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NAC-based Ionic Liquids for GLP-1 Delivery: A Mechanistic Understanding of *In Vivo* Performance

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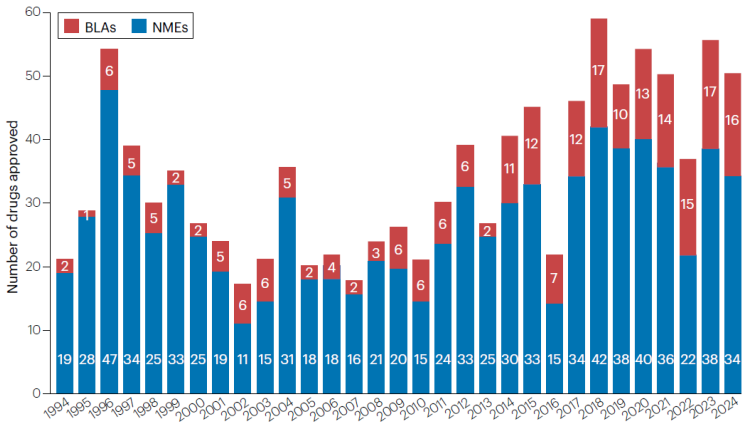
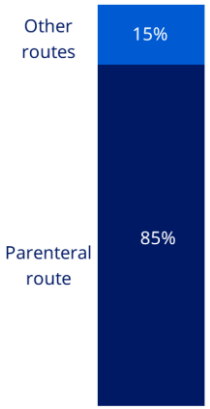
NEXT-GENERATION DELIVERY INNOVATIONS

Growing peptide market & Preference for oral treatment

FDA approvals 1994-2024 [1,2]

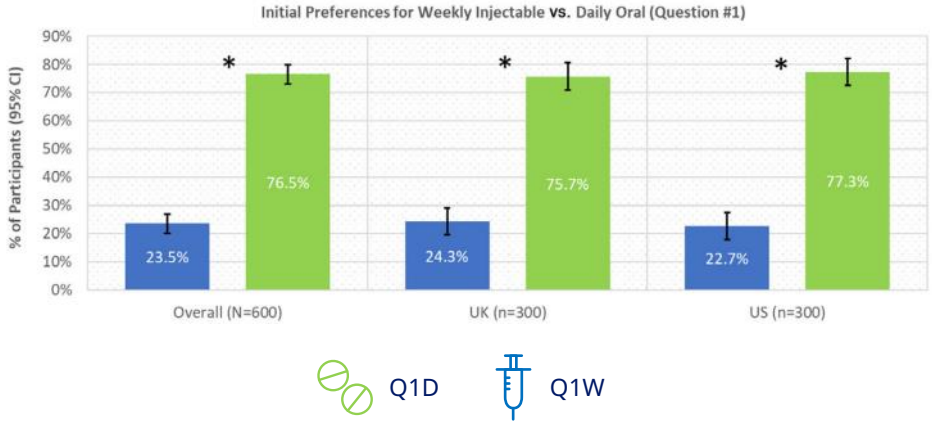




- Global peptide market **$53 B** in 2025 and rapidly expanding (CAGR 5.31%)
- Increasing approval rate for biologics

Heavily dominated by parenteral treatment

Patient preference [3]



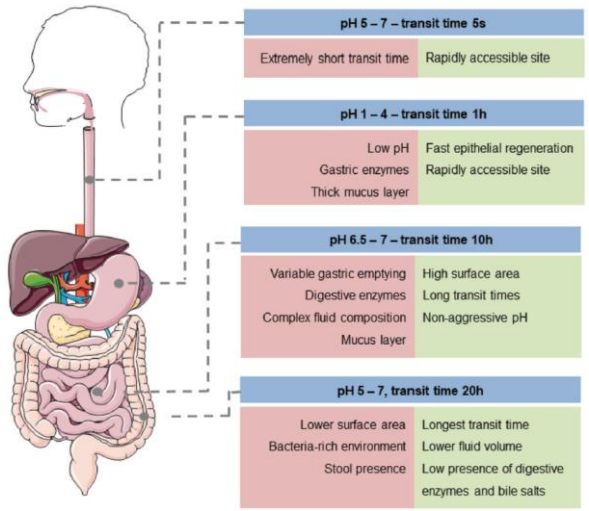
Daily oral treatment is preferred over weekly S.C

There is a clear unmet need and rational for improving the oral bioavailability of peptides

1. Asher Mullard, 2024 FDA approvals. *Nature Reviews Drug Discovery*, 2025, 24: 75-82
2. Peptide Therapeutics Market Size And Share Report, 2030 (grandviewresearch.com)
3. Boye K et al., Patients' preferences for once-daily oral versus once-weekly injectable diabetes medications: The REVISE study. *Diabetes, Obesity and Metabolism*, 2021, 23 (2): 508-519

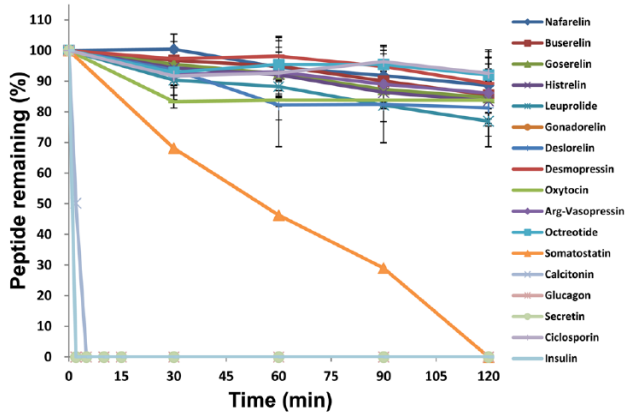
Low oral bioavailability remains the main obstacle - Stability

