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Crossing the "Triple Barrier": Challenges, Strategies, and Future of Oral Delivery for Peptide Drugs

The In the field of biomedicine, peptide drugs have become powerful tools for treating chronic diseases such as diabetes, obesity, and osteoporosis due to their high activity, specificity, and low toxicity. However, an awkward reality remains: the vast majority of peptide drugs still rely on injection for administration. This creates a "glass wall" for patients—the drugs are effective, but inconvenient to use. Enabling peptides to be taken orally as easily as a single aspirin tablet is a dream pursued by scientists and the pharmaceutical industry, and one of the most challenging frontiers in this field. This journey of exploration is an ongoing battle to overcome the "triple barrier" the human body has built to protect itself.

I. Why Is Oral Administration So Challenging? — The Triple Barriers Peptides Must Conquer

After oral administration, peptides must endure an exceptionally perilous journey before reaching the bloodstream to exert systemic effects, facing the rigorous challenges of three major physiological barriers:

First Gate: The “Chemical and Biological Degradation Barrier” Within the Digestive Tract

Extreme pH environments: The highly acidic gastric environment (pH 1–3) can cause acid hydrolysis or conformational changes in many peptides, leading to inactivation.

Enzymatic “Meat Grinder”: The digestive tract is rich in proteases and peptidases (such as pepsin, trypsin, chymotrypsin, and various brush border oligopeptidases). These act like precision scissors, systematically cleaving peptides into inactive fragments or individual amino acids. This is the primary reason for extremely low oral bioavailability (typically <1-2%).

The Second Gate: The “Physical and Biochemical Permeability Barrier” of the Intestinal Epithelium

Even if they manage to evade degradation, peptides still need to penetrate the intestinal wall to enter the bloodstream.

Hydrophilicity and High Molecular Weight: Most peptides have molecular weights between 500-5000 Da. Being highly hydrophilic and charged, they cannot pass through the lipid bilayer of intestinal epithelial cells via passive diffusion like small-molecule lipophilic drugs.

Restrictions of Tight Junctions: The “tight junctions” between intestinal epithelial cells act like the ‘cement’ in a “brick wall,” strictly limiting the permeation of macromolecules through cellular bypass pathways.

Export Pump Efflux: Intestinal epithelial cells express multiple efflux transporters (e.g., P-glycoprotein) that actively “pump back” peptides that have entered the cell into the intestinal lumen, further reducing their absorption.

The Third Gate: The Liver's “First-Pass Metabolic Barrier”

Small amounts of absorbed peptides first reach the liver via the portal vein. Within this “chemical factory,” a rich array of enzyme systems further metabolizes and eliminates them, resulting in only a negligible amount ultimately entering systemic circulation.

II. Breakthrough Strategies: How to Design a “Trojan Horse”?

To escort peptides through these three barriers, researchers have developed two complementary core strategies: First, modifying the peptides themselves to make them more resilient and stealthy; second, constructing sophisticated delivery systems to create customized “vehicles” or “passes” for them.

Strategy 1: Structural “Armoring” of Peptide Molecules

This is a direct approach to fundamentally enhance their survival capacity.

Cyclization and Cross-linking: Connecting the ends or side chains of linear peptides into ring structures (e.g., via disulfide bonds) restricts conformational flexibility, shields partial cleavage sites, and significantly boosts protease resistance. The orally administered cyclic peptide drug cyclosporine exemplifies this successful approach.

Non-Natural Amino Acid Substitution: Introducing D-amino acids or specially modified amino acids can effectively “confuse” proteases specific to natural L-amino acids.

Chemical Modification: Polyethylene glycolation or attachment of fatty acid chains not only increases stability but may also aid absorption by promoting interactions with the intestinal mucosa or forming micelles.

Strategy Two: Intelligent Design of Delivery Systems

This represents the most active and promising research direction, aiming to provide comprehensive protection and navigation for peptides throughout their journey.

1. Permeation Enhancers: Temporarily “Pry Open” Tight Junctions

This is a relatively traditional yet effective strategy. Utilizing certain small molecules (e.g., sodium decanoate, SNAC), surfactants, or medium-chain fatty acids can temporarily and reversibly open the tight junctions between intestinal epithelial cells. This increases paracellular pathway pores or disrupts the lipid structure of cell membranes, thereby promoting passive transport of peptides. The successful commercialization of somatropin oral tablets hinged on a novel permeation enhancer, SNAC. This compound locally elevates gastric pH to protect peptides while facilitating absorption through the gastric mucosal epithelium, thereby circumventing primary intestinal enzyme systems.

