Formulating Peptides for the Gut: A Case Study on Exenatide in Lipid-Based Formulations using Enteric Capsules

Vincent Jannin, PharmD, PhD, HDR, FCRS
Innovaform™ Accelerator, Capsugel SAS France

Oral Drug Delivery – Technology of Today and Tomorrow Workshop
July 14th, 2025

CRS 2025 ANNUAL MEETING & EXPOSITION
PHILADELPHIA, PA
JULY 13-18, 2025

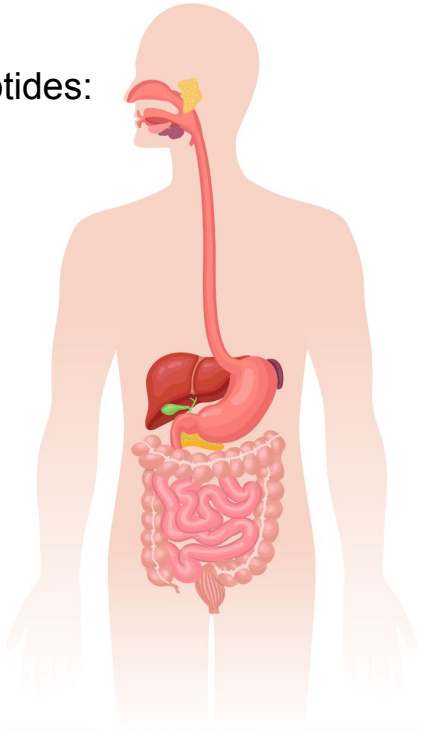
NEXT-GENERATION DELIVERY INNOVATIONS

What limits oral bioavailability of peptides?

Bioavailability: the rate and extent at which a drug reaches the general circulation from an administered dosage form

Main limitations to oral bioavailability of peptides:

- **Acid** sensitivity
- Sensitivity to digestive **enzymes**
- Poor **permeability** across stomach and intestinal barriers



Main attributes of Lipid Based Formulations can overcome several bioavailability issues

LBF: Isotropic mixtures of drug in liquid or semi-solid lipid excipients

Physiological advantages

Lipidic environment can provide **protection from enzymatic degradation**

Favoring efficient diffusion through the mucus layer to reach the intestinal epithelium

Permeability improvement : open tight junction and favor paracellular uptake and compatible with permeation enhancers

Formulation advantages

Simple formulation preparation process with soft conditions

Ease of **scale-up**

Liquid state: Improve homogeneity of drug products (low dose)

Reduction of dust exposure: de-risking handling of high-potent API

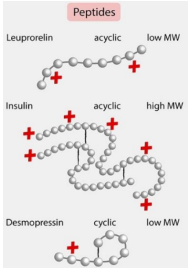
Hydrophobic Ion Pair: a validated strategy to maximize peptide loading in LBF

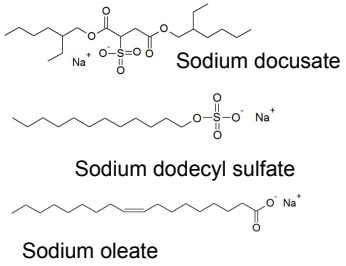
Principle

- Replace hydrophilic counter-ion (HCl, acetate) by hydrophobic counter-ion
- Pre-requisite: peptide needs to be ionizable in either acidic or basic conditions
- Advantage: no alteration of peptide chemical structure

Ionizable AA	pKa
Arginine	13
Histidine	6
Lysine	11
Aspartic acid	4
Glutamic acid	4

Scientific evidence





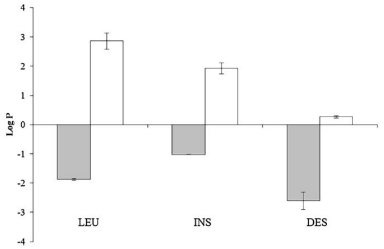


Fig. 5. Log P of indicated peptide drugs (LEU, INS and DES) (gray bars) and the corresponding HIP complexes LEU-docusate 2:1, INS-docusate 6:1 and DES-docusate 1.5:1 (white bars). Indicated values are means ($n \geq 3$) ± SD.

