Applications of Physiologically - Based Pharmacokinetic Modelling in Oral Peptide Drug Development

Ricardo Diaz de Leon Ortega, 14th July 2025

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

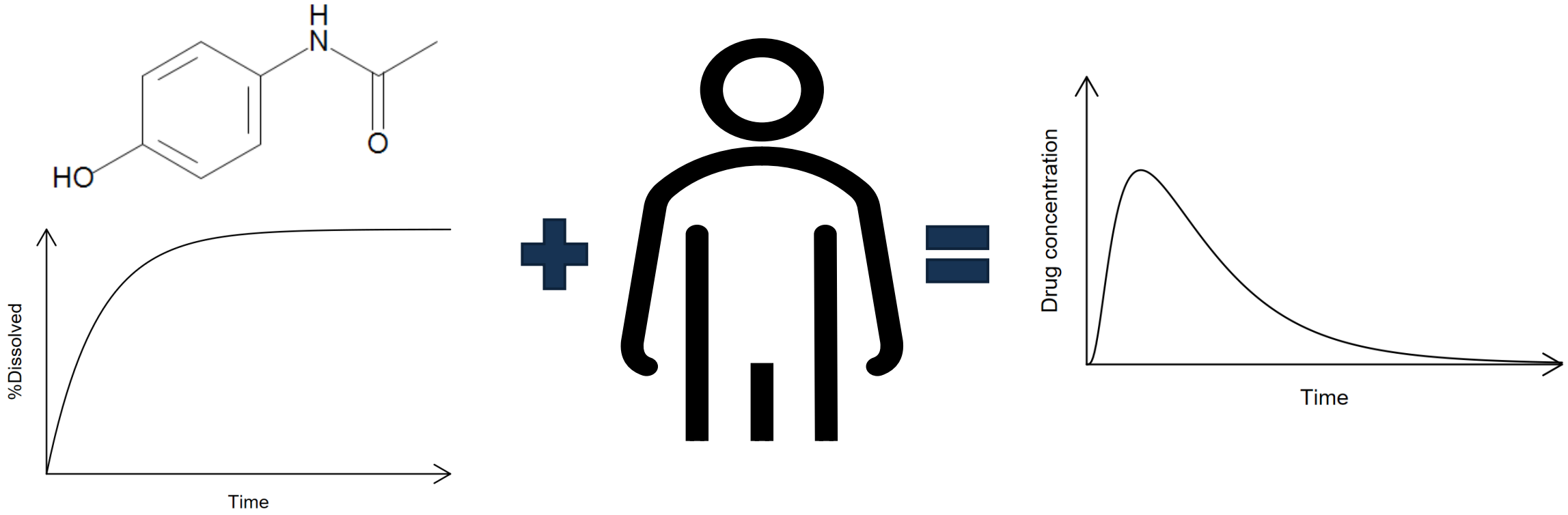
NEXT-GENERATION DELIVERY INNOVATIONS

Outline

- Introduction: Physiologically – based pharmacokinetic modelling and simulation
- Case study 1: A retrospective analysis of SNAC effect on peptide absorption (dosed as an enteric coated formulation)
- Case study 2: Use of modelling and simulation to evaluate potential drug – drug interactions of Rybelsus® (semaglutide) as perpetrator

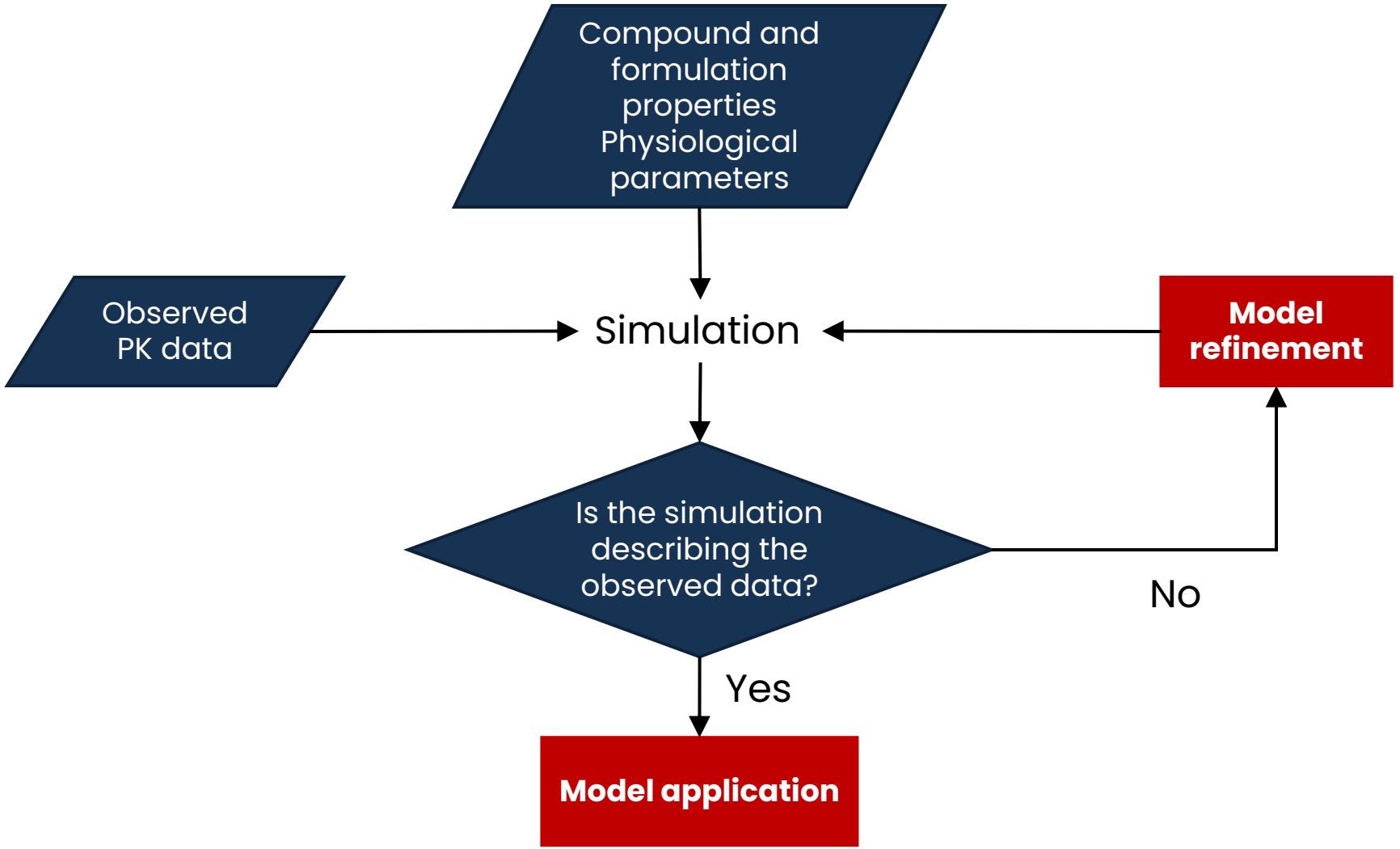
Physiologically - based pharmacokinetic (PBPK) modelling

- An approach that integrates compound (physicochemical and in vitro DMPK) and formulation properties (e.g. dissolution) with physiological parameters (e.g. tissue volumes, blood flows) through a set equations

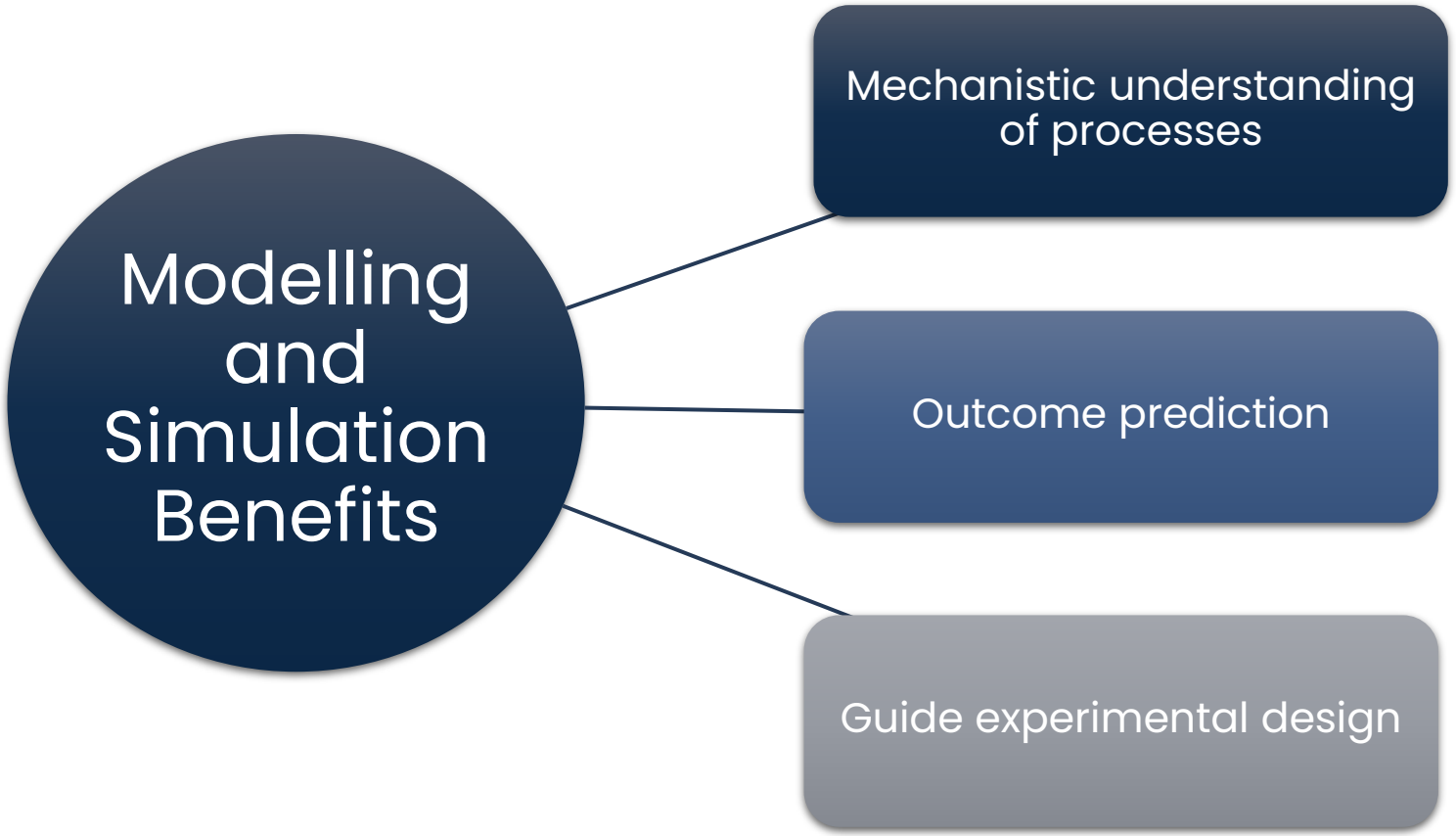


Espié P, et al. Physiologically based pharmacokinetics (PBPK). Drug Metab Rev. 2009

PBPK flow chart

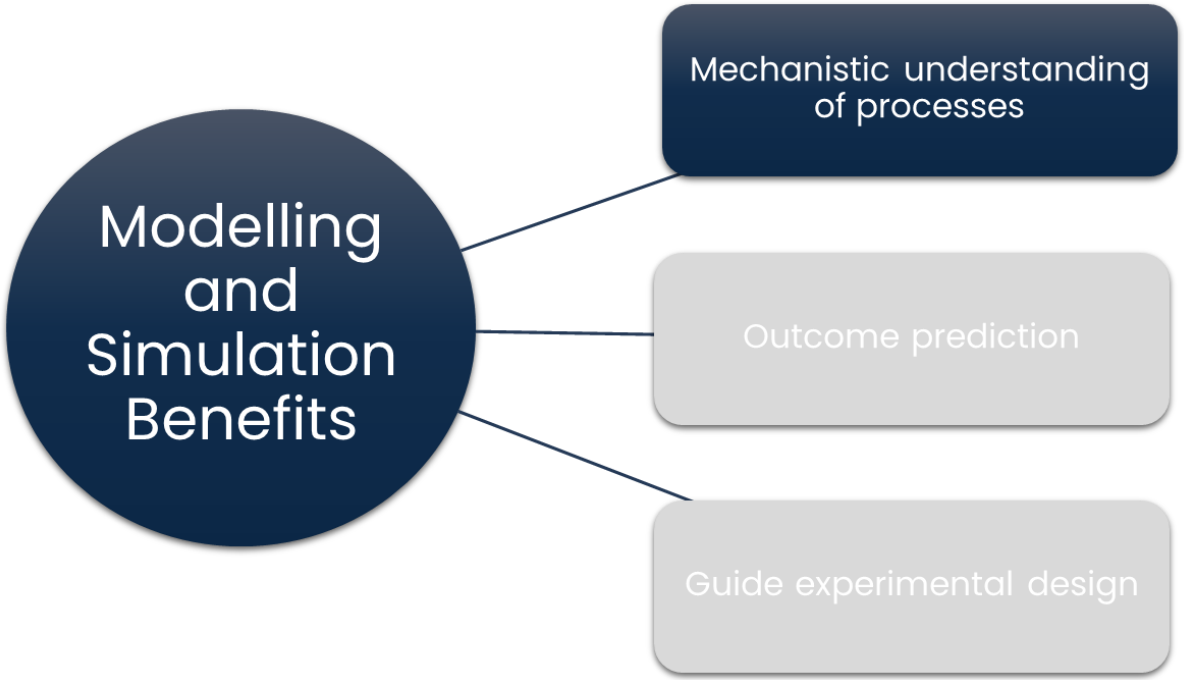


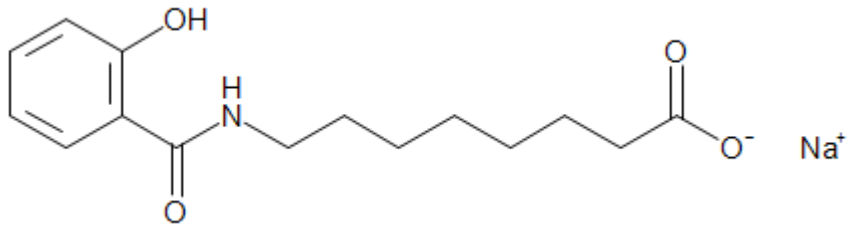
Kuepfer, L., et al. Applied Concepts in PBPK Modeling: How to Build a PBPK/PD Model. CPT: pharmacometrics & systems pharmacology, 2016



