Beijing Dilun Biotechnology Co., Ltd.
Specializes in R&D and manufacturing of peptide synthesis equipment, providing comprehensive technical solutions and services.
Web: www.peptidescientific.com. Email: chengchao.wei@dilunbio.com

Review of Research Progress in Oral Peptide and Protein Drugs

Peptide and protein therapeutics play a pivotal role in treating diabetes, cancer, autoimmune diseases, and metabolic disorders due to their high potency, specificity, and low toxicity. However, their oral bioavailability remains extremely low, forcing the vast majority of products to rely on injectable administration. This severely impacts patient compliance and the accessibility of long-term treatment. Developing efficient oral delivery technologies represents a core challenge in the biopharmaceutical field. In recent years, significant progress has been made in this field through advances in materials science, formulation technology, and physiological understanding. This paper aims to provide a systematic review of the key challenges, major technical strategies, and recent breakthroughs in the oral delivery of peptide/protein drugs.

I. Three Major Physiological Barriers Facing Oral Delivery

After oral administration, peptide and protein drugs must sequentially overcome the following barriers to enter the systemic circulation and exert their therapeutic effects:

1. Chemical and Enzymatic Degradation Barriers: The highly acidic environment of the stomach (pH 1–3) can cause drug denaturation or chemical hydrolysis. Numerous proteases and peptidases exist within the gastrointestinal tract, such as pepsin, trypsin, chymotrypsin, and intestinal brush border enzymes, which systematically degrade macromolecular drugs into inactive peptides or amino acids.

2. Intestinal Epithelial Permeability Barrier: Drug molecules are typically large (>500 Da), highly hydrophilic, and charged, making passive diffusion through the lipid bilayer of intestinal epithelial cells difficult. Tight junctions between epithelial cells also strictly limit paracellular transport.

3. Hepatic First-Pass Metabolism Barrier: A small fraction of absorbed drugs undergoes clearance by abundant hepatic metabolic enzymes during first-pass metabolism through the liver via the portal vein.

These barriers result in oral bioavailability below 1% for most therapeutic peptides/proteins, necessitating targeted strategies for systematic breakthroughs in drug development.

II. Core Technology Strategies for Overcoming Barriers

Current research focuses on four key areas: enhancing drug stability, inhibiting enzymatic degradation, promoting intestinal epithelial permeability, and developing advanced delivery systems.

1. Molecular Structure Modification: Enhancing Intrinsic Stability

Chemically modifying drug molecules to strengthen their inherent

resistance to degradation and improve absorption properties.

Cyclization and Crosslinking: Connecting linear molecules end-to-end or via side chains forms ring structures that constrain conformations and shield enzymatic cleavage sites.

Introduction of Non-Natural Amino Acids: Replacing L-amino acids with D-amino acids effectively counters protease-specific cleavage.

Fatty Acid Chain Modification: Attaching fatty acid chains enhances drug interaction with intestinal mucus and epithelial cells, potentially extending half-life through micelle formation or plasma albumin binding. For instance, the success of liraglutide and semaglutide partly stems from fatty acid chain modifications.

2. Application of Permeation Enhancers: Temporarily Opening Absorption Pathways

This represents one of the strategies closest to clinical implementation. Permeation enhancers promote drug absorption by reversibly and transiently altering epithelial barrier properties.

Mechanisms of action include temporarily opening tight junctions, dissolving membrane lipids, or inhibiting efflux pumps. Examples include medium-chain triglycerides, surfactants, and novel absorption enhancers.

Landmark Case: The successful commercialization of oral somatropin tablets represents a revolutionary breakthrough. Its core innovation lies in the use of SNAC. SNAC exerts multiple local effects in the stomach:

mildly elevating local pH to protect the drug, reducing pepsin activity, and promoting transcellular drug transport by interacting with gastric epithelial cell membranes. This strategy ingeniously circumvents the primary enzymatic environment of the intestine.

3. Enzyme Inhibitor Use: Buying Time for Drugs

Co-administering protease inhibitors with drugs creates a temporary "low-enzyme-activity window" locally in the gastrointestinal tract.

Common Inhibitors: Include peptazime inhibitors, trypsin inhibitors, etc.

Strategic Limitations: Typically requires combination with permeation enhancers. Long-term safety (e.g., potential impact on nutrient digestion) warrants careful evaluation.

