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Review Article
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Oral Delivery of Proteins and Peptides: Current Advances and Future Opportunities

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Abstract
Oral delivery of protein and peptide therapeutics represents one of the most challenging yet impactful goals in modern drug delivery. Despite the clinical success of injectable biologics, patient compliance, chronic dosing requirements, and healthcare costs drive the need for oral alternatives. However, enzymatic degradation, poor epithelial permeability, chemical instability, and first-pass metabolism severely limit oral bioavailability. This review provides a comprehensive analysis of biological barriers, formulation strategies, chemical and biological modification approaches, device-assisted technologies, clinical progress, regulatory considerations, and emerging future opportunities for oral protein and peptide delivery.

Keywords: *Oral biologic delivery, Protein and peptide therapeutics, gastrointestinal, barriers, Formulation strategies, Permeation enhancers*

INTRODUCTION

Protein and peptide therapeutics constitute a rapidly expanding class of pharmaceuticals due to their high specificity, potent pharmacological activity, and reduced off-target toxicity compared with conventional small molecules [1-3]. More than 400 peptide-based drugs are currently approved or in clinical development, addressing diseases such as diabetes, cancer, autoimmune disorders, and hormonal deficiencies [4]. Despite their therapeutic promise, most protein and peptide drugs require parenteral administration, limiting patient acceptance and long-term adherence [5].

Oral delivery remains the most desirable route, offering ease of administration, improved patient compliance, and reduced healthcare costs [6]. However, the physicochemical properties of proteins and peptides-large molecular size, hydrophilicity, conformational instability, and susceptibility to enzymatic degradation-pose formidable challenges to oral absorption [7,8]. Significant research efforts over the past three decades have led to notable technological advances, yet widespread clinical translation remains limited.

PHYSIOLOGICAL BARRIERS TO ORAL DELIVERY

1. Gastrointestinal Enzymatic Degradation

The gastrointestinal tract is rich in proteolytic enzymes, including pepsin in the stomach and trypsin, chymotrypsin, elastase, and carboxypeptidases in the intestine [9]. These enzymes rapidly hydrolyze peptide bonds, drastically reducing the fraction of intact drug available for absorption [10].

2. Mucus Barrier

The intestinal mucus layer acts as a viscoelastic hydrogel that traps and clears foreign particles, limiting drug diffusion to the epithelial surface [11]. Electrostatic and hydrophobic interactions between mucus glycoproteins and protein drugs further restrict penetration [12].

3. Epithelial Cell Barrier

Proteins and peptides exhibit poor permeability across intestinal epithelial cells due to their size and polarity [13]. Tight junctions restrict paracellular transport, while transcellular diffusion is limited by the lipophilic cell membrane [14].

4.Efflux Transporters and First-Pass Metabolism

Efflux transporters such as P-glycoprotein and extensive hepatic first-pass metabolism further reduce systemic exposure following oral administration [15].

FORMULATION AND DELIVERY STRATEGIES

1. Enzyme Inhibition and Protective Formulations

Co-administration of protease inhibitors (e.g., aprotinin, soybean trypsin inhibitor) has been explored to reduce enzymatic degradation [16]. Enteric coatings and pH-sensitive polymers protect protein drugs from gastric acidity and enable targeted intestinal release [17].

2. Permeation and Absorption Enhancers

Absorption enhancers, including medium-chain fatty acids, bile salts, surfactants, and chelating agents, transiently open tight junctions or increase membrane fluidity to enhance permeability [18-20]. While effective, safety concerns related to epithelial damage and long-term use remain a challenge [21].

3. Nanotechnology-Based Delivery Systems

Nanocarriers such as polymeric nanoparticles, liposomes, solid lipid nanoparticles, and nanomicelles protect proteins from degradation and improve mucosal uptake [22–24]. Surface modification with polyethylene glycol (PEG) or mucus-penetrating ligands enhances stability and transport across the mucus layer [25].

4. Lipid-Based Systems

Self-emulsifying drug delivery systems (SEDDS) and lipidic formulations facilitate lymphatic transport, bypassing hepatic first-pass metabolism [26]. Lipidation of peptides improves membrane affinity and systemic exposure [27].

CHEMICAL AND MOLECULAR MODIFICATION APPROACHES

1. PEGylation and Cyclization

PEGylation improves proteolytic stability and prolongs circulation half-life but may reduce biological activity [28]. Cyclization of peptides enhances conformational rigidity and enzymatic resistance [29].

1. Prodrug Strategies

Prodrugs are designed to improve stability and permeability, converting into the active drug after absorption [30]. Several peptide prodrugs have demonstrated improved oral bioavailability in preclinical studies [31].

DEVICE-ASSISTED AND MECHANICAL APPROACHES

Innovative ingestible devices capable of injecting proteins directly into the intestinal wall have emerged as a disruptive technology [32]. These systems physically bypass enzymatic and permeability barriers and have demonstrated promising clinical results for insulin and other peptides [33].

CLINICAL ADVANCES AND REGULATORY LANDSCAPE

The approval of oral semaglutide represents a milestone in oral peptide delivery, validating the feasibility of this route [34]. However, regulatory approval requires stringent demonstration of safety, reproducibility, and long-term tolerability of absorption enhancers and novel excipients [35].

FUTURE OPPORTUNITIES

1. Receptor-Mediated and Targeted Transport

Exploiting endogenous transport pathways such as transferrin or neonatal Fc receptors may enable efficient transcytosis of proteins across the intestinal epithelium [36].

2. Microbiome-Based Therapeutics

Engineered gut bacteria capable of producing therapeutic peptides in situ offer a novel paradigm for oral biologic delivery [37].

3. Artificial Intelligence and Formulation Design

AI-driven formulation optimization and predictive modeling may accelerate the identification of optimal carrier systems and excipient combinations [38].

CONCLUSION

Oral delivery of proteins and peptides remains a formidable but achievable goal. Advances in formulation science, nanotechnology, chemical modification, and device-based approaches have significantly expanded the therapeutic landscape. Continued interdisciplinary innovation and clinically focused research are essential to translate these technologies into safe, effective, and commercially viable oral biologics.

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