Lipid Formulations in Customized Enteric Capsules Show Promising Results For Oral GLP-1 RA Delivery

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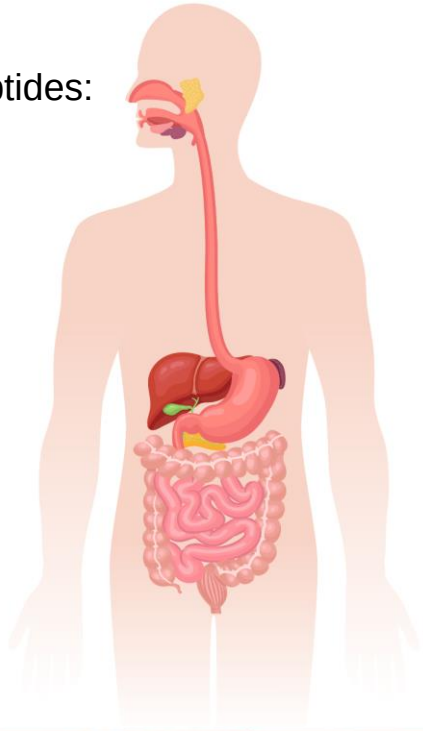
NEXT-GENERATION DELIVERY INNOVATIONS

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

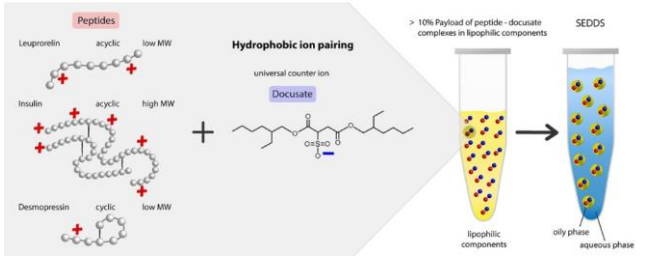


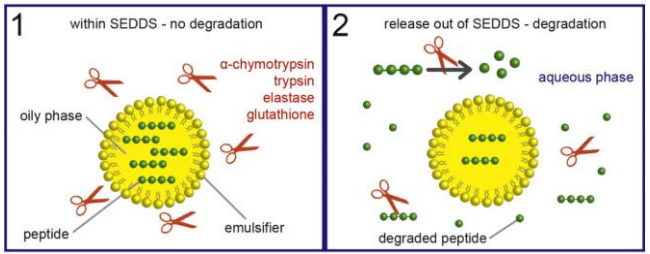
Exenatide (GLP-1 receptor analog)

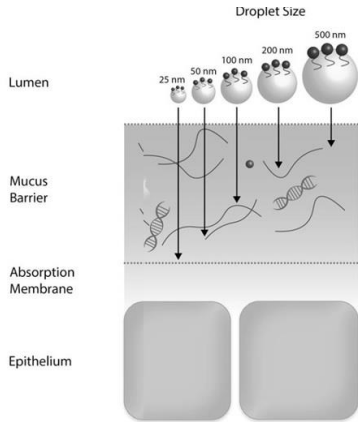
- Sensitivity to enzymes (**pepsin, α-chymotrypsin**)
- Limited permeation due to size (~**4.2 kDa**)

Formulation strategy to improve oral bioavailability of Exenatide

Literature







Griesser, J., et al. ***2017***. https://doi.org/10.1016/j.ijpharm.2017.02.019
Hetényi, G., et al. ***2017***. https://doi.org/10.1016/j.ijpharm.2017.03.027
Griesser, J. et al. ***2018***. https://doi.org/10.1016/j.ijpharm.2018.01.018

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

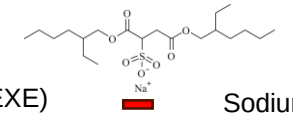
(2) Develop a **customized capsule**:

- Compatible with developed formulation
- Enabling enteric delivery to avoid Exenatide degradation in the upper GI tract