Payloads of to 10.7% peptide in LBF were achieved using HIP formation, corresponding to an increase in peptide payload of:

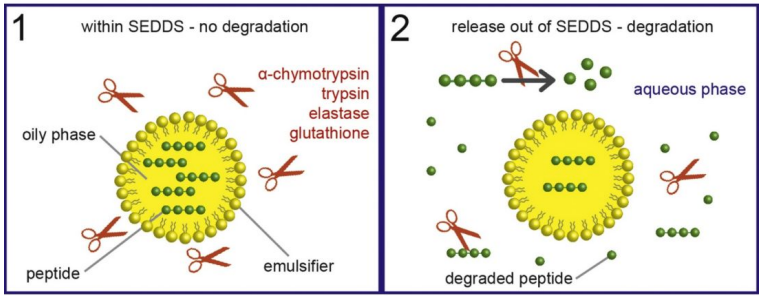
- 25-fold for Leuprorelin
- 6-fold for Insulin
- 40-fold for Desmopressin

Griesser, J., et al. ***2017***. https://doi.org/10.1016/j.ijpharm.2017.02.019

LBF offer protective environment against proteolytic degradation

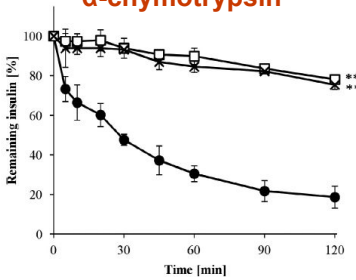
Principle

- Proteases are hydrophilic enzymes, not soluble in lipid hydrophobic environment.
- Peptides are protected if they remain in the oily phase.

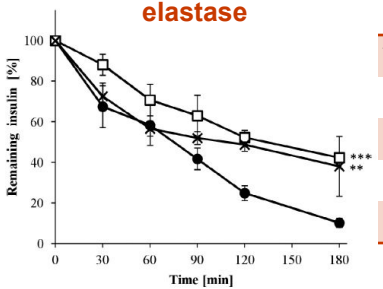


Scientific evidence

Enzymatic degradation of insulin in presence of **α-chymotrypsin**



Enzymatic degradation of insulin in presence of **elastase**



Composition (%)	C (X)	D (□)
Tetraglycol	10	30
Propylene glycol	10	-
Peceol™	10	30
Labrasol®ALF	60	40
Labrafil® M1925CS	10	-

● Native insulin

LBF provided a protective effect towards protease-induced degradation

Hetényi, G., et al. ***2017***. *https://doi.org/10.1016/j.ijpharm.2017.03.027*

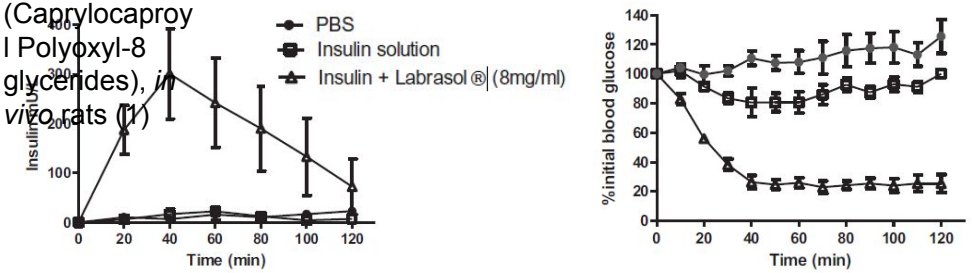
Lipid excipients can increase gastrointestinal permeability of large molecules

Principle

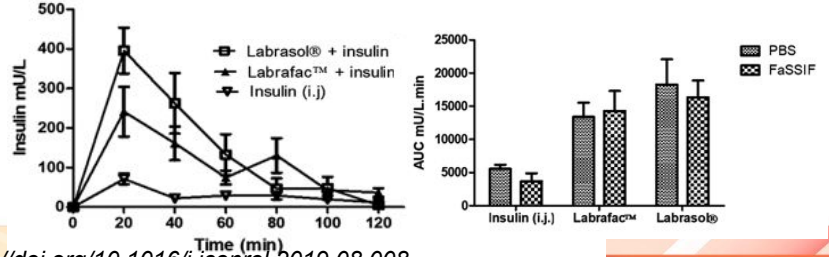
- Medium chain fatty acids (MCFA) can transiently open tight junctions and/or fluidify intestinal cell membranes
- Reversible process (concentration dependent)
- MCFA can be generated in situ upon LBF digestion
- Excipients with proven efficiency as intestinal permeation enhancers soluble in LBF: SNAC (Semaglutide, Rybelsus®); Medium chain fatty acids: C8 (Octreotide, MyCapssa®), C10, Labrasol®; Labrafac®MC60; Bile salts; Sucrose laurate esters