Low stability and permeability [1]



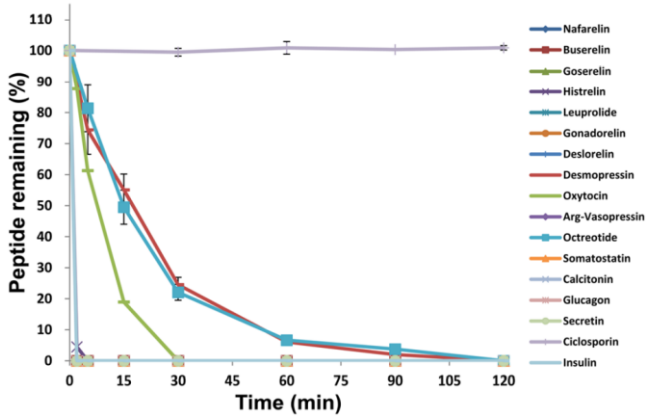
- Prone to proteolysis in the GIT
- Absorption limited by large molecular size

Stability in human gastric fluids [2]



- **T1/2 < 2 min** when Mw > 3kD (> 25 AA), despite pI, Log P, H acceptors or doners
- Peptides < 1.4 kD (< 10 AA) remain stable

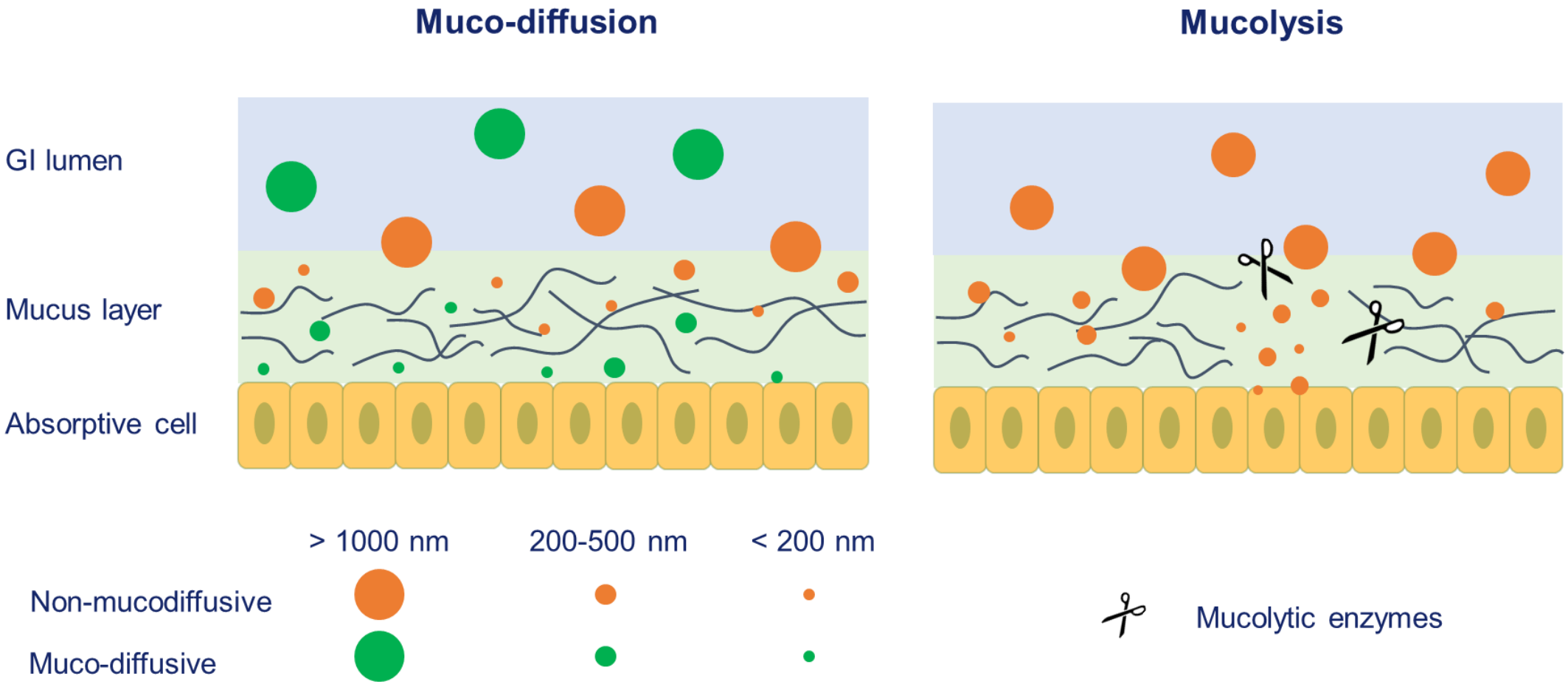
Stability in human intestinal fluids



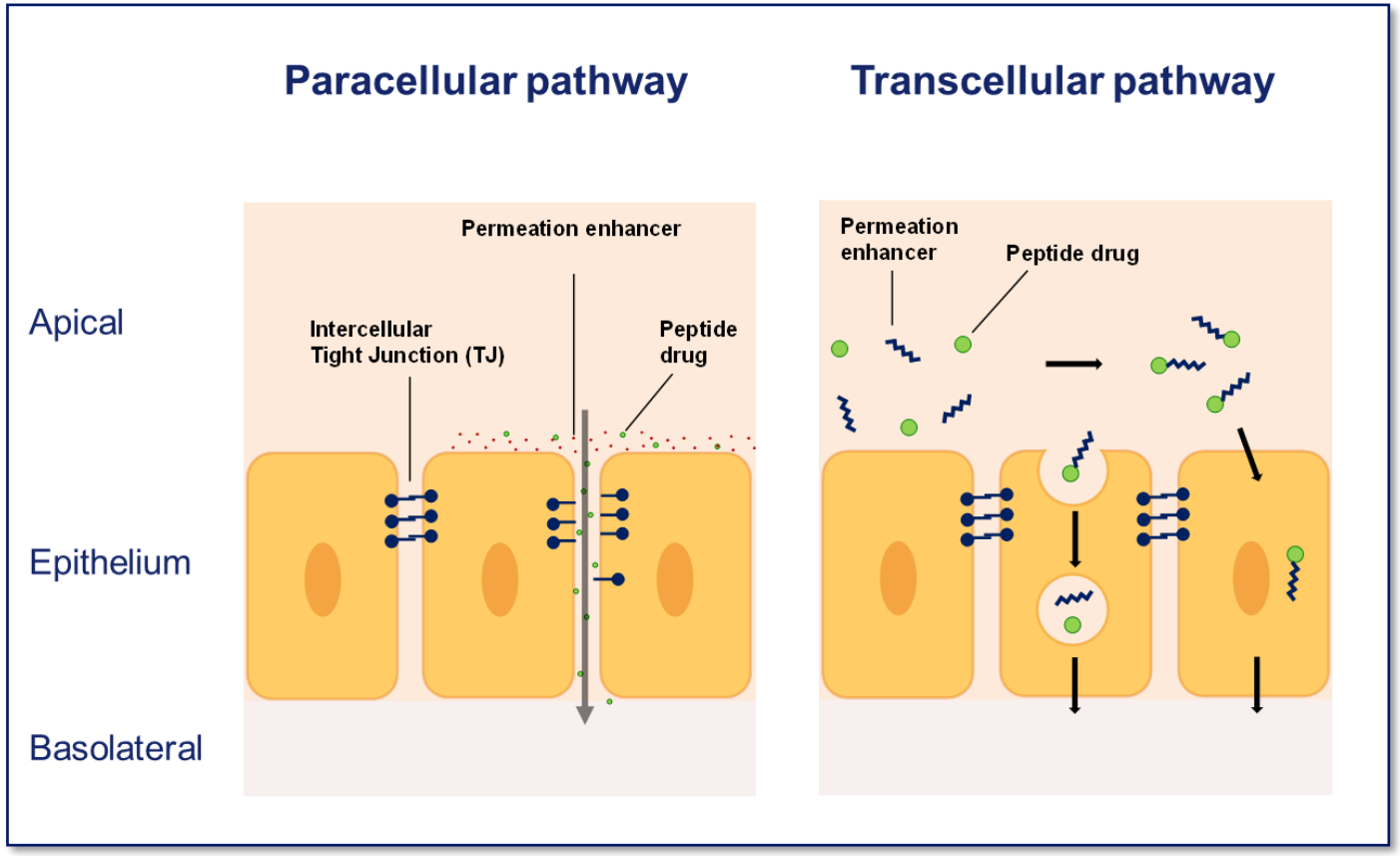
- **T1/2 < 2 min** for most tested peptides
- Cyclic peptides last over 15 min (i.e. cyclosporin, desmopressin, octreotide)

1. Durán-Lobato M, Niu Z, and Alonso MJ, Oral delivery of biologics for precision medicine. *Advanced Materials*, 2020, 32, 1901935
2. Wang J, Yadav V, et al., Toward oral delivery of biopharmaceuticals: an assessment of the gastrointestinal stability of 17 peptide drugs. *Molecular Pharmaceutics*, 2015, 12 (3): 966–973

Low bioavailability remains the main obstacle - Permeability



Low bioavailability remains the main obstacle - Permeability



Common permeation enhancers:

- ❑ SNAC families
- ❑ Medium-chain fatty acids (e.g. C10, C8)
- ❑ Bile salts
- ❑ Cell penetrating peptides
- ❑ Others (Lauryl carnitine, EDTA, etc.)

SNAC: Sodium N-(8-(2-hydroxybenzoyl) amino) caprylate, or sodium salcaprozate; C10: Sodium caprate; C10: Sodium caprate EDTA: Ethylenediaminetetraacetic acid

