"An assessment of the trends in oral peptide administration"

4th CRS Workshop on Oral Peptide Administration

David Brayden, University College Dublin

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

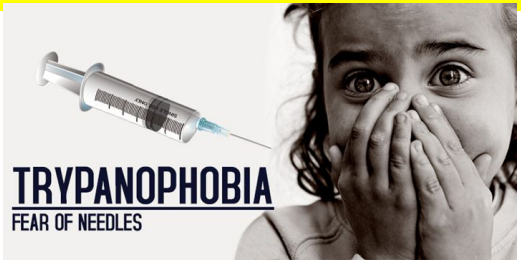
NEXT-GENERATION DELIVERY INNOVATIONS

Agenda

- Current state of play for oral peptide translation
- What have we learned about medium chain fatty acid-based permeation enhancers?
- Can established excipients be repurposed as permeation enhancers?
- Will combinations of enhancers raise the oral bioavailability ceiling?
- Translating enhancers and peptides into new oral dosage form designs

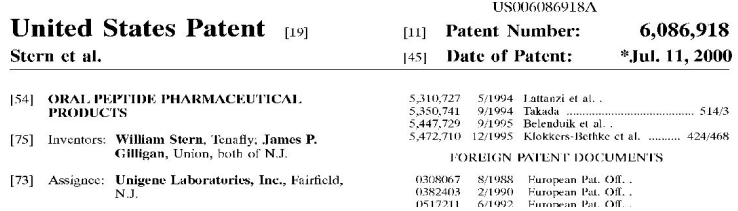
Why oral peptide administration?

Convenience/compliance



https://www.healthtopia.net/disease/mental-health/phobia/trypanophobia-causes-symptoms-treatment

Commercial: patent extensions



US006086918A

United States Patent [19]
Stern et al.

[11] **Patent Number: 6,086,918**
[45] **Date of Patent: *Jul. 11, 2000**

[54] **ORAL PEPTIDE PHARMACEUTICAL PRODUCTS**

[75] Inventors: **William Stern**, Tenafly, **James P. Gilligan**, Union, both of N.J.

[73] Assignee: **Unigene Laboratories, Inc.**, Fairfield, N.J.

5,310,727	5/1994	Lattanzi et al. .	
5,350,741	9/1994	Takada	514/3
5,447,729	9/1995	Belenduik et al. .	
5,472,710	12/1995	Klekkers-Bethke et al.	424/468

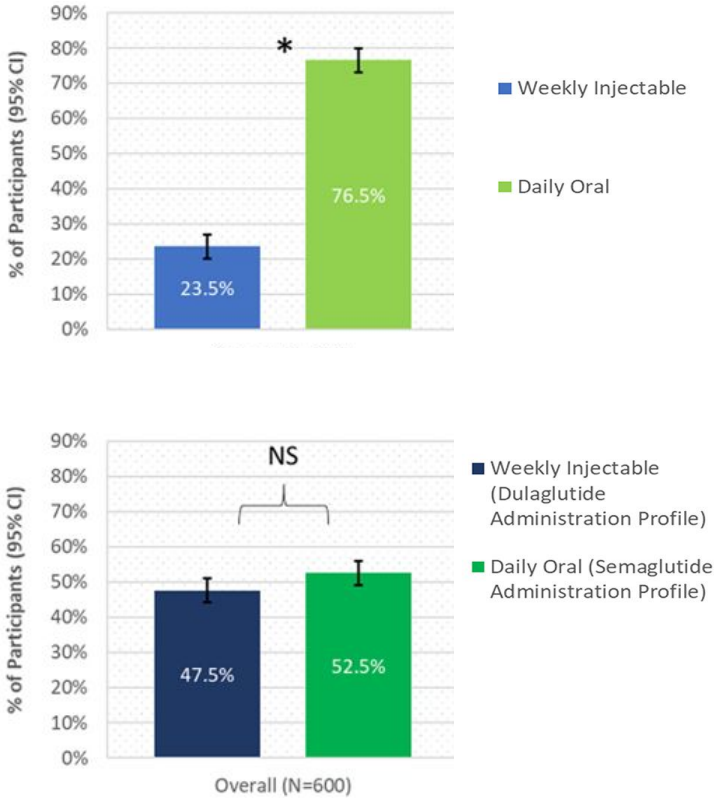
FOREIGN PATENT DOCUMENTS

0308067	8/1988	European Pat. Off. .
0382403	2/1990	European Pat. Off. .
0517211	6/1992	European Pat. Off. .

Earlier peptide take up in Type 2 diabetes leads to better outcomes

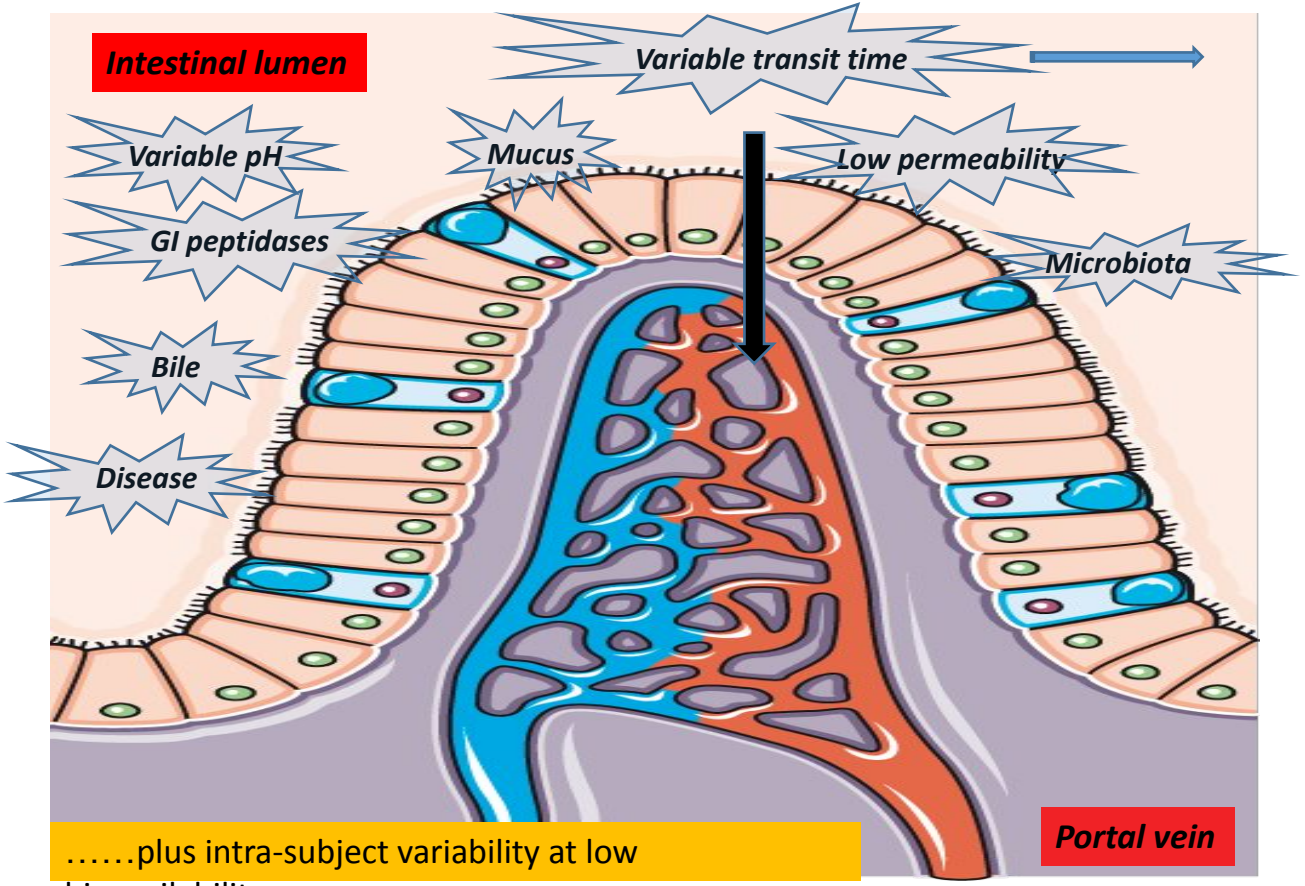
More physiological route to liver for some peptides

The convenience argument is quite subtle: the REVISE Study



Adapted from Diabetes Obesity Metabolism, 23, (2), 508-519, (2020) DOI: 10.1111/dom.14244

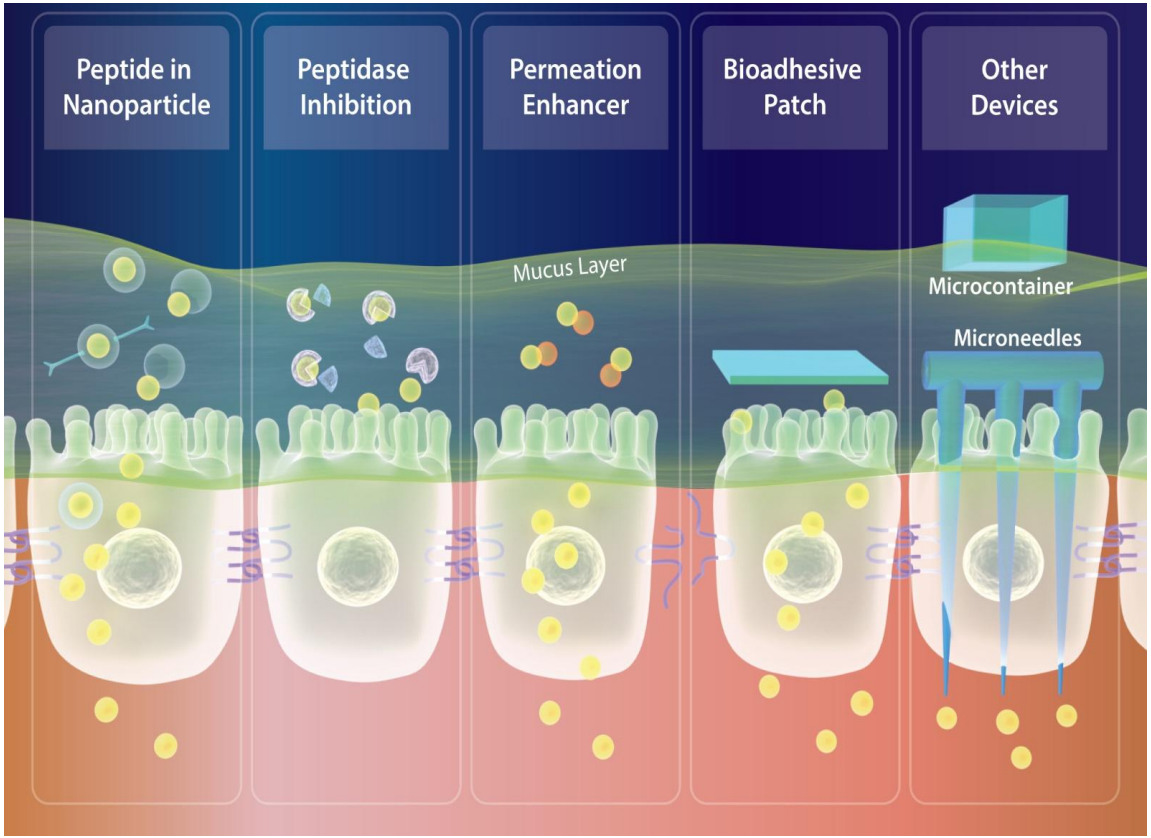
The problems for oral peptide administration….



