Unlocking the potential: Challenges & opportunities in Oral Delivery of Peptides and Proteins.

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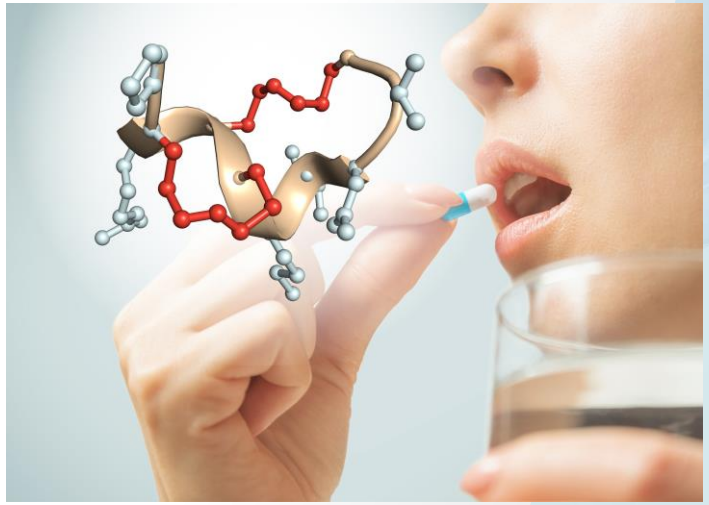

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Agenda

- Oral Peptide Market
- Pros and cons of oral Protein - Peptide drug delivery
- Approved protein - peptides in the market,
- Peptides in Clinical Development
- Protein/Peptide characterization
- Preformulation
- Formulation strategies for oral delivery (pH, absorption enhancer, enteric coating, mucoadhesive & lipid-based delivery)
- In process testing and finished product characterization
- Conclusion

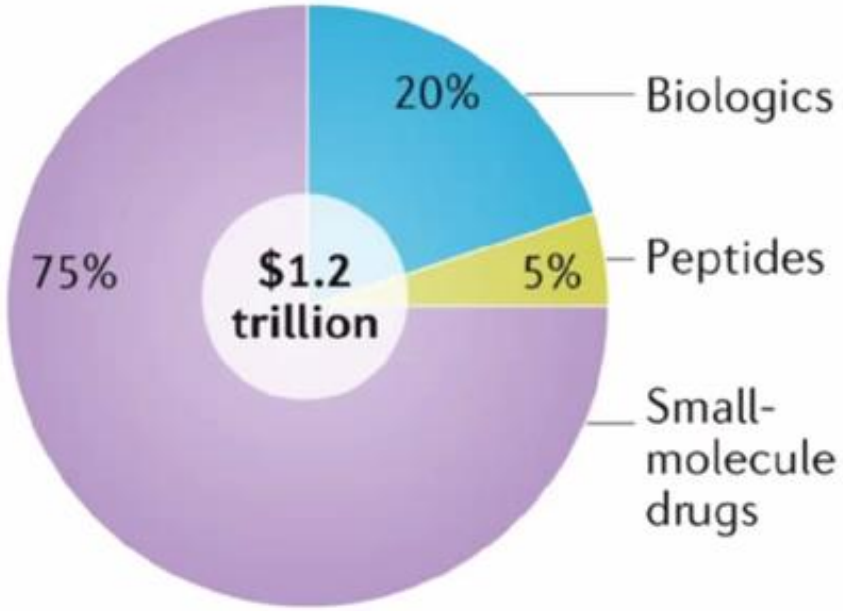
Therapeutic Large Molecules

Oligonucleotides	• Contain a few amino acids (e.g., 2 to 20) linked by peptide bonds
Peptides	• Peptides are short chains of amino acids (fewer than 50 residues) linked by peptide bonds
Proteins	• Large molecules made up of > 50 amino acids
Enzymes	• Enzymes are proteins and often highly specific—each one targets a particular substrate or reaction. Proteases are evaluated as potential therapeutic agents

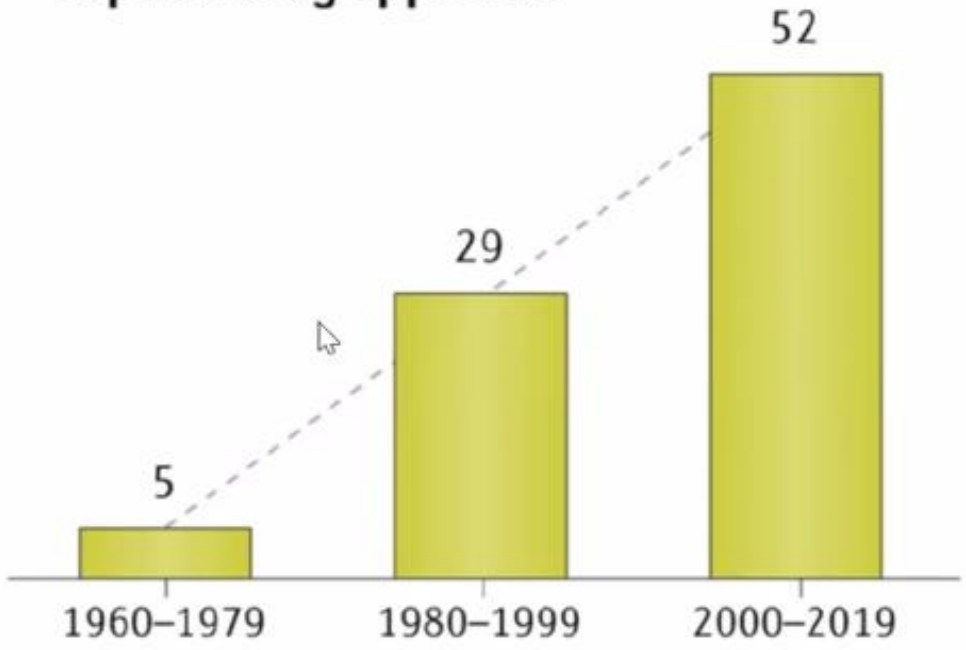
Peptide Market Growth

- Peptide therapeutic market was valued at USD 26.98 Billion in 2019 and is projected to reach USD 51.24 Billion by 2027.

Global pharmaceutical market (2019)



Peptide drug approvals



Technologies for Oral Delivery, Puneet Tyagi, CRS Symposium 2023

Peptide Market Growth

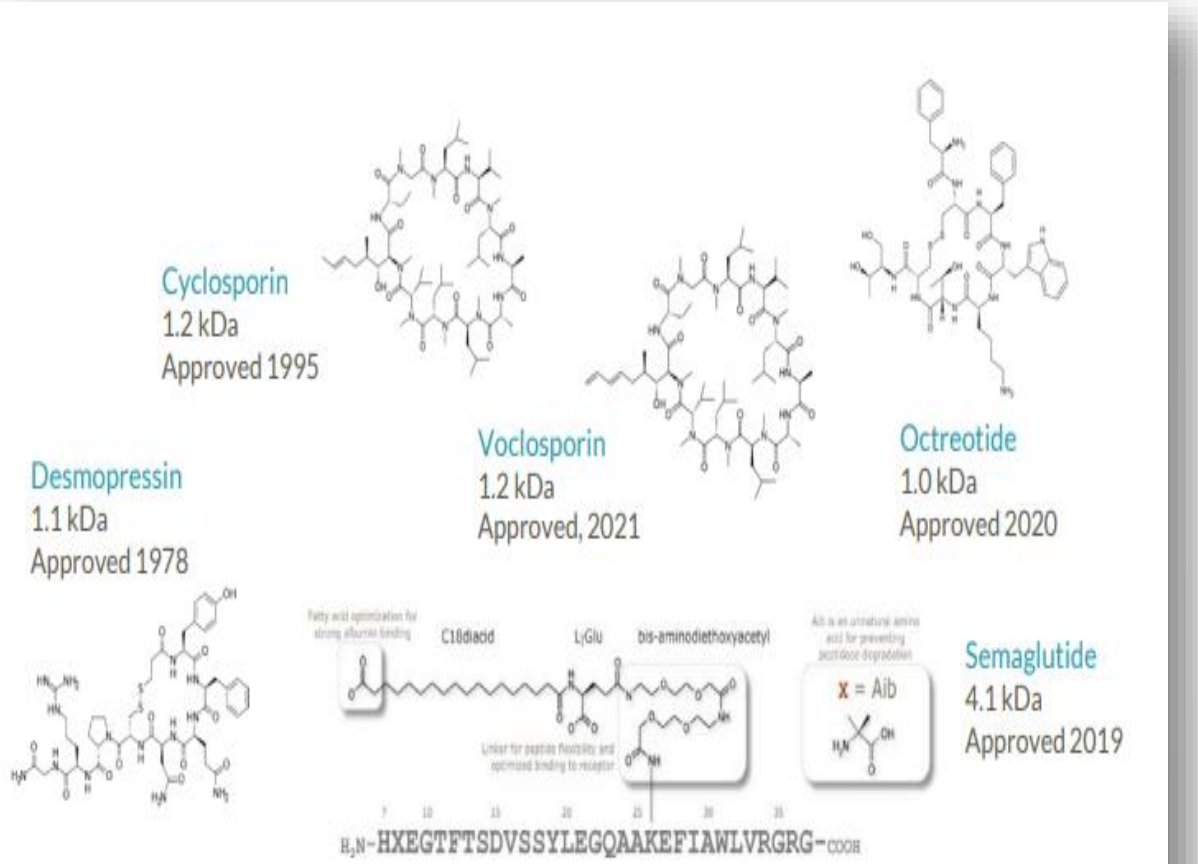
Oral Proteins And Peptides Market size was valued at USD 1.2 Billion in 2022 and is projected to reach USD 7.8 Billion by 2030, growing at a CAGR of 11.5% from 2023 to 2030.

