necessarily mean intracellular delivery. Internalization kinetics should be linked to therapeutic activity. If the payload is extracellularly active, excessive internalization may be unnecessary. If intracellular release is beneficial, endosomal escape and intracellular bioactivity should be measured. A well-designed study therefore connects receptor binding to uptake, uptake to intracellular fate and intracellular fate to pharmacodynamic response [64-66].

Protein Corona and Biological Identity

Once administered, nanoparticles rapidly adsorb plasma proteins, creating a protein corona that can alter apparent size, surface charge and receptor accessibility. A ligand that is highly exposed in phosphate-buffered

saline may become partially hidden in plasma. Therefore, targeting should be tested in physiologically relevant protein-containing media. The biological identity of a nanoparticle can thus differ from its manufactured identity. This is a central translational issue. Surface characterization should include corona studies and biodistribution should be evaluated in the presence of the full biological environment. Targeting claims based solely on cell culture in serum-free conditions are insufficient for clinical translation [67].

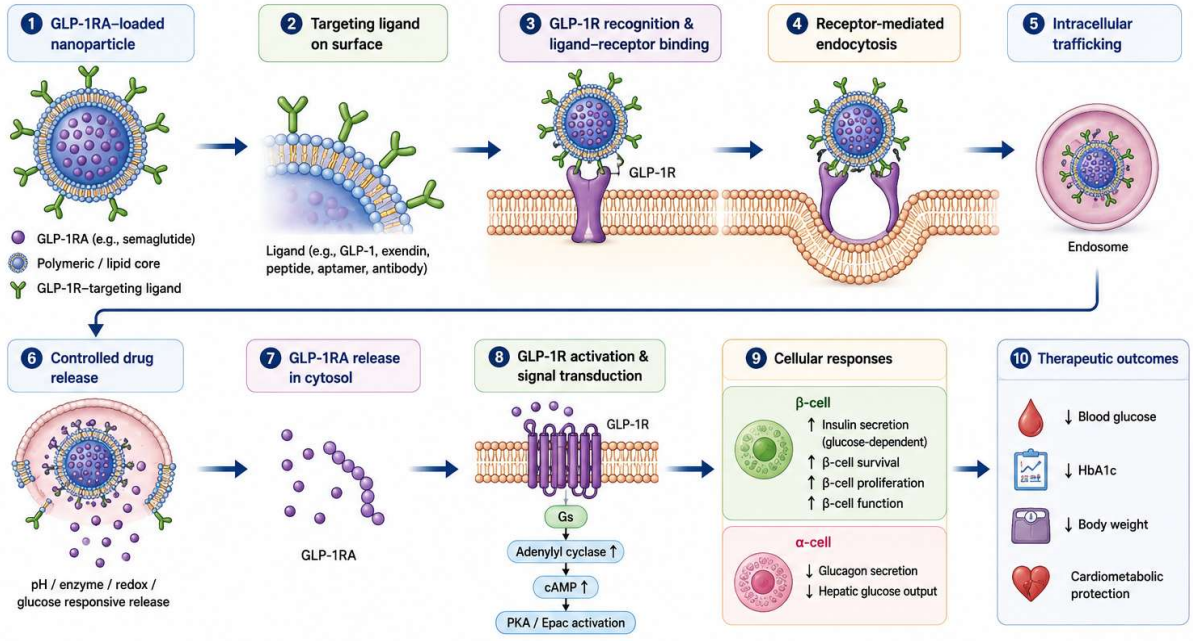

Figure 3. GLP-1 Receptor-Targeted Nanoparticle Delivery: Mechanism of Cellular Targeting and Therapeutic Action.

Oral GLP-1 Nanomedicine: 2020-2026 Research Progress

Oral delivery has become the most active area of GLP-1 formulation research because it directly addresses injection burden. Research from 2020 onward has moved from general oral peptide protection toward barrier-specific and receptor-mediated strategies. In 2020, targeted nanoparticles were developed to increase L-cell stimulation as part of an oral peptide strategy for incretin-based diabetes treatment [39]. This work demonstrated that a nanocarrier could be designed not simply to carry an incretin but also to interact with intestinal biology. An additional 2020 study described oral lipid nanocapsules containing exenatide and demonstrated the possibility of combining oral peptide protection with stimulation of GLP-1-related intestinal pathways [40]. These findings established a conceptual basis for dual-action oral systems.