……plus intra-subject variability at low bioavailability

Brayden DJ, et al. (2020). Adv Drug Deliv. Rev. 157:2-36.

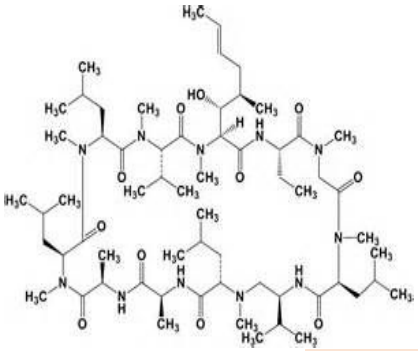
Administration strategies



Plus
Medicinal chemistry efforts on potency, GI stability, and extension of t½

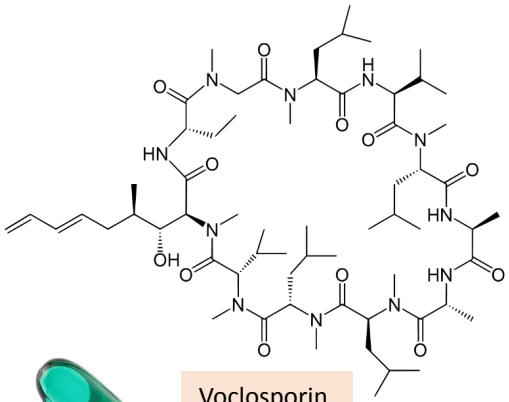
Brayden DJ, *et al* (2020). Adv Drug Deliv Rev. 157: 2-36 .

Five oral peptide formulations are approved for humans



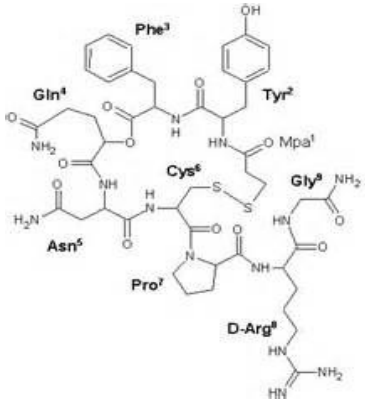
Cyclosporine

F=40 %



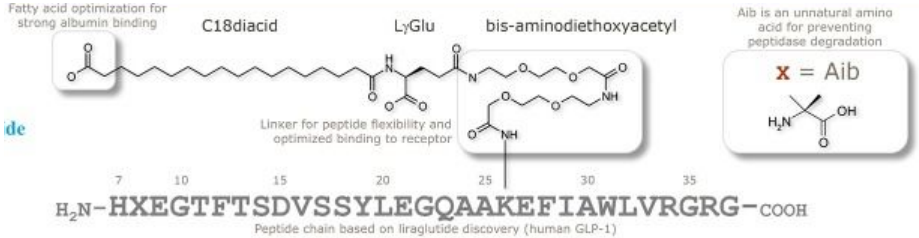
Voclosporin

F= 8 -30 %



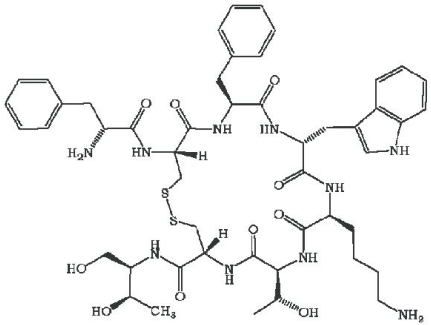
Desmopressin

F=0.2 %



Semaglutide

F=0.4-1.0 %



Octreotide

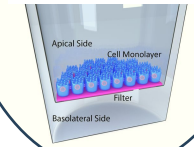
F=0.5-0.8 %

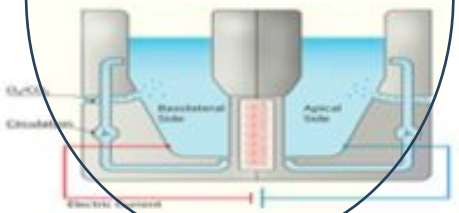
Current clinical development of oral peptides

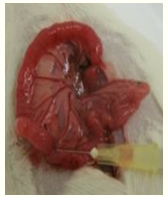
Company	Peptide	Technology	Specifics	Phase
Merck	MK-0606 (macrocycle PCSK9 antagonist)	Permeation enhancer	C_{10}	III, ongoing
Enteris	Leuprolide	Peptelligence™ enhancers	Acyl carnitines/citric acid	II; ongoing
Janssen	JNJ-2113 (macrocycle IL-23R antagonist)	Permeation enhancer	C_{10} (in patents)	III; ongoing
Oratech JV	Insulin (ORMD-0801)	POD™ enhancers	EDTA, SBTI, bile salts (in patents)	II; completed
Chugai Pharma	Luna-18 (macrocycle RAS inhibitor)	mRNA display and med chem	No enhancer	I (2025)
Sciwind Biosciences	XW004, Ecnoglutide (acylated GLP-1 RA)	Permeation enhancer	Not disclosed	I (2024)
Viking	VK2735 (GLP-1/GIP RA)	Permeation enhancer	Both C_{10} and SNAC in WO 2024/192219	II (2025)
Proxima Concepts	Insulin	Permeation enhancers	Propyl gallate and aromatic alcohols	IIa (2025)
Rani	Octreotide, PTH	Robotic pill	Device	I; (2020, 2024)

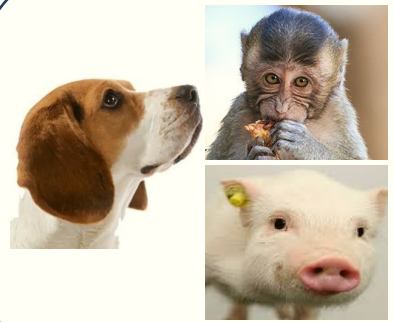
What have we learned about medium chain fatty acid-based permeation enhancers?

Mixtures









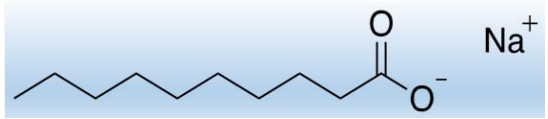
Variables:
Species
GI physiology
Lumen contents
Concentrations
Mixtures v solid dosage

Solid dosage forms

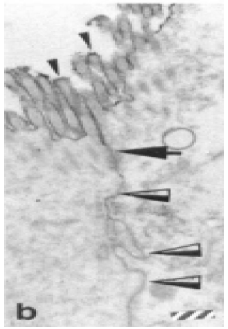
See also: Emeh P, et al. Mol Pharm. 2024 Jan 1;21(1):313-324.

C_{10}

Mw: 194 Da, pKa = 5



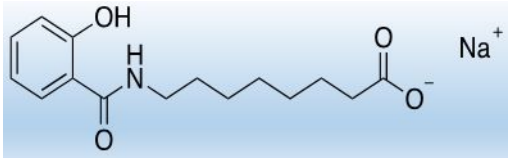
Epithelial tight junction opener (1995)



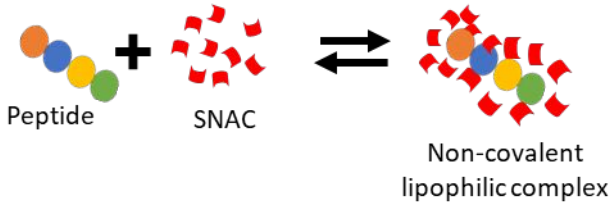
Lindmark, T *et al*. (1998)
doi:10.3109/10611869808995876

SNAC

Mw: 301 Da, pKa = 5

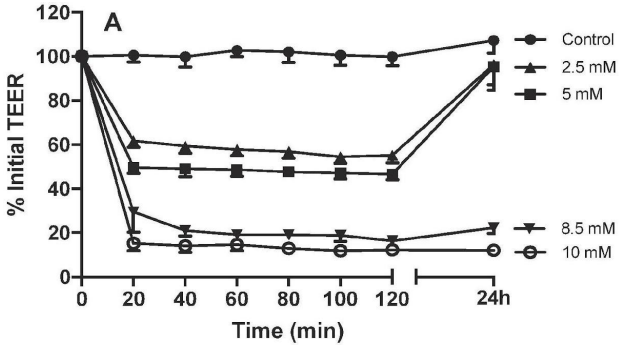


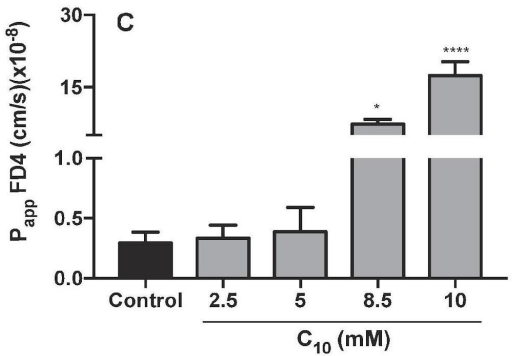
The chaperone hypothesis (1995)



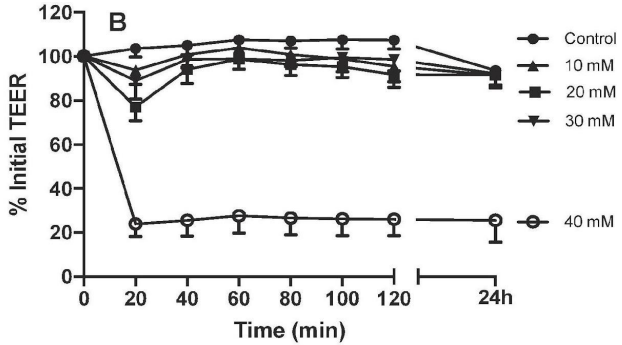
Effects of C_{10} and SNAC on FD4 flux across Caco-2 monolayers

