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Review paper

Peptide Therapeutics and Next Generation Drug Delivery Systems

Emerging Frontiers in Drug Discovery and Medicinal Chemistry

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ABSTRACT

Peptide based therapeutics occupy a distinctive middle ground between small molecule drugs and large biologics, combining the target specificity and low off-target toxicity characteristic of proteins with a synthetic tractability that has made them an increasingly attractive drug class. Seven of the ten best-selling pharmaceuticals worldwide are now based on amino acid sequences, reflecting the clinical and commercial maturation of this modality. Yet the same physicochemical properties that confer peptides their selectivity, namely their size, conformational flexibility, and susceptibility to proteolytic degradation, also render them vulnerable to rapid enzymatic breakdown and poor membrane permeability, historically restricting most peptide drugs to parenteral administration. This review surveys the structural and physiological barriers that limit peptide bioavailability, summarizes the principal chemical and formulation strategies developed to overcome them, including chemical modification, permeation enhancers, and lipid-based nanoparticulate carriers, and evaluates the clinical translation of oral peptide delivery through the case study of oral semaglutide. We conclude by considering the formulation and regulatory trends likely to shape the next generation of peptide therapeutics.

1. Introduction

Peptides are short chains of amino acids, typically fewer than fifty residues in length, linked by peptide bonds, occupying a molecular weight range intermediate between conventional small molecules and larger protein biologics (Liu et al., 2025). This intermediate position confers a distinctive pharmacological profile: peptides can achieve the high target specificity and mechanistic diversity associated with proteins, including the ability to disrupt protein-protein interactions that are notoriously difficult to target with small molecules, while retaining a degree of synthetic accessibility, chemical tunability, and lower manufacturing complexity relative to monoclonal antibodies and other large biologics.

The clinical and commercial success of this modality has been substantial. Beginning with the introduction of insulin therapy over a century ago, peptide and protein therapeutics have become deeply embedded in the treatment of diabetes, oncology, and a widening range of chronic and metabolic diseases (Mehrdadi, 2023). More recently, the emergence of glucagon-like peptide-1 (GLP-1) receptor agonists as both antidiabetic and weight-management therapies has driven a further surge of interest in the field, contributing to a peptide and protein therapeutics

market valued at approximately $42.8 billion in 2023 and projected to exceed $80 billion within the following decade (Zhu et al., 2021; Mehrdadi, 2023).

Despite this commercial and clinical momentum, the pharmacokinetic liabilities intrinsic to peptide structure remain a central challenge. This review examines those liabilities in detail, surveys the delivery technologies developed to address them, and considers how far the field has progressed toward the long-standing goal of non-invasive, patient-friendly peptide administration.

2. Physiological and Structural Barriers to Peptide Delivery

The pharmacokinetic challenges facing peptide therapeutics are best understood as arising from an inherent tension between the structural features that confer biological activity and those that would be required for favorable drug like behavior. Three barriers are of particular importance.

2.1 Enzymatic Degradation

Peptides are highly susceptible to proteolytic degradation by a wide range of endogenous enzymes, beginning in the stomach and small intestine and continuing at the brush border membrane and within enterocytes. This enzymatic vulnerability is particularly acute for orally administered peptides, which must survive an extremely hostile gastrointestinal environment characterized by extreme pH variation, high concentrations of pepsin, trypsin, and chymotrypsin, and a dense population of brush-border peptidases, before any absorption can occur (Zhu et al., 2021).

2.2 Poor Membrane Permeability

Even peptides that survive enzymatic attack face a substantial permeability barrier. The intestinal epithelium is designed to exclude large, hydrophilic molecules, and most therapeutic peptides, owing to their size, polarity, and hydrogen-bonding capacity, permeate the intestinal mucosa poorly via either the transcellular or paracellular route. This combination of degradation and poor permeability results in oral bioavailability figures for unmodified peptides that are frequently below one percent (Liu et al., 2025).