Enhancer-based oral peptide products in the market

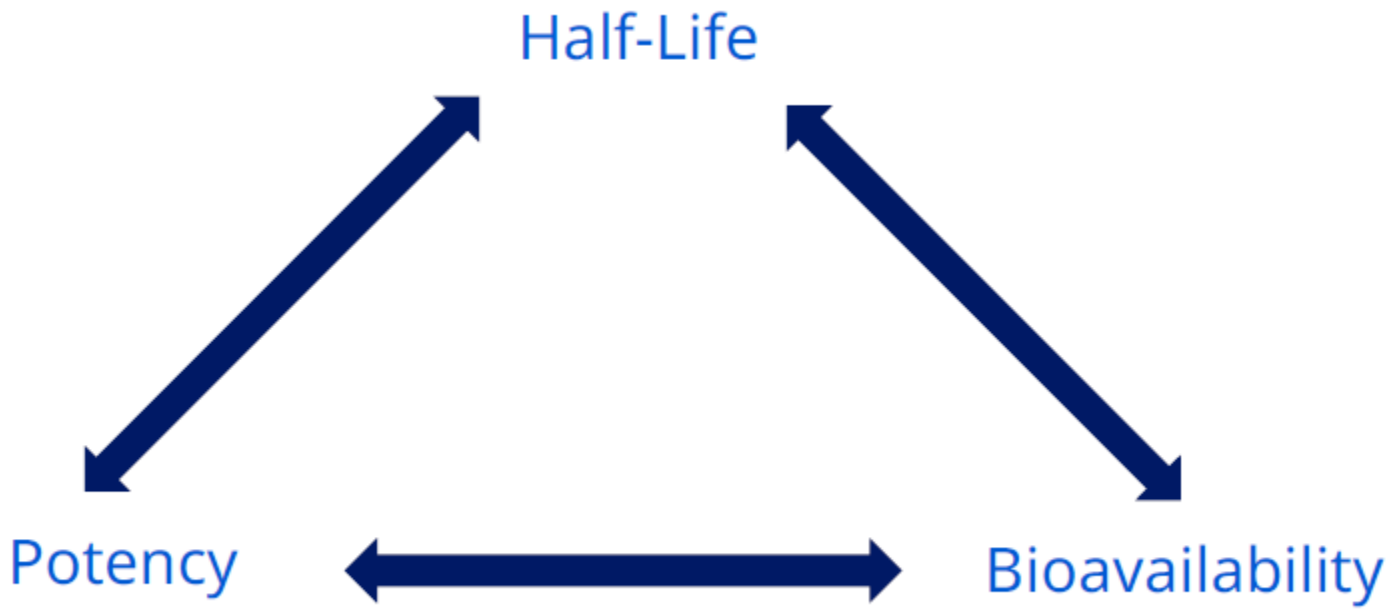
Semaglutide tablets
(FDA approved in 2019)

SNAC (sodium salcaprozate)

Octreotide capsules
(FDA approved in 2020)

C8 (sodium caprylate)

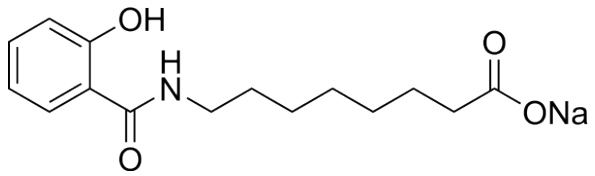
Interplay between potency, half-life & bioavailability



Parameters are interlinked and all crucial for oral peptide delivery

Tablet co-formulation with SNAC for gastric delivery

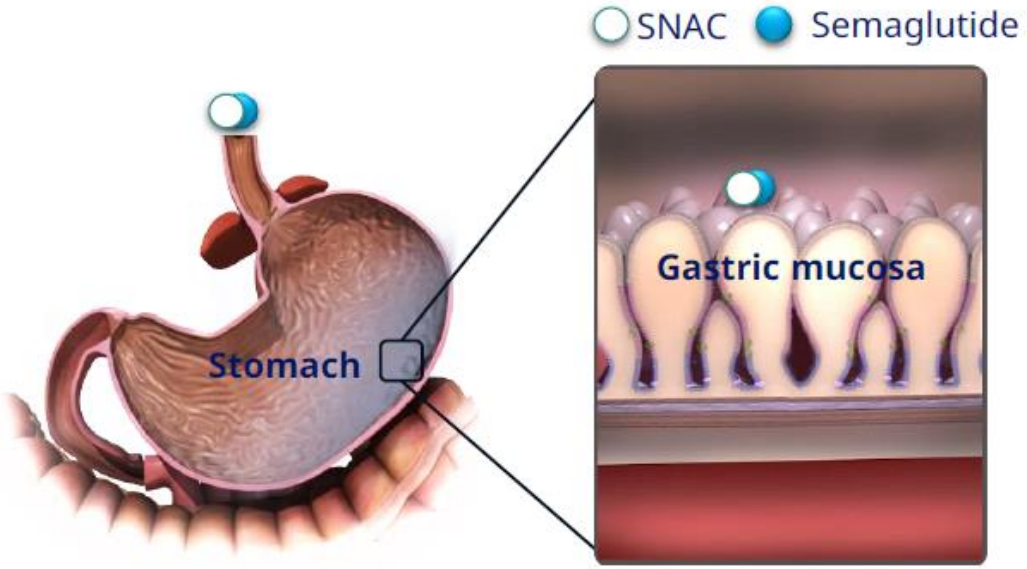
SNAC (sodium salcaprozate)[1]



SNAC, a small fatty acid derivative, is an absorption enhancer that facilitates absorption