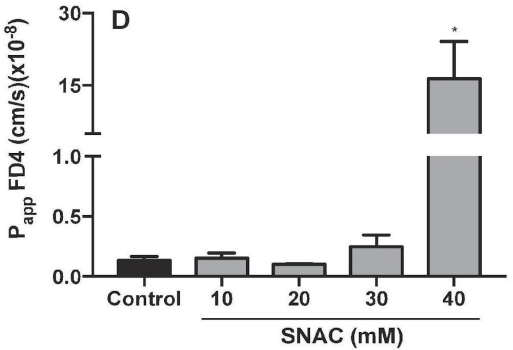
C_{10}

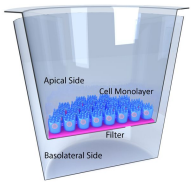




SNAC

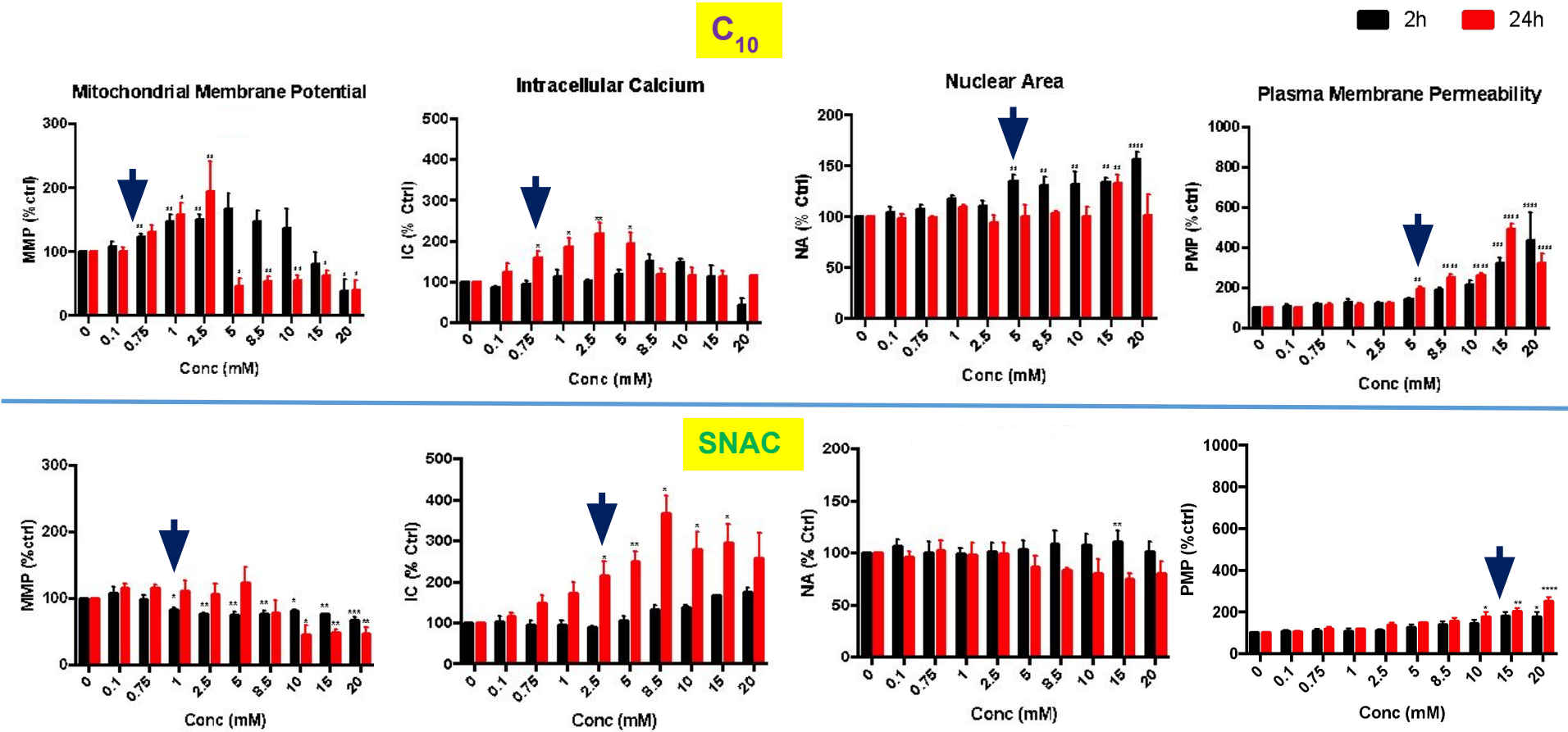






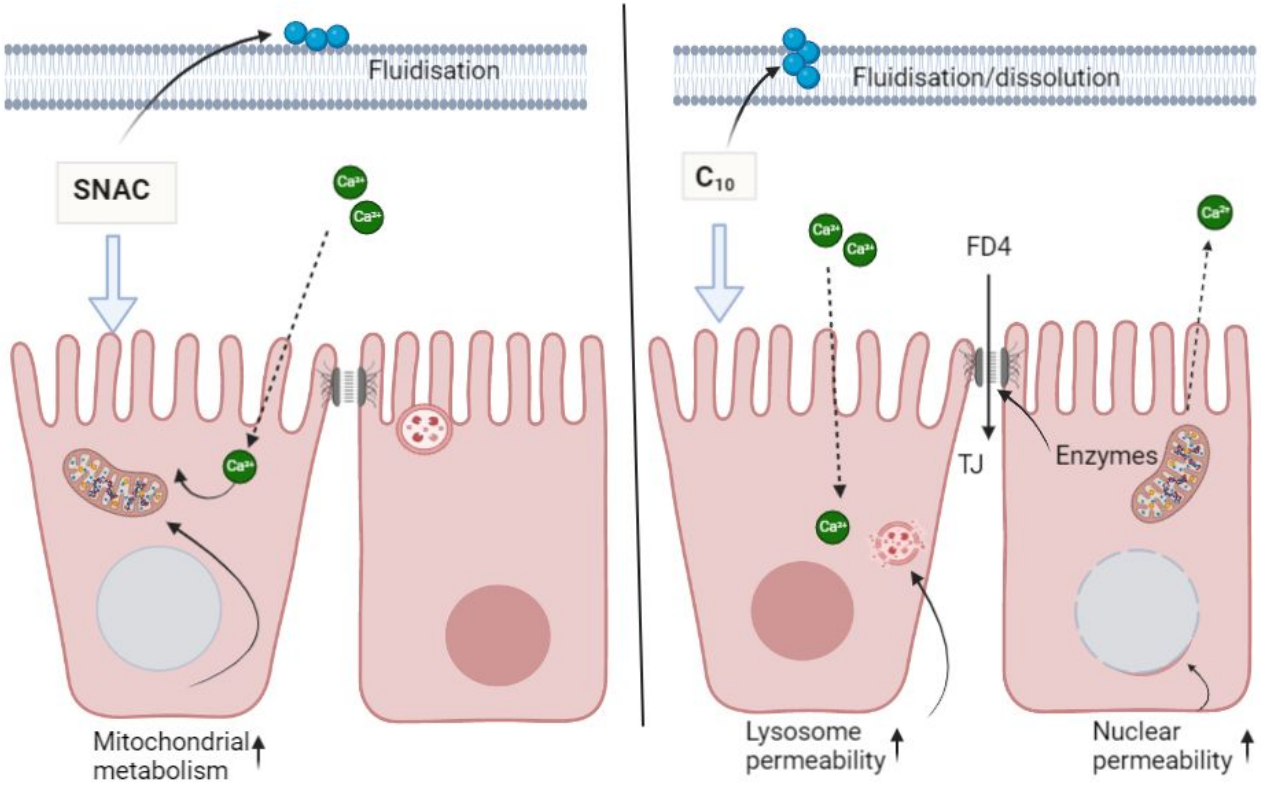
Twarog, C. et al. (2020). Eur J Pharm Biopharm. doi: 10.1016/j.ejpb.2020.04.023

High content imaging in live Caco-2 cells



Twarog, C. et al. (2020). Eur J Pharm Biopharm. doi: 10.1016/j.ejpb.2020.04.023

In vitro assays suggested some similarity for SNAC with C_{10}



Adapted using BioRender® from Twarog, C. et al. (2020). Eur J Pharm Biopharm. doi:

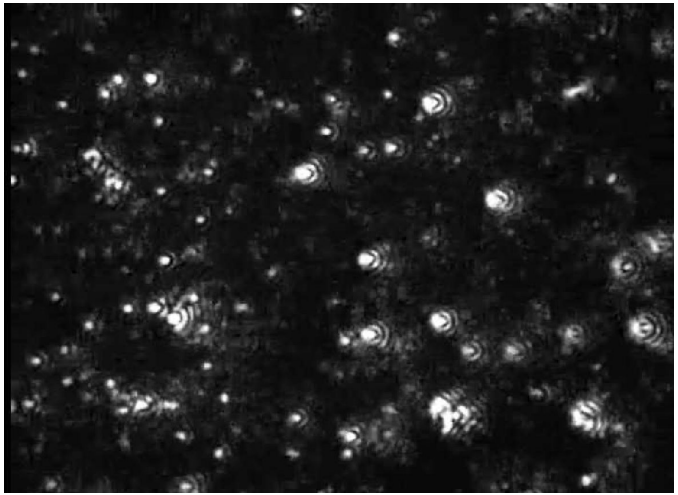
Biophysical techniques reveal that interactions between exenatide and SNAC/ C_{10} are…

- ✔ Weak: *several media*
- ✔ Influenced by the PE total concentration: *evidence of enhancer self-association*
- ✔ Especially weak in more complex buffers: *Likely due to competitive interaction with bile salts*

	ITC		SPR	ACE	
Media	H_2O	PBS	HBS	PBS	FaSSIF/FeSSIF
System configuration	Exenatide in solution		Exenatide immobilized	Exenatide in solution	
	[PE] constant, Exenatide variable		[PE] variable, Exenatide constant	[PE] variable, Exenatide constant	
K_d (μM)	1 - 100	ND	weak	10	100

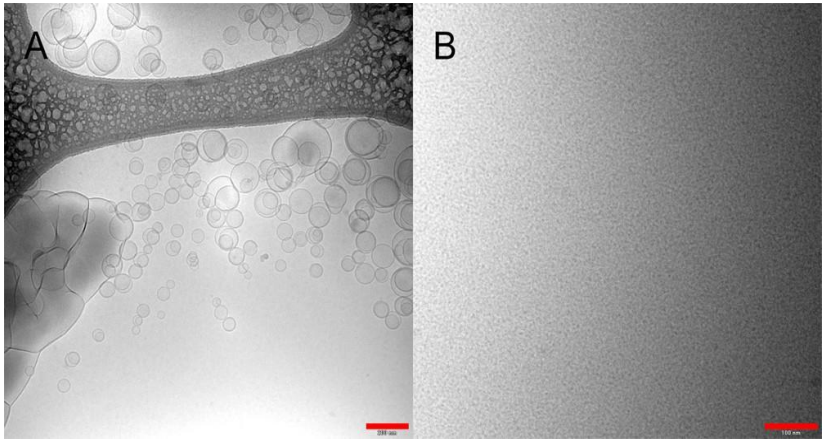
Twarog C, et al. Int J Pharm. 626 (2022):122131. doi: 10.1016/j.ijpharm.2022.122131.