2.3 First-Pass Hepatic Metabolism and Short Systemic Half-Life

Peptides that do reach the systemic circulation are often rapidly cleared through renal filtration and further proteolytic degradation, resulting in short circulating half-lives that can necessitate frequent dosing, an important consideration for chronic disease management where patient adherence is closely tied to dosing convenience (Mehrdadi, 2023).

Table 1 Principal Barriers to Peptide Bioavailability and Their Physiological Basis

Barrier	Physiological Basis	Consequence for Peptide Drugs
Enzymatic degradation	Gastric and pancreatic proteases; brush-border and intracellular peptidases	Rapid breakdown before or during absorption; near-complete loss of intact peptide after oral dosing
Poor membrane permeability	Tight intestinal epithelial junctions; peptide size, polarity, and hydrogen-bonding capacity	Oral bioavailability typically below 1% for unmodified peptides
First-pass hepatic metabolism	Portal circulation routes absorbed peptide through the liver before systemic distribution	Further reduction in the fraction of intact peptide reaching systemic circulation
Short plasma half-life	Renal filtration and continued proteolysis in circulation	Frequent dosing required; reduced patient adherence for chronic conditions

3. Strategies to Overcome Delivery Barriers

3.1 Chemical Modification

Chemical modification strategies aim to alter the intrinsic physicochemical properties of a peptide to improve its stability and permeability without abolishing biological activity. Common approaches include cyclization, which reduces conformational flexibility and can confer resistance to exopeptidase degradation; substitution of L-amino acids with D-amino acids or non-natural residues at sites of proteolytic cleavage; N-methylation of the peptide backbone, which can simultaneously improve metabolic stability and membrane permeability; and PEGylation or lipidation, which extend circulating half-life by reducing renal clearance and, in the case of lipidation, can promote reversible albumin binding (Liu et al., 2025).

3.2 Enzyme Inhibitors and Absorption Enhancers

Co-formulation with protease inhibitors can transiently reduce enzymatic degradation within the gastrointestinal lumen, while permeation enhancers, including medium-chain fatty acid derivatives such as sodium caprate and salcaprozate sodium (SNAC), act to transiently increase paracellular or transcellular permeability of the intestinal epithelium. SNAC, notably, is the enabling excipient behind the first

orally approved GLP-1 receptor agonist formulation, discussed further below (Mehrotra & Kalyan, 2024).

3.3 Lipid-Based Nanoparticulate Delivery Systems

Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) encapsulate peptide cargo within a lipid matrix, offering simultaneous protection from enzymatic degradation, improved membrane interaction through their small particle size and high surface area, and the potential for mucoadhesive surface modification to prolong intestinal residence time (Mehrdadi, 2023). Because these carriers can accommodate both hydrophilic and lipophilic payloads, they have been investigated across a wide range of peptide and protein classes, from insulin to larger monoclonal antibody fragments, although manufacturing scalability and long-term stability remain active areas of formulation research.

3.4 Physical and Device-Based Delivery Technologies

Beyond chemical and formulation strategies, physical delivery technologies, including microneedle patches for transdermal administration and ingestible robotic capsules capable of mechanically injecting peptide formulations directly into the intestinal wall, represent an emerging category of delivery innovation that bypasses the enzymatic and permeability barriers of conventional oral or subcutaneous administration altogether (Liu et al., 2025).