Scientific evidence

Labrasol® (Caprylocaproyl Polyoxyl-8 glycerides), *in vivo* rats (1)



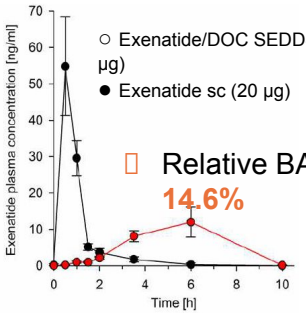
Labrafac®MC60 (Glyceryl Monocaprylocaprate), *in vivo* rats (2)

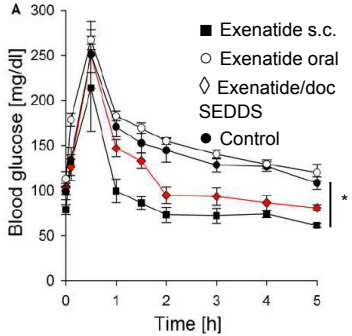


(1) McCartney, F., et al. ***2019***. https://doi.org/10.1016/j.jconrel.2019.08.008
(2) McCartney, F. et al. ***2024*** https://doi.org/10.1016/j.ijpharm.2024.124353

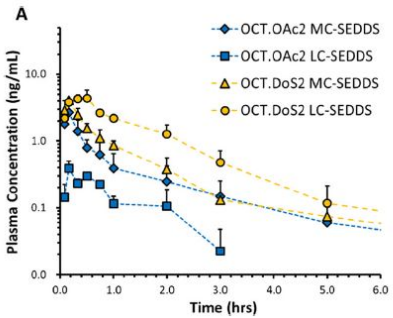
LBF improve oral bioavailability of loaded peptides

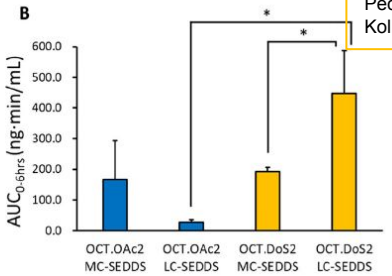
HIP exenatide/docusate 1:4 + SEDDS, rats (1)





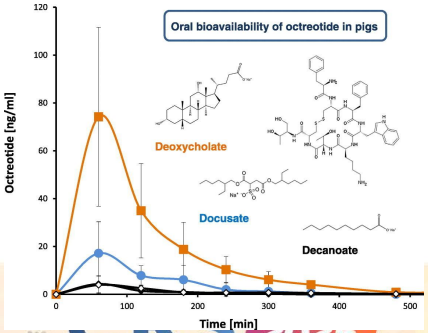
HIP octreotide + SEDDS, rats (3)





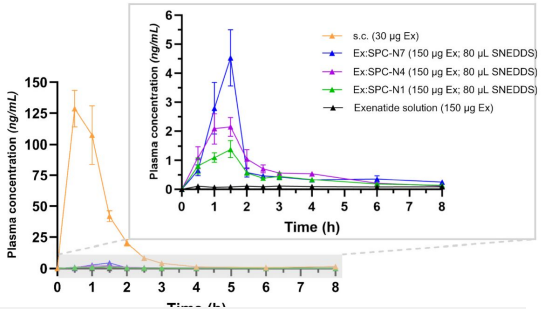
LC triglycerides 32.5%
Peceol® 32.5%
Kolliphor EL 35%

HIP octreotide + SEDDS, pigs (2)