Peters, S.A., Physiologically-Based Pharmacokinetic (PBPK) Modeling and Simulations: Principles, Methods, and Applications in the Pharmaceutical Industry, 2012

Case 1:
A retrospective analysis of SNAC effect on peptide absorption (dosed as an enteric coated formulation)

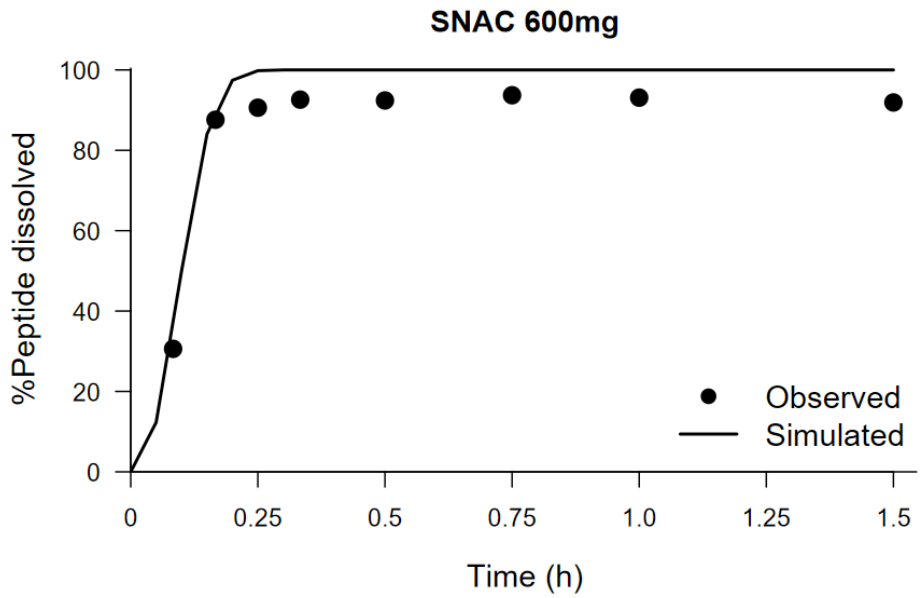




SNAC (permeation enhancer)

Enteric coated formulation: Peptide + SNAC

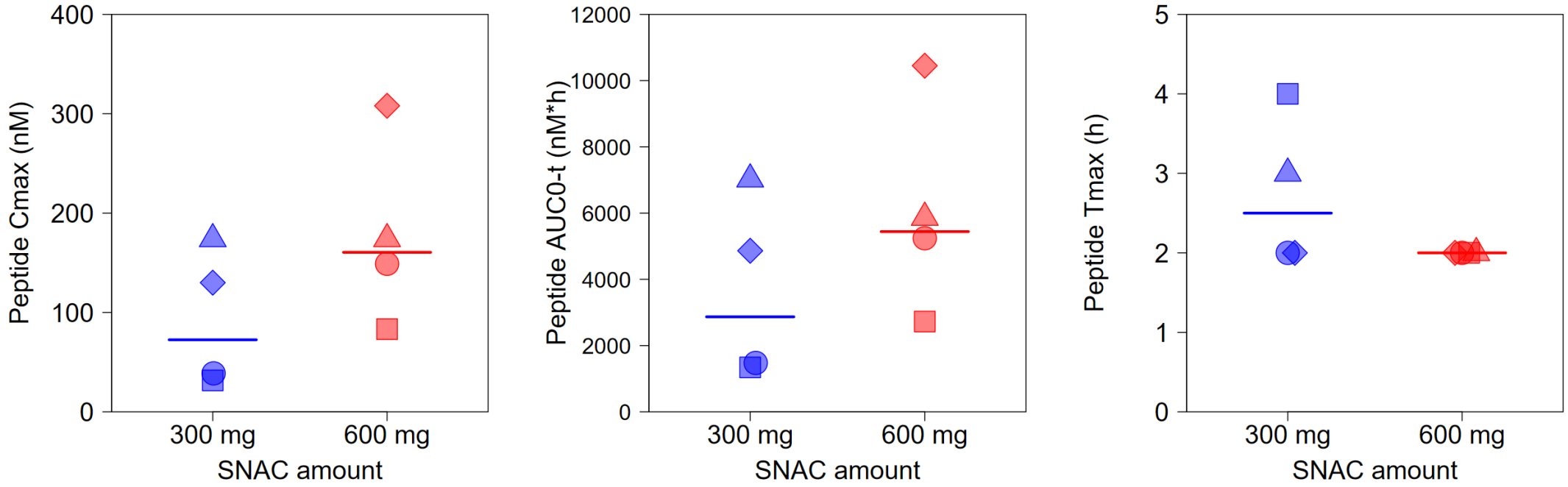
- **Highly soluble but poorly permeable peptide**
- **Tablets had the same amount of peptide but with either 300mg or 600mg of SNAC**
- **A Weibull model was fitted to the observed dissolution data of the tablet with 600mg of SNAC**
- **Key assumptions**
  - Peptide and SNAC dissolve at the same rate
  - SNAC amount does not impact dissolution



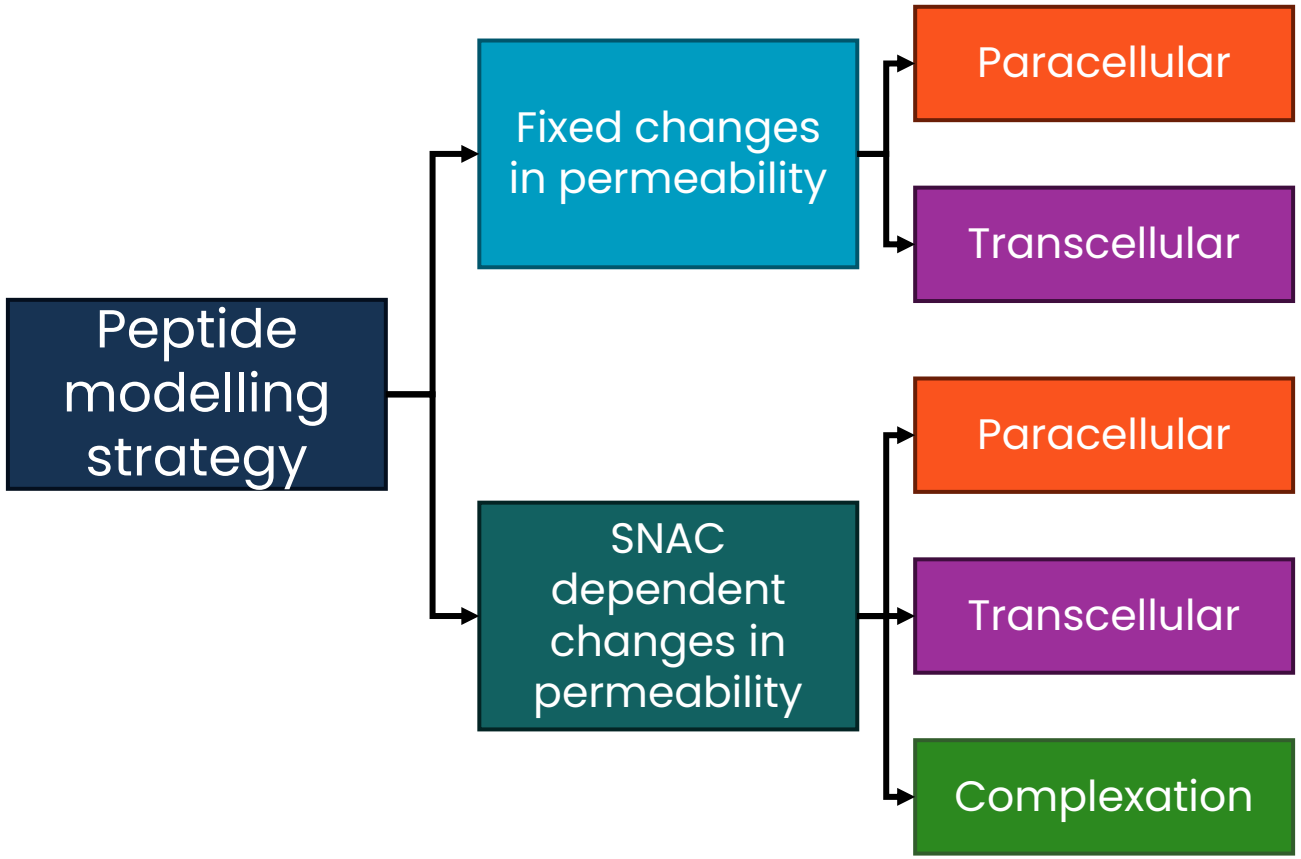
Component	Condition
Apparatus	Apparatus II (paddle)
Medium	**50 mM sodium phosphate buffer, pH 6.8**
Volume of Medium	500 mL
Rotation Speed	75 rpm (with 250 rpm between 60 and 90 minutes)
Sampling Time Points	5, 10, 15, 20, 30, 45, 60 and 90 (infinity) minutes.

Oral administration (dog)
Peptide PK parameters

- **Peptide PK data showed that decreasing SNAC by half, decreased AUC and Cmax proportionally, while Tmax is consistent around 2 h**



Line: geometric mean for Cmax and AUC, median for Tmax



Permeability value was fitted to the peptide Cp-t profile from the SNAC 600 mg tablet

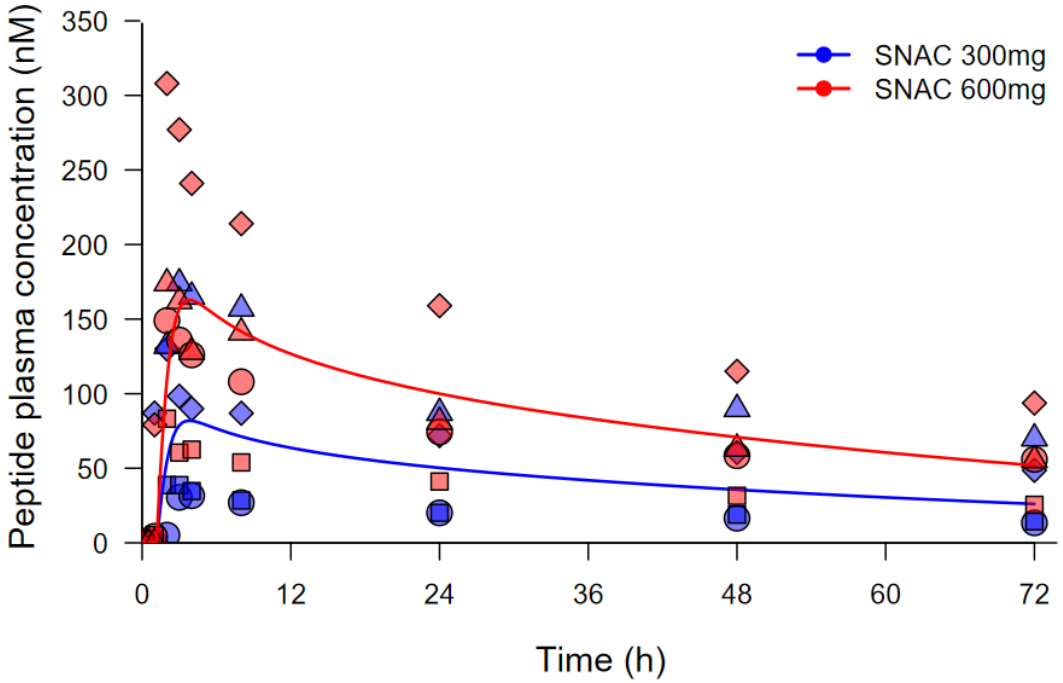
For SNAC 300mg, the value was reduced by half

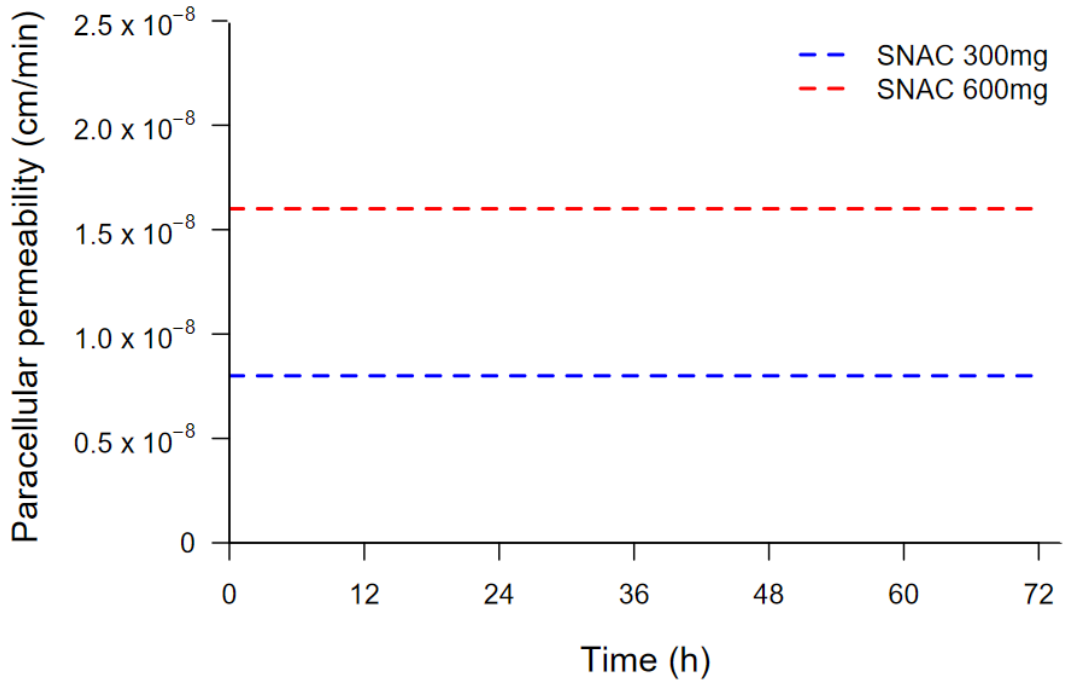
A linear relationship was established between the predicted SNAC concentration in the gut and the predicted changes in permeability