https://www.verifiedmarketresearch.com/product/oral-proteins-and-peptides-market/

The global oral protein and peptide market is growing rapidly; it is estimated to be worth USD 1.5 billion in 2023 and is anticipated to reach USD 8.4 billion by 2032. It is expected to grow at a compounded annual growth rate (CAGR) of 20% during the forecast period from 2022 to 2032.

https://www.prnewswire.com/news-releases/oral-proteins-and-peptides-market-size-to-be-worth-usd-8-4-billion-by-2032--roots-analysis-302036998.html

Oral PPs in Market & Historical Major Milestones of Oral Delivery Systems of PPs



Approved therapeutic peptides for oral delivery*

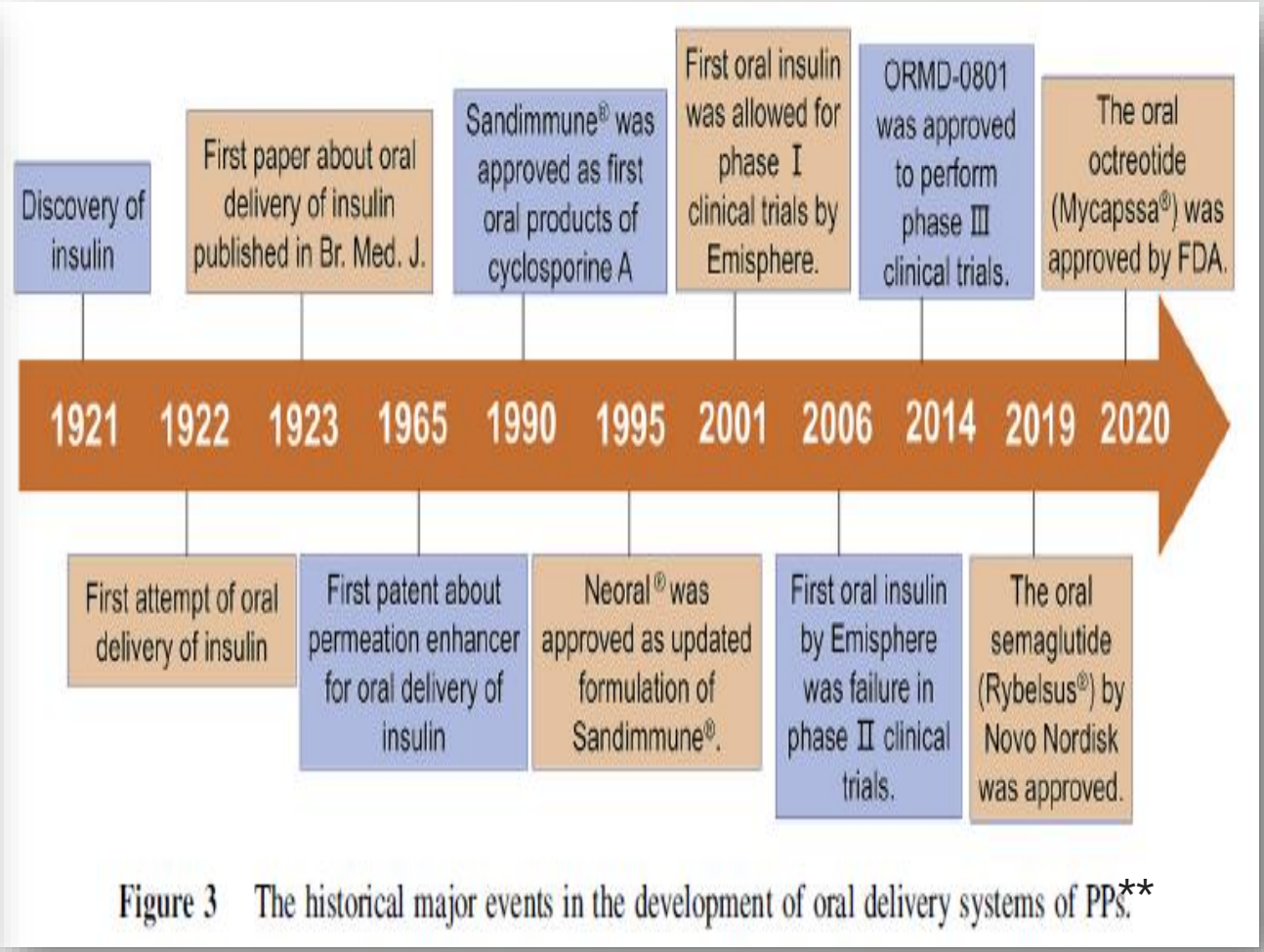


Figure 3 The historical major events in the development of oral delivery systems of PPs.**

*https://www.adocia.com/composants/uploads/2023/09/Adocia-Corporate-Presentation-AUG-2023-EN.pdf

**Acta Pharmaceutica Sinica B 2021;11(8):2416e2448 - Oral delivery of proteins and peptides: Challenges, status quo and future perspectives

Examples of Peptides under clinical evaluation

Company Name	Drug Name	Phase
Ascletis	ASC-30	Phase I
BrightGene Bio-Medical Technology	BGM-0504	Phase I
Boehringer Ingelheim	BI-3006337 (YH-25724)	Phase I
Novo Nordisk	cagrilintide + semaglutide	Phase III
Roche / Carmot Therapeutics	CT-388	Phase II
Roche / Carmot Therapeutics	CT-868	Phase II
MetaVia	DA-1726	Phase I
Zealand Pharma	dapiglutide	Phase II
D&D Pharmatech	DD-01	Phase II
Merck & Co. (Hanmi Pharma)	efinopegdutide	Phase I
Hanmi Pharmaceutical	efocipegtrutide (HM-15275)	Phase I
Apollo Therapeutics	HEC-88473	Phase I
Kailera Therapeutics	HRS-9531	Phase III
Amgen	maridebart cafraglutide	Phase II
Eli Lilly	mazdutide	Phase II
Metsera Inc	MET-097i	Phase II
Novo Nordisk	NN-9541 (NN-9542, NNC0519-0130)	Phase II
Novo Nordisk AS	NNC-04870111 (Amycretin)	Phase II
Altimmune	pemvidutide	Phase II
Eli Lilly	retatrutide	Phase III
Rose Pharma	ROSE-010	Phase I
Boehringer Ingelheim/Zealand	survodutide	Phase III
Viking Therapeutics	VK-2735	Phase II

Peptides under evaluation

Commonly prescribed GLP-1 receptor agonists:

- Dulaglutide - weekly
- Liraglutide - daily
- Semaglutide - weekly subcutaneously, daily orally
- Exenatide BID - twice daily
- Exenatide QW - weekly
- Tirzepatide - weekly
- Albiglutide - weekly (withdrawn from the market)

Other peptides

- Octreotide – octapeptide
- Ecnoglutide –
- Cagrilinitide + Semaglutide
- Dapiglutide