Vesicles and micelles are formed by C_{10} above its CMC



200 mM C_{10} in PBS. Diameter of vesicles ranged between 40–400nm.

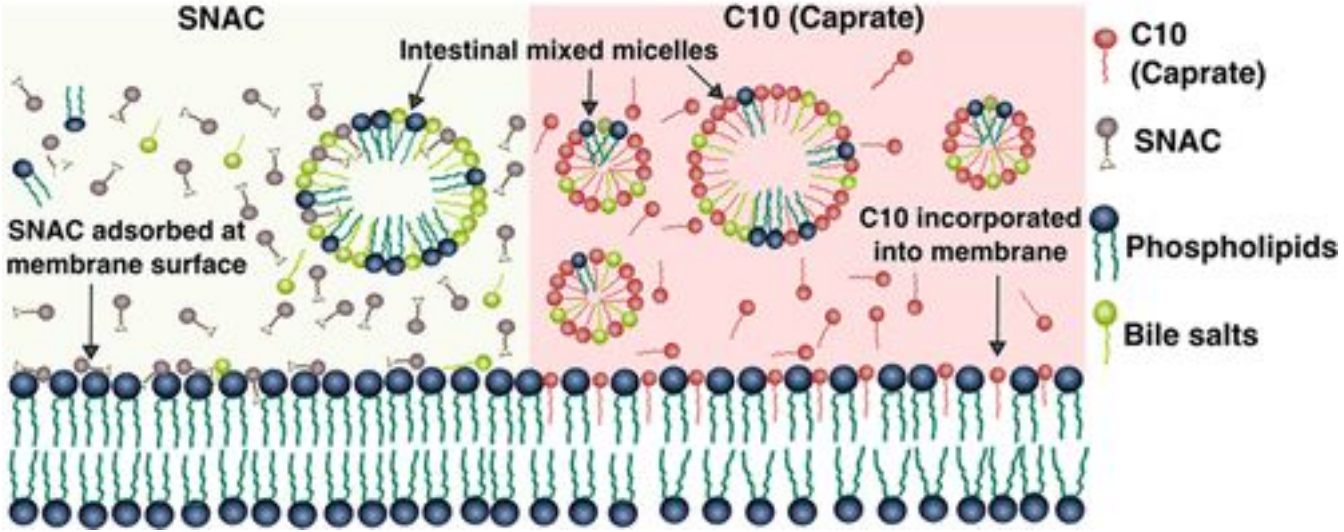
Maher S, et al. Adv Drug Deliv Rev. 2009;61(15):1427-49.



(A) 100 mM C_{10} pH 6.5. 50 to 200 nm vesicles.
(B) 300 mM C_{10} pH 8.5. <5 nm micelles

Berg S, et al. Mol Pharm. 2022;19(1):200-212.

Molecular dynamic simulation reveals differences between C_{10} and SNAC in interacting with lipid bilayers

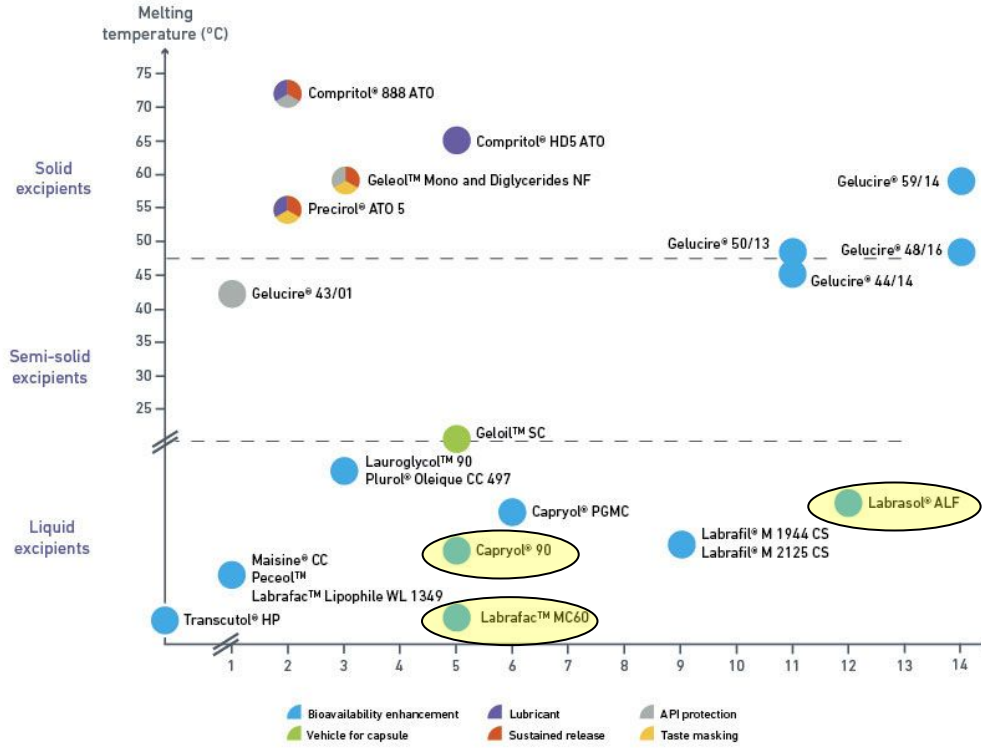


Hossain S*, et al*. (2020) Mol Pharm. 17(11):4226-4240.

Can established excipients be repurposed as permeation enhancers?

J Control Release. 2019;310:115-126. doi: 10.1016/j.jconrel.2019.08.008.

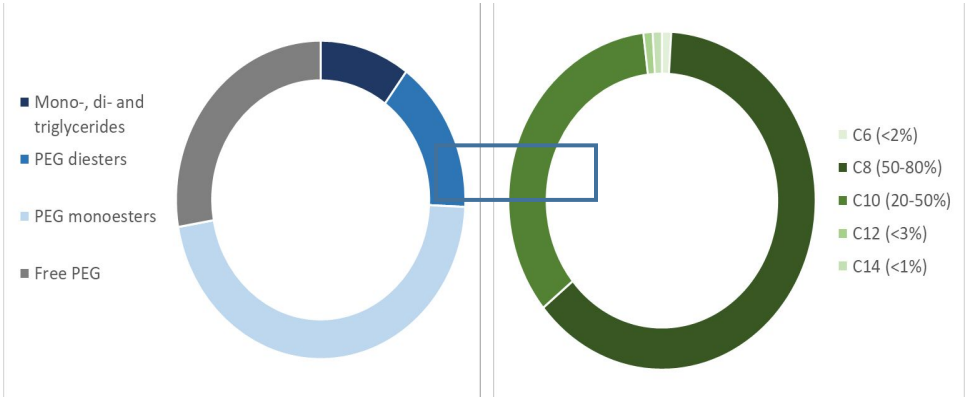
Int J Pharm. 2024; 15;661:124353. doi: 10.1016/j.ijpharm.2024.124353.



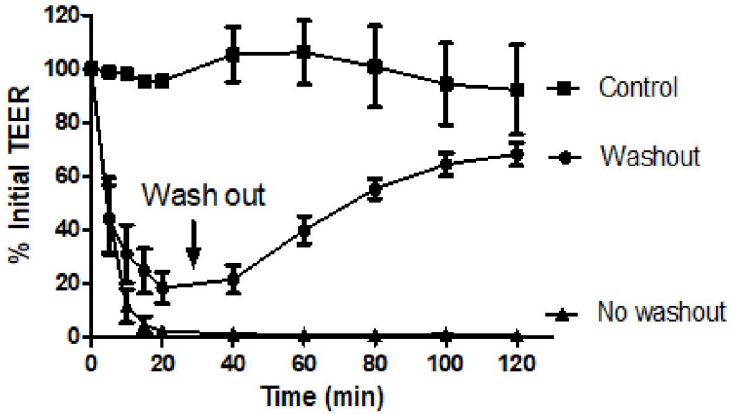
GATTEFOSSÉ

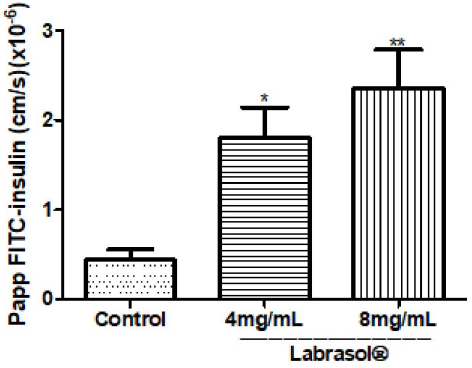
Labrasol®
(Caprylocaproyl polyoxyl-8 glycerides)

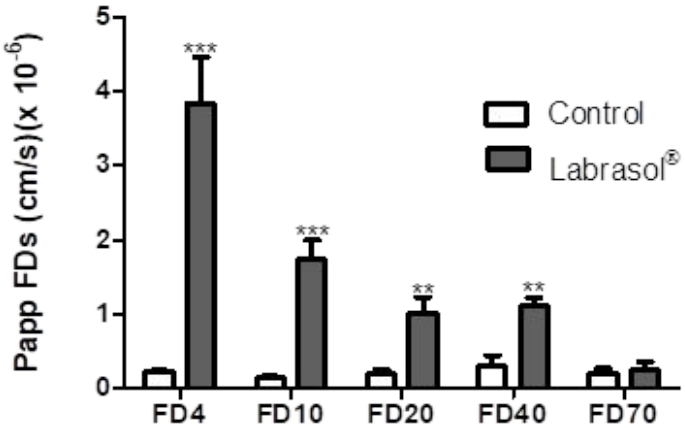
- Self-emulsifying non-ionic surfactant
- Well established solubiliser
- FDA approved in Enzalutamide (Xtandi®, Astellas Pharma)
- Miscible with other common excipients
- HLB = 12

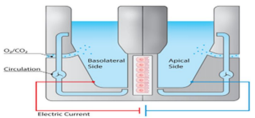


Labrasol® ALF: a competitive enhancer ex vivo





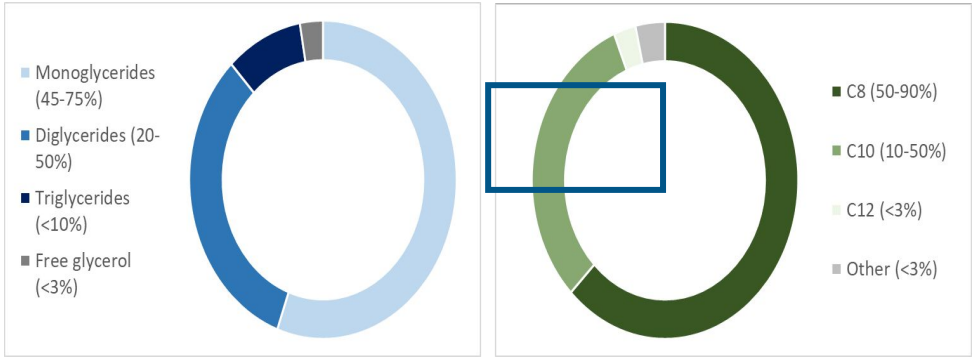




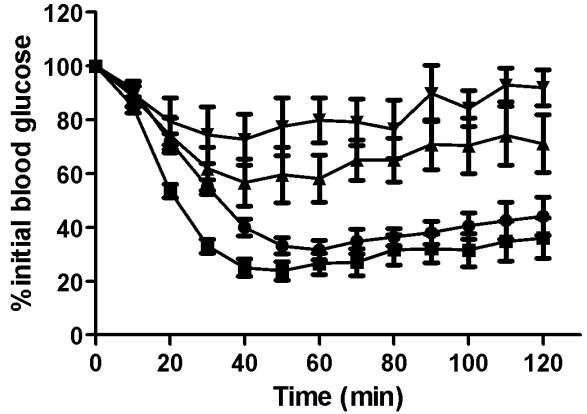
McCartney *et al*. J Control Release. 2019;310:115-126.