Importance of counter-ion type: 17.9-fold higher BA vs oral octreotide solution

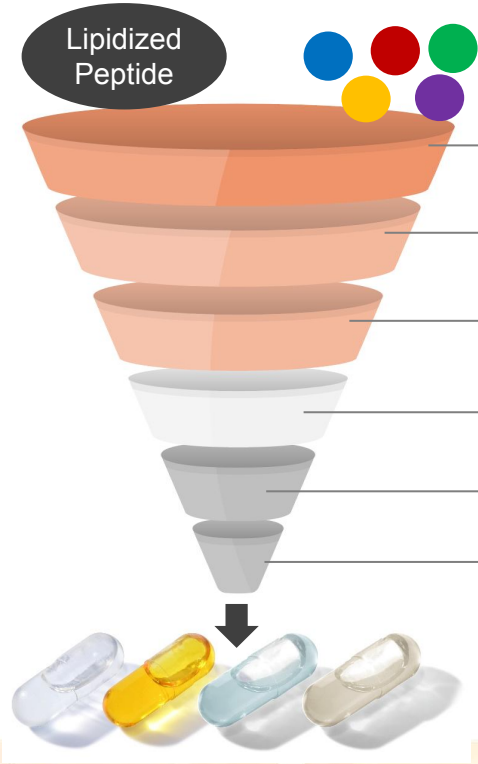
HIP exenatide + SEDDS, rats (4)



SEDDS composition influences:
- Particle size
- Digestion (*in vitro*)
- Proteolytic protection (*in vitro*)
- Permeation (*in vitro*)
- AUC

(1) *Menzel, C et al.* ***2018*** *https://doi.org/10.1016/j.jconrel.2018.03.018*
(2) *Bonengel, S.* ***2018*** *https://doi.org/10.1016/j.jconrel.2018.01.012*
(3) *Li, P. et al.* ***2021*** *DOI: 10.1007/s11095-021-03063-3*
(4) *Venkatasubramanian, R.et al.,* ***2025*** *https://doi.org/10.1016/j.jconrel.2025.01.013*

LBF design: a well-defined stage gate process



Range of lipid excipients exhibiting various functionalities

Solubility evaluation – Refining number of excipients based on API solubilization efficiency

Miscibility – Selection of excipient combinations to obtain isotropic mixtures

Dispersibility – Refining number of combinations based on ability to form homogeneous dispersions in aqueous medium at 37°C

***In vitro* performance evaluation** – enzymatic protection / mucus / intestinal permeation

API stability – Selection of formulations in which API is stable or selection of antioxidants

Capsule compatibility – Selection of capsule compatible with designed formulations

Limited number of oral drug products for pre-clinical and clinical evaluation

Formulation strategy to improve oral bioavailability of Exenatide

Limitations

- Exenatide is a **GLP-1 receptor analog** used in type-2 diabetes mellitus treatment
- Current administration via injection:
  - Byetta® (AstraZeneca), administration twice daily
  - Bydureon® (AstraZeneca), administration once daily
- Limited oral bioavailability due to:
  - Sensitivity to enzymes (**pepsin, α-chymotrypsin**)
  - Limited permeation due to size (**~4.2 kDa**)

Formulation strategy

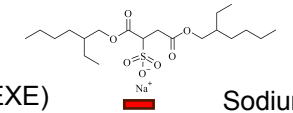
(1) Develop a **lipid-based formulation**:
- With Exenatide HIP to maximize payload in LBF
- To protect exenatide from proteolytic degradation
- Including sodium caprate as permeation enhancer

(2) Develop a **customized capsule**:
- Compatible with developed formulation
- Enabling enteric delivery to avoid Exenatide degradation in the upper GI tract

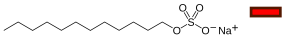
Increase peptide lipophilicity by Hydrophobic Ion Pairing

Method: Hydrophobic Ion Pair

Exenatide (EXE)



Sodium docusate (DOC)



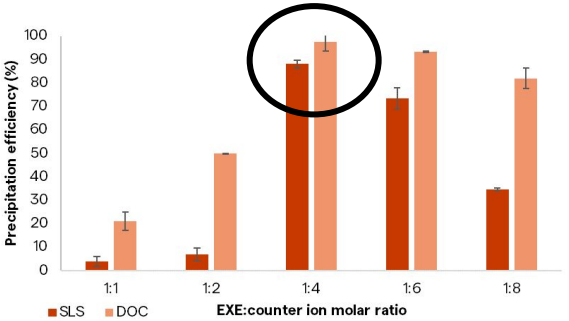
Sodium laurylsulfate (SLS)