Oral GLP-1's in Clinical trials

Four oral GLP-1R products in Phase III trials as race intensifies

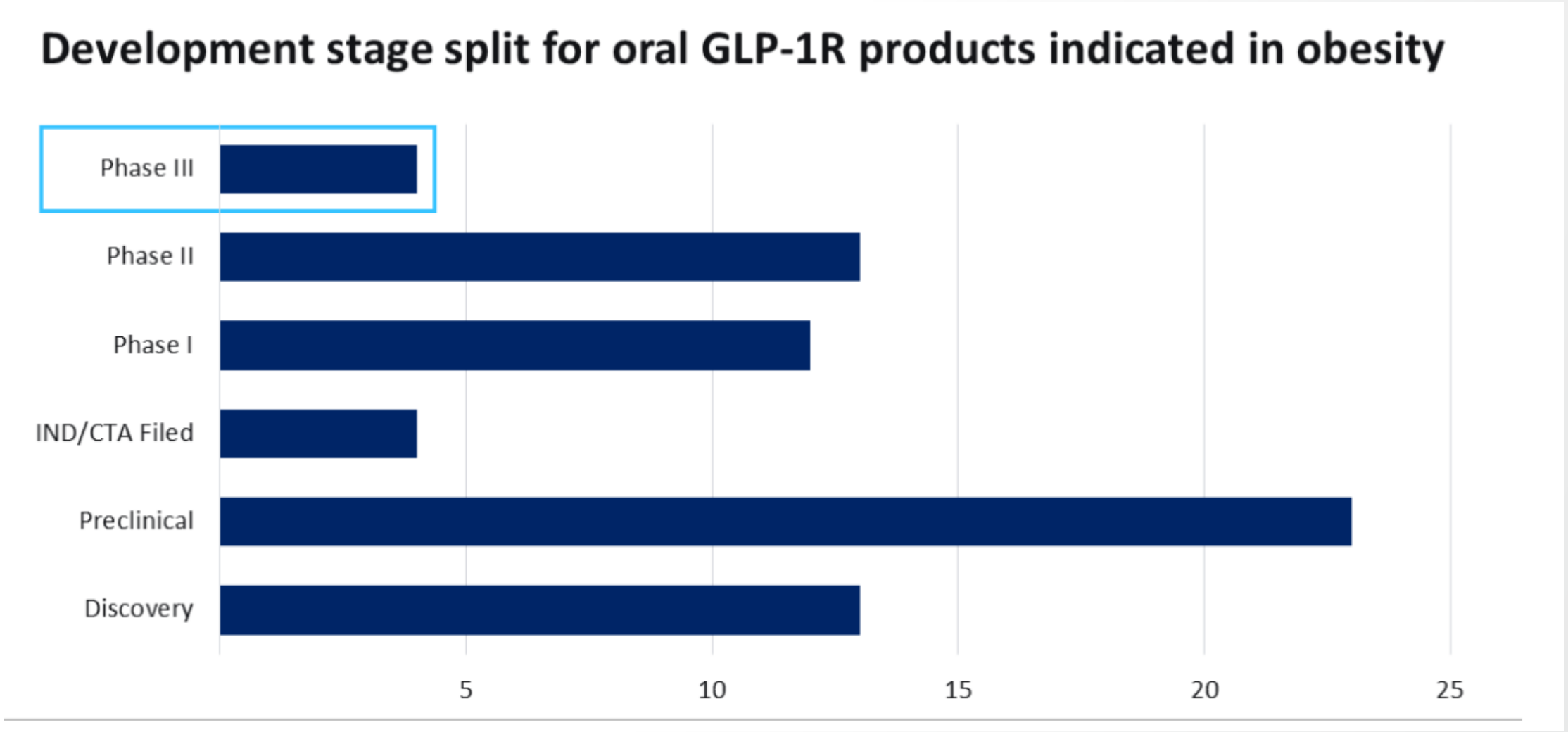
GLP-1R injectable drugs are effective in treating obesity, but their success points to a gap in the market: oral alternatives.

There are currently 63 oral GLP-1R drugs in active development, according to GlobalData's drugs database. Of these, four products are currently in Phase III.

1. Rebelsys — Novo Nordisk
2. NN-9932 — Novo Nordisk
3. Orforglipron calcium — Eli Lilly
4. HRS-953 — Hengrui

https://www.clinicaltrialsarena.com/news/four-oral-glp-1r-products-in-phase-iii-trials-as-race-intensifies/?cf-view&cf-closed

Oral GLP-1's in clinical trials



https://www.clinicaltrialsarena.com/news/four-oral-glp-1r-products-in-phase-iii-trials-as-race-intensifies/?cf-view&cf-closed

Recent Partnerships for Developing GLP-1's

AstraZeneca has recruited a new star to its budding GLP-1 show, picking up an early-stage oral candidate from China's Eccogene in a deal featuring $185 million upfront.

Nov. 2023

https://endpts.com/astrazeneca-licenses-eccogenes-oral-glp-1-for-185m-upfront/

Roche buys obesity and diabetes biotech Carmot Therapeutics in $2.7B merger deal and have will get access to the biotech's three drug candidates,

Dec. 2023

https://endpts.com/roche-buys-obesity-and-diabetes-biotech-carmot-therapeutics-in-2-7b-merger-deal/

Merck is now teaming up with Hansoh Pharma, one of the largest biopharma companies in China, for a candidate known as HS-10535. Merck will dish out $112 million upfront and up to $1.9 billion in biobucks, In China, Hansoh will co-promote or solely commercialize the drug.

Dec. 18, 2024

https://endpts.com/mercks-long-awaited-obesity-move-is-an-oral-glp-1-from-china/

Recent Partnerships for Developing GLP-1's

Verdiva has in-licensed multiple drugs from China-based Sciwind Biosciences. The lead drug is a once-weekly oral formulation of a GLP-1 injectable known as **ecnoglutide**

Jan. 2025

https://endpts.com/aiolos-team-reunites-with-411m-for-new-biotech-with-obesity-drugs-from-china/

Structure Therapeutics Announces First Patients Dosed in Phase 2b ACCESS Clinical Study Evaluating Oral Small Molecule GLP-1 Receptor Agonist, GSBR-1290, for Obesity

Nov. 2024

https://ir.structuretx.com/news-releases/news-release-details/structure-therapeutics-announces-first-patients-dosed-phase-2b

Clinical development of oral peptides

Company	Peptide	Technology	Specifics	Phase
Novo-Nordisk	Semaglutide (Rybelsus®)	Eligen™	SNAC	Approved, 2019
Chiasma	Octreotide (Mycapssa®)	Transient Permeability Enhancer (TPE®)	C_8 in oily emulsion	Approved, 2020
Merck	MK-0606 (macrocycle PCSK9 antagonist)	Permeation enhancer	C_{10}	III, enrolling
Enteris	Leuprolide	Peptelligence™	Acyl carnitines/citric acid	II; ongoing
Novo-Nordisk	Insulin I338	GIPET™	C_{10}	II; terminated
Oramed	Insulin (ORMD-0801)	POD™	Bile salts and EDTA	IIb; terminated (2023)
Biocon	Insulin Tregopil	Acylated PEG-insulin conjugate	C_{10} / pro-drug	II; revised
Janssen	JNJ-2113 (macrocycle IL-23R antagonist)		Not disclosed	Phase IIb (2023)
Rani	Octreotide	Robotic pill	Device	I; completed

Oral bioavailability achieved in animal species

Enhancer(s)	Species/model	Molecule	F	DOI
C10	Cynomolgus monkeys	modified PCSK9 ASO	1.4%*	10.1126/scitranslmed.abe9117
Labrasol®	Cynomolgus monkeys	Macrocycle 44	2.9%	10.1021/acs.jmedchem.1c01599
Propyl gallate, NaCDC	Dogs	MEDI17219	5.9%	10.1038/s41598-021-01750-0
SNAC	Dogs	Semaglutide	0.1-1.2%	10.1126/scitranslmed.aar7047
C10	Dogs	Octreotide	1.2%	10.1016/j.xphs.2020.10.066
PEI (800 Da, end-capped)	Pigs	Oxytocin	6.5%	10.1038/s41551-020-0545-6
C10	Minpigs	GIP-GLP1 agonist (LY)	2%	10.1021/acs.molpharmaceut.2c00443
Labrasol®	Rats (IJ instillation)	Insulin	7%	10.1016/j.jconrel.2019.08.008
Labrasol®	Rats (ID instillation)	Octreotide	2%	10.1007/s11095-019-2682-8
Choline-geranic acid (CAGE)	Rats, (IJ instillation)	Insulin	51%	10.1073/pnas.1722338115
Pelargonidin	Mice (mintab gavage)	Insulin	>80%	10.1073/pnas.2207829119

Oral bioavailability achieved in humans

Enhancer(s)	Molecule	F	DOI
SNAC	semaglutide	0.4-1.2%	10.1126/scitranslmed.aar7047
SNAC	cyanocobalamin	5.1% (from 2% basal)	10.1016/j.clinthera.2011.05.088
Eligen® analogue	sCT	0.5-1.4%	10.1359/jbmr.2002.17.8.1478
C10	I338	2%	10.1016/S2213-8587(18)30372-3
C10	MK-0616	2% estimated	10.1161/CIRCULATIONAHA.122.063372
Labrasol®	MK-0616	2% estimated	10.1161/CIRCULATIONAHA.122.063372
C10	insulin tregopil	2%	10.1007/s40265-023-01925-1
C10	Ionis 301012 (ASO)	5%	Hardee, GE et al (2008). Antisense Drug Technology, 2nd Ed. CRC Press
C8 (oily suspension)	octreotide	0.5%	10.1210/jc.2012-1179
Acyl carnitine/citric acid	sCT	0.4%	US6086918A

Protein and Peptide Delivery Challenges

Protection from the extreme acidity and pepsin in the stomach

(Enzymatic Degradation)