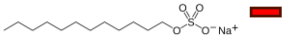
Increase peptide lipophilicity by Hydrophobic Ion Pairing

Method: Hydrophobic Ion Pair

Exenatide (EXE)



Sodium docusate (DOC)



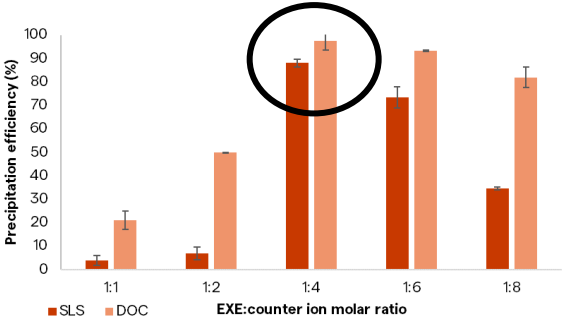
Sodium laurylsulfate (SLS)

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

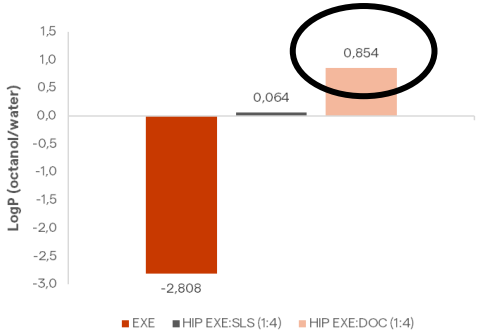
$$Precipitation\ efficiency = 100 - (100 * \frac{[EXE]_{supernatant}}{[EXE]_{total}})$$

- **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

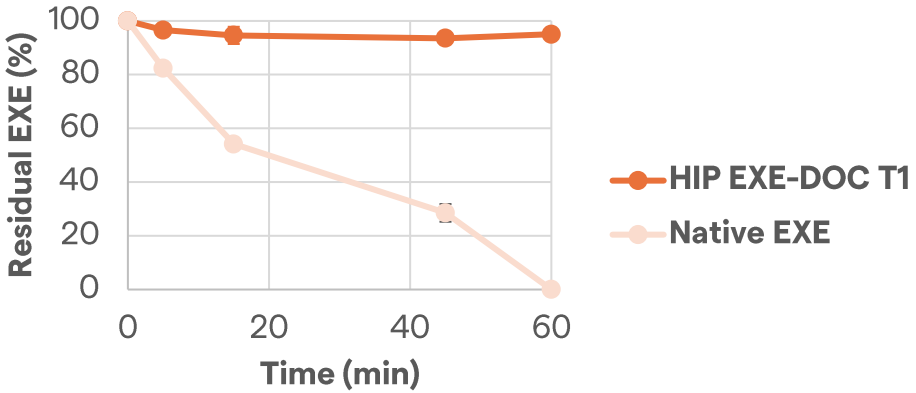
Exenatide is sensitive to:

- 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

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

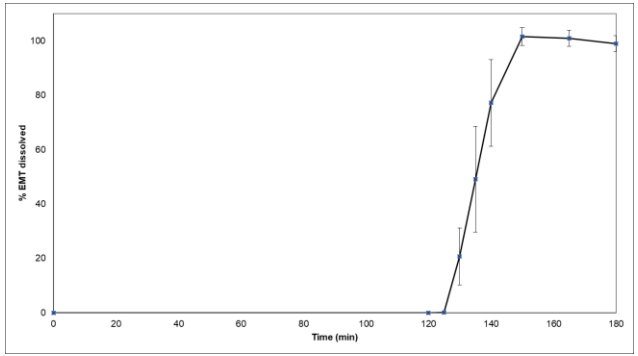
Capsule customization to improve capsule compatibility with fill formulation

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 (**presentation Tech Forum on Thursday 17 July, 9-10am**).
- 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**.