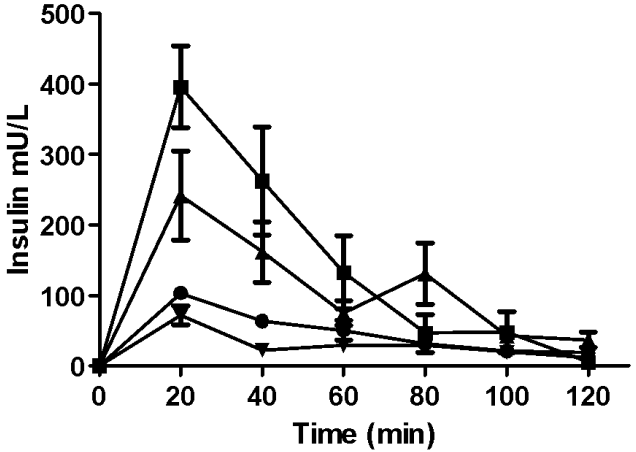
Labrafac™
(Glyceryl mono and dicaprylocaprate)

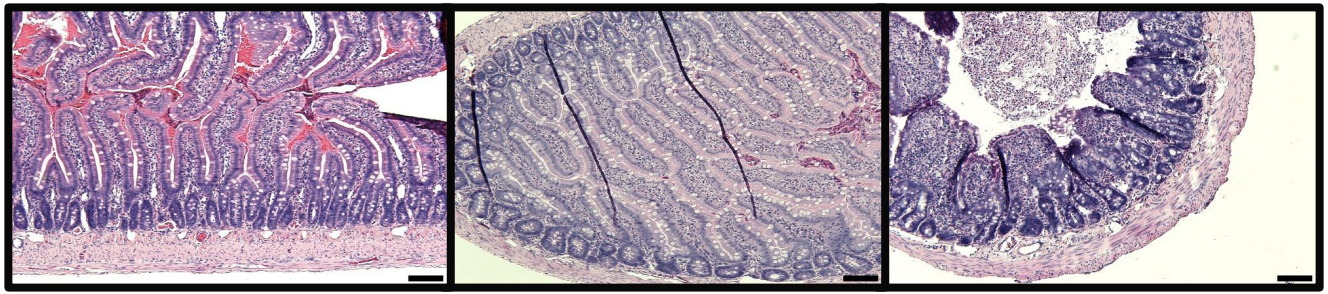
- Liquid excipient at 25°C
- Solubilizer for >20 small molecules
- Multi-compendial excipient
- HLB = 5



Both agents (40mg/kg) increase insulin absorption (rat jejunal instillations)



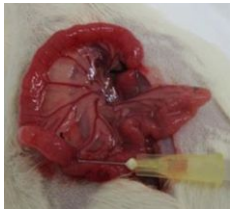




Insulin

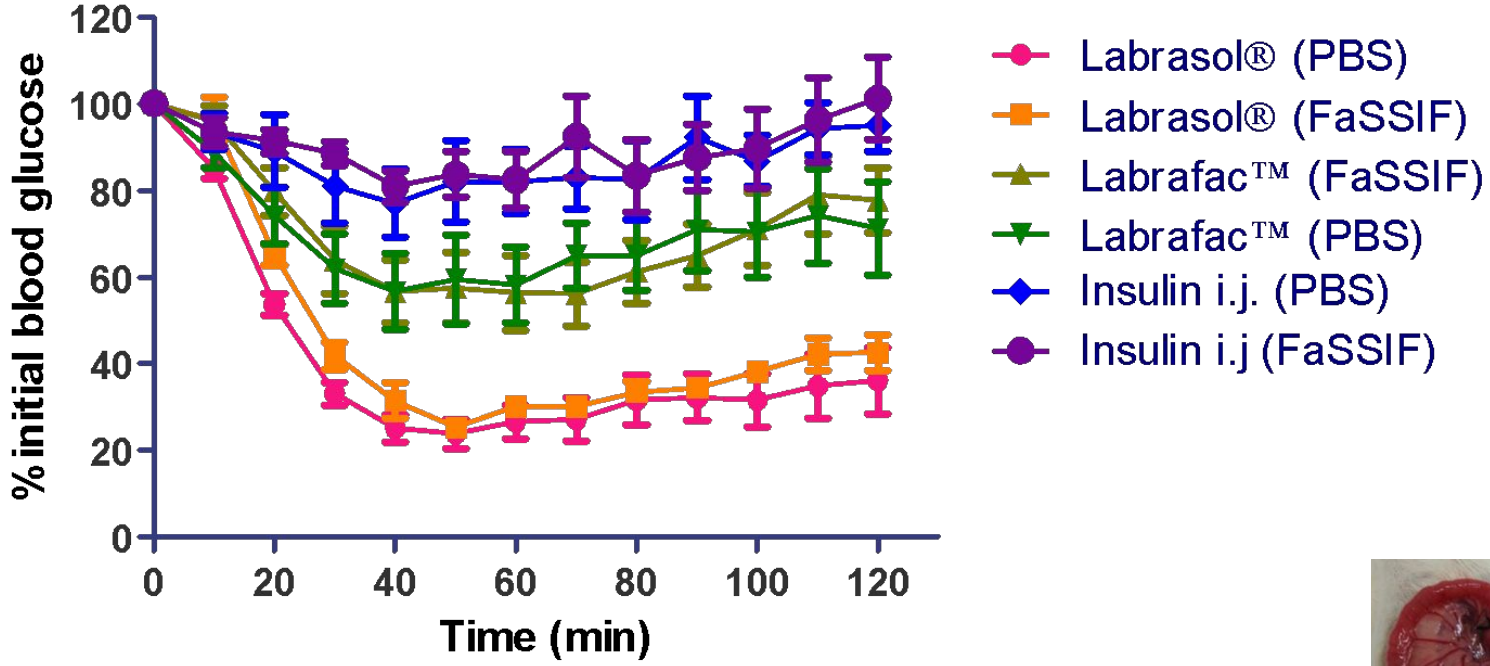
Labrasol®

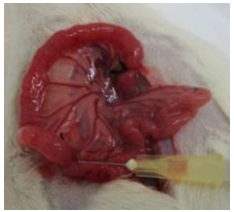
Labrafac™



McCartney et al. (2024) Int J Pharm.; 15;661:124353

In vivo effects maintained in FaSSIF (jejunum)

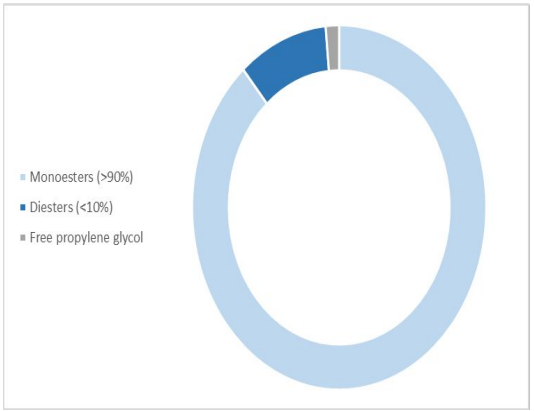


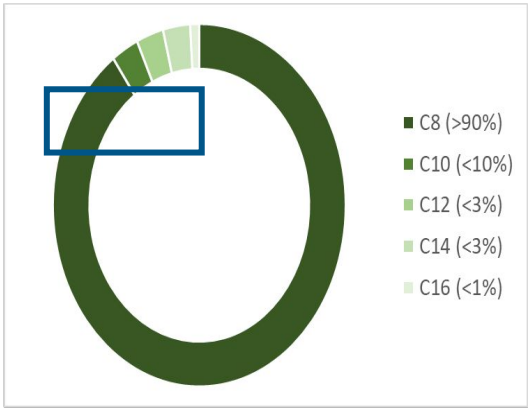


McCartney et al. (2024) Int J Pharm.; 15;661:124353

Capryol® 90

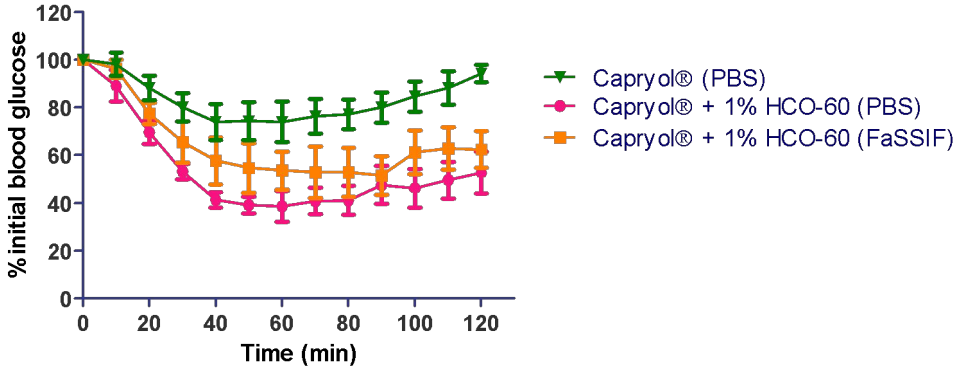
- A non-ionic water-insoluble surfactant used as cosurfactant in oral lipid-based formulation SEDDS and SMEDDS
- Cosurfactant and solubilizer in topical dosage forms
- HLB = 5