Fixed paracellular permeability

Cmax and AUC0-t predicted within ± 20% deviation of the geometric mean value

Tmax was slightly overpredicted

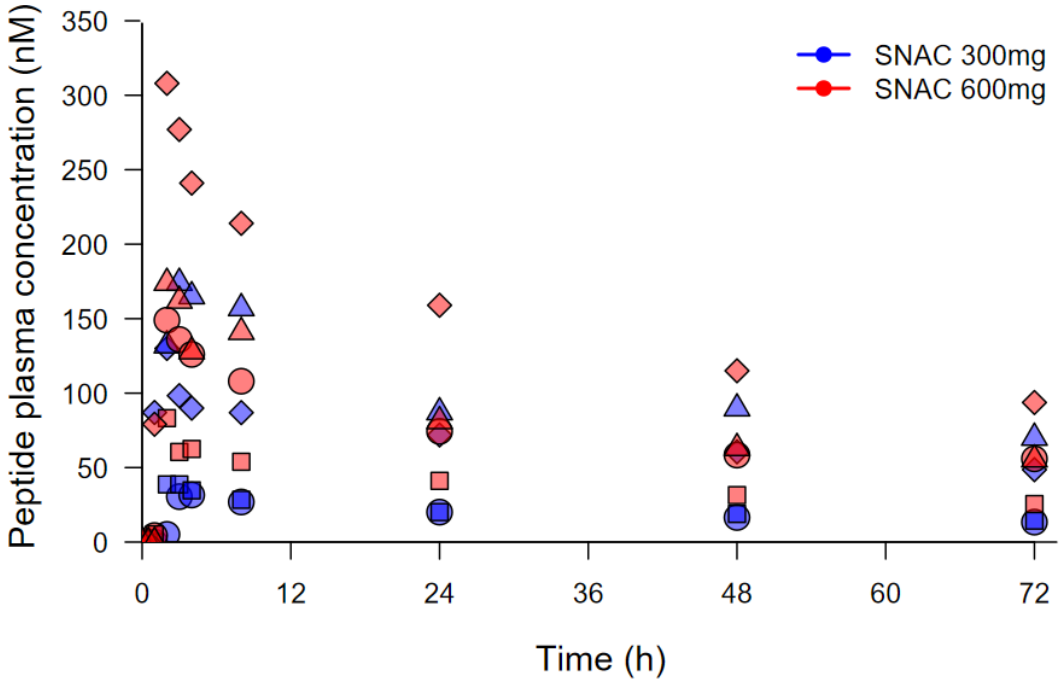


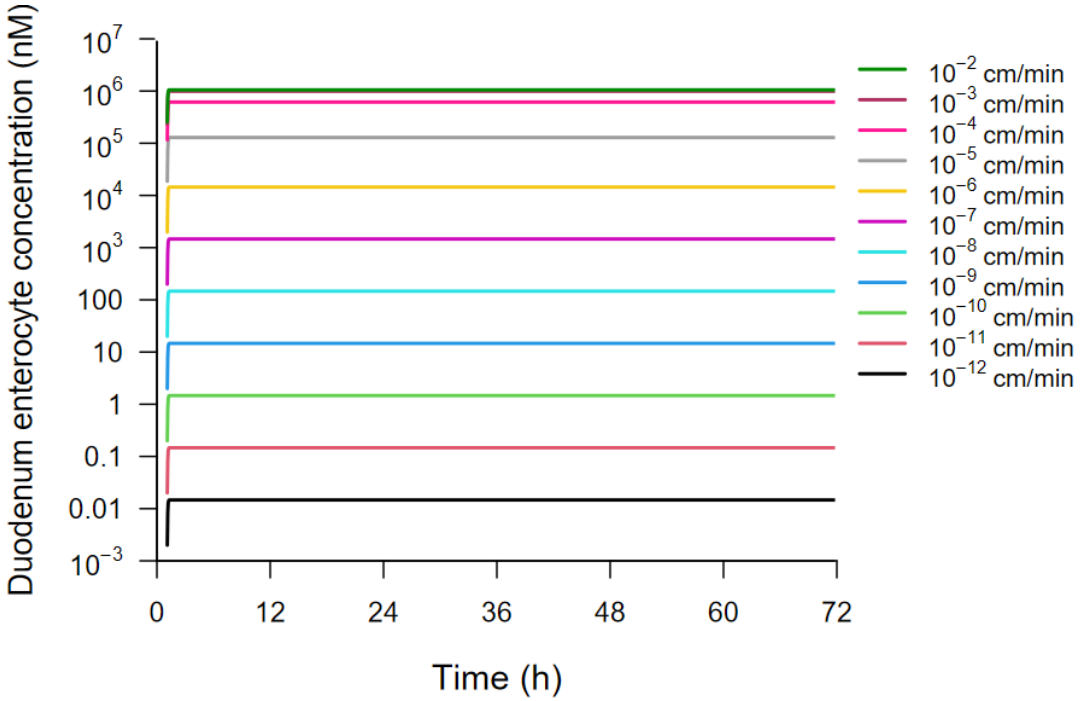


Tmax	
Observed	Predicted
~ 2 h	**3.8 h**

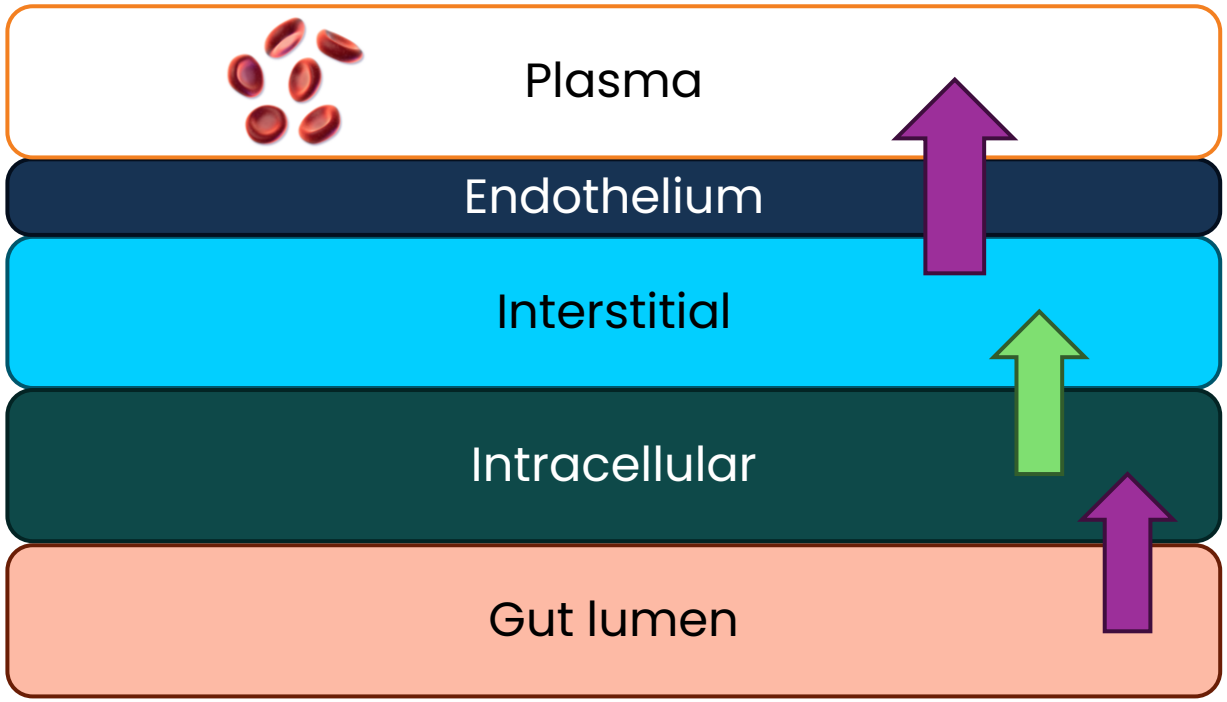
Fixed transcellular permeability

The model, as initially configured, failed to predict the peptide plasma concentration, as peptide was accumulating in the enterocytes





PKSim gut absorption model



P intracellular -> P interstitial

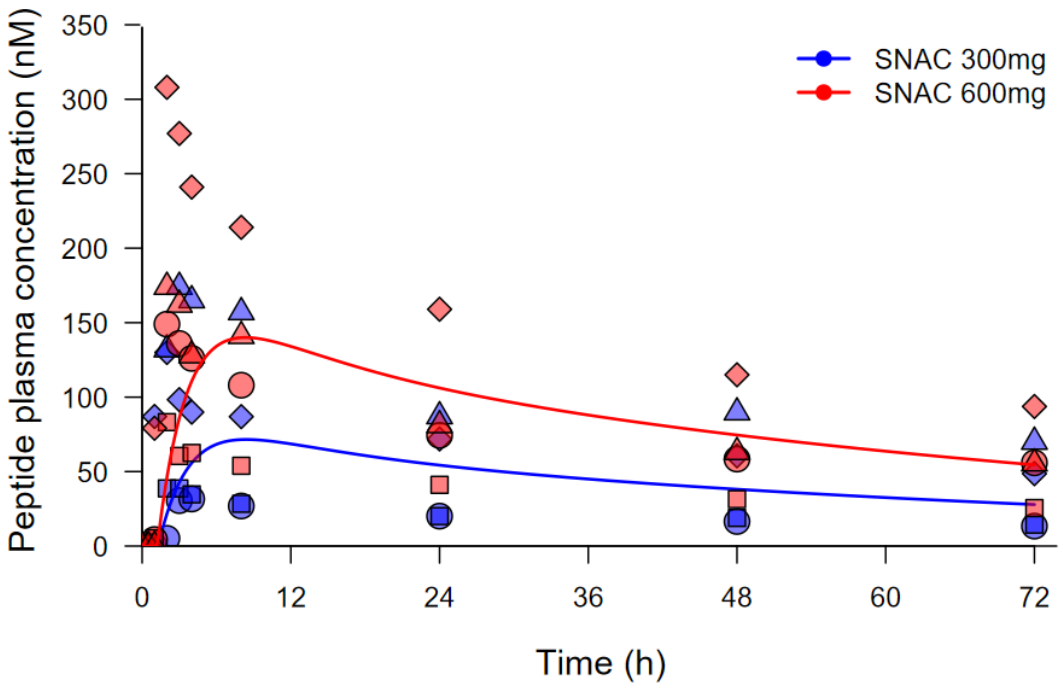
Intestinal transcellular permeability

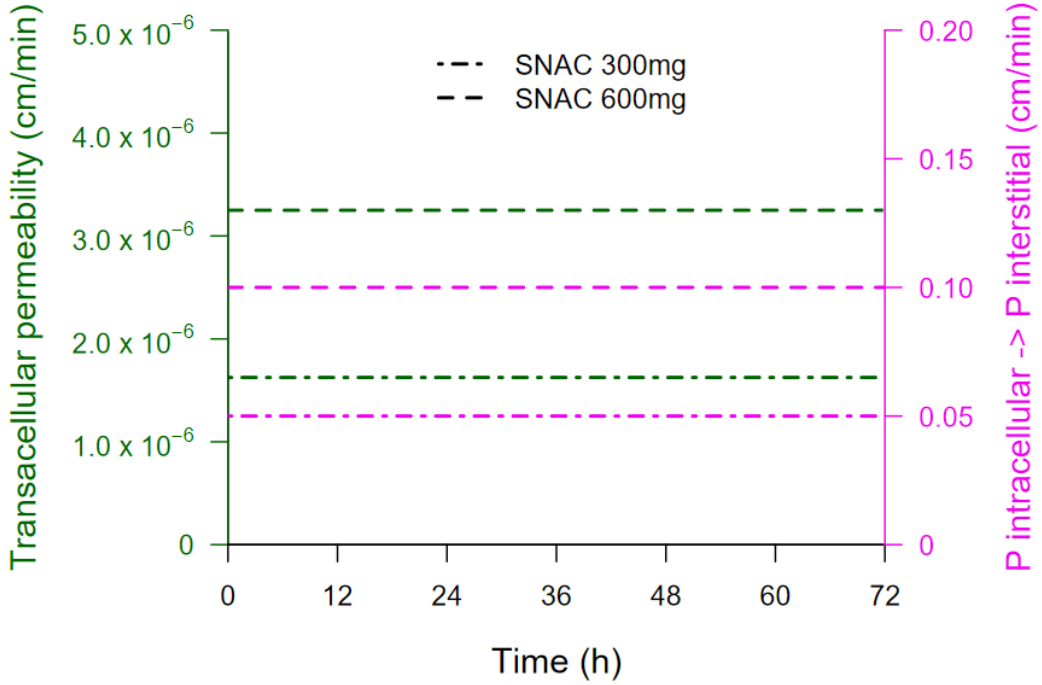
Adapted from Open Systems Pharmacology manual v10, p 89