In 2024, FcRn-targeted semaglutide nanoparticles were developed to improve oral delivery in a type 2 diabetic mouse model. The nanoparticles were functionalized with FcRn-binding peptide or affibody approaches, demonstrating how receptor-mediated transcytosis can be incorporated into oral nanomedicine [38]. This is highly relevant to GLP-1 delivery because it demonstrates targeting of an absorption mechanism rather than relying only on passive permeation [68].

In 2025, glycocholic-acid-modified semaglutide nanoparticles were evaluated with different surface ligand densities. The study assessed mucus penetration, cellular uptake, apparent permeability, intracellular trafficking and oral bioavailability, demonstrating that surface density is a critical formulation variable [26].

In 2026, supramolecular semaglutide nanocomplexes based on positively charged bile-acid derivatives were reported. The optimized system formed particles of approximately 279 nm under aqueous conditions and used electrostatic interactions between modified bile acids and negatively charged semaglutide [41]. This represents a shift toward self-assembled systems in

which the peptide participates directly in nanostructure formation.

Hydrophobic ion pairing provides another 2026 direction. Semaglutide was converted into a hydrophobic ion-paired form to facilitate self-microemulsifying oral delivery [33]. The approach is particularly important because it demonstrates that oral nanomedicine may require coordinated optimization of molecular chemistry and colloidal formulation rather than simply encapsulating the unmodified peptide. Together, these studies show a progression from protection to targeted transport, surface optimization and molecularly enabled self-assembly. The next step is to determine whether these improvements can produce reproducible human exposure.

FcRn-Targeted Semaglutide Nanoparticles

The neonatal Fc receptor is involved in transcytosis and recycling of immunoglobulins and selected macromolecules. FcRn-targeted semaglutide nanoparticles use receptor recognition to facilitate epithelial transport. In the 2024 ACS Nano study, nanoparticles functionalized with FcRn-binding peptide or an affibody were evaluated for oral semaglutide delivery in diabetic mice [38]. The pharmaceutical significance is substantial because it illustrates a general principle: the most useful target for oral delivery may be a transporter or transcytosis receptor rather than the final therapeutic receptor. For GLP-1R-targeted systems, this distinction is crucial. A multi-stage strategy may first use FcRn or another epithelial pathway to cross the intestinal barrier and then exploit GLP-1R targeting after systemic absorption. Such a system would be more complex but could potentially separate the functions of absorption and pharmacological targeting. The major challenges are ligand stability, receptor saturation, species differences in receptor biology and the need to demonstrate that targeting improves human exposure rather than simply increasing uptake in an animal model.

Glycocholic-Acid-Modified Semaglutide Nanoparticles

Bile-acid-derived ligands are attractive for oral delivery because intestinal transport pathways naturally interact with bile acids. The 2025 glycocholic-acid study showed that changing surface density altered several sequential barriers, including surface hydrophobicity, mucus penetration, cellular uptake, apparent permeability and oral bioavailability [26]. This finding has an important formulation implication: targeting ligands can modify multiple physicochemical properties simultaneously. Increasing ligand density may improve receptor interaction but also increase hydrophobicity or alter mucus behaviour. Consequently, optimization should consider a multidimensional response surface rather than a single endpoint. For GLP-1R-targeted nanomedicine, the same principle applies. Increasing GLP-1R ligand density may improve receptor binding but could reduce colloidal stability or change protein-corona formation. Rational formulation therefore requires integrated optimization of particle size, ligand density, charge, hydrophilicity and release.

Mucus-Penetrating Versus Mucoadhesive Nanoparticles

The intestinal mucus layer creates a design paradox for oral nanomedicine. Mucoadhesion can increase residence time and improve the probability of epithelial contact, whereas mucus penetration can facilitate movement through the gel toward the epithelial surface. These strategies are not interchangeable. A strongly mucoadhesive particle may remain close to the luminal surface but become trapped within the mucus, while a mucus-penetrating particle may reach the epithelium more effectively but have a shorter residence time. Surface chemistry is the major determinant of this behaviour. Hydrophilic, low-fouling coatings can reduce interactions with mucin and facilitate diffusion. Polyethylene glycol is widely used for this purpose, although dense PEG layers can reduce cellular interaction. Zwitterionic polymers and hydrophilic polysaccharides provide alternative strategies. For semaglutide nanoparticles, glycocholic-acid density has been shown to influence multiple sequential barriers, emphasizing that the optimal surface is a compromise rather than an absolute property [26, 66].