- Exenatide combined with anionic counter-ion at different molar ratios
- Yield determined by quantification of « unpaired » peptide:

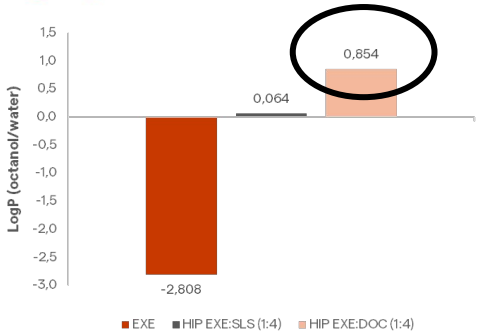
$$Precipitation\ efficiency = 100 - \left(100 * \frac{[EXE]_{supernatant}}{[EXE]_{total}}\right)$$

- **Log P** measurements used to determine lipophilicity increase.

Results:



Highest yield with **1:4 molar ratio**



Highest **lipophilicity** increase with sodium docusate.

HIP EXE:DOC (molar ratio 1:4) was selected for the following stages of LBF development.

Formulation design: solubility and dispersibility

Solubility evaluation

Type	Commercial name	Solubility (mg/g)	
		EXE	EXE:DOC
Oil	Maisine® CC	<LOQ	0.03
	Soybean oil	<LOD	<LOD
Surfactant	Capryol® 90	<LOD	0.02
	Labrafac™ MC60	<LOQ	**9.54**
	Lauroglycol™ 90	<LOD	<LOD
	Labrafil® M1944CS	0.7	<LOD
	Labrasol® ALF	<LOD	5.47
	Kolliphor® ELP	<LOD	<LOD
	Tween® 20	<LOD	0.06
	Tween® 80	<LOD	<LOD
Solvent	PEG 400	<LOD	2.28
	Propylene glycol	9.9	**9.04**
	Glycerin	5.2	0.89

- C10 in Labrafac® MC60 = 20 mg/mL

Miscibility and dispersibility tests

- Test of surfactants with Labrafac® MC60 from 90/10 to 70/30

LBF prototype composition (T1)	
Commercial name	**Amount**
Labrafac MC® 60	85%
Kolliphor® RH40	10%
Propylene glycol	5%
Exenatide	6 mg/g
C10	20 mg/g
Particle size measurements in water, 37°C, 1:1000	
Z-average (nm)	**PDI**
104	0.1
Solubility evaluation, 37°C	
EXE	1.44 ± 0.01 mg/mL
EXE:DOC HIP	7.63 ± 0.17 mg/mL

In vitro evaluation: protection vs proteases

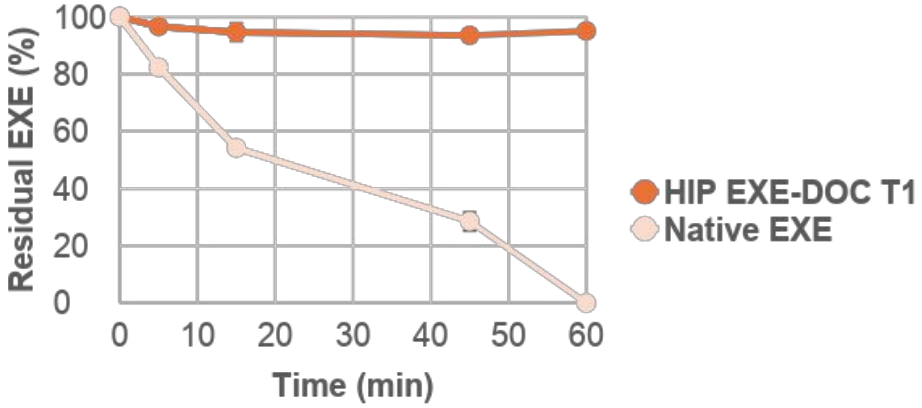
Exenatide is sensitive to:

- Pepsin need for an enteric dosage form
- α-chymotrypsin

Method:

Formulation was dispersed in buffer and incubated with a solution of α-chymotrypsin for 1 hour. At predetermined timepoints, enzyme activity is stopped and peptide quantified.