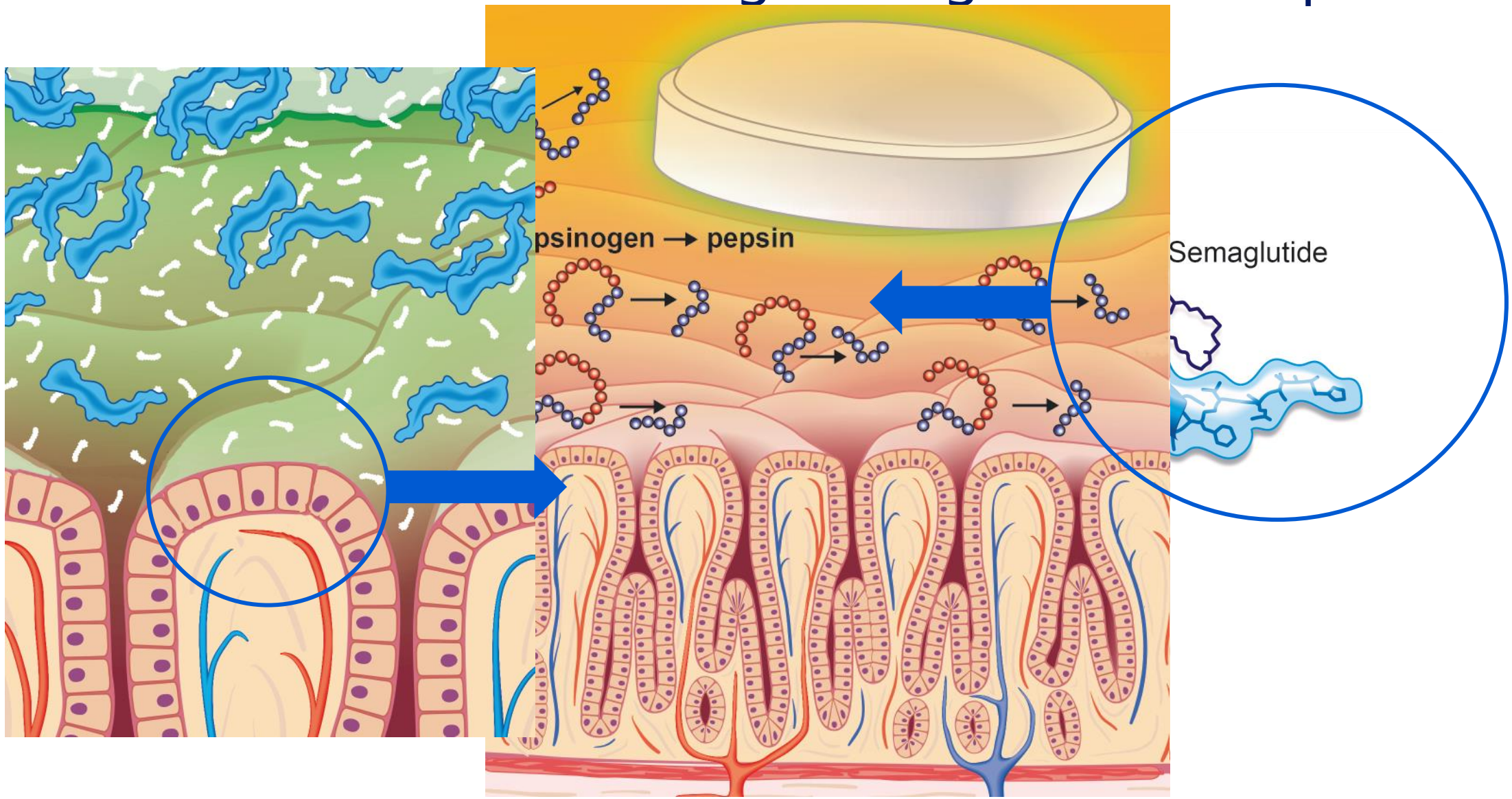
The available data for semaglutide co-formulated with SNAC support that absorption takes place in the stomach in a localised buffered environment

The effect is strictly time-dependent and occurs primarily via transcellular route



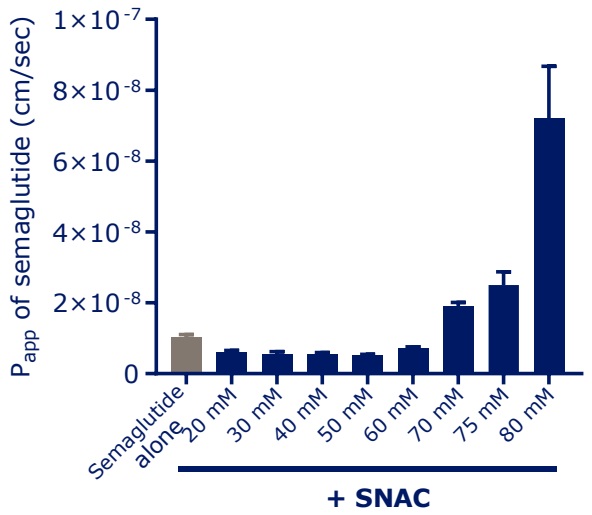
1. Buckley ST et al., Transcellular stomach absorption of a derivatized glucagon-like peptide-1 receptor agonist. *Science Translational Medicine*, 2018, 10, 467

The role of SNAC in semaglutide gastric absorption



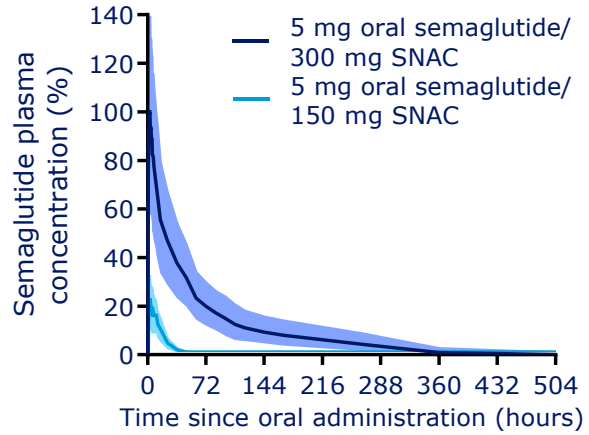
Peptide exposure is dependent on SNAC concentration

In vitro absorption across gastric cell monolayers



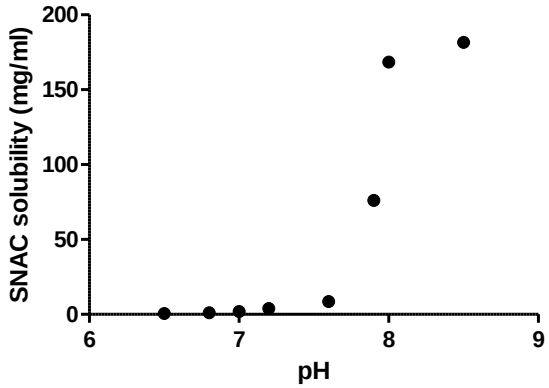
- The permeation of semaglutide depends on SNAC concentration