Particle size also affects mucus transport. Very large particles may show restricted diffusion, whereas smaller particles can move through mucus more readily. However, reducing size can decrease loading and alter clearance. A useful development strategy is therefore to establish a particle-size window in which mucus penetration, epithelial uptake and loading remain balanced. Mucus should also be studied under realistic conditions. Mucin concentration, pH, ionic strength and gastrointestinal motility can influence nanoparticle movement. Artificial mucus models are useful for screening but should be complemented by ex vivo intestinal tissue and in vivo imaging. Fluorescent tracking should distinguish particles that remain in the mucus from particles that reach epithelial cells [45-49]. For GLP-1R-targeted systems, mucus penetration is especially important because a targeting ligand cannot function efficiently if the nanoparticle is trapped several micrometres away from the epithelial surface. Therefore, oral GLP-1R nanomedicine should treat

mucus transport as an upstream prerequisite to receptor targeting.

Long-Acting GLP-1 Nanomedicine

Long-acting systems aim to reduce dosing frequency and maintain a relatively stable concentration-time profile. Although weekly GLP-1RA therapy is already available, longer intervals could further improve adherence. Nanoparticles, microspheres, nanogels and injectable lipid depots can provide sustained release. For polymeric depots, the release mechanism may involve diffusion, polymer erosion or both. PLGA systems can provide weeks of release but may expose the peptide to acidic degradation products. Alternative polymers or buffering excipients may therefore be needed. A useful long-acting formulation should reduce Cmax-related adverse effects without reducing total exposure. Pharmacokinetic evaluation should include Cmax, Tmax, AUC, terminal half-life and fluctuation index. Pharmacodynamic analysis should include fasting glucose, postprandial glucose, HbA1c, body weight and food intake. The development challenge is especially relevant for GLP-1RAs because gastrointestinal adverse effects often occur during initiation and dose escalation. A long-acting system that cannot be rapidly discontinued may create clinical concerns **[69]**. Therefore, release predictability and dose flexibility should be incorporated into the target product profile.

Nanodepots and Controlled Release

Nanodepots can be administered subcutaneously or intramuscularly and designed to release the agonist gradually. The initial burst should be minimized because it can produce transiently high concentrations. Conversely, an excessively slow terminal phase can produce prolonged subtherapeutic exposure. Mathematical release models such as zero-order, first-order, Higuchi and Korsmeyer-Peppas can describe release behaviour, but model fitting should be interpreted mechanistically. A strong development programme should correlate in vitro release with in vivo pharmacokinetics. The ideal long-acting system should show in vitro-in vivo correlation, enabling manufacturing batches to be controlled using release testing. Such correlation can simplify regulatory development and reduce reliance on extensive animal studies during later formulation optimization [44].

Stimuli-Responsive and Glucose-Responsive Nanomedicine

Stimuli-responsive delivery systems attempt to match drug release with a biological signal. In diabetes, glucose is the most obvious stimulus. Glucose-responsive systems commonly use glucose oxidase, phenylboronic acid, concanavalin A or related mechanisms. A rise in glucose can change pH, binding equilibria or network swelling, triggering drug release [34]. For GLP-1 therapy, the advantage is less straightforward than for insulin. GLP-1RAs already stimulate insulin secretion in a glucose-dependent manner. Nevertheless, glucose-responsive delivery could potentially reduce unnecessary exposure and improve postprandial control. The system would need to demonstrate superior pharmacokinetic efficiency or reduced adverse effects compared with a conventional sustained-release formulation. Dual-responsive systems may be more useful. For oral delivery, pH responsiveness can protect the formulation in the stomach, while enzyme or bile-acid interactions can support intestinal transport. After absorption, receptor targeting could provide tissue specificity. This hierarchical design is conceptually stronger than attempting to make one nanoparticle respond to every biological signal. Recent 2024-2026 reviews describe smart nanoparticles as a major direction in diabetes nanomedicine [34,35,42]. However, complexity should be minimized because every additional responsive component introduces manufacturing and analytical variables.