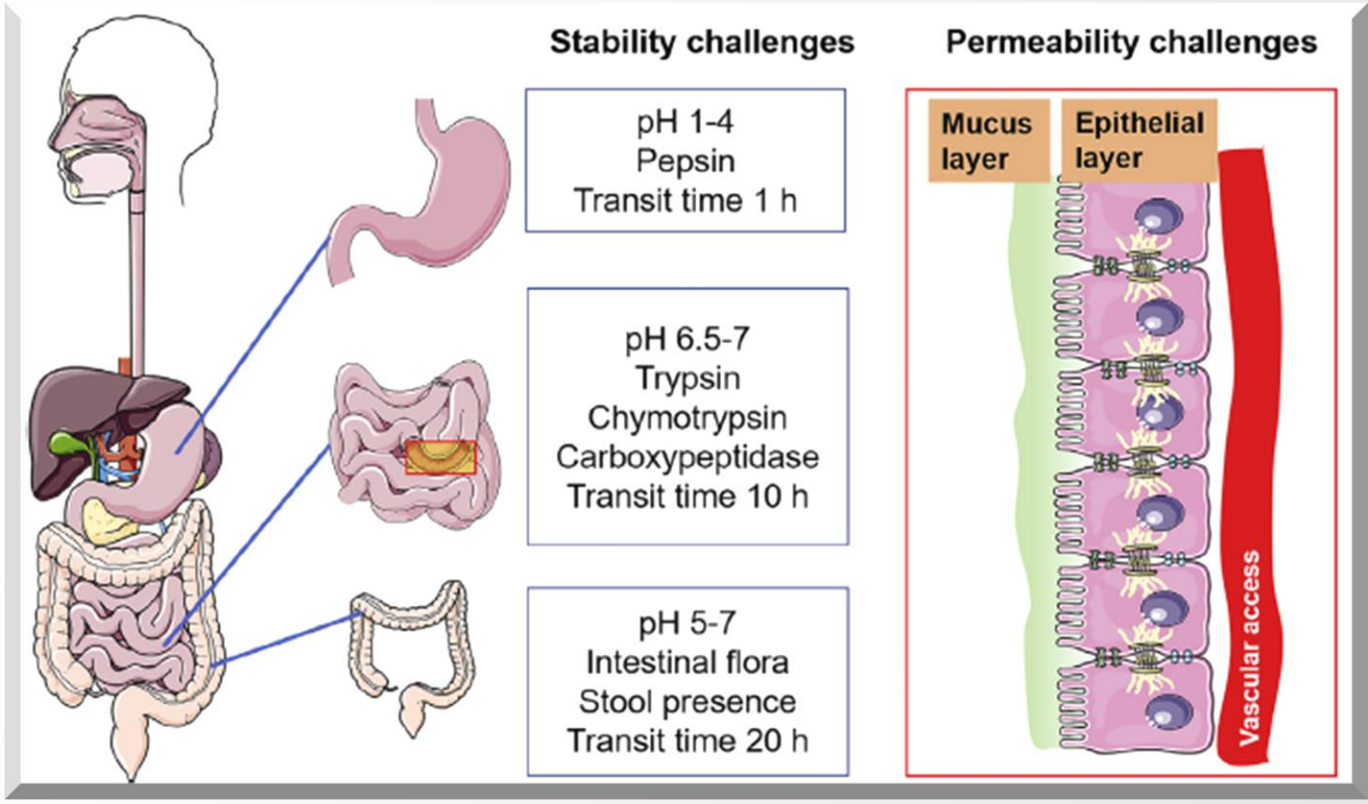
In the intestine, the drug should be protected from the plethora of enzymes that are present in the intestinal lumen.

Formulating a protein and peptide drug for delivery though GI tract requires a multitude of strategies.

The dosage form must initially stabilize the drug making it easy to take orally.

In addition, the formulation must facilitate both aqueous solubility at near-neutral pH and lipid layer penetration for the protein to cross the intestinal membrane and then basal membrane for entry into the bloodstream.

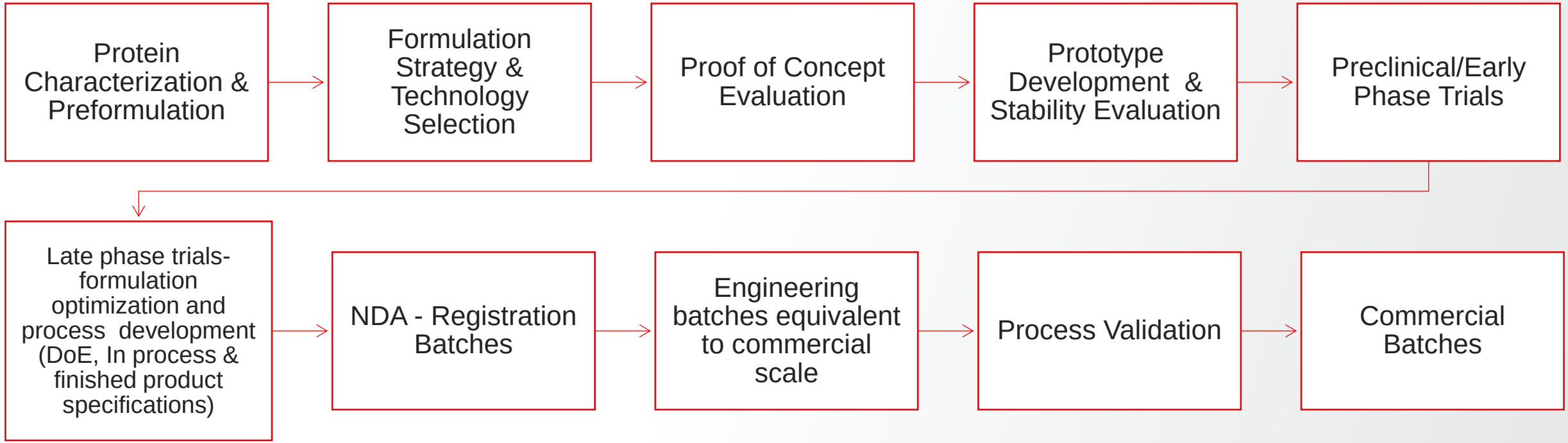
(Membrane Permeability)



Schematic representation of physiological barriers and permeability challenges in GI tract*

*Acta Pharmaceutica Sinica B 2021;11(8):2416e2448

Oral PPs Development Process Flow



End to end services at Thermo Fisher
Detailed discussion in the subsequent slides

PPs Characterization & Preformulation

Peptide/Protein Characterization

Test	Details	Instrument/Techniques
Amino acid sequence	This is the method of determining the order and identity of the amino acids that make up the peptide.	Mass spectrometry (MS), Edman degradation, or N-terminal sequencing .
Peptide mapping	This is the method of breaking down the peptide into smaller fragments by using enzymes or chemicals, and then separating and identifying the fragments. Peptide mapping can provide information about the primary structure, disulfide bonds, post-translational modifications, and sequence variants of the peptide.	(HPLC), capillary electrophoresis (CE), or MS
Host cell protein	This is the method of detecting and quantifying the residual proteins from the host cell that may contaminate the peptide product during the production process. Host cell proteins can affect the safety, efficacy, and stability of the peptide product, and therefore need to be minimized and monitored.	Enzyme-linked immunosorbent assay (ELISA), mass spectrometry, or western blotting .
Host cell DNA	This is the method of detecting and quantifying the residual DNA from the host cell that may contaminate the peptide product during the production process. Host cell DNA can pose a potential risk of immunogenicity, mutagenicity, or viral transmission, and therefore need to be minimized and monitored.	Polymerase chain reaction (PCR), quantitative PCR, or hybridization assays
SDS-PAGE	This is the method of separating proteins based on their molecular weight by using sodium dodecyl sulfate (SDS) and polyacrylamide gel electrophoresis (PAGE). SDS is a detergent that denatures the proteins and gives them a uniform negative charge, while PAGE is a technique that applies an electric field to a gel matrix that acts as a sieve. SDS-PAGE can provide information about the size, purity, and identity of the peptide.	Sodium dodecyl sulfate (SDS) and Polyacrylamide gel electrophoresis (PAGE)

Peptide/Protein Characterization (Contd..)