In vivo plasma exposure in human subjects



- Clinical trials support that more enhancer yields superior exposure

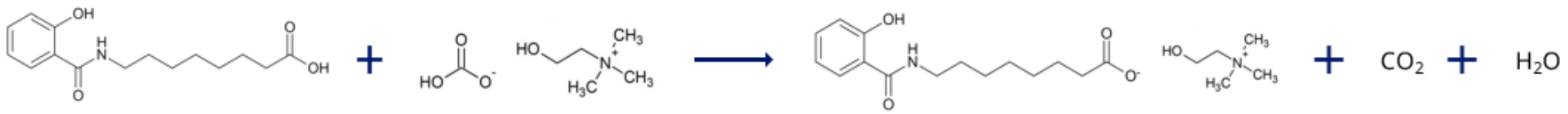
pH dependent solubility of SNAC



- Low solubility below pH 7.5

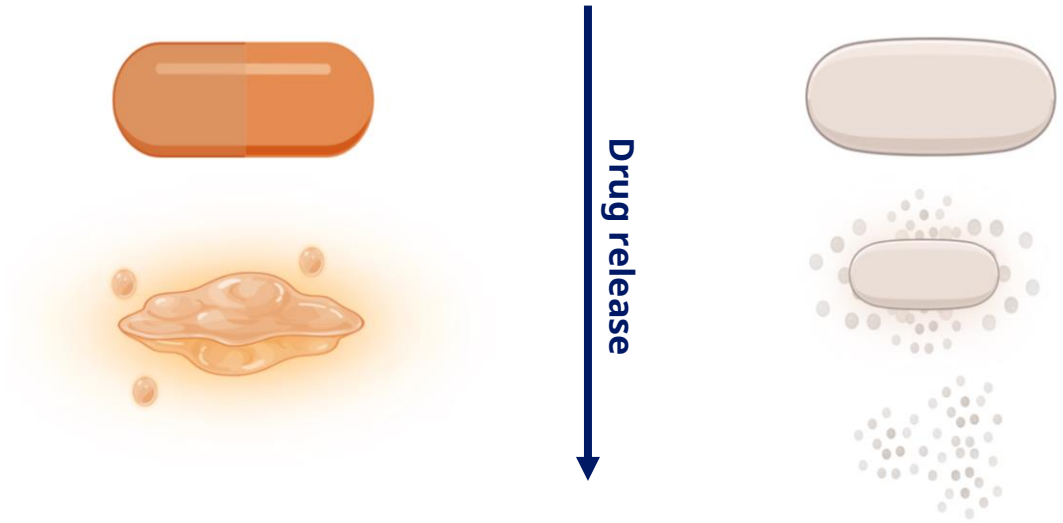
1. Buckley ST et al., Transcellular stomach absorption of a derivatized glucagon-like peptide-1 receptor agonist. *Science Translational Medicine*, 2018, 10, 467

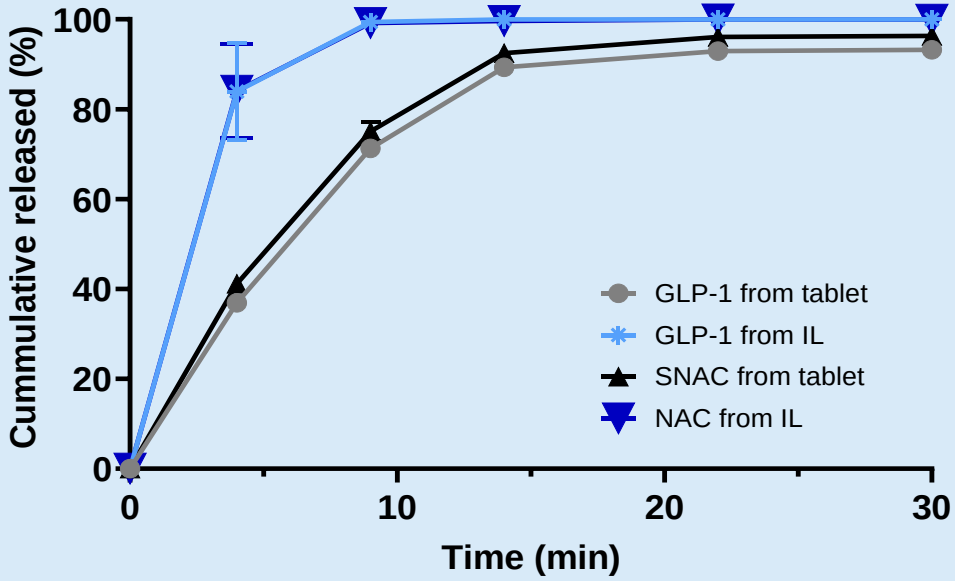
Ionic liquids (CHONAC) formed by acid-base neutralization