Fixed transcellular permeabilities

Cmax and AUC0-t predicted within ± 20% deviation of the geometric mean value

Tmax was overpredicted

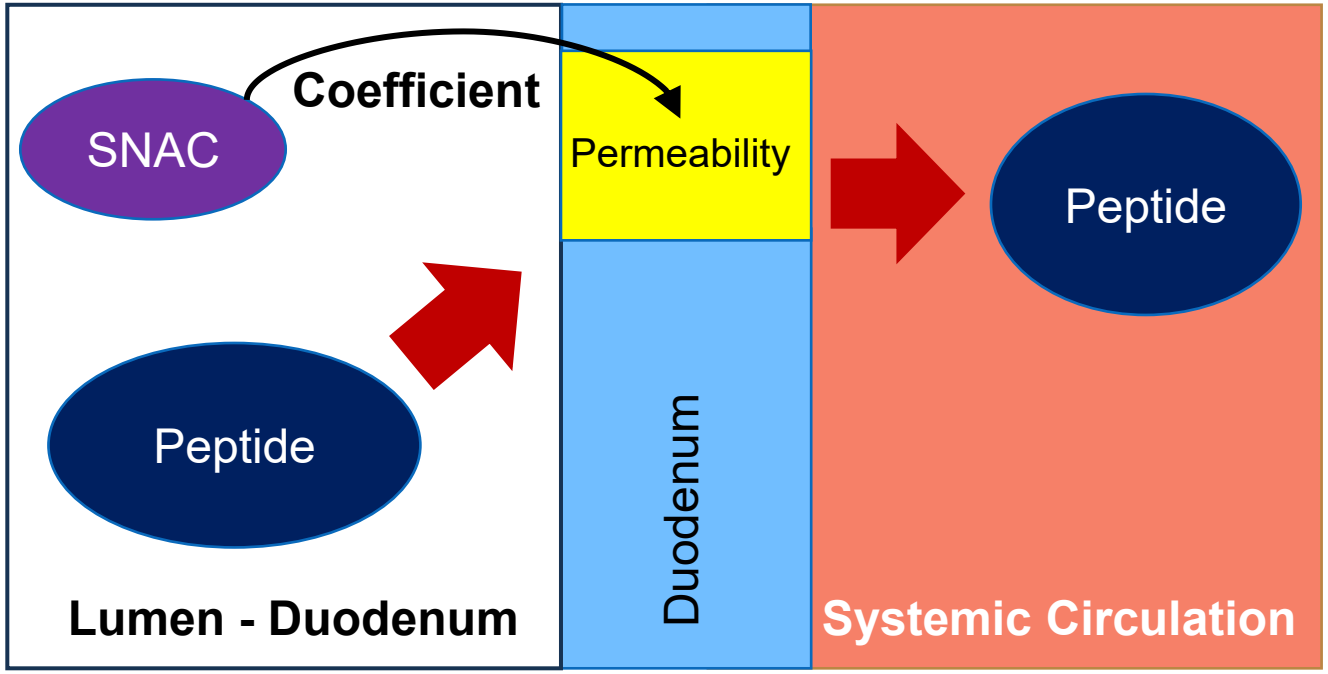




Tmax	
Observed	Predicted
~ 2 h	**8.5 h**

SNAC dependent peptide permeability models

- **It is reported that SNAC enhances permeability during a time window of ~20 mins**
- **To simulate the time activity window, a linear relationship was established between the predicted SNAC concentration in duodenum to predicted permeability changes**
  - Duodenum transit time is ~ 20 mins



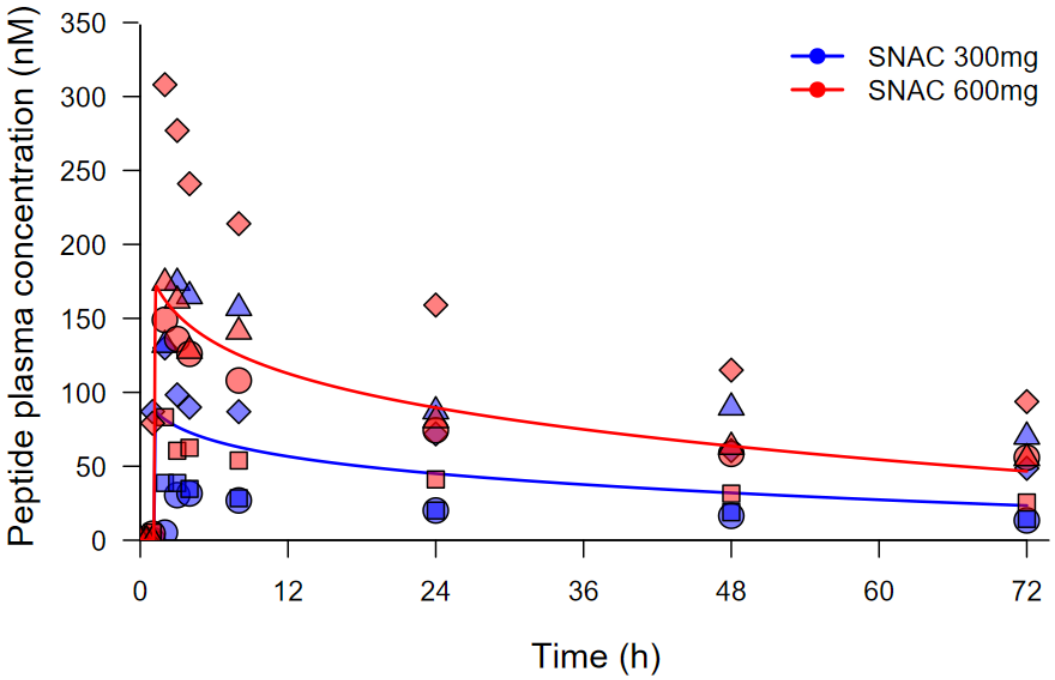
$$Permeability = SNAC\ conc\ duodenum\ lumen\ (\mu M) * coefficient\left(\frac{cm}{min * \mu M}\right)$$

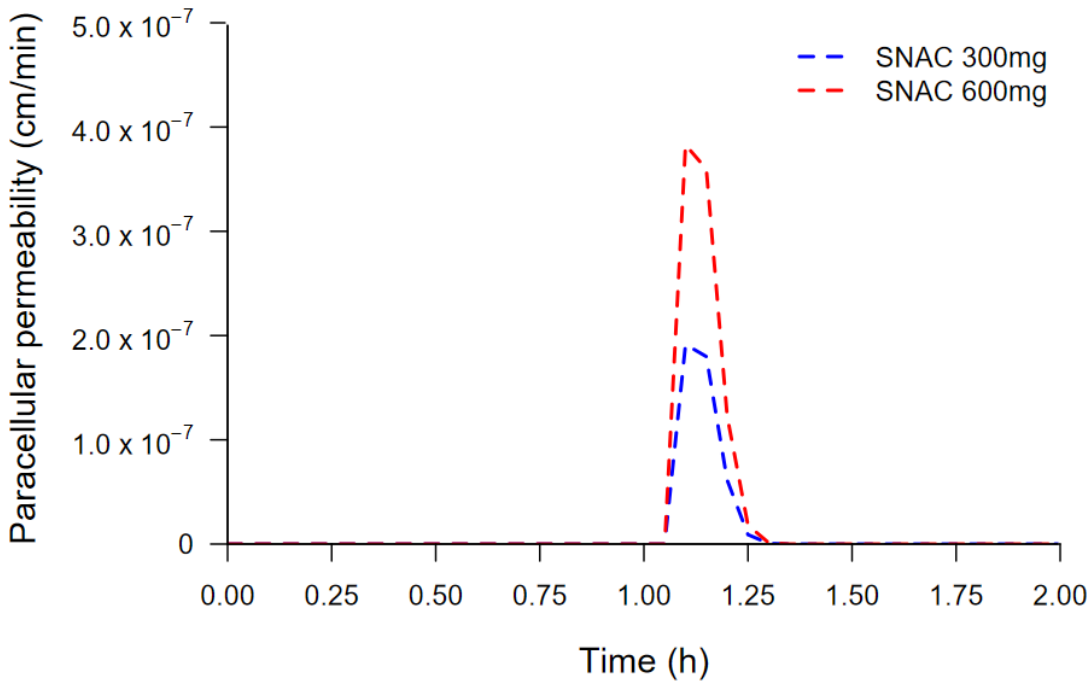
Twarog C, et al. Pharmaceutics (2019) 11, 78

SNAC dependent paracellular permeability

Cmax and AUC0-t predicted within ± 20% deviation of the geometric mean value

Tmax prediction improved



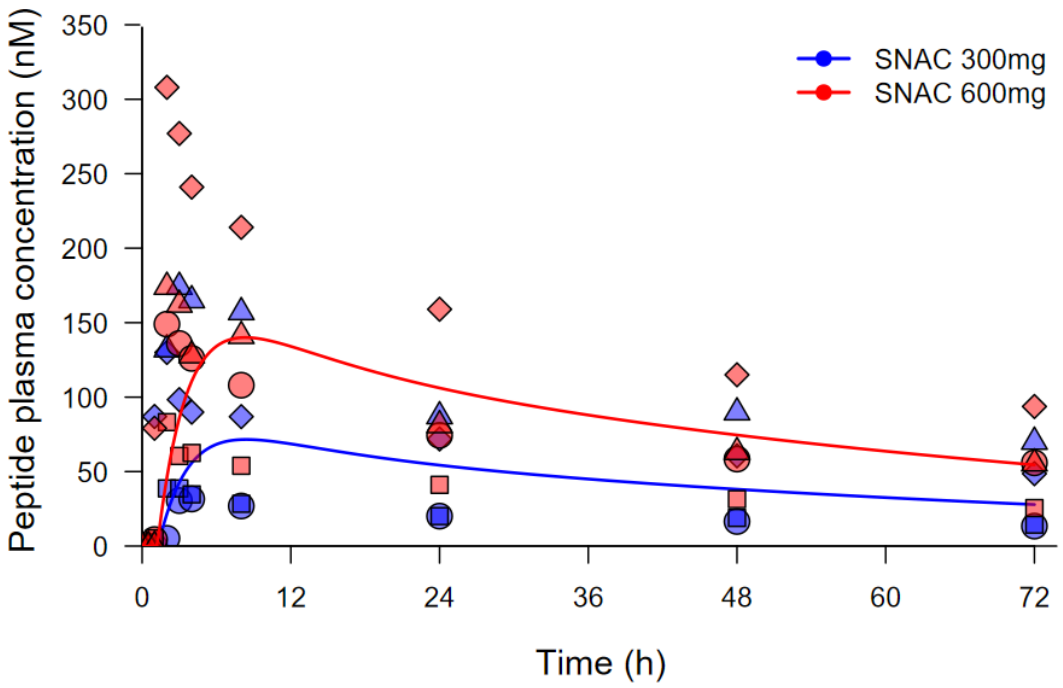


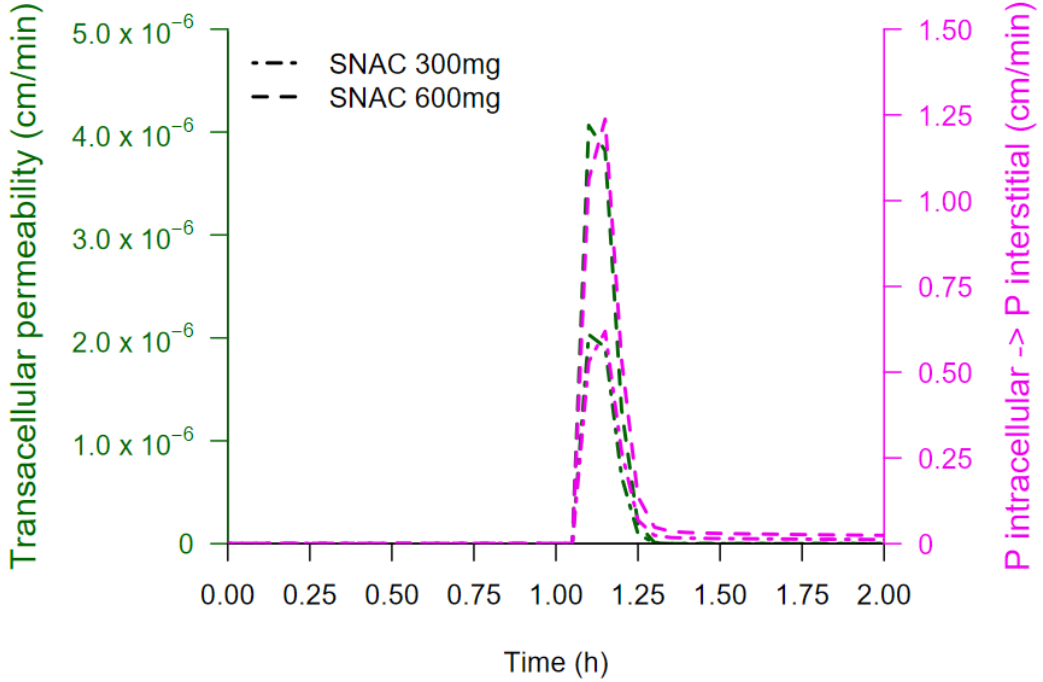
Tmax	
Observed	Predicted
~ 2 h	**1.3 h**

SNAC dependent transcellular permeability

Cmax and AUC0-t predicted within ± 20% deviation of the geometric mean value

Tmax was overpredicted





Tmax	
Observed	Predicted
~ 2 h	**8.3 h**

Complexation: Peptide + SNAC

SNAC may form a complex with the peptide either by hydrophobic ion pairing or by forming micelles

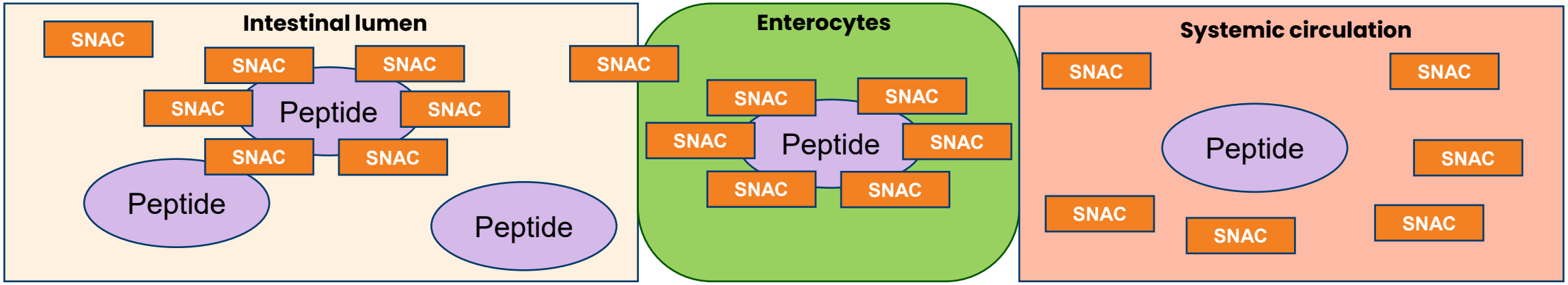
- Model assumptions:
  1. 1 peptide + 30 SNAC = 1 complex
  2. The complex is highly permeable (transcellular)
  3. Association and dissociation are separated processes