Table 2 Comparison of Major Peptide Delivery Strategies

Strategy	Mechanism of Benefit	Advantages	Limitations
Cyclization / D-amino acid substitution	Reduces susceptibility to exopeptidase cleavage; stabilizes conformation	Improved metabolic stability; can preserve receptor binding	May require extensive structure-activity optimization; risk of activity loss
PEGylation / lipidation	Reduces renal clearance; enables reversible albumin binding	Extended plasma half-life; reduced dosing frequency	Potential immunogenicity; added synthetic complexity
Permeation enhancers (e.g., SNAC)	Transiently increases epithelial permeability	Enabled first oral GLP-1 receptor agonist formulation	Bioavailability still low (single-digit percent); food/fasting-state sensitivity
Lipid-based nanoparticles (SLNs/NLCs)	Physical encapsulation shields peptide from enzymatic attack	Protects labile cargo; potential for mucoadhesion	Manufacturing scale-up and long-term stability challenges
Microneedle patches / ingestible devices	Bypasses gastrointestinal enzymatic and permeability barriers mechanically	Avoids GI degradation entirely; needle-free (microneedles)	Device cost and complexity; patient acceptance considerations

4. Case Study: Oral Semaglutide

The regulatory approval of an oral formulation of semaglutide, a GLP-1 receptor agonist historically administered by subcutaneous injection, represents one of the most significant recent milestones in peptide delivery science. The oral formulation co-formulates semaglutide with SNAC, a permeation enhancer that transiently raises local gastric pH and facilitates monomeric peptide absorption across the gastric epithelium when taken on an empty stomach with a minimal volume of water (Mehrotra & Kalyan, 2024). Although the resulting oral bioavailability remains modest, on the order of single-digit percentages, it is sufficient to achieve therapeutically meaningful systemic exposure when combined with appropriate dose escalation, demonstrating that permeation-enhancer-based strategies can translate from formulation science into a commercially successful, patient-preferred alternative to injectable peptide therapy.

Comparative pharmaceutical development work has also explored solid oral dosage forms for other peptides, including vancomycin and semaglutide, using high-throughput excipient screening approaches to identify formulations that improve intraduodenal and ultimately oral bioavailability beyond what earlier enteric or solution-based formulations achieved, illustrating how systematic, data-driven formulation screening is beginning to complement traditional trial-and-error approaches to peptide delivery optimization.

5. Remaining Challenges and Future Outlook

Despite the clinical success of oral semaglutide, oral bioavailability for most peptide therapeutics remains too low to be considered a fully solved problem, and considerable heterogeneity exists in absorption depending on individual peptide physicochemical properties, formulation, and even gastric emptying and dietary conditions at the time of dosing (Zhu et al., 2021). Bitter taste perception and gastrointestinal tolerability also present formulation challenges for certain bioactive peptides intended for oral administration, particularly in nutraceutical and

functional food contexts adjacent to pharmaceutical peptide development.

Looking forward, several converging trends are likely to shape the field. Machine learning-guided formulation screening is increasingly being applied to identify optimal combinations of excipients and permeation enhancers from very large combinatorial design spaces, potentially accelerating the identification of viable oral formulations for peptides that would otherwise require years of empirical optimization. Continued refinement of chemical modification strategies, including next-generation lipidation and cyclization chemistries, is expected to further extend peptide half-life and stability. Finally, growing clinical experience with device-based delivery technologies may expand the range of peptides amenable to non-invasive administration beyond what chemical modification alone can achieve.

6. Future Directions

- Systematic, high-throughput screening of excipient and permeation-enhancer combinations, increasingly guided by machine learning models, to accelerate oral formulation development.
- Development of next-generation lipidation and cyclization chemistries to further extend peptide stability and half-life without compromising potency.
- Expanded clinical evaluation of device-based delivery technologies, including microneedle patches and ingestible robotic capsules, for peptides not amenable to chemical or nanoparticulate strategies alone.
- Greater attention to patient-centric formulation attributes, including taste-masking and dosing convenience, particularly for chronic disease indications requiring long-term adherence.
- Harmonization of regulatory frameworks for novel excipients and delivery devices to reduce translational barriers for innovative peptide delivery technologies.