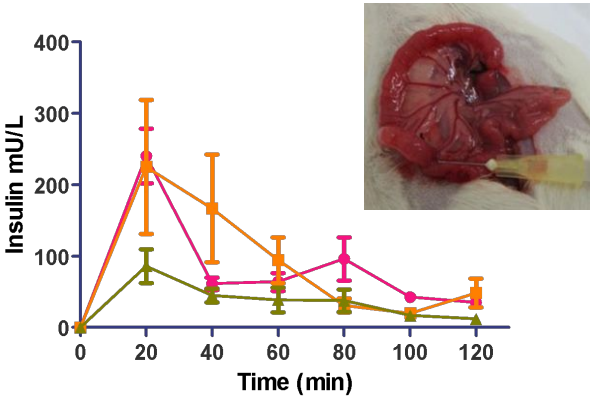




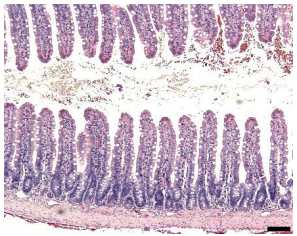
Ukai etal, (2020). Enhanced Intestinal Absorption of Insulin by Capryol 90, a Novel Absorption Enhancer in Rats: Implications in Oral Insulin Delivery. Pharmaceutics. 18;12(5):462

Capryol® 90 with 1% HCO-60 with insulin in rat jejunum





Treatment	% F
SC insulin (1 IU/kg)	-
Capryol® (PBS)	1.7
Capryol® + HC060 (PBS)	3.8
Capryol® + HCO60 (FaSSIF)	4.1



McCartney et al, in preparation

Insulin bioavailability in rat jejunal instillations (summary)

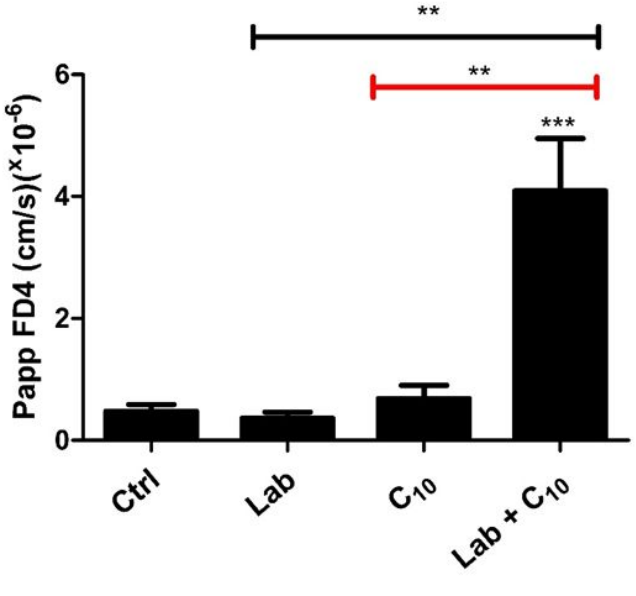
Treatment	Tmax (min)	Cmax (mU/L)	AUC (0–120) (mU/L.min)	Relative F (%)
S.C. insulin (1 IU/kg)	27±7	104±3	5544±642	-
PBS				
Labrafac®	43±12	267±60	13377±2144	4.8
Labrasol®	23±3	420±58	18272±3800	6.6
Capryol®	30±10	257±33	10447±629	3.8
FaSSIF				
Labrafac®	30±7	316±75	14297±3007	5.2
Labrasol®	23±3	380±69	16340±2537	5.9
Capryol®	47±16	258±82	11237±3896	4.1

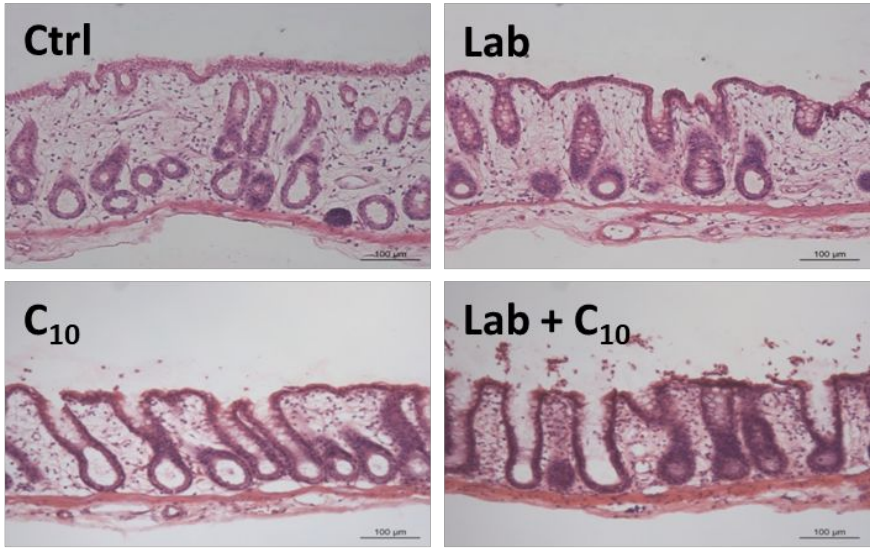
50 IU/kg insulin dose for instillations, excipents 40 mg/kg

Conclusions on Gattefosse project

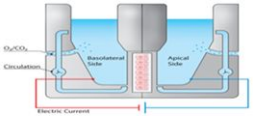
- Labrasol® ALF acts as a permeation enhancer ex vivo and in vivo
- Labrafac™ MC60 does likewise, but to a lesser extent
- Both lipid based excipients are still effective in FaSSIF buffer
- Capryol 90 is also efficacious, but requires solubility improvement using HCO-60
- Excipient selection is based on many parameters: HLB, compatibility with API, dose level required…

Will combinations of enhancers raise the oral bioavailability ceiling?



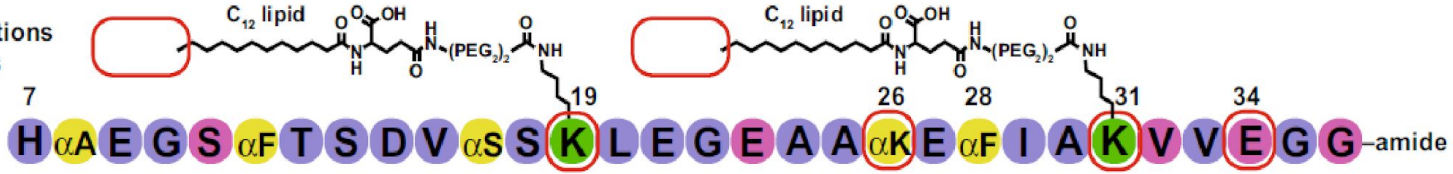


Heade J, et al (2018) J Pharm Sci. ;107(6):1648-1655.



Combining sodium chenodeoxycholate and propyl gallate gave superior oral bioavailability for a GLP-1-RA peptide (MEDI7219) compared to SNAC with semaglutide

MEDI7219
- 12 amino acid substitutions
- 5 α-methyl amino acids
- Bis-lipidation

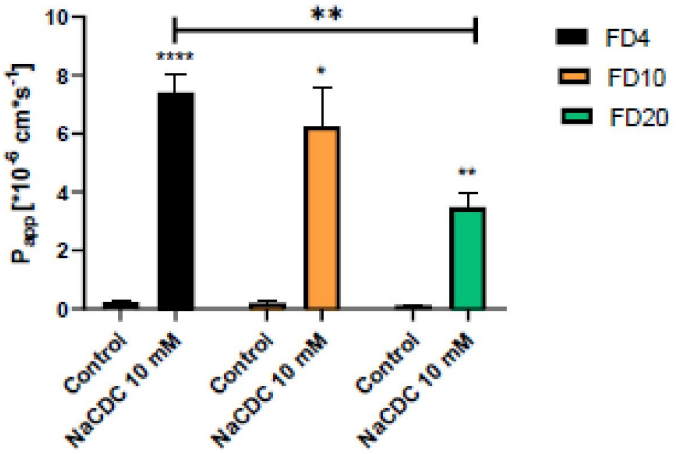


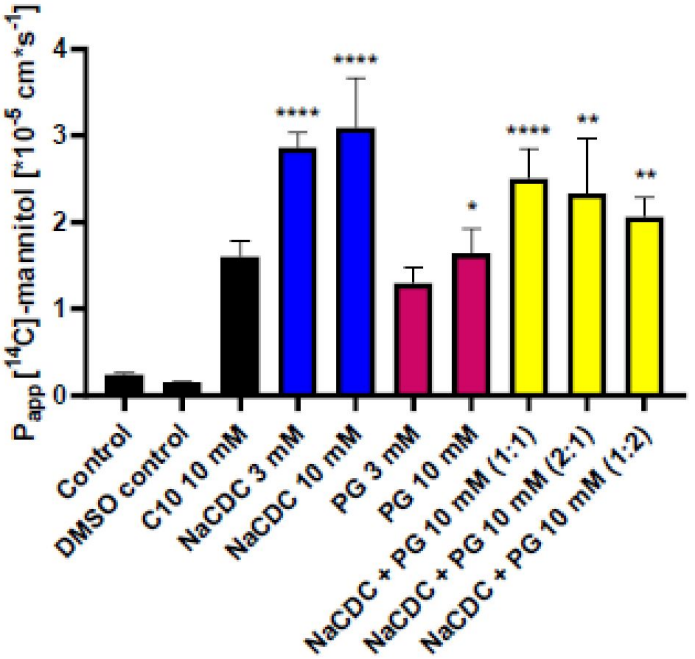
	Peptide	
	Semaglutide	MEDI7219
Peptide dose, mg/dog	20	20
PE dose, mg/dog	300 (SNAC)	300 (100 mg NaCDC and 200 mg PG)
Coating	none	pH 5.5 enteric
$t_{½}$, hours	60.5 (13.6)	9.8 (13.2)
T_{max}, hours	2.0 (1.5–2.5)	1.5 (1.0–4.5)
C_{max}, ng/mL	21.1 (72.5)	1,450 (63.2)
$AUC_{0\text{-}inf}$, ng·h/mL	1,440 (45.8)	13,500 (54.2)
F, %	0.08 (45.8)	5.92 (54.2)
CL/F, mL/h	16,000 (47.4)	1,880 (52.1)

Tablets in dogs….

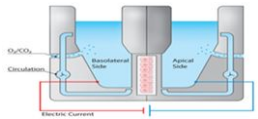
Pechenov S, et al. Sci Rep. 2021:22521. doi: 10.1038/s41598-021-01750-0.

What was the rationale for the NaCDC/PG combination ?