$$1\ Peptide + 30\ SNAC \rightarrow 1\ Complex$$

$$kon * [Peptide] * [SNAC]$$

$$1\ Complex \rightarrow 1\ Peptide + 30\ SNAC$$

$$koff * [Complex]$$

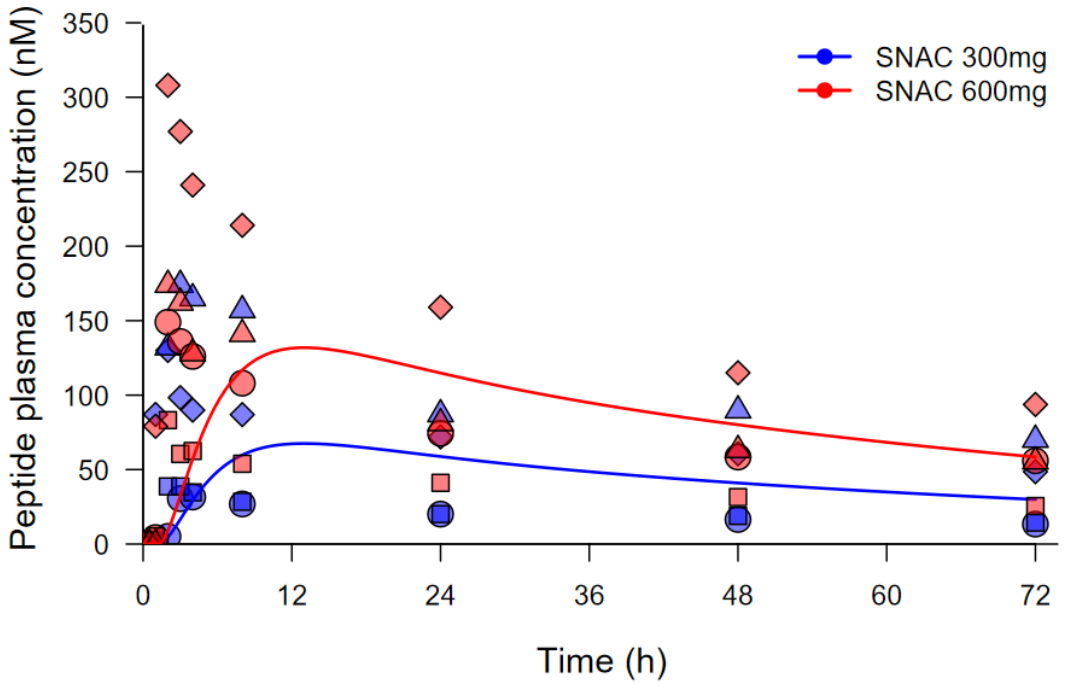


Twarog C, et al. Pharmaceutics (2019) 11, 78

Complexation: Peptide + SNAC

Cmax and AUC0-t predicted within ± 20% deviation of the geometric mean value

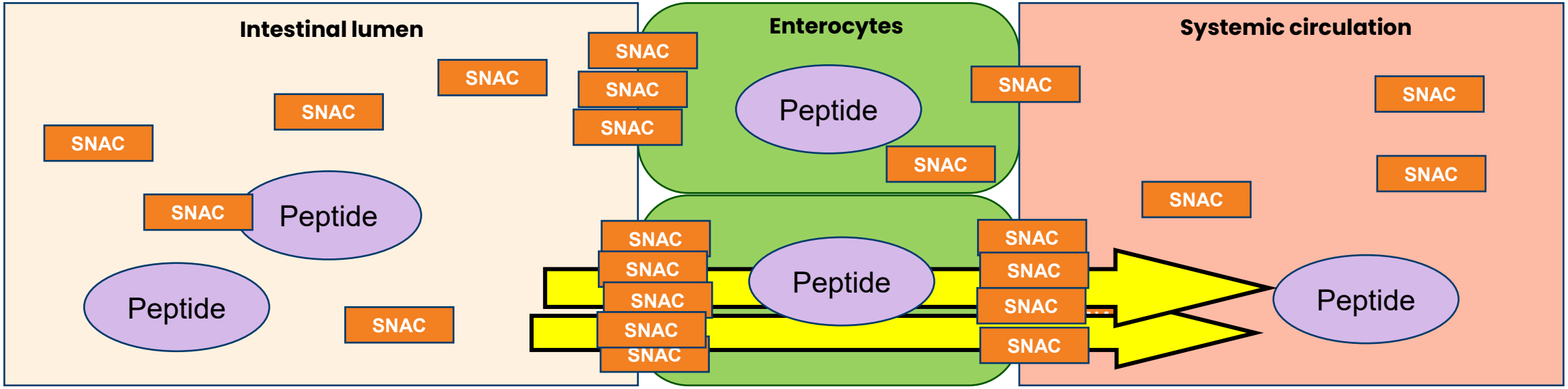
Tmax was overpredicted into a larger extent



Tmax	
Observed	Predicted
~ 2 h	**13 h**

SNAC - Proposed mechanisms of action: Transcellular (paracellular-like) route

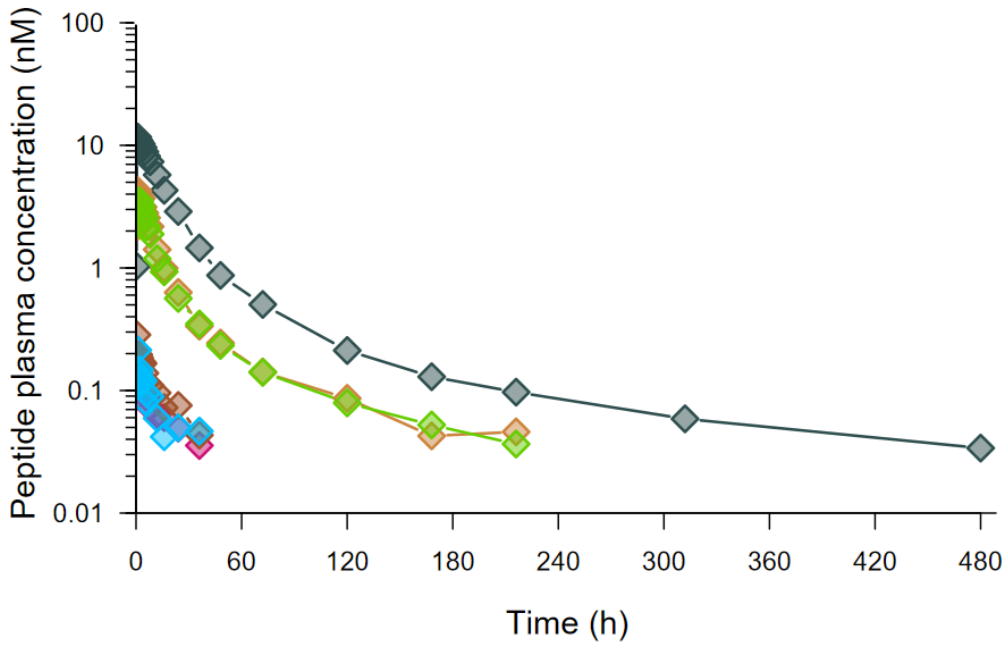
- SNAC might insert in both sides of the enterocyte's membranes leading to fluidisation and increased permeability
- These can be considered as channels where the peptide can cross through the cells
- In the model, this channel could be simulated as paracellular permeability



Oral administration (human): Observed data

- **Tablet 600 mg SNAC was administered to human healthy subjects (n = 6)**
- **High variability was observed**

- **Plasma concentration profiles could be classified into three different exposure levels:**
  - Low
  - Medium
  - High

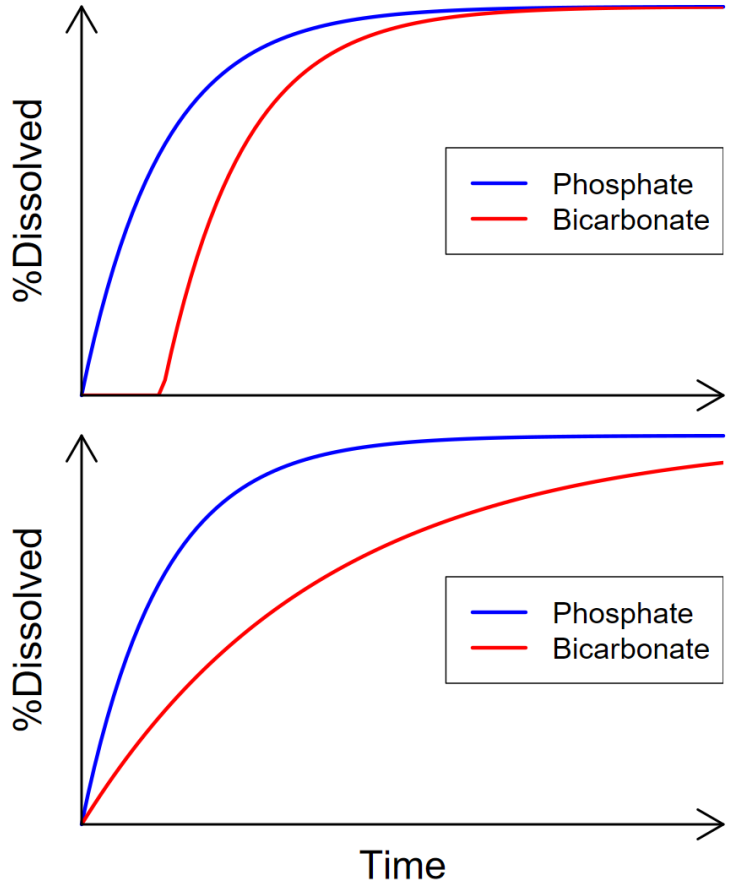


In vitro dissolution testing of EC formulations

- **It has been reported that in vitro dissolution testing using 50 mM phosphate buffer might lead to an overestimation of in vivo dissolution of enteric coated formulations**

- **One explanation could be the differences in buffer capacity of the medium used**
  - Buffer capacity of phosphate buffer ~ 29 mM/ΔpH
  - Buffer capacity of bicarbonate buffer ~ 2.5 – 13 mM/ΔpH

- **The differences may result in**
  - A lag time for dissolution
  - Slower dissolution

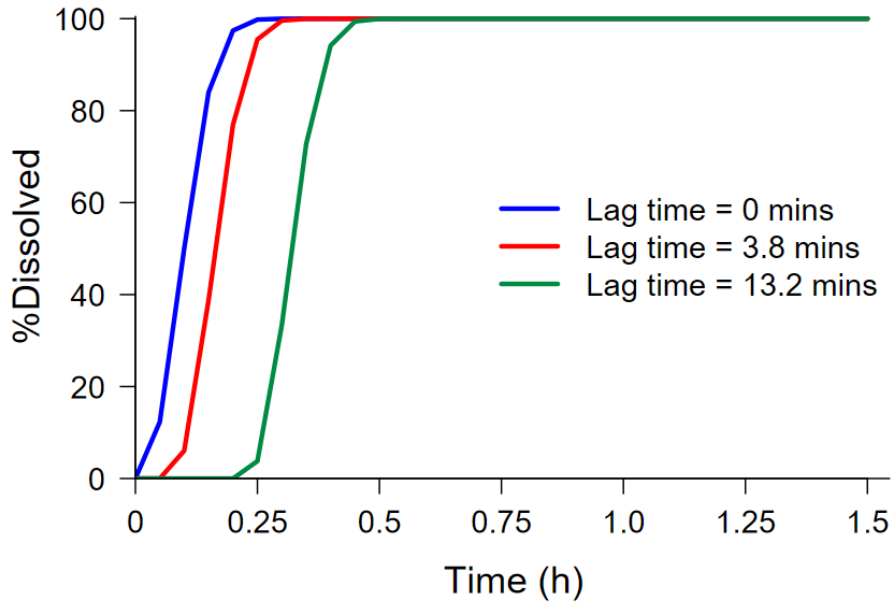


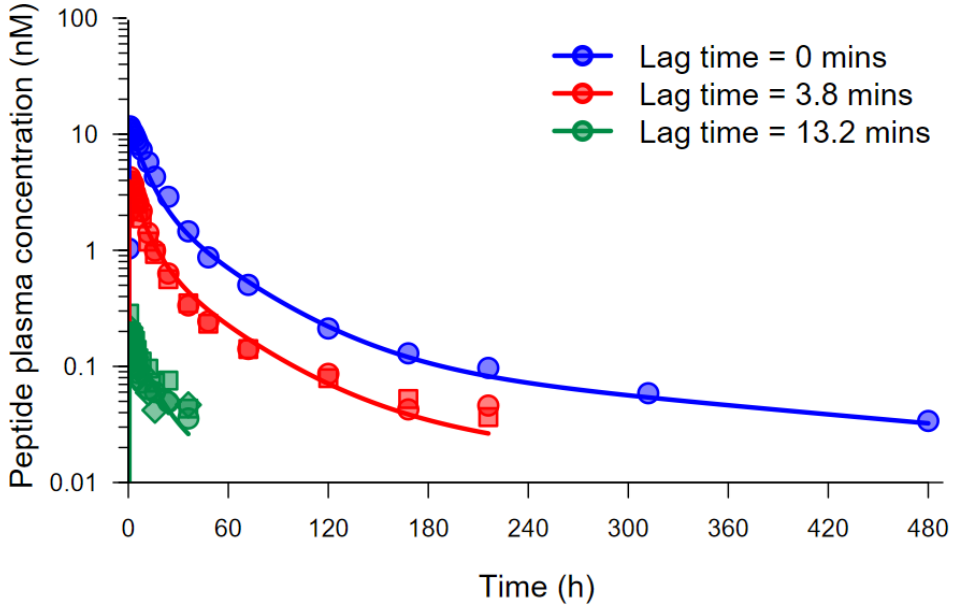
Amaral Silva D, et al. J Control Release. 2020 Sep 10;325:323-334

Model application – lag time

Simulating dissolution with an initial lag time, in vivo Cp-t profiles can be predicted

