Chanlleges & Advances In Oral Peptide Therapeutics

Peptide drugs have poor oral bioavailability due to the complex physiological barrier of gastrointestinal tract, making most of the listed peptide drugs are administered by injection, which is not only cumbersome to operate, but also brings great challenges to patients who need long-term injection of peptide drugs (such as insulin), including pain, aversion to injection and local irritation, seriously reducing the patient's compliance.

In order to improve patients' compliance with medication, oral administration becomes the best way of drug delivery. However, **how to overcome various barriers to oral absorption of peptide drugs and develop oral drug delivery technology with high bioavailability** has become a hot spot and a difficult area of research at present.

Challenges Of Oral Peptide Therapeutics

When taken orally, peptide drugs must overcome four major barriers in the gastrointestinal tract before they enter the circulation and begin to work (Figure 1).

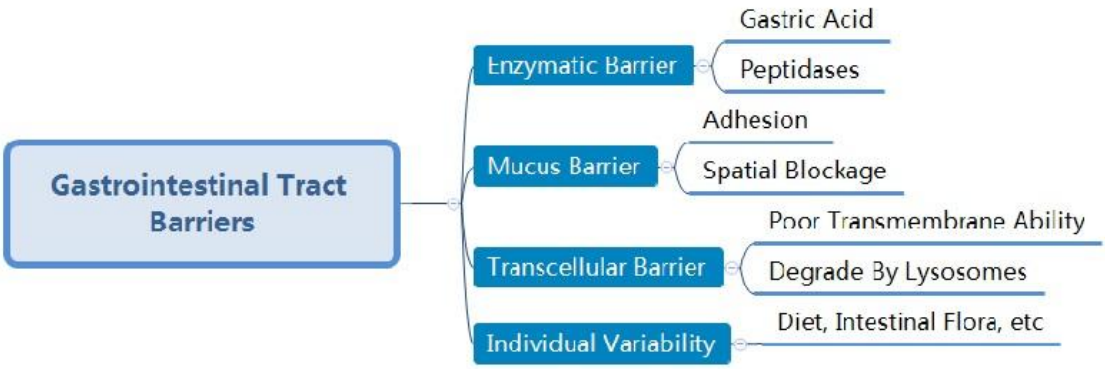

Figure 1. Challenges of oral peptide drugs

Enzymatic barrier: Peptides are subject to destruction by gastric acid and enzymatic degradation in the gastrointestinal tract. The pH of gastric acid is around 1 to 2.5, and most peptides lose their biological activity. And the small intestine contains gram quantities of peptidases secreted by the intestinal mucosa include trypsin, carboxypeptidase and many dipeptidases and aminopeptidases, which can degrade both peptides.

Mucus barrier: The mucus layer of the gastrointestinal tract is a physicochemical barrier to peptides. Foreign drug-containing particles are "trapped" by the mucus layer due to adhesion or spatial blockage and are

removed within the next few minutes to hours, resulting in decreased drug bioavailability.

Transcellular barrier: The absorption of peptide drugs in the gastrointestinal tract is mainly dependent on the transcellular pathway. However, the epithelial cell surface of the GI tract lacks peptide transport receptors and the peptide has poor ability to cross the cell membrane directly, at the same time the cell will also deliver the peptide into the cell and degrade it by lysosomes.

Individual variability: Individual variability is also a barrier that limits the development of oral peptides. The absorption process of peptides in the gastrointestinal tract is influenced by various individualized factors such as meal intake, gastrointestinal digestive fluid and mucosal surface area and intestinal flora, in addition to the co-morbidities of patients.

Oral Peptide Therapeutics Development

Oral peptide drugs are difficult to develop, yet the attention is high. However, there are relatively few successfully developed drugs.