HNAC Choline bicarbonate CHONAC

Ionic liquids offer faster dissolution and higher solubility

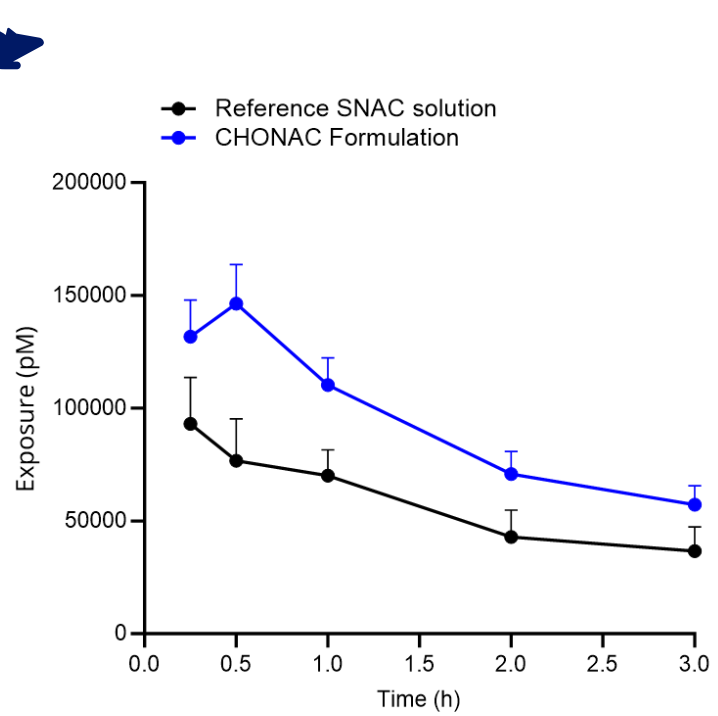




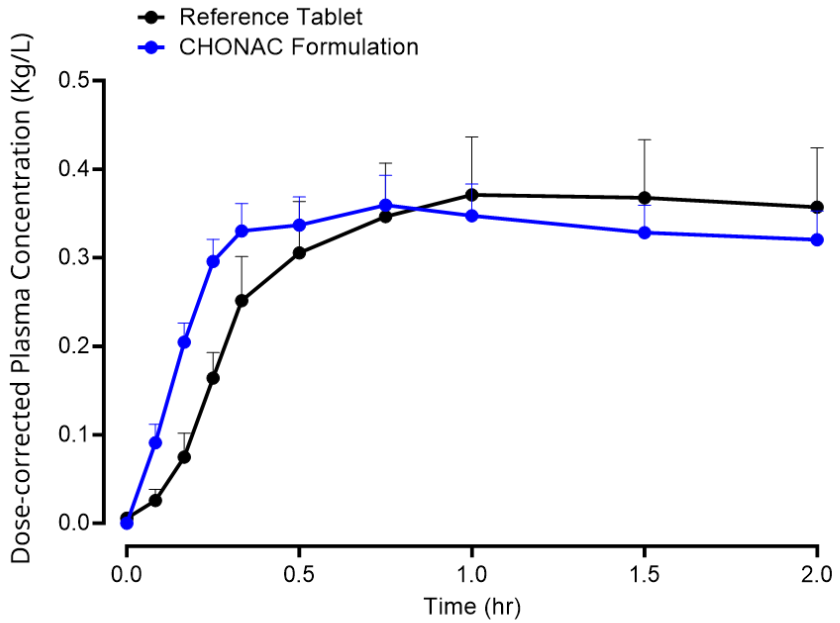
- Liquid formulation circumvents hydration and dissolution, rapidly increasing concentration of available enhancers
- Dissolution of ionic liquid in an immediate release capsule is faster than from a SNAC tablet [1]

1. Rebollo R et al., Salcaprozate-based ionic liquids for GLP-1 gastric delivery: A mechanistic understanding of in vivo performance. *Journal of Controlled Release*, 2025, 377, 267-276

In vivo dosing in anesthetized animals showed superior initial uptake of GLP-1 from ionic liquid formulation

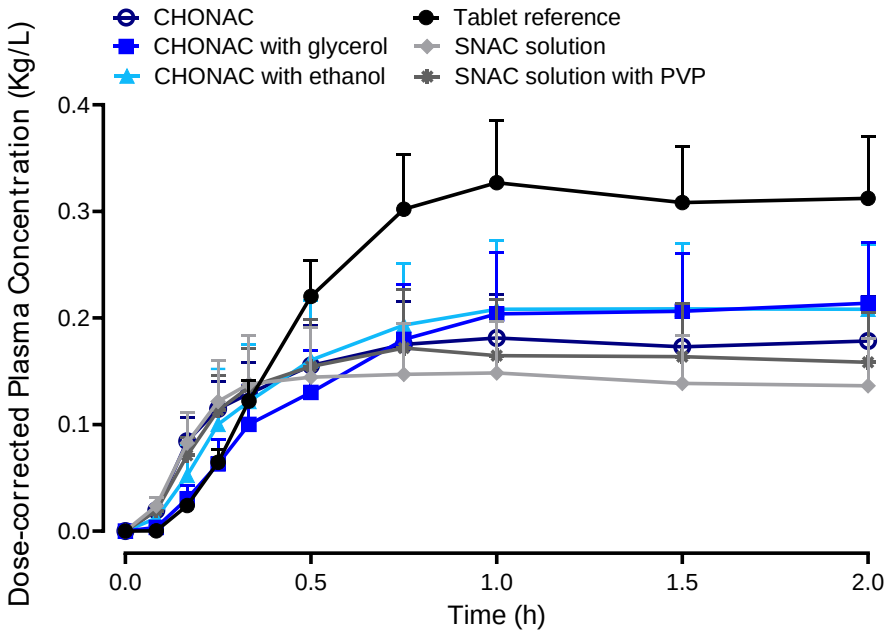


- Superior initial uptake of GLP-1 from ionic liquid than from **liquid formulation** comprising SNAC and GLP-1