A longer lag time results in a lower exposure

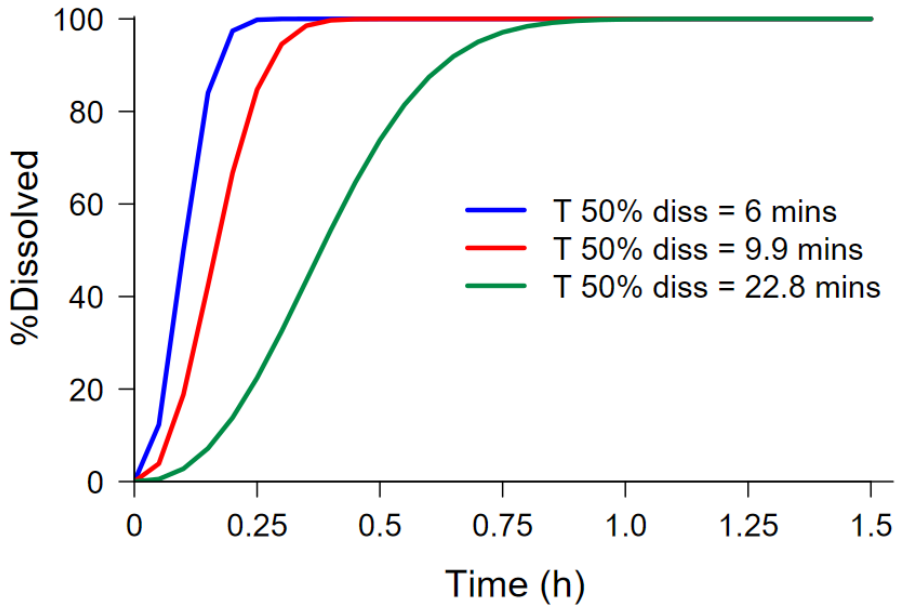


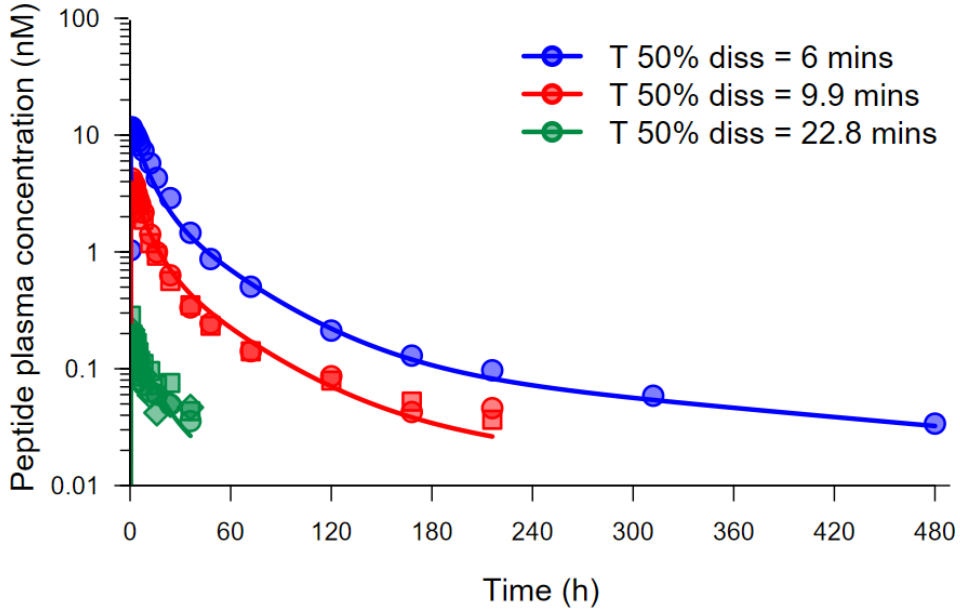


Model application – slower dissolution

Simulating dissolution with different dissolution rates, in vivo Cp-t profiles can be predicted

A slower dissolution results in a lower exposure





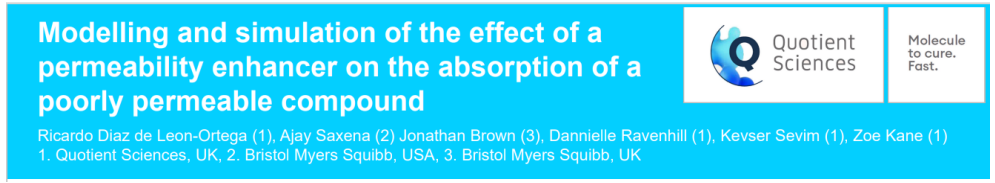
Case 1
Conclusions

- **The best way to simulate the effect of SNAC on the permeability of this particular peptide, dosed as an enteric coated formulation, was by modifying the paracellular permeability dynamically**
  - This could be reflecting a modified transcellular permeability process

- **Variability in the peptide Cp-t profiles could be explained by differences in in vivo dissolution**
  - For enteric coated formulations, dissolution in biorelevant media would be preferred

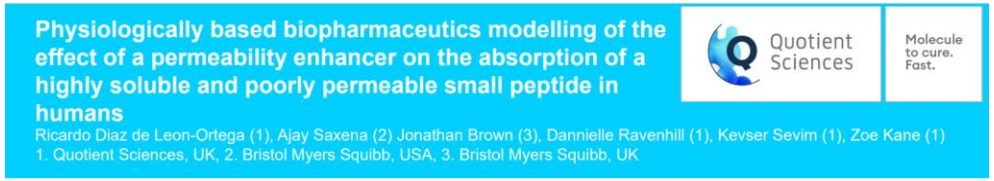
- **Permeation enhancers are functional excipients**
  - Measuring their concentration in dissolution profiles and plasma will lead to a better model development

PAGE meeting 2024



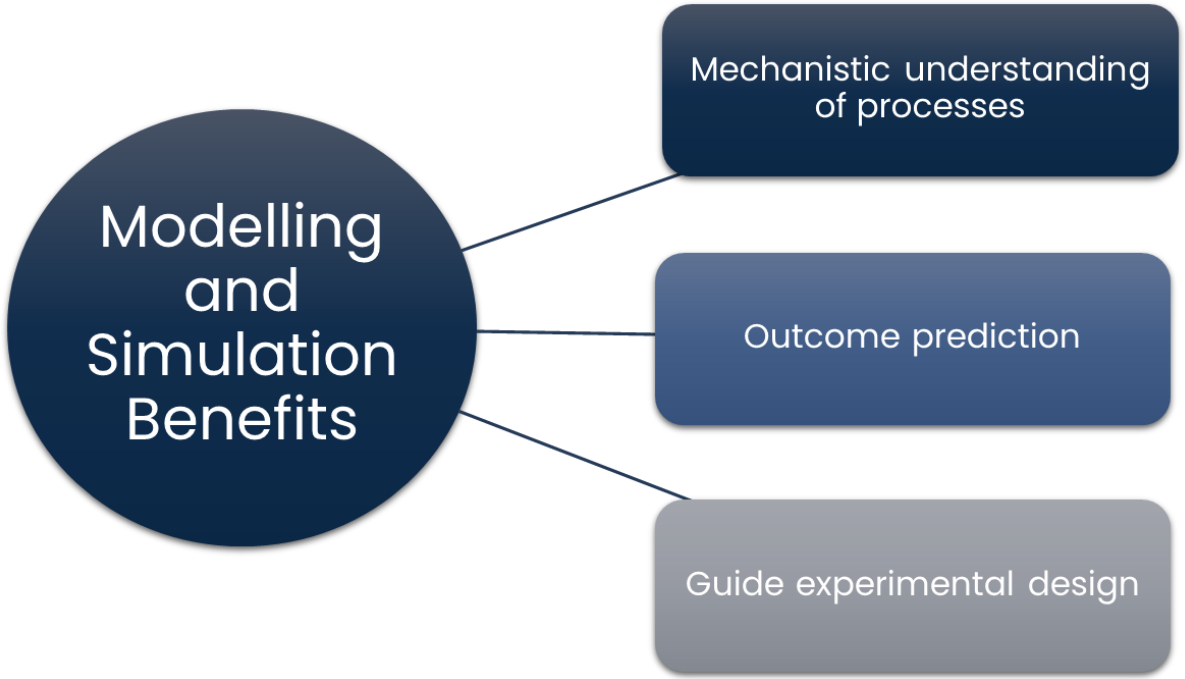
Diaz de Leon Ortega, R., Saxena, A., Brown, J., Ravenhill, D., Sevim, K., & Kane, Z. (2024). *Modelling and simulation of the effect of a permeability enhancer on the absorption of a poorly permeable compound*. [Poster presentation]. PAGE meeting 32 2024, Rome, Italy
Abstract 10793 [www.page-meeting.org/?abstract=10793]

ISSX conference 2024



Diaz de Leon Ortega, R., Saxena, A., Brown, J., Ravenhill, D., Sevim, K., & Kane, Z. (2024). *Physiologically based biopharmaceutics modelling of the effect of a permeability enhancer on the absorption of a highly soluble and poorly permeable small peptide in humans* [Poster presentation]. ISSX-JSSX Meeting 2024, Hawaii, USA

Case 2:
Use of modelling and simulation to evaluate potential drug – drug interactions of Rybelsus® as perpetrator



Rybelsus® (semaglutide)

- **Rybelsus® is an oral medication used to manage type 2 diabetes by improving blood sugar levels**

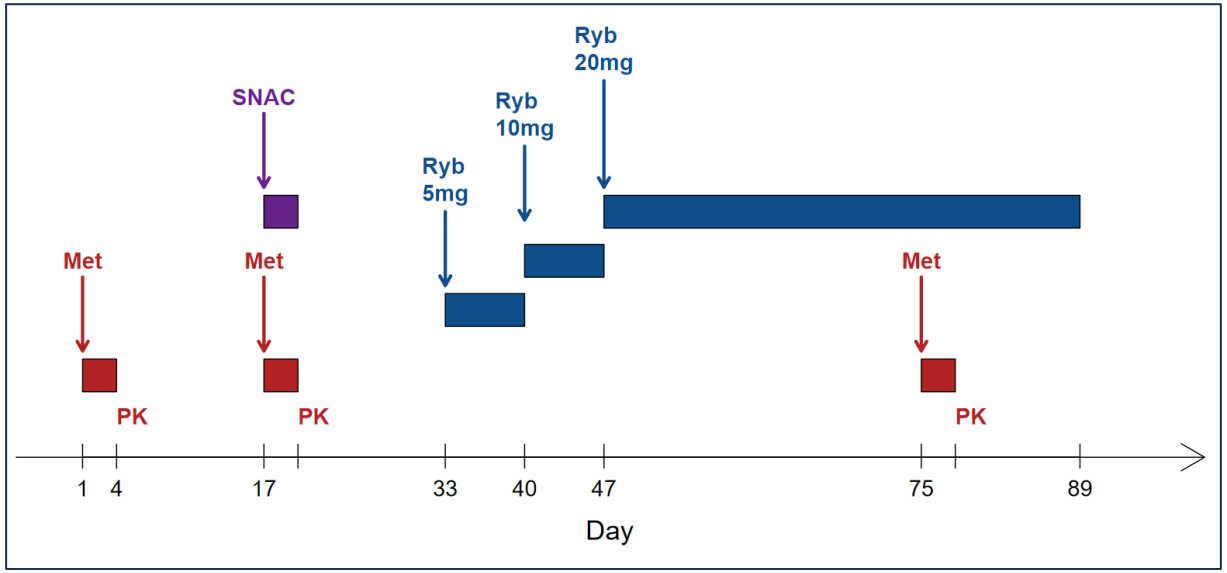
- **Semaglutide is a GLP-1 receptor agonist peptide, and one of its effects is to slow gastric transit**
  - In vitro studies showed that semaglutide have a very low potential to inhibit or induce CYP enzymes, and to inhibit drug transporters

- **SNAC is used to improve the absorption of poorly permeable compounds**
  - There are CYP and transporter interactions reported for SNAC, but they are considered of low risk