Drug Name	Company	Indications	Status
Octreotide	Chiasma	acromegaly	Marketed
Semaglutide	Novo Nordisk	Type 2 diabetes	Marketed
Desmopressin	Ferring Pharmaceuticals	Diabetes insipidus, bedwetting, hemophilia A, von Willebrand disease, and high blood urea levels	Marketed
Vancomycin	ANI Pharmaceuticals	Infections	Marketed
Cyclosporine	Novartis	Prevent organ rejection in people who have received a liver, kidney, or heart transplant	Marketed
Ixazomib	Takeda	Multiple myeloma	Marketed
Plecanatide	Synergy	Chronic idiopathic constipation and irritable bowel syndrome with constipation	Marketed
Linaclotide	Ironwood	Irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC)	Marketed
Voclosporin	Aurinia	Active lupus nephritis	Marketed
Radha108	Biomix	HIV Infection	Marketed

Gepon	Immutic	Virus infection	Marketed
Difelikefalin	Cara	Moderate to severe itching	Marketed
Leuprorelin	Foresee Pharmaceuticals / ScinoPharma	Prostate cancer	Marketed
Octreotide	Chiasma	Acromegaly	Marketed
Larazotide	Alba	Celiac disease	Phase III
Trofinetide	Neuren	Rett Syndrome	Phase III
Traneurocin	NeuroActiva	COVID 2019 infections	Phase III
PN-235	Protagonist / Janssen	Plaque psoriasis	Phase II
PN-943	Protagonist	Ulcerative colitis	Phase II
LAT 8881	Lateral	Migraine; Neuropathic pain	Phase II
Emodepside	Bayer	Hookworm infections	Phase II
PAC-113	Demegen / General Biologicals	Candidiasis	Phase II
Solnatide	Apeptico	Acute Lung Injury	Phase II
BBT-401	Bridge	Ulcerative colitis	Phase II
Teriparatide oral	Entera	Hypoparathyroidism; Osteoporosis	Phase II
PCS-20%52	Yuhan	Diabetic gastroparesis; Dyspepsia; Gastroparesis	Phase II
Dolcanatide	Bausch	Ulcerative colitis	Phase II
B27PD	Enzo Biochem	Uveitis	Phase I/II
Val-201	Valirx	Prostate cancer; Solid tumours	Phase I/II
PTG-100	Protagonist	Ulcerative Colitis	Phase I
Macrocyclic peptides	Merck/Ra Pharmaceuticals	Cardiovascular disorders	Phase I
T20K	Cyxone AB	Multiple sclerosis	Phase I
PRI-002	Priavoid	Mild cognitive impairment	Phase I
NNZ-2591	Neuren	Angelman syndrome	Phase I
LY-3493269	Eli Lilly	Type 2 diabetes mellitus	Phase I
ARG 301	arGentis	Rheumatoid arthritis	Phase I
NCT-025	Seachaid	Postmenopausal osteoporosis	Phase I

Table 1: Oral Peptide Drugs Approved and In Pipeline

Frontier Technology and Application of Peptide Oral Delivery

In recent years, the development of peptide oral delivery technologies has been in full swing, but most of them have come to no avail. At present, peptide oral delivery technologies are mainly divided into 3 major types, 1 permeability enhancers; 2 chemical modification; 3 mechanical devices.

Permeability Enhancers

Permeability enhancers are generally small molecules, some of which can instantly and reversibly open biofilm channels for transmembrane or intercellular transport, some of which can instantly open tight junctions between cells, etc. **The following five novel drug delivery technology platforms are currently being used.**

1) Emisphere's Eligen®

Eligen Technology uses small molecule carriers to orally deliver biologics and other normally impermeable drugs into the bloodstream. The key technology is the use of a carrier, SNAC, Sodium N-[8-(2-hydroxybenzoyl)amino]caprylate, which is non-covalently bonded to the protein and protects the peptide from degradation by gastrointestinal enzymes by changing the peptide conformation, and also enhances membrane permeability to facilitate peptide absorption. This technology is currently approved and commercialized in two products, oral vitamin B12 and oral semaglutide.