2. Enzyme Inhibitors: Locking the “Scissors”

Co-formulating with protease inhibitors (e.g., pepinase, trypsin inhibitor) temporarily suppresses digestive enzyme activity locally, creating a time window for peptide passage through the gastrointestinal tract. This strategy is often combined with permeation enhancers.

3. Carrier Delivery Systems: Crafting Multifunctional “Nano-Warriors”

This frontier research focuses on achieving targeted delivery, protection, and controlled release.

Nanoparticles/Nano-Micelles: Utilizing polymeric or lipid materials to encapsulate peptides within nanoscale particles. These particles shield peptides from enzymatic degradation and enhance absorption through phagocytosis by intestinal M cells or the adhesion-retention effect. For instance, chitosan-based nanoparticles are extensively studied for their bioadhesivity and ability to disrupt tight junctions.

Liposomes and Pre-Liposomes: Phospholipid bilayer vesicles effectively encapsulate hydrophilic and lipophilic drugs, offering robust protection. Pre-liposomes (dry lipid powders) self-assemble into liposomes upon hydration, resolving their liquid instability.

Cell-penetrating peptide conjugation: Linking peptide drugs to transmembrane peptides, these “molecular guides” efficiently transport cargo across cell membranes. For instance, conjugation with transmembrane peptides derived from HIV-Tat protein is a common strategy to enhance intracellular delivery efficiency.

Bionic and Bioadhesive Systems: Mimicking pathogens or utilizing bioadhesive materials (e.g., lectins) enables delivery systems to specifically bind to targeted regions of the intestinal wall, prolonging residence time and enhancing absorption.

III. Breakthroughs and Future Outlook

In recent years, this field has achieved substantial breakthroughs from concept to product:

Milestone Product: Novo Nordisk's oral semaglutide tablets represent the world's first successfully commercialized oral GLP-1 receptor agonist. Its ingenious combination of acylation modification (enhancing stability and albumin binding) and SNAC permeability-enhancing technology demonstrates the commercial and technical viability of oral peptide therapeutics.

Trend Toward Technological Convergence: Future oral peptide delivery systems will feature multifunctional integration. For instance, an ideal nanocarrier may simultaneously incorporate: pH-responsive coating (for gastric protection and intestinal release), enzyme inhibitor loading, surface-modified transmembrane peptides, and targeting ligands.

Nevertheless, significant challenges remain:

1. Efficiency vs. Safety Balance: Achieving efficient, reversible barrier opening without causing long-term mucosal damage or nutrient absorption

impairment.

2. Inter-Individual Variability & Reproducibility: Ensuring consistent therapeutic efficacy remains challenging due to intra- and inter-individual differences in gastrointestinal physiology (pH, motility, microbiota).

3. Cost and quality control in large-scale production: Complex manufacturing processes for delivery systems pose significant hurdles in ensuring uniformity and stability during industrial-scale manufacturing.

Looking ahead, research on oral peptide delivery will evolve in the following directions:

Artificial Intelligence and Rational Design: Leveraging AI to predict peptide stability, membrane permeability, and carrier compatibility, accelerating virtual screening for optimal molecules and delivery strategies.

Novel biomaterials: Developing smarter, safer, and more biocompatible delivery materials.

Beyond small intestinal absorption pathways: Exploring alternative routes like colon-targeted delivery, sublingual administration, or buccal mucosal absorption to bypass harsh intestinal environments.

Personalized delivery: Integrating genomics and microbiome research may enable tailored oral peptide delivery regimens for individual patients.

IV. Conclusion

The journey toward oral delivery of peptide drugs represents an interdisciplinary challenge that converges molecular pharmacology, pharmaceutics, materials science, and physiology. Human strategies have continuously evolved—from attempting to “forcefully breach” physiological barriers to learning to utilize or “outsmart” them. The success of oral semaglutide shines like a beacon, proving the viability of this path and greatly inspiring the entire field. Despite formidable challenges ahead, deepening fundamental science and advancing engineering techniques give us reason to believe that an increasing number of peptide drugs will shed their “injectable” form and enter patients' lives as tablets. This will truly achieve the perfect union of efficacy and convenience, reshaping the treatment paradigm for chronic diseases. This journey through the “triple gate” will ultimately usher us into a new era of oral biologics.