7. Beyond the Oral Route: Complementary Administration Strategies

While oral delivery has attracted the greatest research and commercial attention, owing to its clear advantages for patient convenience and long-term adherence, it is not the only non-invasive or patient-friendly route under active investigation for peptide therapeutics. Transdermal delivery via microneedle arrays allows peptides to bypass both the gastrointestinal enzymatic environment and the stratum corneum permeability barrier of intact skin, delivering peptide cargo directly into the dermis with minimal invasiveness and, in many designs, without the pain associated with conventional hypodermic injection (Liu et al., 2025). Pulmonary and nasal delivery routes exploit the large surface area and relatively high permeability of respiratory and nasal mucosa, and have been explored for peptides requiring rapid systemic absorption or, in the case of nasal delivery, direct access to the central nervous system via the olfactory pathway.

Each of these alternative routes carries its own formulation-specific challenges. Pulmonary delivery requires careful control of particle size and aerodynamic properties to achieve deep lung deposition, while nasal delivery is constrained by the limited volume that can be administered per dose and by mucociliary clearance mechanisms that limit residence time. Transdermal microneedle approaches, meanwhile, must balance mechanical robustness sufficient to penetrate the skin with a dissolution or degradation profile that reliably releases the full peptide payload. Despite these challenges, the diversity of routes now under active investigation reflects a broader shift in the field away from viewing subcutaneous injection as the default fallback and toward a more deliberate, indication specific matching of delivery route to the pharmacokinetic and patient adherence requirements of a given therapeutic peptide (Mehrotra & Kalyan, 2024).

Table 3 Comparison of Non-Invasive and Minimally Invasive Peptide Administration Routes

Route	Key Advantage	Principal Limitation	Illustrative Application
Oral (with permeation enhancer)	Highest patient preference and adherence potential	Low absolute bioavailability; food/fasting sensitivity	Oral semaglutide (GLP-1 receptor agonist)
Transdermal microneedle	Bypasses GI tract entirely; minimal pain	Limited payload volume; manufacturing complexity	Investigational insulin and vaccine-peptide patches
Pulmonary (inhaled)	Large absorptive surface area; rapid onset	Requires precise particle engineering; variable lung deposition	Inhaled insulin formulations (historical and investigational)
Intranasal	Potential direct CNS access via olfactory pathway	Small administrable volume; mucociliary clearance	Investigational neuropeptide and hormone therapies

8. Conclusion

Peptide therapeutics have matured from a niche modality, historically confined to injectable insulin and a handful of hormone analogs, into one of the most commercially significant and clinically versatile classes of medicine, a transformation exemplified by the success of GLP-1 receptor agonists. This progress has been made possible not by resolving the fundamental physicochemical liabilities of peptides, but by developing an increasingly sophisticated toolkit of chemical modification, permeation enhancement, nanoparticulate encapsulation, and device based delivery strategies that work around these liabilities. The continued convergence of formulation science, medicinal chemistry, and computational screening is likely to further expand the range of peptides that can be delivered non-invasively, bringing this important therapeutic class closer to the accessibility long associated with conventional small-molecule medicines.

9. Manufacturing and Regulatory Considerations

Delivery innovation for peptide therapeutics does not occur in isolation from manufacturing and regulatory realities. Lipid-based nanoparticulate formulations, permeation-enhancer co-formulations, and device-based delivery systems each introduce additional excipients, manufacturing unit operations, and, in the case of novel devices, engineering validation requirements that must be characterized to the same rigorous standard as the active peptide itself. Regulatory agencies have increasingly published specific guidance addressing the qualification of novel permeation enhancers and delivery excipients, reflecting recognition that the delivery system itself can materially influence both efficacy and safety and therefore warrants dedicated regulatory scrutiny distinct from that applied to the peptide active ingredient alone. Navigating this expanded regulatory scope, alongside the chemistry, manufacturing, and controls complexity introduced by multi-component formulations, represents a nontrivial translational hurdle that companies developing next-generation peptide delivery systems must plan for well in advance of clinical development (Mehrotra & Kalyan, 2024).

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