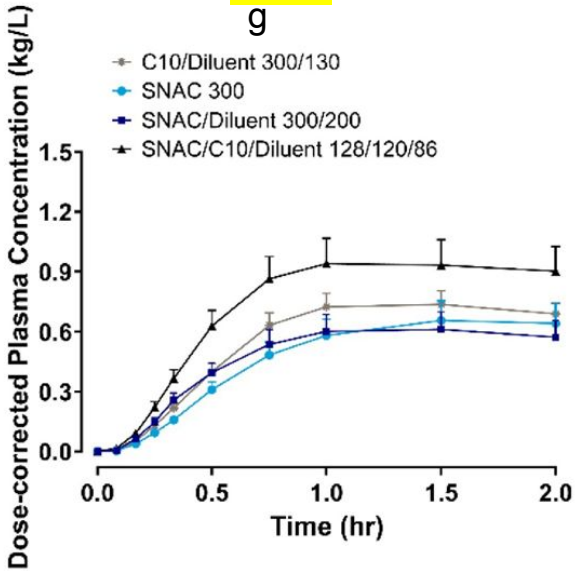


Rindchen, A. et al. 5th Eur Pharm Conference, (Porto, 2025)

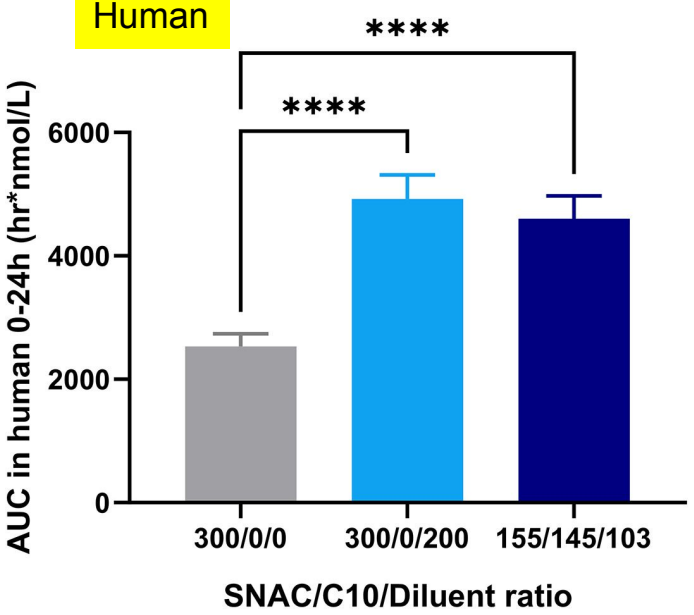


Combining SNAC and C_{10} in a gastric tablet

Dog

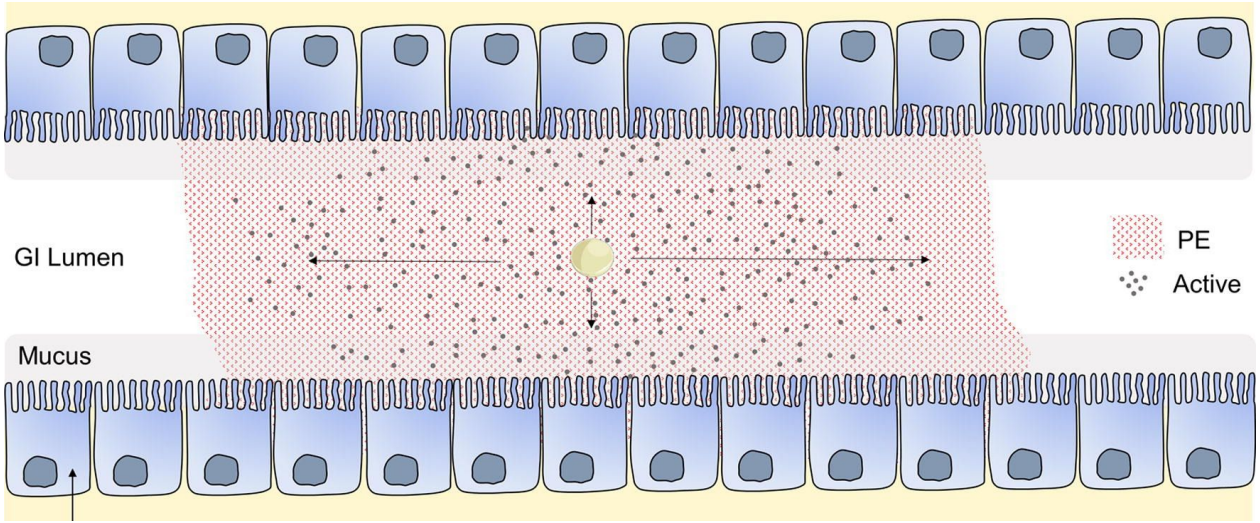


Human



Niu Z, et al. J Control Release. 2024;378:92-102.

Translating enhancers and peptides into new oral dosage form designs

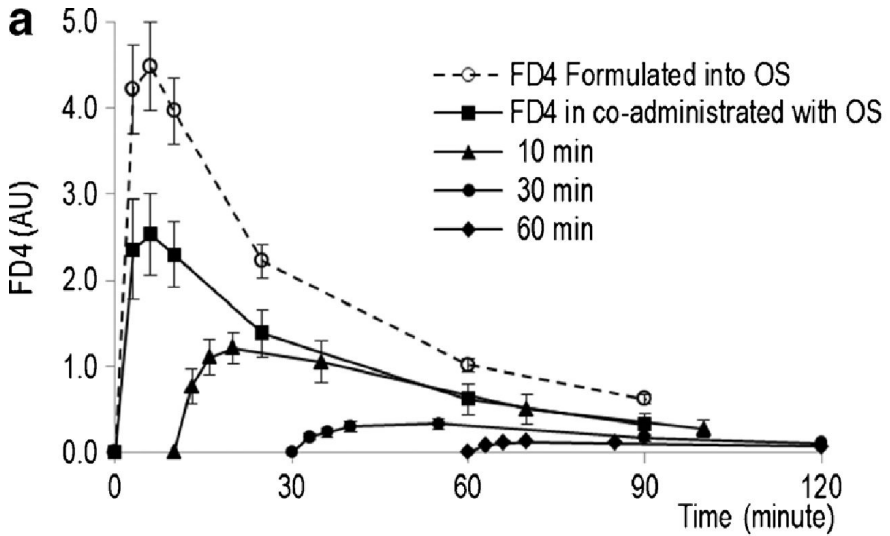


Maher S, Brayden DJ. (2021) *Adv Drug Deliv Rev.*177:113925.

Designs

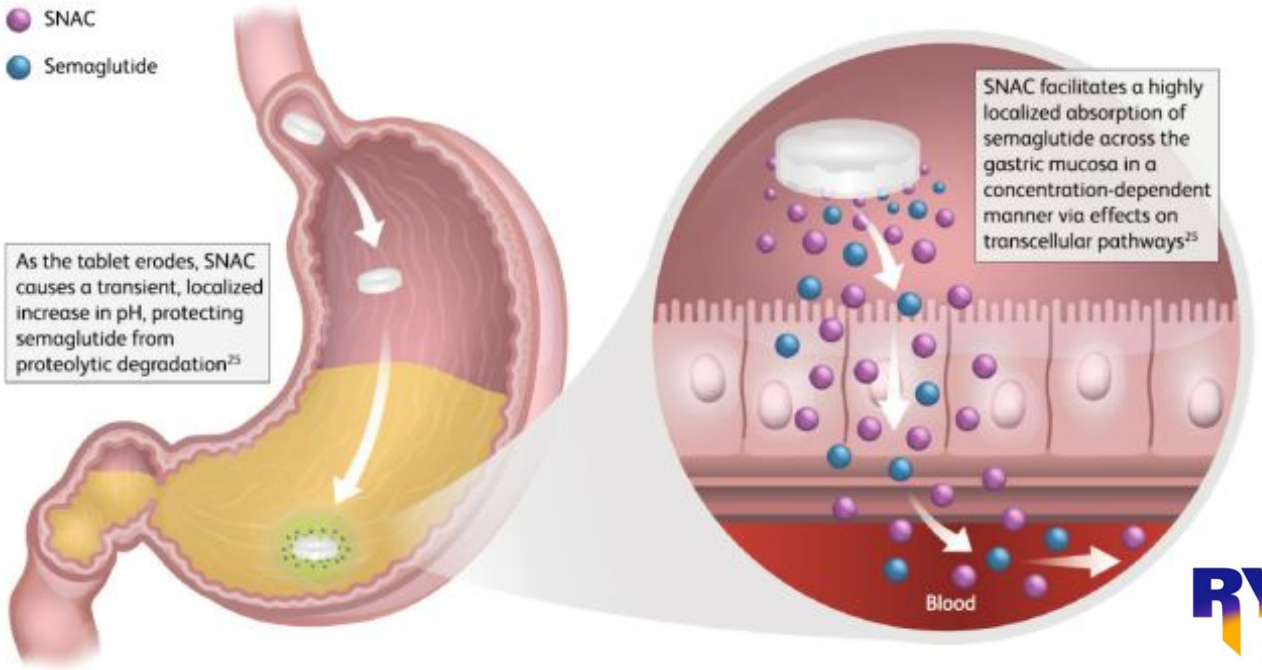
- *IR of both*
- *Burst for both, followed by second PE phase*
- *PE released first, then peptide*
- *SR of both over 60 min*

Core principle: rapid co-release and presentation of PE and peptide



Tuvia S, et al (2014) Pharm Res. ;31(8):2010-21.

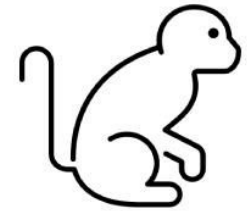
SNAC's gastric mechanism for semaglutide requires fast dissolution

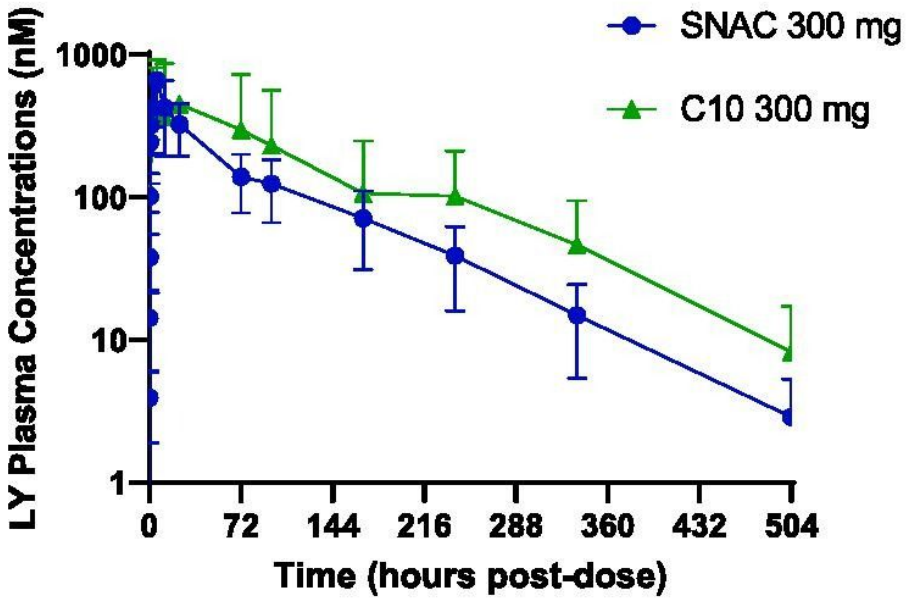


RYBELSUS® semaglutide tablets

Andersen A, et al (2021) 81(9):1003-1030. doi: 10.1007/s40265-021-01499-w.