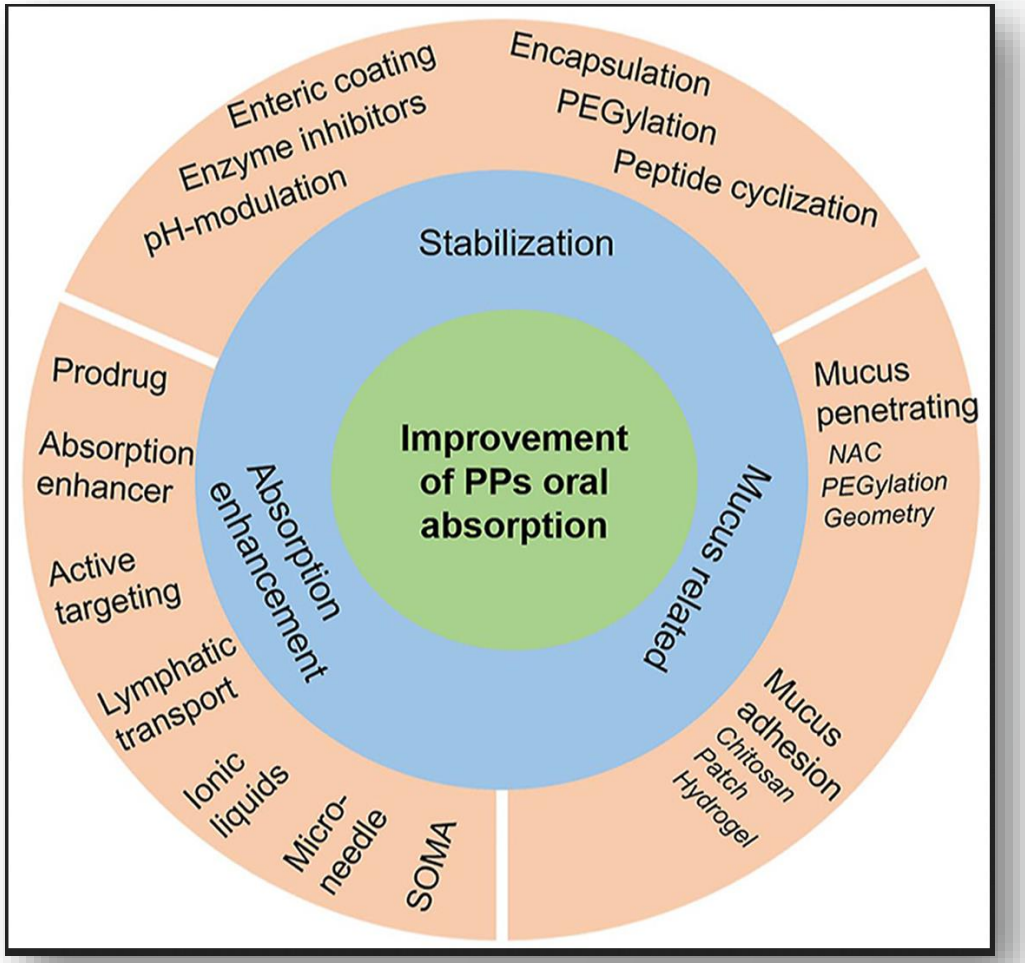
Test	Details	Instrument/Techniques
Intact mass (Molecular Weight)	This is the method of measuring the molecular weight of the intact peptide without any fragmentation or modification. Intact mass can provide information about the accuracy, consistency, and heterogeneity of the peptide.	Matrix-assisted laser desorption/ionization (MALDI) or electrospray ionization (ESI) mass spectrometry
Capillary isoelectric focusing (CIEF)	This is the method of separating proteins based on their isoelectric point (pI) by using capillary isoelectric focusing (CIEF). pI is the pH at which the protein has no net charge and does not migrate in an electric field. CIEF can provide information about the charge, purity, and identity of the peptide.	CIEF is a technique that applies an electric field to a capillary tube that contains a pH gradient
pH stability	This is the method of testing the stability of the peptide under different pH conditions. This can be done by exposing the peptide to various pH buffers and measuring its activity, solubility, aggregation, or degradation. pH stability can provide information about the optimal pH range, shelf life, and storage conditions of the peptide.	HPLC, MS
Manganese content	This is the method of detecting and quantifying the amount of manganese (Mn) in the peptide product. Mn is a trace element that can be present in the peptide due to the use of MnCl2 as a catalyst in the peptide synthesis. Mn can affect the activity, stability, and toxicity of the peptide, and therefore need to be controlled and monitored.	Atomic absorption spectroscopy (AAS), inductively coupled plasma mass spectrometry (ICP-MS), or colorimetric assay
Endotoxin	This is the method of detecting and quantifying the amount of endotoxin in the peptide product. Endotoxin is a lipopolysaccharide (LPS) that is released from the cell wall of gram-negative bacteria. Endotoxin can cause fever, inflammation, and shock in humans, and therefore need to be eliminated and monitored.	Limulus amebocyte lysate (LAL) assay, kinetic turbidimetric assay, or chromogenic assay

Preformulation (Physicochemical Characterization)

- Particle size
- Bulk and tap density
- Flow properties
- Compressibility and the impact of shear on Protein properties
- Compaction simulation studies
- Hygroscopicity
- Moisture Analysis
- pH related solubility
- pH related stability
- ASAP stability
- Force Degradation
- Excipient compatibility studies
- Define the drug product development process based on the preformulation studies and data

Formulation Strategies

Strategies for Improving Oral Absorption of Proteins and Peptides (PPs)



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Potential Dosage Form for Oral Delivery of Peptides

- Tablets with functional Targeted Release
- Mucoadhesive tablets
- Capsules with functional targeted release
- Lipid Based Drug Delivery
- Other

Stabilization Approaches

pH Modulation – to Protect from the GI pH and Enzymes

- pH Modulation – GI enzymes need optimal pH to exert their effect. Incorporation of acid or alkaline salts can minimize the PPs degradation.

  - Modulate stomach pH
    - Eg- Pepsin starts to lose their effect pH above 3. The in vitro studies have shown that Salcaprozate Sodium increases the local pH around the tablet. This results in reduced pepsin activity and thereby reduced metabolism of Semaglutide in the stomach.*

  - Modulate Intestinal pH
    - Eg - Luminal proteases, such as trypsin and chymotrypsin, exhibit maximum activity at pH > 6.5. Some organic acids, such as citric acid, tartaric acid have been generally used as pH-lowering agents to inhibit the activity of intestinal enzymes.
    - Tarsa Therapeutics (Philadelphia, USA) phase III trial for oral delivery of Salmon Calcitonin (ORACAL) which comprises of an enteric coated capsule to bypass the stomach and citric acid to modulate the pH microenvironment in intestine.**

*Rybelsus, INN-semaglutide (europa.eu)

**Oral delivery of proteins and peptides: Challenges, status quo and future perspectives - ScienceDirect

pH Modulating Excipients Selection and Challenges

Selection & Optimization

- Select the salt based on the target site (eg- alkaline salts for stomach and acids for the small intestine)
- Salt and PPs compatibility
- Optimize the salt amounts using the invitro studies containing different salt to drug ratios (pH measurements)
- Formulations with different salt to drug ratios can be tested in preclinical or early phase trials. Based on the clinical data, an optimized quantity of salt can be selected

Challenges

- Any novel excipients would require extensive information in the dossier
- Extensive stability and tox data may be required
- Drug & salt incompatibilities
- Salt induced stability issues

Enteric Coating – Small Intestine & Colon-Specific Delivery

- Enteric coating offers protection to PPs from low pH and pepsin in stomach completely.
- Commonly used polymers are Eudragit – L 10055, L100 & S100 , HPMCP (Phthalate), Acryl-EZE®
- Colon is a more suitable absorption site for PPs when compared to stomach and small intestine due to its low enzyme activity, long residence time and neutral pH value

- **Challenge** - Oral bioavailability of PPs can't be improved significantly if only enteric coating is used because of the digestive enzymes in intestine.

- **Solution** – Enteric coating in combination with protease inhibitors or permeation enhancers (PE) or pH modulating agents can improve permeation and/or reduce the metabolism – (Details of a marketed product using the combination of PE & enteric coat is presented in lipid-based formulations section)
- Tarsa Therapeutics (Philadelphia, USA) phase III trial for oral delivery of Salmon Calcitonin (ORACAL) which comprises of an enteric coated capsule to bypass the stomach and citric acid to modulate the pH microenvironment in intestine.*

*Oral delivery of proteins and peptides: Challenges, status quo and future perspectives - ScienceDirect

Enteric coated Dosage Forms for Oral PPs

Proof of concept or Early phase clinical trials

- Can be achieved using readily available functional coated capsules

  EUDRACAP® , Enprotect® (HPMC and HPMC-AS polymers)
- Targeted drug delivery to small intestine and colon
- Ideal for active ingredients (PPs) which are sensitive to gastric acid heat and moisture
- Reduce the development cost and accelerate time to clinic

Traditional Approaches

- Enteric coated capsule – Dry blend filled into the capsules followed by an enteric coat on top of the capsule shell
- Mini Tablets – Enteric coated mini tablets filled into the capsule or core mini tablets filled into the capsules followed by an enteric coat on top of the capsule shell
- Single unit matrix tablet – Tablet coated with an enteric coating

Absorption/Permeation Enhancers

Absorption/Permeation Enhancers

Mechanism - Fluidity and permeability of the membrane

- Absorption enhancers can facilitate oral absorption of PPs either paracellularly via the opening of tight junctions or transcellularly through increasing membrane permeability, or a combination of both.

- There are over 250 substances that have been used in preclinical studies as absorption enhancers for oral delivery of PPs, some of typical which have been listed in Table 2.*

Table 2 List of some typical permeation enhancers for oral absorption of PPs.

Enhancer	Mechanism	Application
EDTA	Chelating agents; paracellular	ORMD-0801; ORMD-0901 (Oramed Pharma, USA)
Citric acid	Chelating agents; paracellular	Peptelligence™ (Tarsa, USA)
Bile salts	Multimodal	IN-105 (Biocon, India)
Sodium caprate (C_{10})	Multimodal	GIPET® (Merrion Pharma, Ireland)
Sodium carprylate (C_8)	Multimodal	TPE® (Chiasma, Israel)
SNAC/5-CNAC	Transcellular	Eligen® (Emisphere, USA)
Chitosan	Multimodal	Oral insulin (NanoMega, USA)
Penetratin/PenetraMax	Transcellular	Reported for various peptides

*Acta Pharmaceutica Sinica B 2021;11(8):2416e2448

Permeation enhancers

Over 250 PEs have improved intestinal permeability of poorly absorbed drugs including peptides in every conceivable pre-clinical drug delivery model. Yet there is a relatively poor translation of PE-based delivery systems for oral peptides.

https://www.sciencedirect.com/science/article/abs/pii/S0169409X16301892

Oral Peptides & Proteins (PPs) - Potential for approval when right technology is used

- The FDA approval of oral Semaglutide for type 2 diabetes (2019) and oral Octreotide for acromegaly (2020) is evidence that selected niche peptides can be administered orally if formulated with suitable technologies such as permeation enhancers and enteric coating.*

*https://doi.org/10.1080/17425247.2021.1942838 - Transient Permeation Enhancer® (TPE®) technology for oral delivery of octreotide: a technological evaluation

FDA Approved Oral Peptide using Absorption Enhancer - Rybelsus (Semaglutide Tablets)

- **Formulation Design** - Primarily driven by optimizing the Semaglutide bioavailability using **Salcaprozate sodium** as an absorption enhancer**.