Enzyme-Responsive Release

Enzyme-responsive nanocarriers are attractive because the gastrointestinal tract contains defined proteolytic environments. A carrier can be designed with peptide or protein cross-links that remain stable during one phase of transit and are cleaved in another. For oral GLP-1 delivery, the preferred system would protect the peptide from luminal proteases while releasing it after reaching an absorptive region. An important challenge is avoiding premature cleavage. If the carrier is exposed to the same enzyme that is intended to trigger release before reaching the absorption site, the payload may be released too early. Protective coatings or sequential layers can solve this problem. Enzyme-responsive systems can also be useful intracellularly. Endosomal proteases may trigger release after receptor-mediated uptake. This creates a two-stage formulation in which extracellular stability and intracellular release are controlled by different mechanisms. The design should therefore identify the enzyme concentration, catalytic rate and expected residence time in the relevant compartment. Triggering thresholds should be experimentally determined rather than assumed from literature values. This is particularly important because enzyme activity varies among individuals and can be altered by disease, diet and medication [70-72].

Redox-, pH- and Temperature-Responsive Systems

Redox-responsive nanoparticles often use disulfide linkers that are stable extracellularly but cleaved in reducing intracellular environments. Such systems can facilitate release after receptor-mediated endocytosis. For GLP-1R-targeted particles, redox-responsive release may be useful if intracellular delivery improves pharmacological activity or protects the peptide from extracellular degradation. pH-responsive systems are more directly relevant to oral delivery. Enteric polymers can protect particles in the stomach and dissolve at higher intestinal pH. However, a single pH threshold may not perfectly match physiological transit. Multi-layer coatings can provide more gradual transitions. Temperature-responsive systems are less attractive for routine diabetes therapy because external thermal triggering reduces convenience. Nevertheless, thermoresponsive depots may have research value for controlled-release implants or localized delivery. The general principle is that a stimulus should be selected because it is present at the intended site, reproducible, sufficiently different from background conditions and capable of producing a useful change in release. Complexity without a meaningful physiological trigger should be avoided [73-75].

Recent Clinical Evidence Supporting GLP-1-Based Nanomedicine

The clinical evidence for GLP-1RAs provides the biological justification for developing advanced delivery systems. Oral semaglutide has demonstrated that clinically meaningful GLP-1R activation can be achieved through the gastrointestinal route. The PIONEER programme established reductions in HbA1c and body weight, while higher-dose oral regimens have shown additional efficacy [19-22]. Semaglutide has also demonstrated clinically relevant cardiovascular outcomes. A 2020 analysis of SUSTAIN and PIONEER data reported cardiovascular event reduction across different baseline risk categories [23]. In SELECT, semaglutide 2.4 mg reduced major adverse cardiovascular events by approximately 20% compared with placebo in the studied population, establishing an outcome-level benefit beyond glycaemic control [25]. The relevance to nanomedicine is strategic. A future nanoparticle should preserve this clinically validated pharmacology. The key development question is therefore not whether nanoparticles can lower glucose in rodents, but whether they can deliver a clinically validated GLP-1RA in a way that is more convenient, more stable, more selective or more cost-effective. The rise of oral small-molecule GLP-1R agonists also increases competitive pressure. Orally active non-peptide agonists such as orforglipron can avoid some peptide-delivery barriers [43]. Nanomedicine will therefore need to demonstrate advantages that cannot be readily achieved by small molecules, including peptide-specific pharmacology, prolonged exposure or targeted delivery.

Oral Semaglutide: Pharmaceutical Lessons

Oral semaglutide uses salcaprozate sodium (SNAC) as an absorption-enhancing component. The formulation illustrates how a peptide can be administered orally by combining chemical modification with a localized absorption mechanism. However, the requirement for specific administration conditions and the relatively low absolute bioavailability demonstrate that oral peptide delivery remains technically demanding. Recent 2026 research has raised additional questions regarding the gastrointestinal effects of SNAC-enabled delivery, including interactions with the gut environment [44]. This illustrates why next-generation oral nanomedicine should be evaluated not only for systemic exposure but also for gastrointestinal physiology and microbiome interactions. Nanoparticles could potentially improve oral peptide delivery by protecting the drug over a larger intestinal region and providing controlled interaction with epithelial receptors. The development goal should therefore be a reproducible exposure profile rather than simply a high apparent bioavailability in a single animal model.