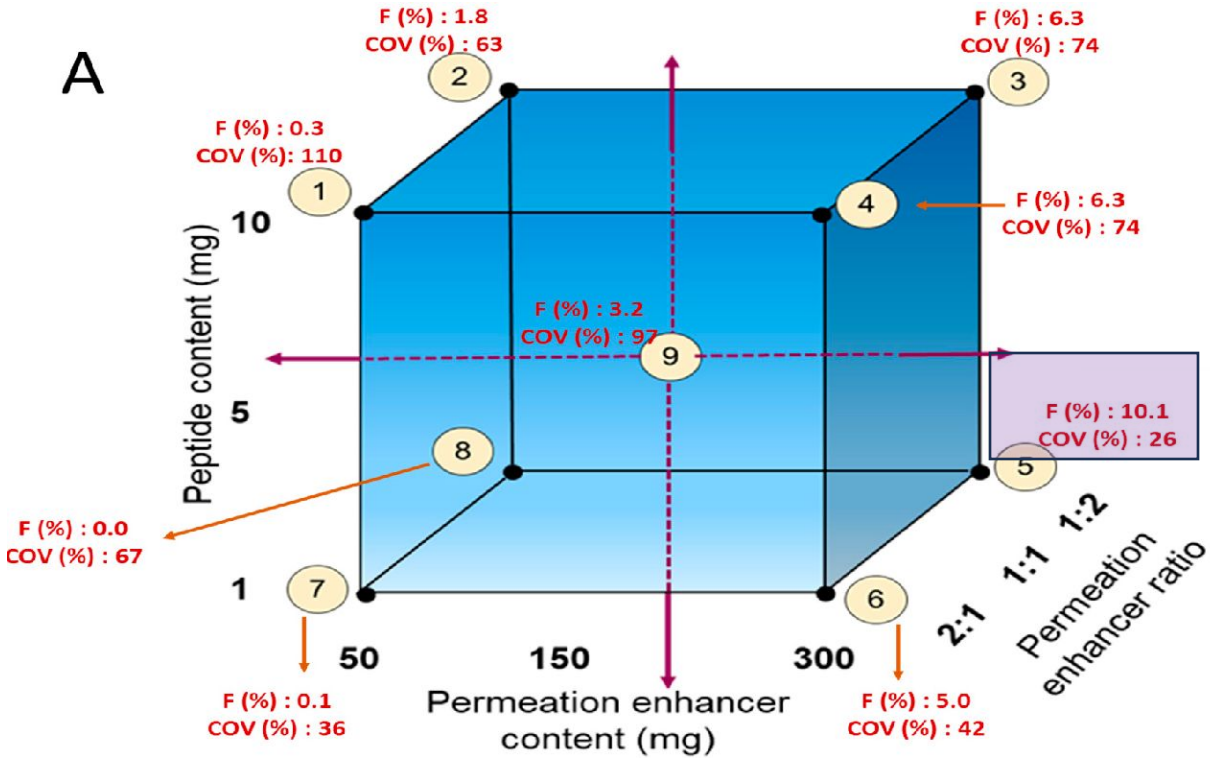
C_{10} also worked in the stomach with a Lilly GLP-1/GIP dual peptide agonist in fast erodible tablets





Tran H, et al (2024). Int J Pharm;650:123680. doi: 10.1016/j.ijpharm.2023

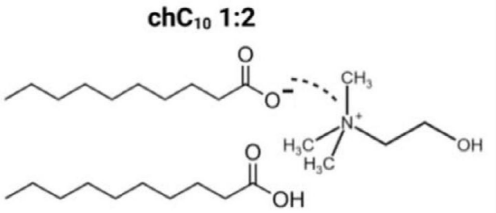
MEDI7219 tablet designs for dogs: IR dominant

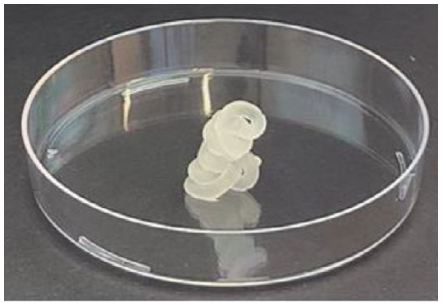


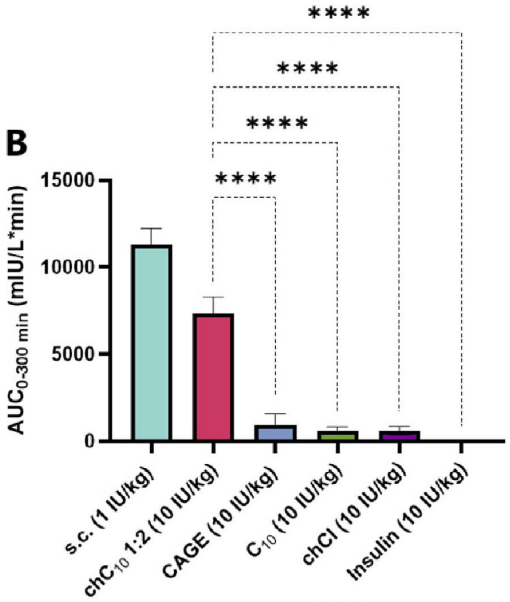
10 mg peptide, 300 mg PE total, IR tablet, released pH 5.5

https://www.mdpi.com/1999-4923/15/10/2436

‘Ionogels’ can offer sustained release: choline and C_{10}



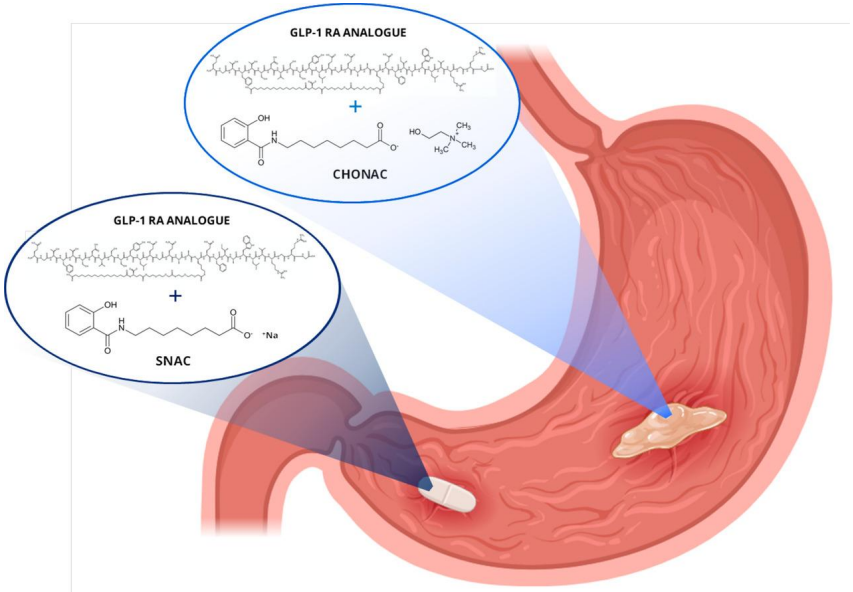


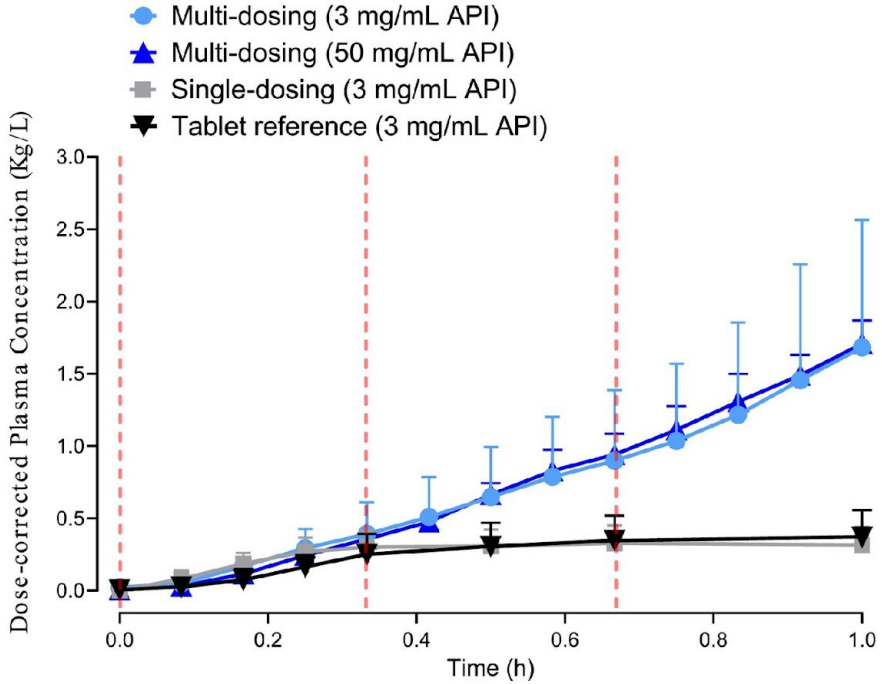


….benefits of a gel localising to wall and releasing caprate in situ?

Raptis K, et al. Adv Healthc Mater. 2025 :e2500946. doi: 10.1002/adhm.202500946.

Clues to optimal intestinal dosage form in dogs with a ionic liquid/GLP-1 RA construct





Rebollo R, et al (2025). J Control Release;377:267-276.

Conclusions

- PE selection is focussed on bioavailability improvements and compatibility in the dosage form
- In vitro and ex vivo models allow mechanistic data to be achieved, but models are limited by narrow non-damaging concentrations
- In our hands, in situ rat gut instillations have been a useful PE screen as predictors for large animal formulations, but it is case by case
- C_{10} and SNAC are still the benchmark PEs, with bile salts also popular. They are all anionic MCFA structures that perturb plasma membranes
- There are ongoing efforts in combining enhancers
- Effort is going into dosage form design to optimise co-presentation over time because the best PEs are absorbed too rapidly

Acknowledgments

- Research Ireland and the European Regional Development Fund (Grant Number 13/RC/2073) “CURAM Medical Devices;” a CIFRE grant from the French Government, with additional funding from Sanofi Pharma (Caroline Twarog) and Gattefosse (Dr. Fiona McCartney)
- Ann Rindchen, MSc, was funded by an Erasmus + grant in collaboration with Prof. Claus Michael Lehr (University of Saarbruecken, Germany)
- Dr. Joanne Heade, carried out the combination studies with Labrasol and C10 and was funded by a commercialisation grant from Research Ireland
- Declaration: DB is on the SABs of Ashland, Biograil, Nimble Therapeutics, and Arecor and had a project funded by Gattefosse. He consults for some companies mentioned in this talk.

Fiona McCartney

Joanne Heade

Caroline Twarog

Anne Rindchen

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