4. Advanced Delivery Systems: Providing Full-Pathway Protection and Smart Delivery

This is the most active frontier of research, aiming to construct multifunctional integrated "nanoscale carriers."

Nanocarrier Systems: Including polymeric nanoparticles, liposomes, solid lipid nanoparticles, and nanoemulsions. These systems encapsulate drugs, protect them from degradation, and increase intestinal retention time and absorption through mechanisms like adhesion and endocytosis.

Bioadhesive Systems: Employ adhesive materials like chitosan to prolong delivery system attachment to the intestinal mucosa, extending the

absorption time window.

Targeted and Responsive Systems: Modify carrier surfaces with targeting ligands for specific binding to intestinal regions or cell receptors; or design pH-responsive or enzyme-responsive carriers for drug release exclusively at target sites.

III. Significant Research Advances and Case Studies

1. Oral Semaglutide: As the first approved oral GLP-1 receptor agonist, it integrates acylation modification for enhanced stability with SNAC permeation-enhancing technology. This demonstrates the commercial viability and technical pathway for oral peptide drugs, significantly boosting industry confidence.

2. Application of Cell-Penetrating Peptides: Covalently linking or co-delivering therapeutic peptides/proteins with membrane-penetrating peptides significantly enhances their transmembrane transport efficiency. Strategies combining them with CPPs like Tat or Penetratin demonstrate substantial potential in preclinical studies.

3. Bionic and Microbe-Inspired Delivery: Designing carriers based on bacteria or viruses' natural mechanisms for intestinal invasion. Examples include mimicking the GM1 receptor-binding domain of cholera toxin or utilizing engineered non-pathogenic bacteria as living delivery vehicles.

4. Colon-Targeted Delivery: Leveraging the lower protease activity in the colon, pH-dependent or time-controlled colon-localized release systems

have been developed, offering an alternative oral delivery approach for drugs like insulin.

5. Microneedle capsules and device-assisted delivery: Examples include the “smart insulin capsule,” which deploys microneedle patches within the stomach to deliver drugs directly to submucosal capillaries, completely bypassing the primary barrier in the gastrointestinal lumen. This represents a disruptive physical delivery approach.

IV. Current Challenges and Future Outlook

Despite progress, large-scale clinical application still faces multiple challenges:

Balancing efficiency and safety: How to promote efficient absorption while ensuring reversible, harmless effects on intestinal barrier function and avoiding long-term risks.

Individual variability and reproducibility: Gastrointestinal physiology is significantly influenced by diet, disease, and microbiota. How to ensure stable and consistent drug efficacy.

Production Feasibility and Cost: Mass-producing complex delivery systems at low cost and high quality presents a major engineering challenge.

Regulatory and Evaluation Standards: The unique mechanisms of novel delivery technologies necessitate establishing corresponding nonclinical and clinical evaluation guidelines.

Future development directions are expected to focus on:

1. Artificial Intelligence and Rational Design: Leveraging AI to predict molecular stability, membrane permeability, and carrier compatibility to accelerate the discovery of optimal drug-carrier combinations.

2. Multi-mechanism synergistic systems: Developing next-generation smart delivery platforms integrating protection, permeation enhancement, targeting, and responsive release.

3. Exploration of novel absorption pathways: Investigating absorption routes beyond the small intestine, such as gastric absorption, colonic absorption, and alternative oral pathways like sublingual and buccal mucosal absorption.

4. Personalized delivery: Tailored oral administration strategies may emerge by integrating individual gut physiology and microbiome characteristics.

V. Conclusion

The development of orally administered peptide and protein therapeutics represents a multidisciplinary challenge integrating molecular pharmacology, formulation science, materials science, and physiology. From early simple coatings to today's combination of molecular modifications and complex delivery systems, technical strategies have continuously evolved. The success of oral somatropin marks the field's transition from proof-of-concept to a new phase of product realization,

charting a course for the entire industry. Although a universally effective, safe, and economical oral solution remains elusive, breakthroughs in fundamental science and continuous engineering innovation will gradually break the “injection curse” for large-molecule drugs. This will deliver more convenient and patient-friendly treatment options, ultimately reshaping the therapeutic landscape and management experience for numerous chronic diseases. This challenging R&D journey is paving the way toward a new era of oral biologics.