Recent Research Data, 2020-2026

Research published from 2020 through 2026 shows a clear evolution in the field. In 2020, oral peptide nanocarriers were increasingly designed around intestinal biology, including L-cell stimulation and lipid nanocapsules for incretin-based therapy [39,40]. During 2021-2022, research broadened toward nanostructured lipid carriers, oral peptide nanoparticles and transporter-assisted absorption [45-49]. By 2024, the focus had shifted toward disease-specific nanomedicine and receptor-mediated transport. FcRn-targeted semaglutide nanoparticles demonstrated the potential of epithelial receptor targeting in a diabetic mouse model [38]. Reviews published in 2024 described nanomedicine approaches spanning glucose-responsive systems, gene delivery, oral insulin and regenerative therapy [30,42]. The 2025 literature introduced more precise surface engineering. Glycocholic-acid density was optimized for sequential oral barriers [26], while reviews of smart nanoparticles and nano-based diabetes delivery systems emphasized responsive release, controlled exposure and improved bioavailability [27,28,34].

The 2025 GLP-1R-targeting review consolidated lipid, polymeric, inorganic and biomimetic approaches and explicitly framed GLP-1R-targeting as a multimodal

precision strategy [37]. The 2026 literature then moved toward molecularly enabled nanostructures, including hydrophobic-ion-paired semaglutide self-microemulsifying delivery and supramolecular semaglutide nanocomplexes [33,41]. This progression suggests that the field is moving through four stages: (1) peptide protection, (2) barrier-specific transport, (3) receptor-directed targeting and (4) programmable multifunctional delivery. The next stage should be translational validation rather than simply increasing formulation complexity.

Table 3: Representative advances in GLP-1 and peptide nanomedicine research, 2020-2026.

Year	Nanomedicine strategy	Active agent / payload	Target or delivery mechanism	Major reported feature	Pharmaceutical significance	Reference
2020	Targeted nanoparticles for oral peptide delivery	Incretin-based peptide	Intestinal L-cell interaction	Designed to increase L-cell stimulation and improve oral peptide delivery	Demonstrated that nanocarriers can interact with intestinal biological targets rather than simply protect peptide cargo	**[14]**
2020	Oral peptide nanocapsule strategy	Exenatide	Intestinal delivery and peptide protection	Combined oral peptide protection with intestinal biological interaction	Supported development of oral incretin-based nanomedicine	**[13]**
2020	Nanoparticle-based oral peptide delivery	Peptide/protein therapeutics	Transport and absorption enhancement	Nano/microscale systems explored for improved oral bioavailability	Established formulation approaches for overcoming oral peptide barriers	**[16]**
2021	Multi-unit particulate delivery	Peptide therapeutics	Permeation-enhancer-assisted oral transport	Layered drug and permeation-enhancer approach	Demonstrated engineering of sequential oral delivery functions	**[47]**
2021	Lipid-based oral peptide nanocarriers	Therapeutic peptides	Surface-decorated nanostructured lipid carriers	Surface modification investigated for oral peptide delivery	Highlighted the importance of ligand/surface engineering	**[49]**
2022	Oral peptide nanoparticles	Peptide therapeutics	Nanoparticle-mediated intestinal transport	Advanced nanoparticle approaches for diabetes therapy	Expanded the role of nanocarriers in peptide delivery	**[46]**
2022	Lipid-based nanocarriers	Therapeutic peptides/proteins	Oral lipid-mediated transport	Lipid nanocarriers reviewed for oral macromolecule delivery	Supported lipid systems as a major oral peptide platform	**[48]**
2024	FcRn-targeted nanoparticles	Semaglutide	FcRn-mediated epithelial transcytosis	Receptor-targeted oral delivery demonstrated in diabetic mice	Showed that absorption-receptor targeting may overcome epithelial barriers	**[38]**
2024	Nanomedicine for diabetes	Multiple antidiabetic agents	Nanocarrier-mediated delivery	Broad development of oral, responsive and regenerative nanomedicine	Demonstrated expansion from simple encapsulation to multifunctional systems	**[10,42]**
2025	Glycocholic-acid-modified nanoparticles	Semaglutide	Bile-acid-associated intestinal transport	Surface ligand density influenced mucus penetration, uptake, permeability and oral bioavailability	Demonstrated that ligand density is a multidimensional optimization variable	**[26]**
2025	Smart nanoparticles	Antidiabetic therapeutics	Stimuli-responsive delivery	Responsive systems designed for controlled exposure	Shifted emphasis toward programmable and environment-responsive delivery	**[27]**
2025	GLP-1R-targeting nanoplatforms	GLP-1-related therapeutics	GLP-1R-directed targeting	Lipid, polymeric, inorganic and biomimetic architectures reviewed	Consolidated receptor-targeted nanomedicine as a precision strategy	**[37]**
2025	Nano-based diabetes delivery systems	Insulin and antidiabetic agents	Barrier-specific and responsive systems	Advances in oral delivery, controlled	Strengthened translational framework	**[12,28]**