Results:



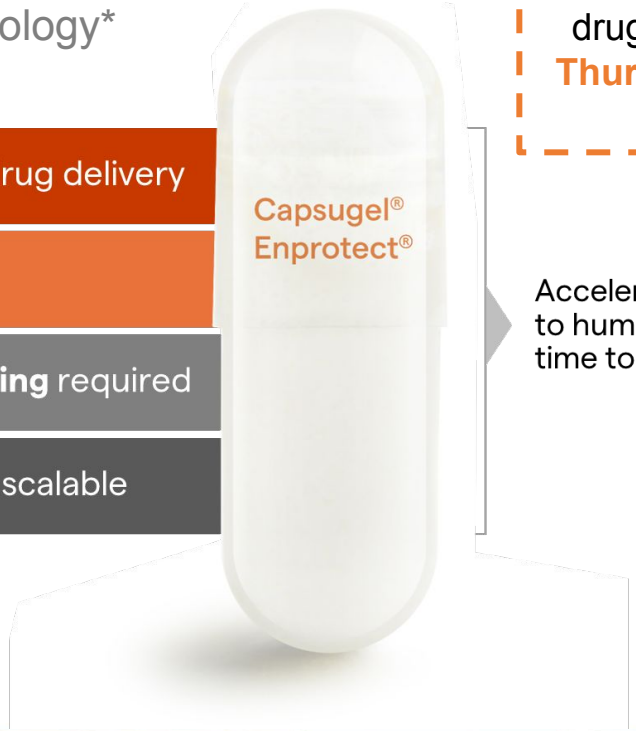
LBF provide a protective effect towards α-chymotrypsin induced degradation.

Capsugel® Enprotect® capsule

Our breakthrough enteric manufacturing technology*

Meets compendial enteric delivery requirements and enables accelerated development and commercialization processes

- **Targeted** enteric drug delivery
- Acid **protection**
- **No additional coating** required
- **Customizable** and scalable



Accelerates time to human and time to market

Tech Forum
'Oral delivery of new drugs modalities'
Thursday 17 July, 9-10am

*Pending patent for double-dipping process (patent EP4251126A1)

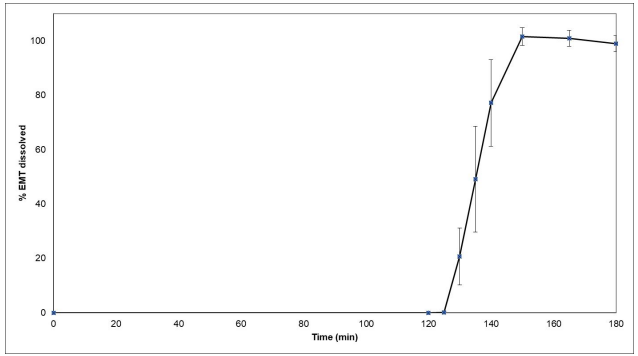
Capsule customization to improve capsule compatibility with fill formulation

Need for customization

Problem statement: Poor compatibility between HPMC polymers and Labrafac®MC60 (major component of LBF in Exenatide case study)

Customization: Gelatin/HPMC-AS double layer capsule

Dissolution test Esomeprazole



Enteric properties as defined by USP (dissolution test type 2)

Disintegration test with LBF

Exemplar image of customized filled capsules after 1 h in HCl 0.1N:

Filled with LBF (including C10)

Filled with LBF (including C10) and EXE:DOC HIP

Enteric properties confirmed

Conclusions

- Lipid-based formulations are a viable and scalable solution for oral bioavailability of peptides.
- Capsugel® Enprotect® capsules demonstrate high performance through *in vitro* and *in vivo* evaluations.
- Lonza CHI capsules can be customized to address specific needs.
- Innovaform™ Accelerator can support your **formulation development** and collaborates with its customers to overcome drug delivery challenges through **capsule innovation**.