** Sources to procure
https://api.drreddys.com/product/salcaprozpate-sodium-snac-excipient-oral-semaglutide
https://www.bocsci.com/product/salcaprozate-sodium-cas-203787-91-1-186805.html
https://lgmpharma.com/product/salcaprozate-sodium/

Absorption Enhancers Evaluation/Optimization

- In vitro experiments using Caco-2 cells
- Preclinical & early phase trials using different absorption enhancers or the concentrations of same absorption enhancer

Table 1 Compositions of the semaglutide drug products

Component	Quantity per tablet (mg/tablet)			Function	Reference to standards
	Semaglutide 3 mg tablet	Semaglutide 7 mg tablet	Semaglutide 14 mg tablet		
Active pharmaceutical ingredient					
Semaglutide	3	7	14	Active ingredient	Novo Nordisk A/S
Excipients					
Salcaprozate sodium	300	300	300	Absorption enhancer	Novo Nordisk A/S
Cellulose, microcrystalline					Ph. Eur., USP, JP
Povidone					Ph. Eur., USP, JP
Magnesium stearate					Ph. Eur., USP, JP
Gross weight[a]	400.7	404.7	411.7	-	-

*https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/213051Orig1s000ChemR.pdf

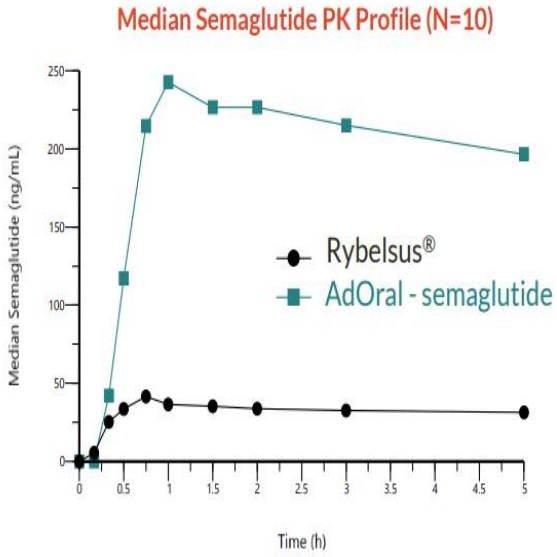
AdOral® - Platform for Oral Delivery of Peptides

AdOral: a promising technology for oral delivery of peptides

- AdOral is a unique formulation based on a new type of permeation enhancer (PE) combined with peptide protection against degradation
- Technology patented until 2042 globally
- The technology has been validated with Semaglutide compared to Rybelsus®, an oral formulation for Type 2 diabetes treatment
- Potential applications to other peptides or proteins

A first feasibility study is ongoing on a partner's protein
Two other feasibility studies are under discussion

Semaglutide formulated with AdOral has shown significantly improved bioavailability in animal



Bioavailability of semagludide formulated with AdOral:
5-fold higher median than Rybelsus

Adocia seeks to establish proof of concept with peptides from future partners

https://www.adocia.com

*https://www.adocia.com/composants/uploads/2023/09/Adocia-Corporate-Presentation-AUG-2023-EN.pdf

Mucoadhesion Approach

Mucoadhesive System

- Mucoadhesive polymers such as Hydroxypropyl Methylcellulose, Chitosan, and Carbopol® can adhere to the mucus layer in the G.I. tract and provide an excellent platform for oral delivery of PPs.

- Mucoadhesion enhances the degree of drug absorption by extending the residence time of the drug carrier and providing higher drug concentration to the absorption site

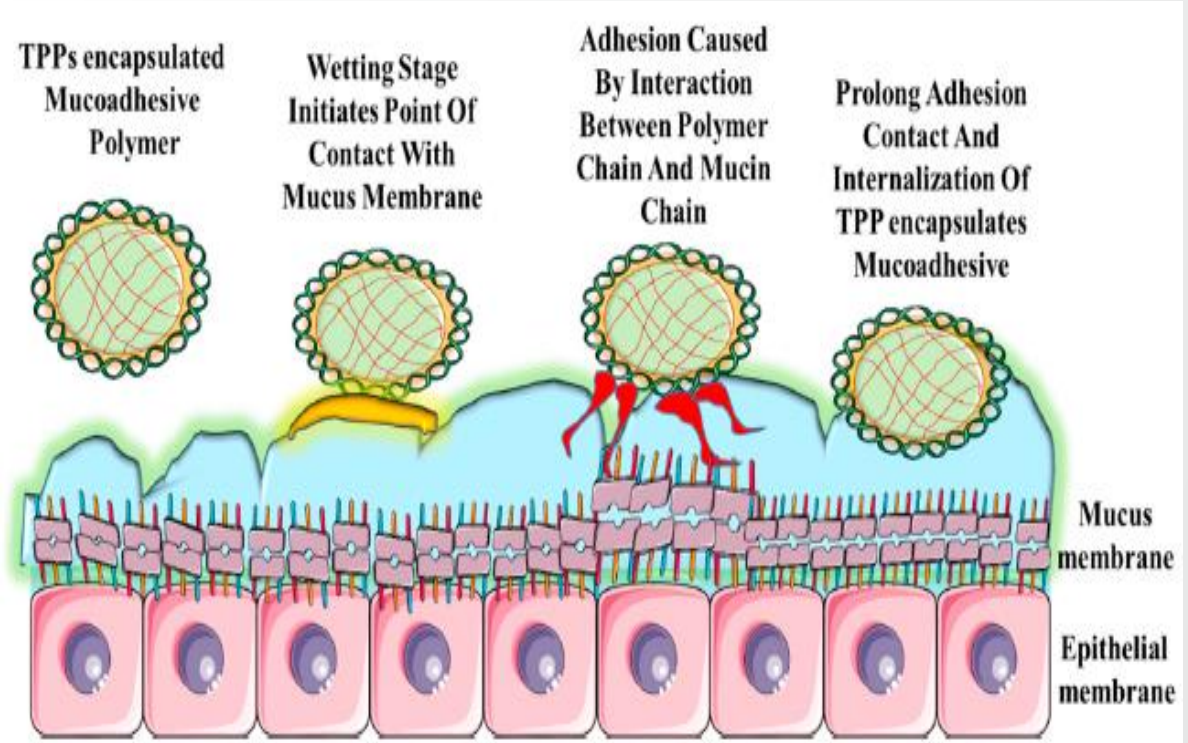


Figure 3. Steps in mucoadhesion for the mucoadhesive polymeric system. At the first stage the mucoadhesive polymer swells (contact stage). The swelling occurs because the polymer has an affinity for water. In the second stage, the polymer interacts with the mucus membrane. Weak chemical bonds form in the entangled polymer chains.

*Children **2020**, 7, 307; doi:10.3390/children7120307 - **An Update on Pharmaceutical Strategies for Oral Delivery of Therapeutic Peptides and Proteins in Adults and Pediatrics**

Mucoadhesive System coupled with an enteric coating

Limitation & Solution - Mucoadhesion may not offer the protection from the low pH and enzymatic degradation of the upper GI region. Therefore, addition of an enteric coating can deliver the dosage form to the target site for mucoadhesion.