Semaglutide oral tablet Rybelsus®, for the treatment of type 2 diabetes, was approved for marketing by the U.S. FDA in 2019. With sales of nearly $500 million in the U.S. in the first three quarters of 2021 and projected sales of $3 billion in 2024, it is the most successful oral peptide formulation available.
It is hypothesized that SNAC protects semaglutide from degradation and facilitates its oral absorption in the stomach by transiently increasing the transcellular permeability of gastric epithelial cells, or by buffering the local environment near the site of action.

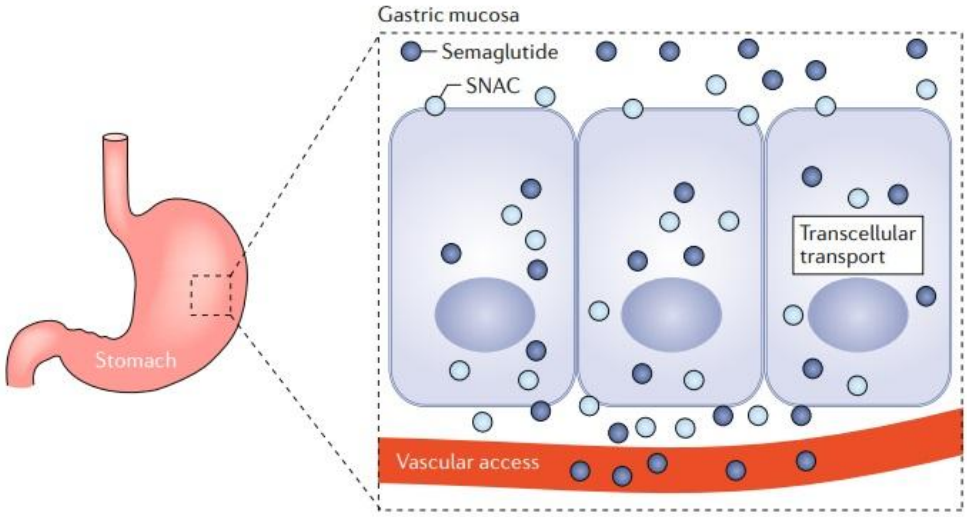

Figure 2. Absorption of Semaglutide

In addition, Entera Bio's oral parathyroid hormone (PTH) program utilizing SNAC and protease inhibitors is in Phase II clinical trials.

2) Merrion's GIPET®

GIPET uses specifically designed oral formulations of patented absorption enhancers which activate micelle formation, facilitating transport of the drug and substantially increasing absorption with good reproducibility and a strong safety profile. **However, its mechanism of action still needs further refinement, and no product has been listed or entered pivotal clinical trials so far.** Novo Nordisk once introduced GIPET technology to develop oral insulin, which was later terminated due to its low oral bioavailability (<1%) that could not support commercialization, although it showed comparable glucose-lowering effect with the injectable formulation in the clinic.

3) Chiasma's TPE®

TPE® is an oily suspension of octreotide that includes a number of excipients that can transiently alter epithelial barrier integrity by opening of intestinal epithelial tight junctions arising from transcellular perturbation. It was able to improve the bioavailability of the peptide octreotide in a study by Tuvia et al. (2012).

In 2020, **Chiasma's oral octreotide Mycapssa® was approved by the FDA for the long-term treatment of patients with acromegaly.** It is based on C8's TPE® platform and is delivered via an enteric coating to the small intestine for dissolution and absorption by a mechanism thought to increase tight junction permeability. However, the clinical advantage of Mycapssa, which requires daily oral administration, is not very obvious compared to

long-acting octreotide, which is injected once a month. So for the $5 billion global market for acromegaly, its $1.9 million in sales in the first quarter of 2021 seems insignificant.