Rybelsus® - DDI studies

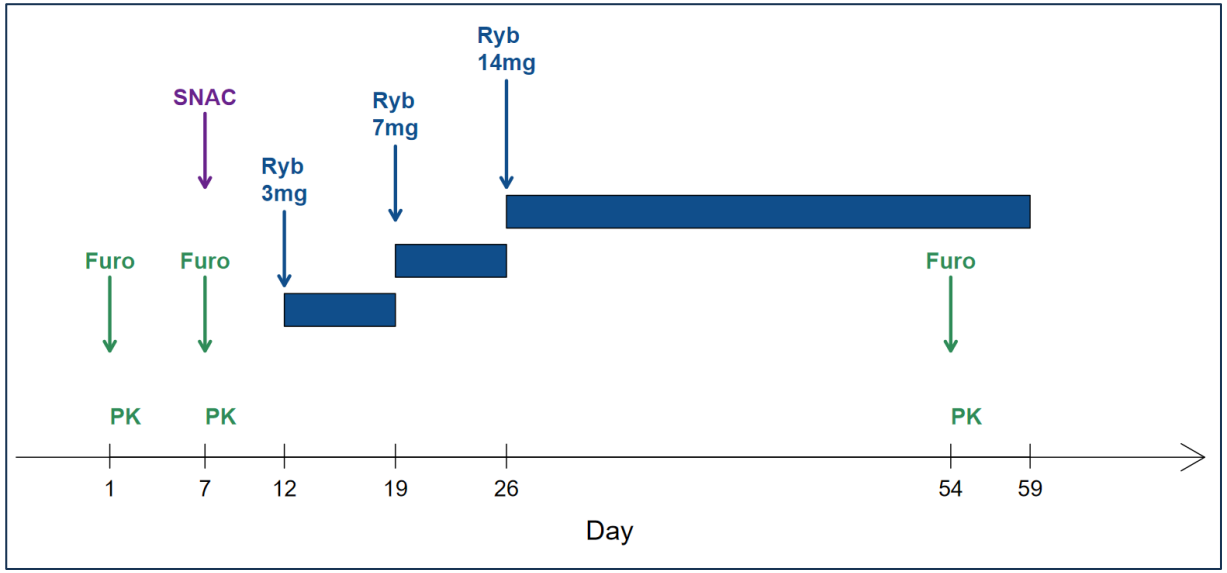
Metformin

- Selected as a low permeability compound



Furosemide

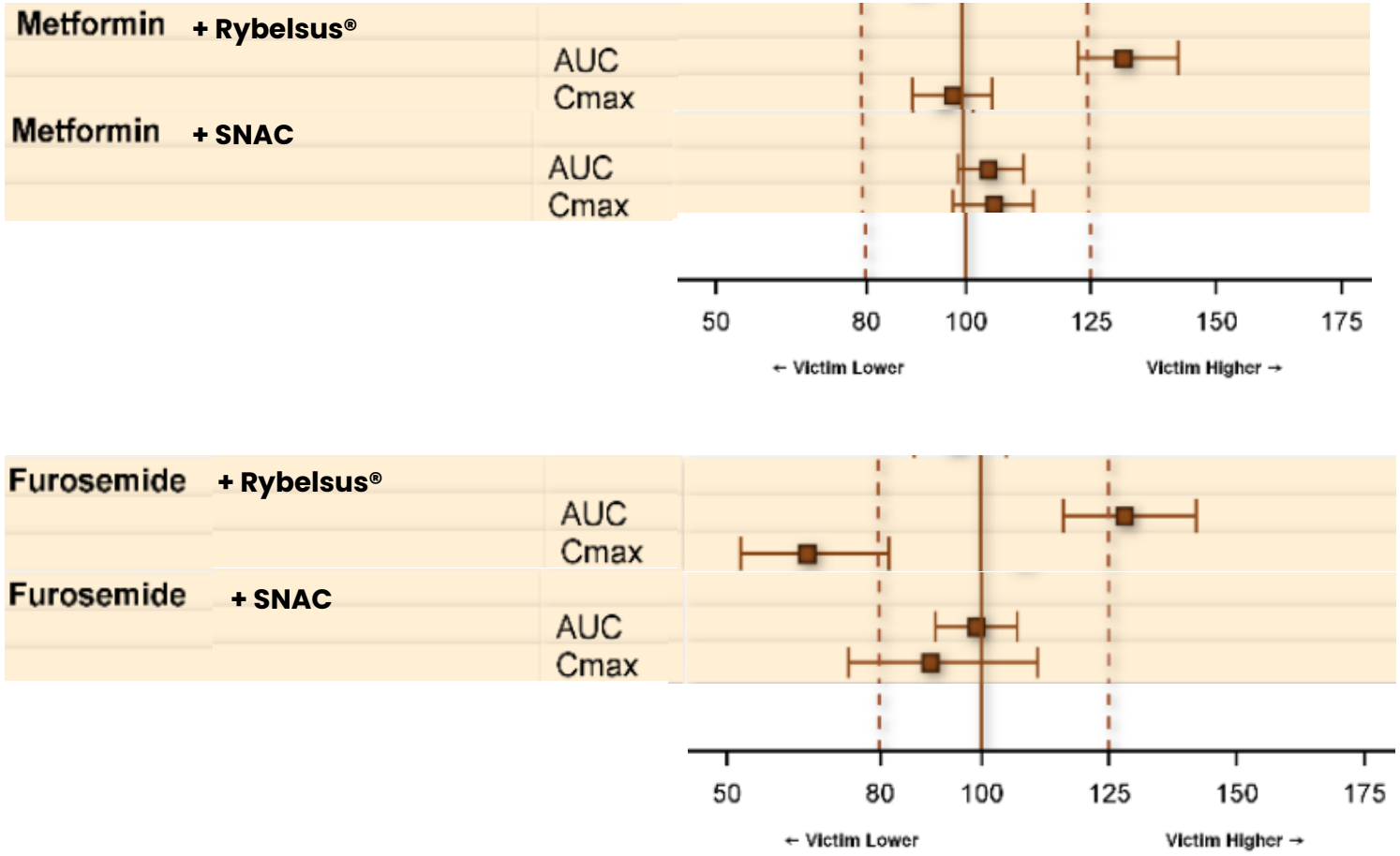
- Selected for being an OAT1 and OAT3 substrate, which SNAC may inhibit



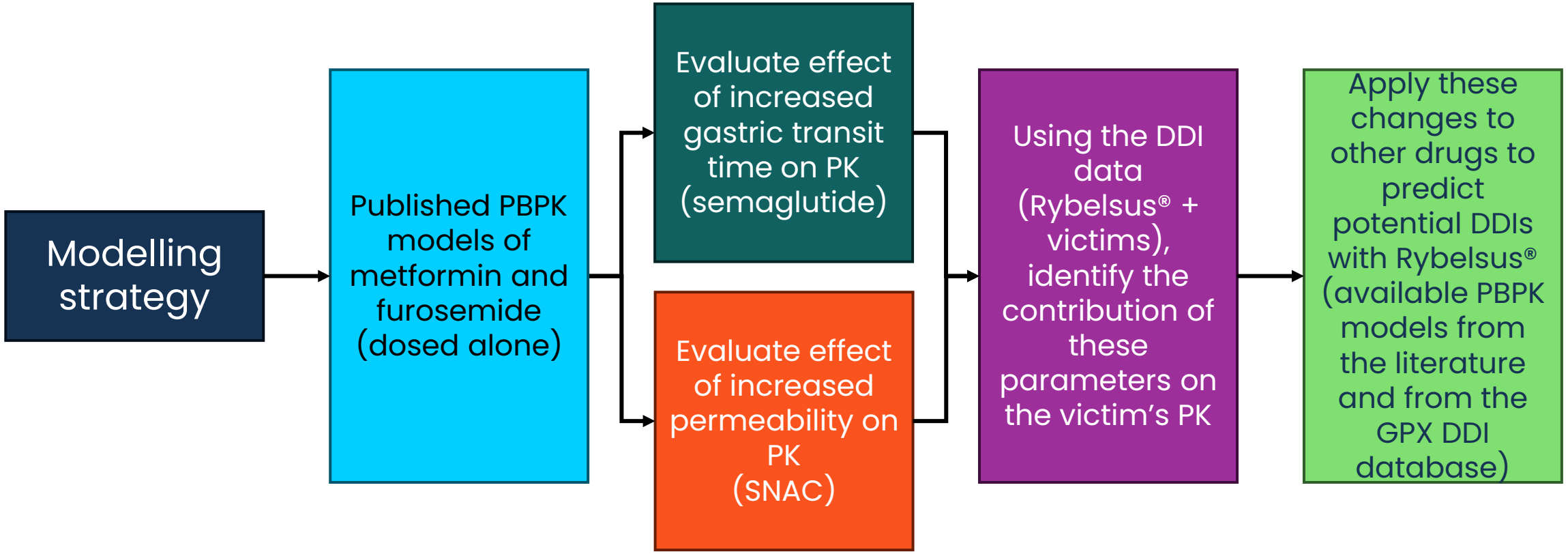
Bækdal TA, et al. Clin Pharmacokinet. 2019 Sep;58(9):1193-1203
Jordy AB, et al. Clin Pharmacokinet. 2021 Sep;60(9):1171-1185

Rybelsus® – DDI studies

Rybelsus® repeated dosing
SNAC single dose



Adapted from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/213051Orig1s000ClinPharmR.pdf

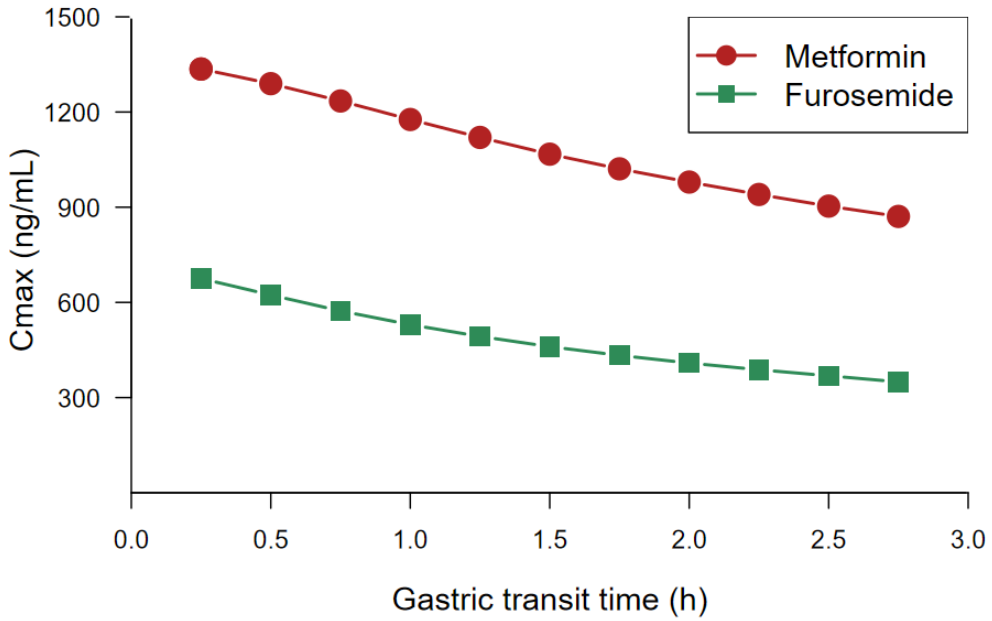


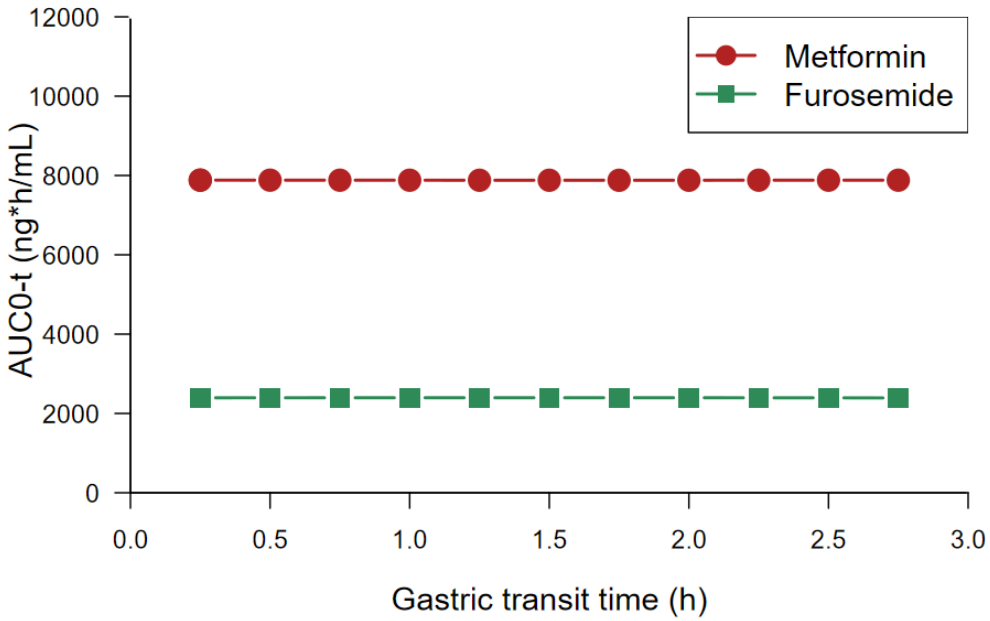
Dahan A, et al. Pharmaceutics. 2021 Nov 5;13(11):1873
Markovic M, et al. Pharmaceutics. 2020 Dec 2;12(12):1175

PBPK: Effect of gastric transit time (GTT)

With a Parameter sensitivity analysis on GTT, it was predicted that with an increase in GTT, Cmax decreased, while AUC is not affected

Another factor is increasing the exposure

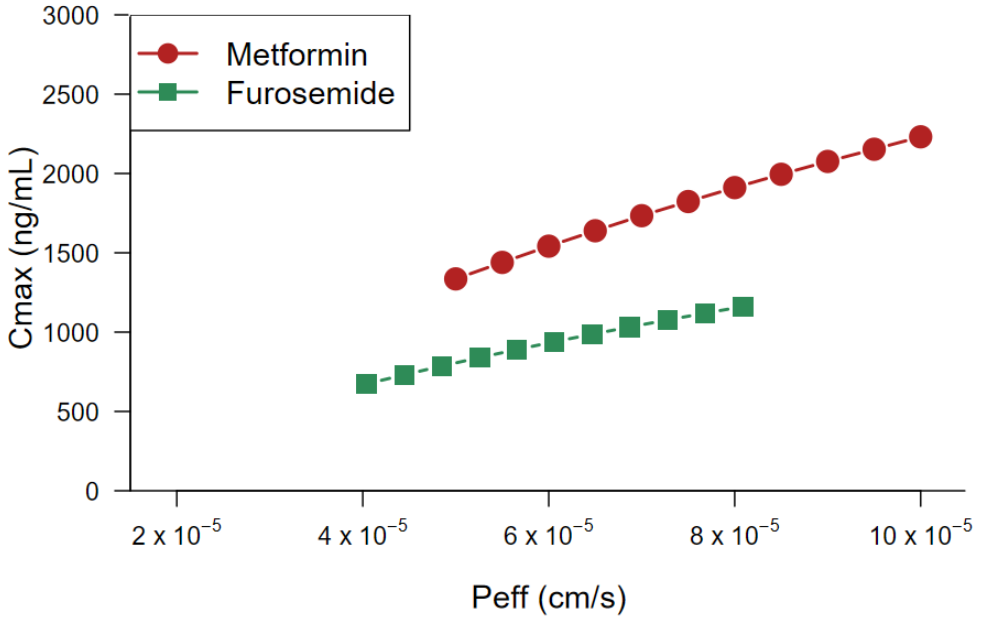


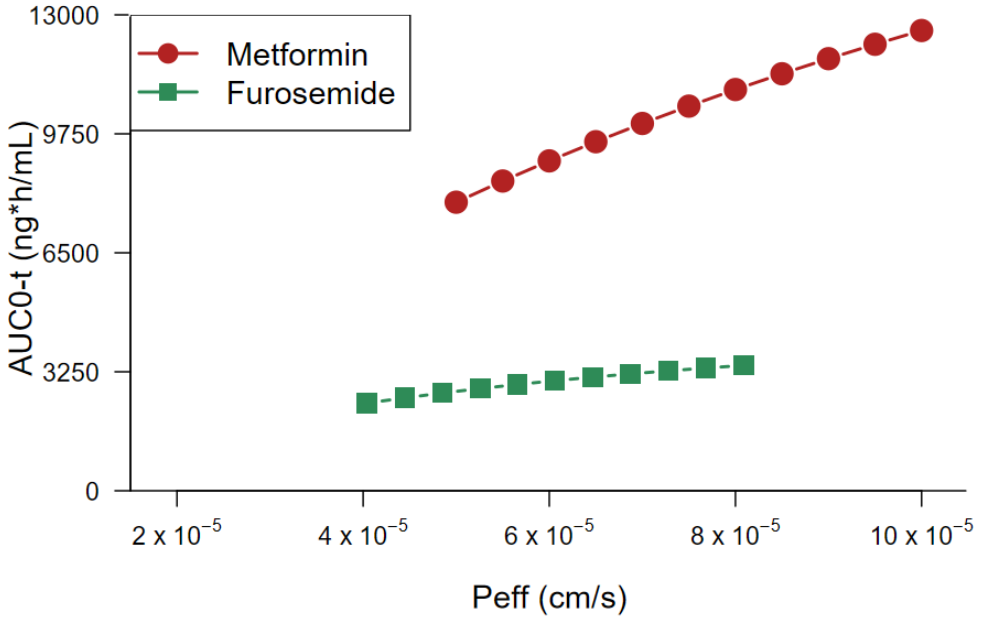


PBPK: Effect of permeability (Peff)

With a Parameter sensitivity analysis on Peff, it was predicted that with an increase in permeability Cmax and AUC increased