				exposure and bioavailability	for diabetes nanomedicine	
2026	Supramolecular nanocomplexes	Semaglutide	Electrostatic self-assembly using modified bile-acid derivatives	Approximately 279 nm particles reported under aqueous conditions	Demonstrated molecularly enabled self-assembly of semaglutide nanostructures	**[41]**
2026	Hydrophobic ion pairing with self-microemulsifying delivery	Semaglutide	Modified physicochemical properties for lipid-based oral delivery	Hydrophobic ion-paired semaglutide incorporated into a self-microemulsifying system	Demonstrated integration of peptide chemistry with nanostructured oral formulation	**[33]**
2026	Emerging multifunctional nanomedicine	GLP-1-related and antidiabetic therapeutics	Receptor targeting, responsive release and biomimetic transport	Increasing emphasis on programmable multifunctional systems	Indicates transition from peptide protection toward precision and sequential delivery	**[29,30,72]**

Combination and Multifunctional Nanomedicine

Although this review focuses on GLP-1R-targeted systems, future nanomedicines may incorporate complementary metabolic agents. The rationale could include simultaneous insulin-sensitization, lipid lowering, anti-inflammatory activity or tissue protection. However, combination loading increases manufacturing complexity and may produce different optimal release kinetics for each drug. GLP-1R agonists can also be combined pharmacologically with glucose-dependent insulinotropic polypeptide receptor agonism. Tirzepatide demonstrates the clinical value of dual GIP/GLP-1 receptor agonism, while newer co-agonist strategies are being investigated [50,51]. A nanomedicine could theoretically co-deliver multiple peptide agonists, but the formulation would need to preserve the relative potency and release ratio. A simpler approach may be a single carrier with modular surface targeting and a single active peptide. Combination systems should be developed only when co-delivery produces a measurable therapeutic advantage over separate administration.

Future Perspectives

The future of GLP-1R-targeted nanomedicine is likely to involve route-specific rather than universal platforms. Oral systems will focus on sequential gastrointestinal barriers and transporter-mediated absorption. Injectable systems will emphasize long-acting exposure and predictable release. Targeted systemic systems may focus on receptor-positive tissues and dose sparing. Multi-stage targeting is particularly promising. An oral nanoparticle could first use mucus-penetrating or bile-acid-mediated transport, then FcRn or another transcytosis mechanism, followed by systemic GLP-1R targeting. Each stage would have a defined function. Such a design is more rational than asking one ligand to solve every biological barrier. Artificial intelligence may also influence formulation development. Machine-learning models can connect composition and process variables to particle size, PDI, encapsulation and release. Combined with automated microfluidics, this could accelerate formulation optimization. Spatial biology may further refine targeting. Single-cell transcriptomics and spatial proteomics can identify GLP-1R-positive populations and heterogeneity among tissues. This could enable patient-specific targeting strategies. Finally, clinical development should focus on meaningful outcomes. A nanoparticle that improves AUC by 20% but offers no patient-level advantage may not justify development. Conversely, a system that enables monthly dosing, substantially reduces gastrointestinal exposure or provides a practical oral alternative could transform treatment.

Conclusion

GLP-1 receptor agonists have substantially expanded the therapeutic approach to diabetes by providing effective glycaemic control together with clinically relevant effects on body weight and cardiometabolic outcomes. However, their peptide-based nature continues to impose important pharmaceutical challenges, including enzymatic degradation, poor gastrointestinal permeability, variable oral absorption, administration burden and the need for controlled exposure. Nanomedicine offers a versatile platform for addressing these limitations by integrating peptide protection, controlled release, barrier-specific transport and receptor-mediated targeting within a single formulation strategy.