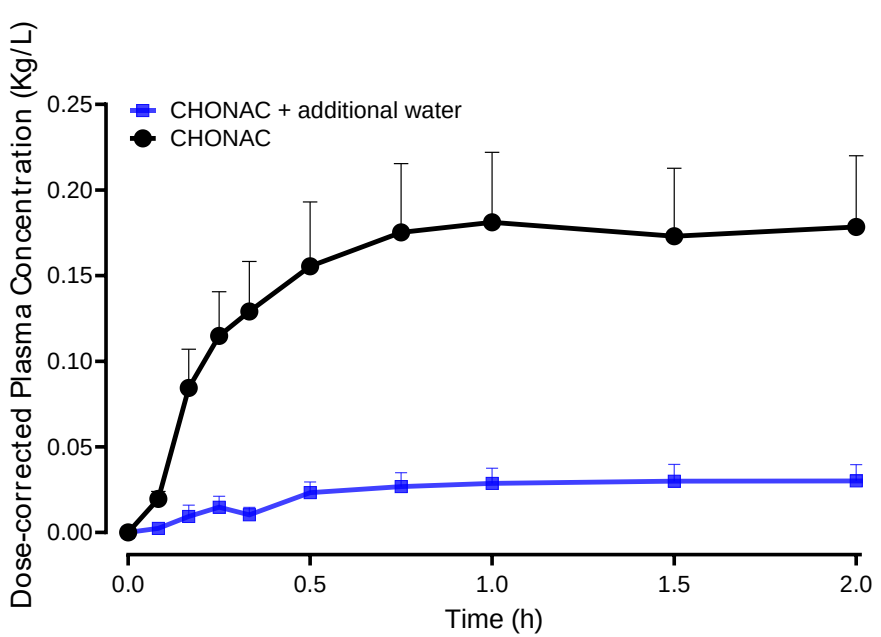


- Superior initial uptake of GLP-1 from ionic liquid than from **tablet formulation** made of SNAC and GLP-1

In vivo dosing in awake dogs showed inferior GLP-1 uptake



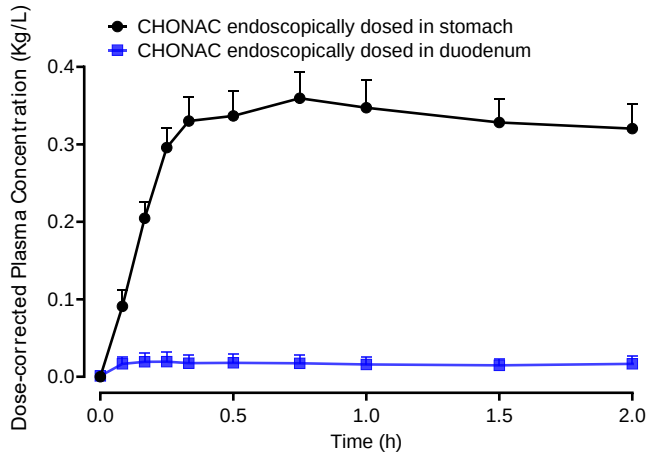
- Variables: viscosity, co-solvents, precipitation inhibitors
- Inferior GLP-1 uptake from liquid formulations in all cases



- GLP-1 uptake sensitive to administration of additional water

Lack of confinement of ionic liquids in the stomach can explain the suboptimal performance of liquid formulations

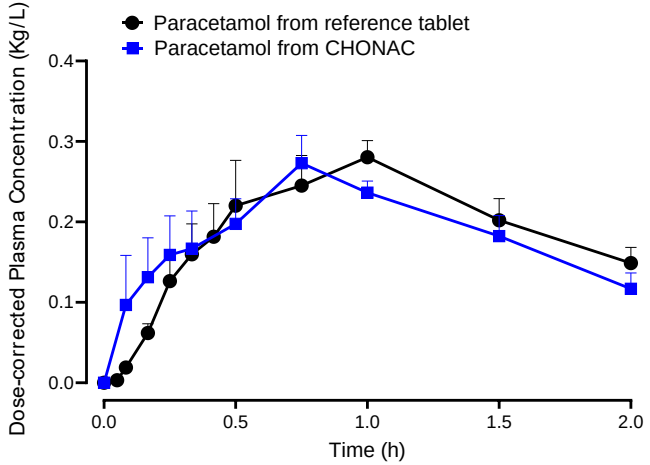
Gastric vs. intestinal dosing



Anesthetized dogs

- Intestinal absorption of GLP-1 is significantly lower than gastric absorption

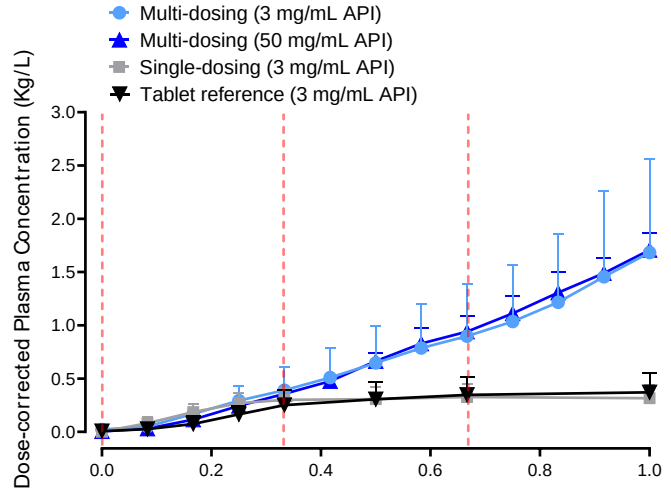
Paracetamol absorption



Awake dogs

- Faster paracetamol absorption indicates faster gastric emptying
- Potential explanation for inferior absorption of GLP-1 in awake dogs

Repeated dosing



Anesthetized dogs

- Repeated dosing of liquid formulation showed continuous linear absorption of GLP-1

Key learnings for ionic liquids and liquid formulations

Ionic liquids offer faster SNAC release, leading to high local concentration

Liquid formulations appear to have an earlier GLP-1 absorption onset compared to solids

Gastric confinement plays a key role in the effectiveness of liquid SNAC formulations

Q&A