Chronic SNAC dosing (as Rybelsus®) could increase the permeability of co-administered drugs

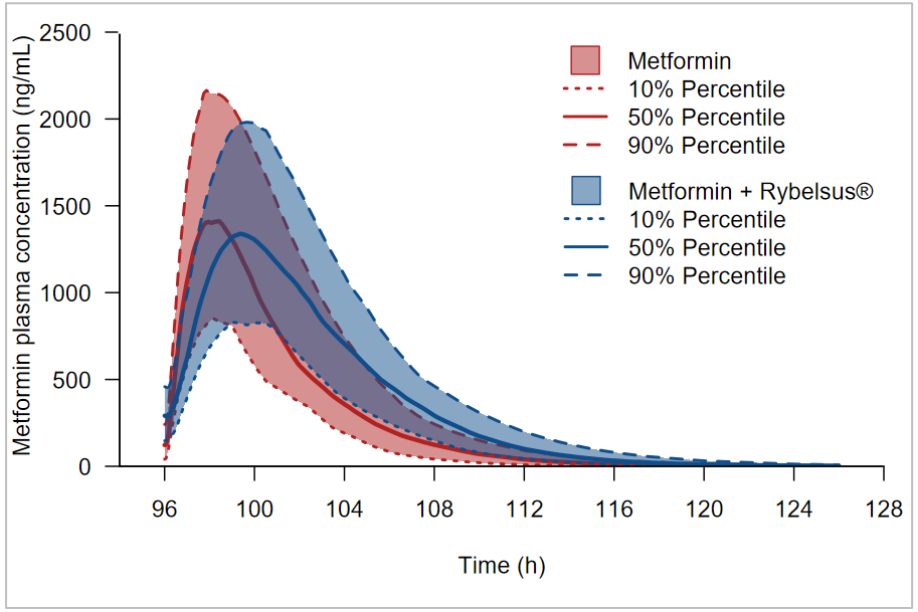




PBPK modelling: Model adjustments

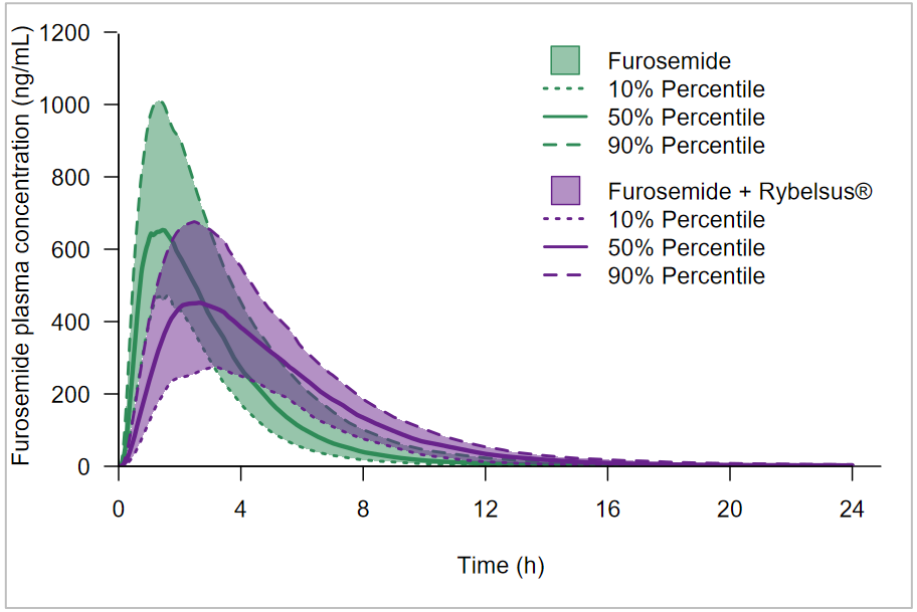
A GTT of 2 h and a Peff of 1.4x of the original value, predicted the ratios of the DDI study for Metformin and Furosemide

Metformin



DDI ratio	Observed	Predicted
Cmax	0.98 (0.90 – 1.06)	0.95 (0.84 – 1.07)
AUC	1.32 (1.23 – 1.43)	1.22 (1.08 – 1.38)

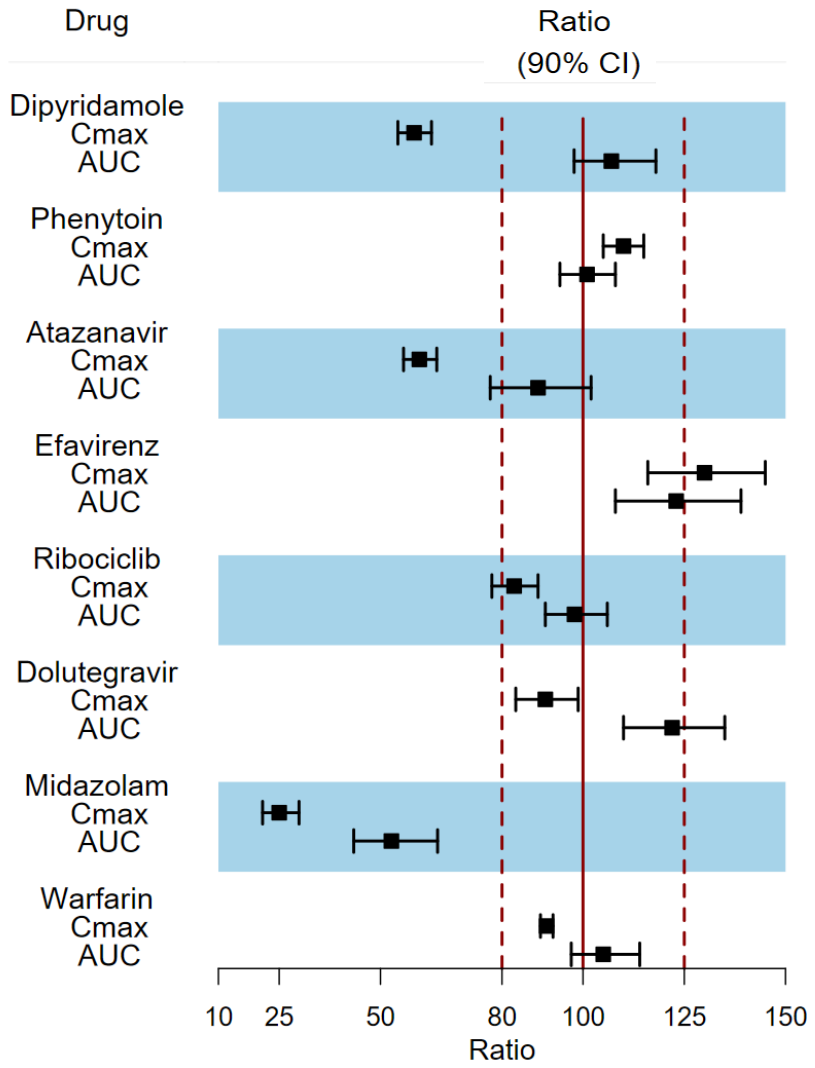
Furosemide



DDI ratio	Observed	Predicted
Cmax	0.66 (0.53 – 0.82)	0.74 (0.68 – 0.81)
AUC	1.28 (1.16 – 1.42)	1.24 (1.13 – 1.35)

Predicted DDIs with Rybelsus® as perpetrator

- **Positive and negative effects**
  - Atazanavir – Efavirenz
- **Different magnitude of effect**
  - Dipyridamole - Midazolam
- **No effect predicted**
  - Phenytoin - Warfarin



Cmax in ng/mL
AUC in ng*h/mL

PBPK modelling application

Victim drug's characteristics

Potential interactions with Rybelsus® depend on the victim's solubility, permeability, ionisation state, and whether there is any saturable metabolism and/or transport in the gut. In PBPK modelling, all these factors are considered dynamically.

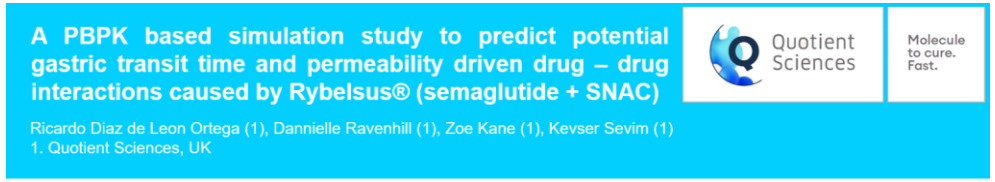
Drug	BCS Class	Acid/Base	Gut metabolism	Transporters	Drug alone			Drug + Rybelsus®		
					Predicted %Fa	Predicted %F	Predicted Max %Diss	Predicted %Fa	Predicted %F	Predicted Max %Diss
Metformin	III	base			33	33	100	43	43	100
Furosemide	IV	acid			52	49	100	63	59	100
Dipyridamole	II	base			100	92	100	100	92	100
Phenytoin	II	acid			98	96	100	99	98	100
Atazanavir	II	base	CYP3A4	P-gp	96	87	100	98	85	100
Efavirenz	II	acid	CYP3A4		74	57	74	84	69	84
Ribociclib	IV	base			88	88	100	94	94	100
Dolutegravir	II	acid	CYP3A4, UGT1A1		72	52	72	81	56	81
Midazolam	I	base	CYP3A4		100	24	100	100	14	100
Warfarin	I	acid			100	100	100	100	100	100

Case 2
Conclusions

- **PBPK modelling is a useful tool to risk assess DDIs caused by changes in GTT and permeability that may result from repeated dosing of Rybelsus®**

- **The same methodology can be applied to other developmental drugs with similar pharmacodynamic effects**
  - Highlighting drug combinations that may benefit from clinical investigation

PAGE meeting 2025



Diaz de Leon Ortega, R., Ravenhill, D., Kane, Z. & Sevim, K. (2025). *A PBPK based simulation study to predict potential gastric transit time and permeability driven drug – drug interactions caused by Rybelsus® (semaglutide + SNAC).* [Poster presentation]. PAGE meeting 33 2025, Thessaloniki, Greece
Abstr 11408 [www.page-meeting.org/?abstract=11408]

Acknowledgements

Bristol Myers Squibb

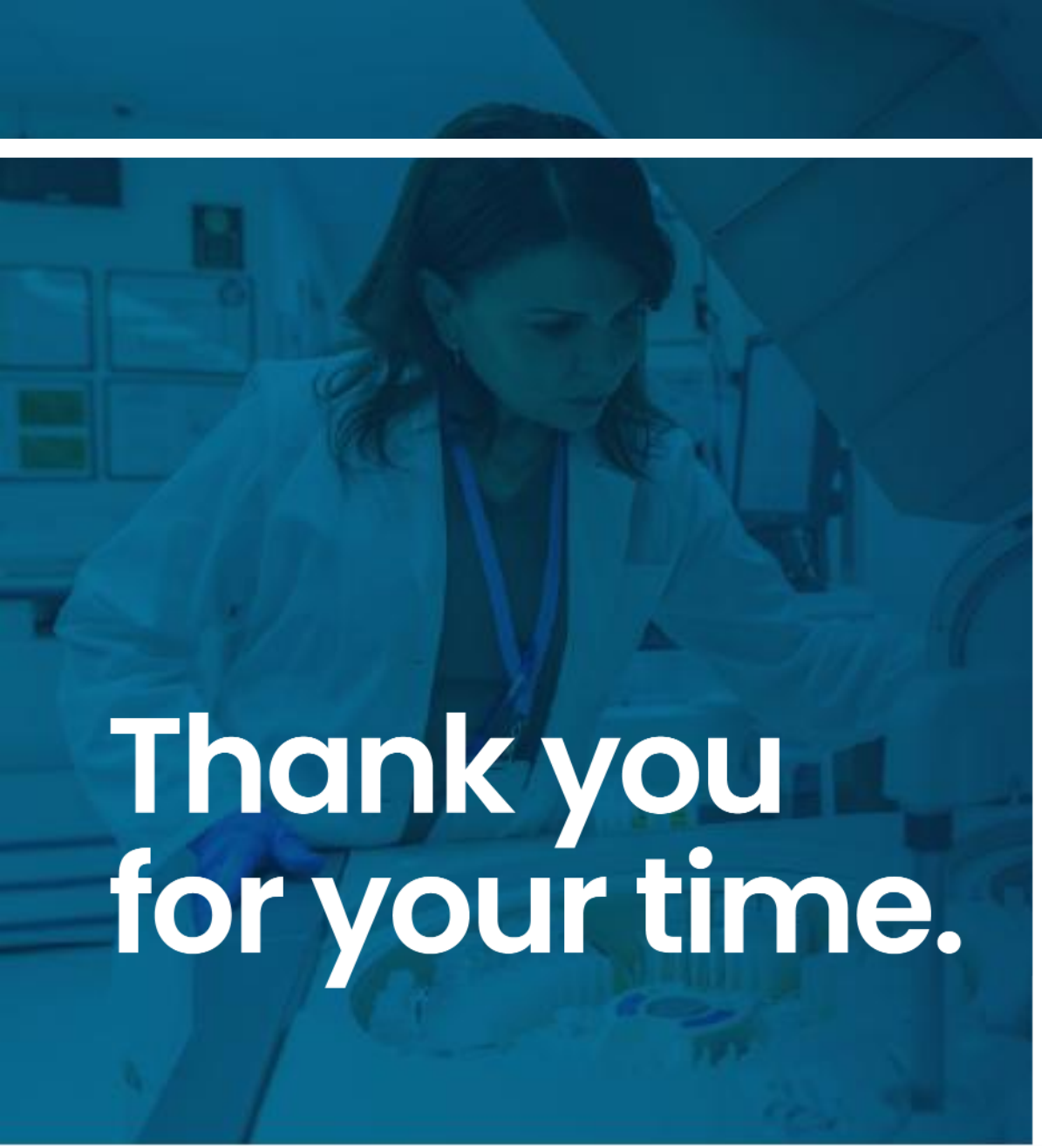
- Ajay Saxena
- Jonathan Brown
- Neil Mathias

Quotient Sciences

- Dannielle Ravenhill
- Zoe Kane
- Kevser Sevim
- John McDermott
- Andy Lewis
- Jane McGuffog

Special thanks

- Prof Nikoletta Fotaki



Thank you for your time.

Quotient Sciences

Molecule to cure. Fast.™

?

Questions?

Ricardo Diaz De Leon Ortega

ricardo.diazdeleon@quotientsciences.com