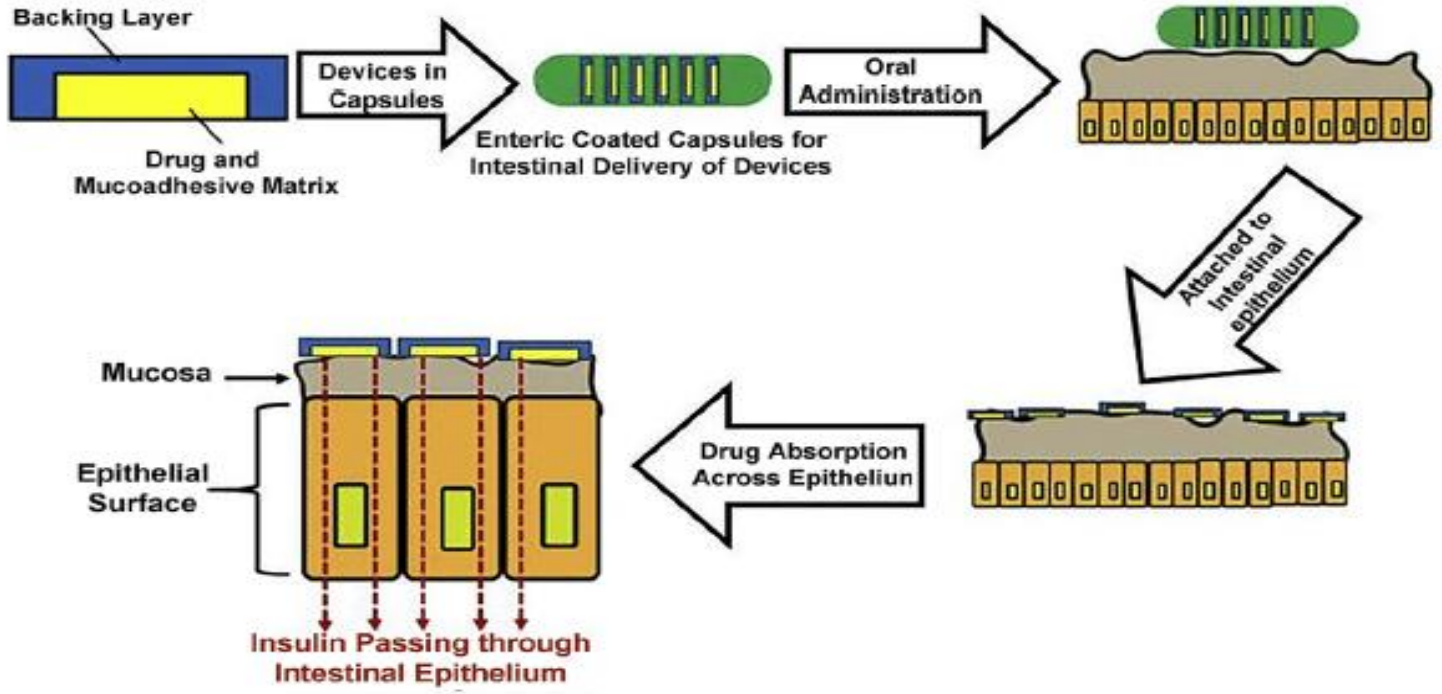


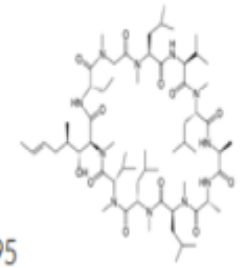
Figure 7 Schematic illustration of structure of intestinal patch and administration device, and *in vivo* mechanism of adhesion, drug release and absorption across intestinal epithelium. Reprinted with the permission from Ref. 176. Copyright © 2016 Springer.

*Acta Pharmaceutica Sinica B 2021;11(8):2416e2448

Lipid Based Systems

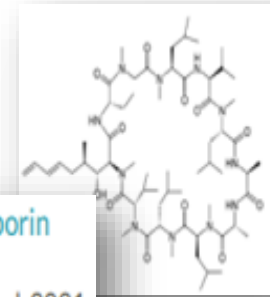
Lipid Based SEDDS in the Market

Specify Neoral (cyclosporine capsules, USP) MODIFIED



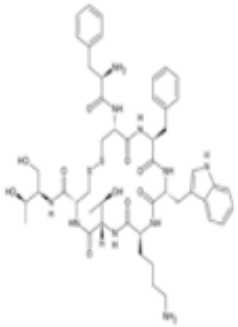
Cyclosporin
1.2 kDa
Approved 1995

Lupkynis (voclosporin) capsules 7.9 mg



Voclosporin
1.2 kDa
Approved, 2021

Mycapssa (octreotide) capsules 20mg



Octreotide
1.0 kDa
Approved 2020

General Benefits of Lipid Delivery

- Enhancement of solubility, bioavailability and absorption of poorly soluble compounds
- Improved stability
- Improved Content Uniformity of low dose actives
- Mitigated containment requirements for potent and hormone compounds
- Targeted drug delivery and controlled release delivery
- Easy to manufacture
- Flexibility of dosing
- Improved patient compliance

SOFTGELS

HARD SHELL CAPS

Liquid Fill Hard Shell Capsules Formulation Development Steps

Formulation Fill development → Banding Solution Development → Prototype development → Scale up Early & late phases

Preformulation/Drug Fill Development

- Vehicle Screening
- Lipid Digestion
- Solubility Studies
- Emulsification Studies
- Melt temp studies
- Precipitation & Dispersibility Studies
- Phase Diagrams
- Material Characterization
- Excipient Compatibility
- Drug characterization
- Gelatin or HPMC capsule shells

Banding solution development

- Polymer Selection (Gelatin or HPMC)
- Color selection (color is recommended for band identification during in-process testing and inspection)
- Solvent/Water Selection
- Band weight

Prototype Development

- Capsule shell size (size 4 -00)
- Develop drug fill preparation process
- Develop encapsulation Process
- Banding process
- In process Testing
  - Fill Weights
  - Band Weight
  - Weight sorting
  - In Process inspection
- Content uniformity
- Stability

Scale up consideration

- Heating time and temperature optimization
- Deaeration
- Maintain the optimum temperature throughout the process
- Accurate Fill weight
- Encapsulation process development
- Equipment to vacuum convey the drug fill to Encapsulator hopper
- Vacuum conveyor from encapsulator to bander
- Banding process (band weight)
- Equipment and Containment (to handle potent compounds)
- Skilled and Trained operators to handle the process

Lipid Based Enteric Coated Capsule (Synergistic combination of PE + target specific)

- **Product** - Mycapssa®, an oral formulation of Octreotide – a cyclic peptide with a relatively low molecular weight (1019.2 g/mol)
- **Technology** - Chiasma's Transient Permeation Enhancer (TPE™) technology
- **Permeation Enhancer (PE)** - Sodium Caprylate (C8) is the key component that acts as a PE in the technology
- **Dosage Form** – Enteric coated capsule containing an oily emulsion
- **Mechanism** - Transiently alter epithelial barrier integrity by opening of intestinal epithelial tight junctions arising from transcellular perturbation.

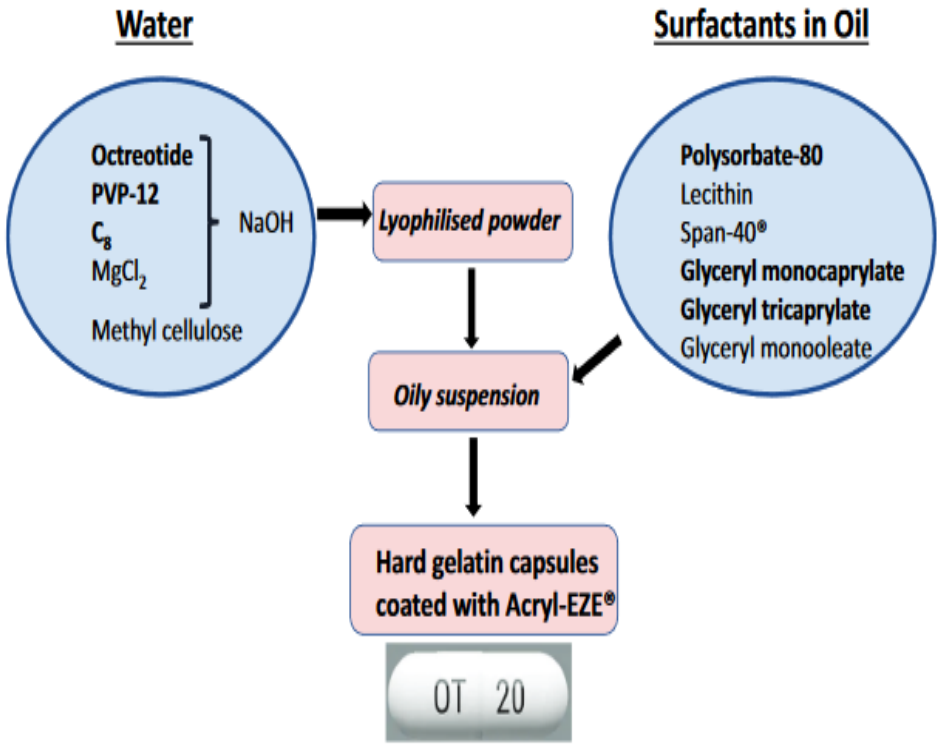


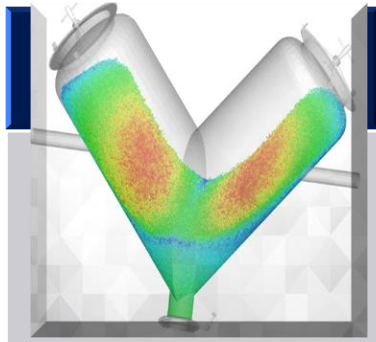
Figure 2. The method of octreotide incorporation into TPE® to form an enteric capsule containing an oily suspension. Details are a composite of information in [37,38]. Octreotide present as the acetate salt. Highlighted substances in the water and oil phases are marked in bold as definitive in the formulation [37]. Components tested in other iterations are also included as described in [38]. Acryl-EZE® (Colorcon, NJ, USA) is a proprietary methacrylic acid-based enteric coating system. Capsule image courtesy of: https:www.Drugs.com/imprints/ot-20-30532.html