The evidence reviewed from 2020 to 2026 demonstrates a progressive evolution from conventional peptide-

protective nanocarriers toward more sophisticated systems involving FcRn-mediated transport, glycocholic-acid-modified surfaces, supramolecular semaglutide nanocomplexes, hydrophobic-ion-paired systems and stimuli-responsive delivery. Importantly, these approaches demonstrate that successful GLP-1 nanomedicine depends not only on particle size or encapsulation efficiency but also on ligand density, receptor affinity, mucus interaction, epithelial transport, peptide integrity, intracellular trafficking and release kinetics. GLP-1R targeting should therefore be distinguished from strategies that target intestinal absorption mechanisms, as both approaches address different pharmaceutical barriers.

Despite encouraging preclinical advances, direct clinical validation of GLP-1R-targeted nanoparticles remains limited. Future development should prioritize mechanistic confirmation of receptor-mediated targeting, reproducible manufacturing, long-term safety, scalable formulation processes and meaningful pharmacokinetic and pharmacodynamic improvements. Multifunctional systems should be developed only when their additional complexity provides a demonstrable therapeutic advantage. Overall, GLP-1-targeted nanomedicine represents a promising but still translationally immature field, with the greatest potential lying in rationally engineered, route-specific and clinically meaningful delivery systems capable of improving peptide stability, exposure, targeting and patient convenience without compromising the established pharmacology of GLP-1 receptor agonists.

List of Abbreviations

GLP-1: Glucagon-Like Peptide-1; GLP-1RA: Glucagon-Like Peptide-1 Receptor Agonist; GLP-1R: Glucagon-Like Peptide-1 Receptor; GPCR: G Protein-Coupled Receptor; GIP: Glucose-Dependent Insulinotropic Polypeptide; GIPR: Glucose-Dependent Insulinotropic Polypeptide Receptor; T2DM: Type 2 Diabetes Mellitus; DM: Diabetes Mellitus; HbA1c: Glycated Haemoglobin; cAMP: Cyclic Adenosine Monophosphate; PK: Pharmacokinetics; PD: Pharmacodynamics; AUC: Area Under the Curve; Cmax: Maximum Plasma Concentration; Tmax: Time to Maximum Plasma Concentration; PDI: Polydispersity Index; EE: Encapsulation Efficiency; NP: Nanoparticle; NLC: Nanostructured Lipid Carrier; SLN: Solid Lipid Nanoparticle; LNP: Lipid Nanoparticle; PLGA: Poly(lactic-co-glycolic acid); PEG: Polyethylene Glycol; PVA: Polyvinyl Alcohol; SNAC: Salcaprozate Sodium; FcRn: Neonatal Fc Receptor; L-cell: Intestinal L Cell; GI: Gastrointestinal; BBB: Blood-Brain Barrier; CNS: Central Nervous System; ROS: Reactive Oxygen Species; DPP-4: Dipeptidyl Peptidase-4; SPR: Surface Plasmon Resonance; BLI: Biolayer Interferometry; mRNA: Messenger Ribonucleic Acid; DNA: Deoxyribonucleic Acid; RNA: Ribonucleic Acid; pH: Potential of Hydrogen; IV: Intravenous; SC: Subcutaneous; IM: Intramuscular; FDA: Food and Drug Administration; AEs: Adverse Events; MACE: Major Adverse Cardiovascular Events; SELECT: Semaglutide Effects on Heart Disease and Stroke in Patients with Overweight or Obesity; PIONEER: Peptide Innovation for Early Diabetes Treatment; SUSTAIN: Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes; PLGA: Poly(lactic-co-glycolic acid); GSH: Glutathione; Lys: Lysosome/Lysosomal; AUC: Area Under the Plasma Concentration-Time Curve; Cmax: Maximum Plasma Concentration; T1/2: Elimination Half-Life; HPLC: High-Performance Liquid Chromatography; TEM: Transmission Electron Microscopy; SEM: Scanning Electron Microscopy; DLS: Dynamic Light Scattering.

Ethical Approval

Not applicable.

Consent for Publication

Not applicable.

Human and Animal Ethical Right

Not applicable.

Conflict of Interest

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Author Contribution

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