4) Oramed's PODTM

Oramed's technology is based on components aimed at providing protection during passage through the GI tract and enhancing absorption. Ethylenediaminetetraacetate sodium (EDTA) and bile salts act as permeation enhancers. The capsule protects insulin from hydrolysis in the stomach, whereas protease inhibitors, such as soybean trypsin inhibitor and aprotinin, protect insulin from protease degradation, especially in the small intestine. **Its oral insulin capsule ORMD-0801 is now in clinical phase III.**

5) Enteris' Peptelligence®

Enteris' Peptelligence® is a technology platform that utilizes the bile salt taurodeoxycholate to open tight junctions for drug transport, and related programs are in clinical trials.
Other technologies, including mucus penetrant, ionic liquids, etc., are focused in relatively early exploratory stages.

Chemical Modification

Currently, the chemical method to improve the lipophilicity of peptides is **lipid modification**, which can be subdivided into two types of synthetic prodrugs and non-prodrugs. **Biocon has developed Tregopil, a prodrug for insulin, which mimics direct delivery to the portal vein and improves patient compliance.** The results of clinical studies have shown Tregopil to have a good safety profile, with significant control of postprandial glucose fluctuations in patients with type 2 diabetes after administration. A pivotal clinical phase II/III study in patients with type 2 diabetes is currently underway.

By modifying the structure of peptide drugs, the degree of absorption of the drug can be improved and the enzymatic degradation can be prevented. After modifying TRH with lauric acid, researchers demonstrated that the lipophilicity of lauric acid-modified TRH was increased, along with improved enzymatic resistance; the bioavailability of insulin was also significantly improved after modifying it with palmitic acid; and the combination of low molecular chitosan with exenatide using disulfide bonds significantly improved the lipophilicity and oral hypoglycemic effect of exenatide.

In addition to enhancing the lipophilicity of peptides, chemical modifications can also improve the transmembrane permeation efficiency of peptides by enabling receptor- or transporter-mediated transmembrane transport through

modified ligands. Various ligands have been successfully applied in the modification strategies of peptides, such as transferrin (Tf), vitamin B12 (VB12), biotin, deoxycholic acid, glycans and cell-penetrating peptide (CPP), etc.

Mechanical Devices

Mechanical system-based platforms including **intestinal patches, intestinal microneedles**, etc. are still in the exploration stage, and their practicality and safety remain to be seen.

Intestinal patches prevent drug degradation in the gastrointestinal tract, facilitate its intestinal absorption by creating a local drug reservoir at the site of administration, and provide a unidirectional, controlled drug release while preventing intraluminal drug loss. The intestinal patch is a unique 2- to 4-layer oral drug delivery device that delivers the drug in a controlled-release manner.

For intestinal microneedles, Rani Therapeutics has developed RaniPill™, a small enterolysis-coated capsule for oral biologics delivery devices (including peptides).The RaniPill™ capsule is swallowed by the patient and passes through the stomach into the intestine. Once the capsule reaches the intestine, the intestinal casing dissolves and the balloon begins to expand, revealing the delivery mechanism, where the pressure inside the balloon pushes the microneedle into the intestinal wall, and the injection is painless because the intestinal wall has no acute pain receptors.

Rani's core product, **RT-101, a RaniPill capsule containing octreotide,** has demonstrated safety in Phase I clinical studies with the same bioavailability as the subcutaneous control, and is expected to start Phase II clinical studies in 2022.

About Huateng Pharma

Huateng Pharma is an innovative pharmaceutical company integrating R&D, manufacturing and sales of drug intermediates, mainly focusing on CMO/CDMO services for intermeiates of antiviral, antineoplastic, diabetic and hypertensive drugs.

Huateng Pharma, founded in 2013, is dedicated to R&D, production and sales of pharmaceutical intermediates related products. Huateng Pharma has an R&D center and a manufacturing base (4 production workshops). It has a step-by-step scale-up technology to meet the needs of different batches, from mg level to 50kg/batch.

We can provide oral peptide drug semaglutide intermediates from lab to GMP production sacle. Contact us at sales@huatengusa.com for more details.

Related Articles:
Overview of Diabetes Treatment Strategies