*https://doi.org/10.1080/17425247.2021.1942838 - Transient Permeation Enhancer® (TPE®) technology for oral delivery of octreotide: a technological evaluation

Site Specific (Target) Delivery

Site Specific Delivery – Pellet / Bead / Minitablet

Delivery Small Intestine or Colon

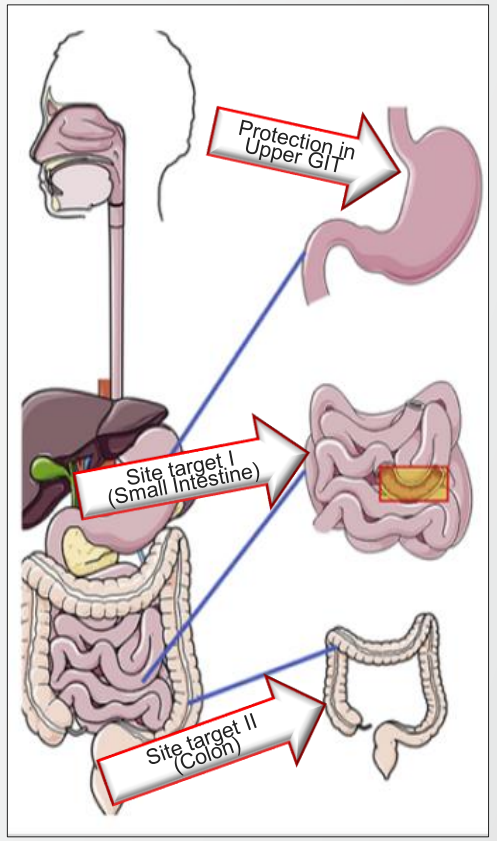


Blend the Protein/Peptide in powder form with excipients

Encapsulate the blend into Hard Gelatin capsule shells

If tablet dosage form is desired, blend can be compressed into a tablet

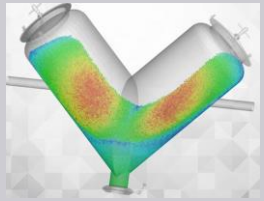
Functional coating will be applied to achieve the site-specific target release



Batch Size Scale Range – Few grams to 300 kg+

Capabilities and Scientific Expertise - Proof of Concept through Commercialization

Site Specific Delivery using Multiparticulates – Small Intestine or Colon

Blending		Compression	Coating	
				 
Blend the Protein/Peptide in powder form with excipients	Compress the blend into a mini tablets		Functional coating will be applied to mini tablets to achieve the site-specific target release	Mini tablets can be filled into capsules or stickpacks

Ideal for Pediatric & Geriatric population with swallowing difficulties

Flexibility with dose titration for the early and late phase clinical studies with stickpack

Finished Product Characterization

In Process Testing during Drug Product Manufacturing

- Moisture (LOD)
- Particle Size Distribution (Sieve Analysis)
- Bulk & Tapped Density
- Angle of Repose
- Flow Properties
- Blend Uniformity
- Assay of the blend (optional)
- Appearance
- Individual unit dose weight (tablets/capsules)
- Weight of 10 units
- Hardness (tablets)
- Thickness (tablets)
- Friability (tablets)
- Locked length (capsules)

Peptide/Protein Drug Product Characterization

Test	Details	Instrument/Techniques
Appearance	This parameter is used to determine the visual appearance of the protein drug product.	Visual inspection of the drug product
Identity	This parameter is used to confirm the identity of the protein drug product. It is usually determined by comparing the protein's sequence, molecular weight, and other physicochemical properties with those of a reference standard	Mass spectrometry and/or U(H)PLC technology.
Purity/assay	This parameter is used to determine the purity of the protein drug product.	Combination of analytical techniques such as chromatography, electrophoresis, and mass spectrometry
SOD (superoxide dismutase) activity	This parameter is used to determine the superoxide dismutase (SOD) activity of the protein drug product. SOD is an enzyme that plays a crucial role in protecting cells from oxidative stress.	The activity of SOD can be determined using a variety of assays
Protein content	This parameter is used to determine the protein content of the drug product.	Combination of analytical techniques such as HPLC, UV spectroscopy, Bradford assay, and bicinchoninic acid assay (BCA)

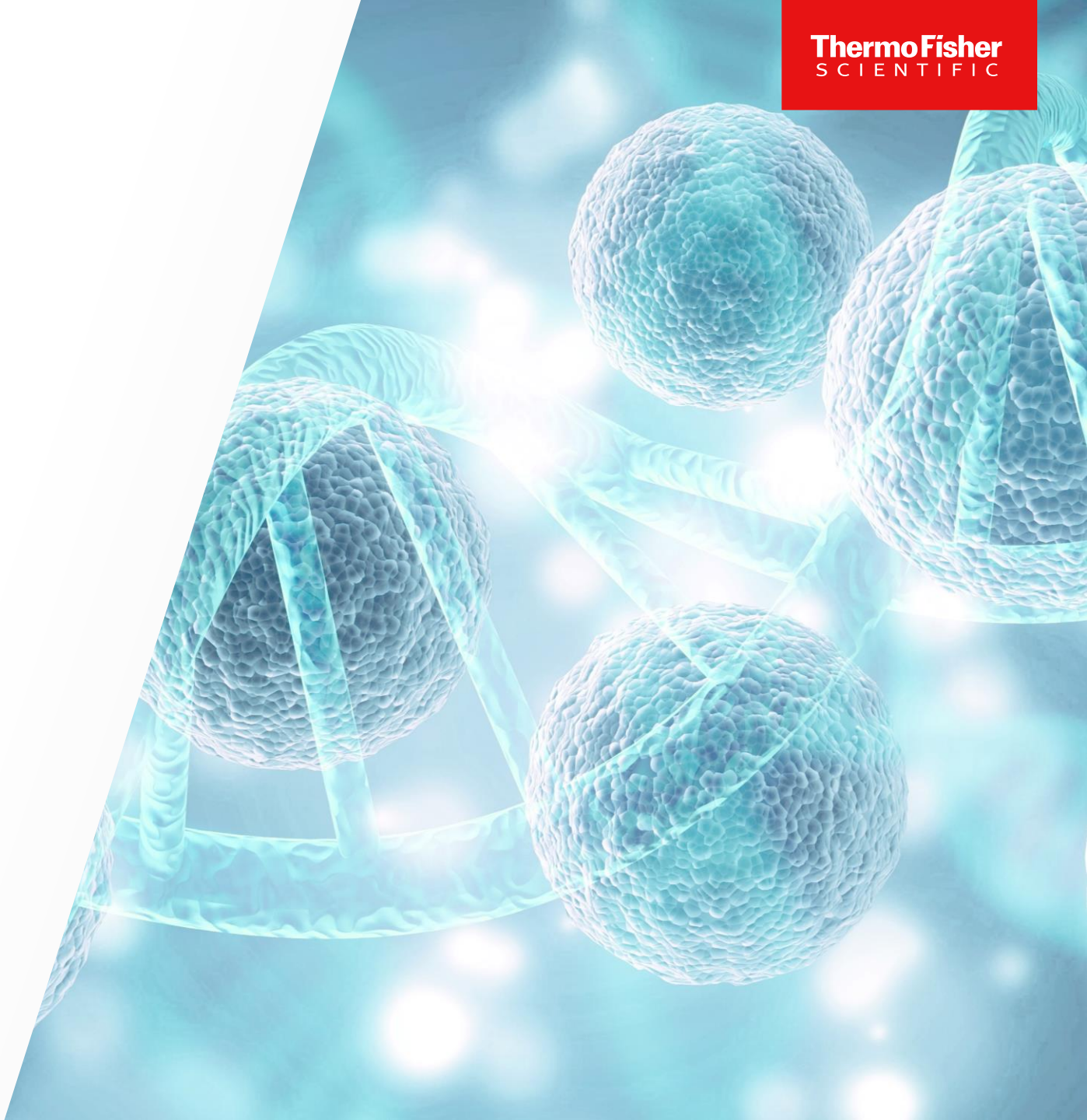
Peptide/Protein Drug Product Characterization

Test	Details	Instrument/Techniques
Water content	This parameter is used to determine the water content of the protein drug product.	Karl Fischer titration and loss on drying
Microbial testing	This parameter is used to determine the presence of microbial contamination in the protein drug product.	Combination of microbiological assays such as plate count, membrane filtration, and direct inoculation
Dissolution	This parameter is used to determine the rate at which the protein drug product dissolves in a given medium.	RP-HPLC
Content uniformity	This parameter is used to determine the uniformity of the protein drug product.	RP-UHPLC & MS
Permeability or Absorption enhancers assay	This parameter is to confirm the presence of absorption/permeation enhancer within the predetermined specification range	RP-UHPLC
HMWP	High molecular weight proteins (HMWP)	SE-HPLC, LCMS, MS

Conclusion

Thermo Fisher can offer

- Development of peptides in oral delivery
- Clinical manufacturing of orally delivered peptides for Phase I – III
- Commercial manufacturing of orally delivered Proteins, peptides, oligos and others in the class
- Bring effective medicines to patients



Thank you