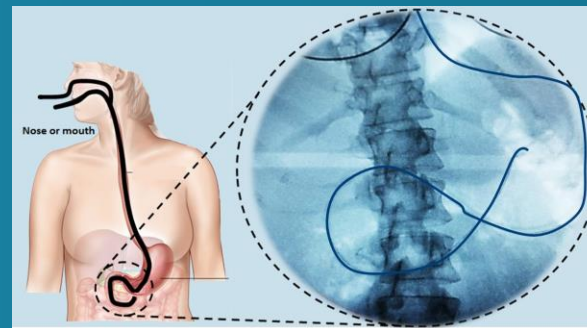


In Vivo Formulation Behavior and Drug Absorption

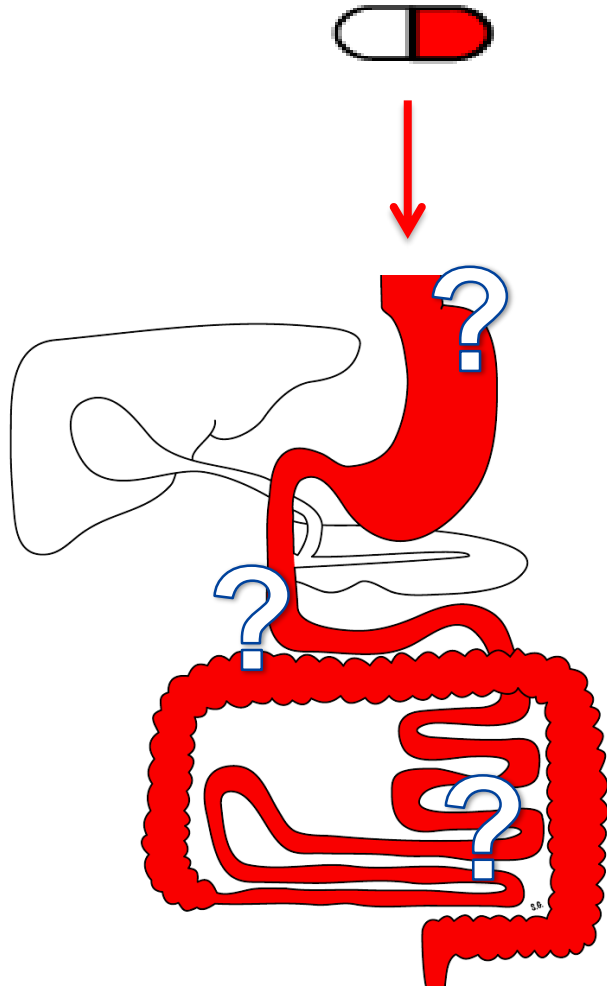
In vivo dissolution and drug absorption



Patrick Augustijns
Drug Delivery and Disposition
KU Leuven, Belgium

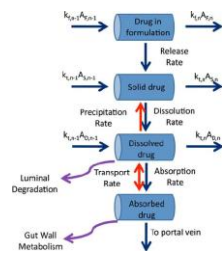
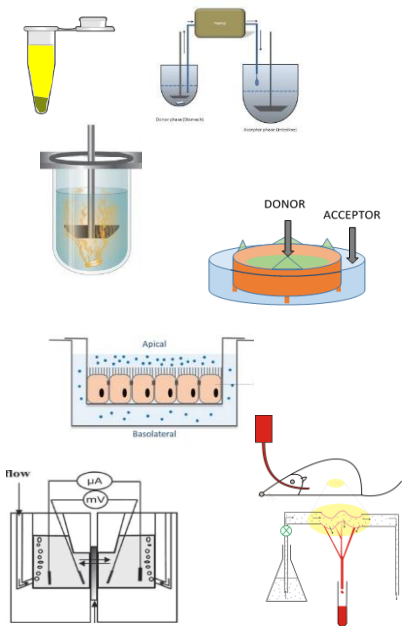
May 23 2023

Gut physiology



- Composition/volume of GI fluids
- Motility
- Digestion / Food effects
- Enzymes and transporters
- Microbiome
- Surgery

Drug behavior in the gastrointestinal tract

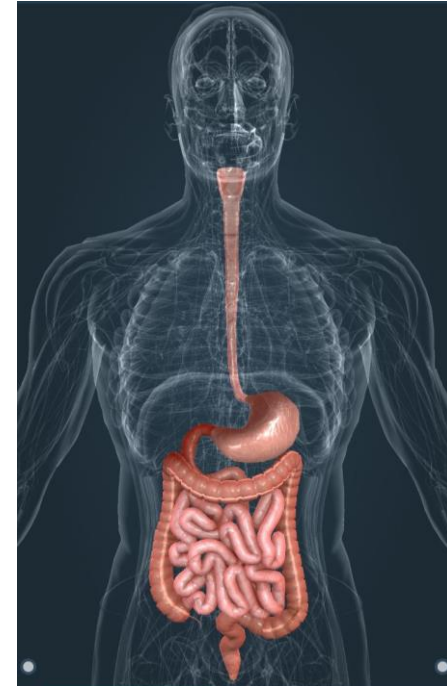


Simulate / Predict

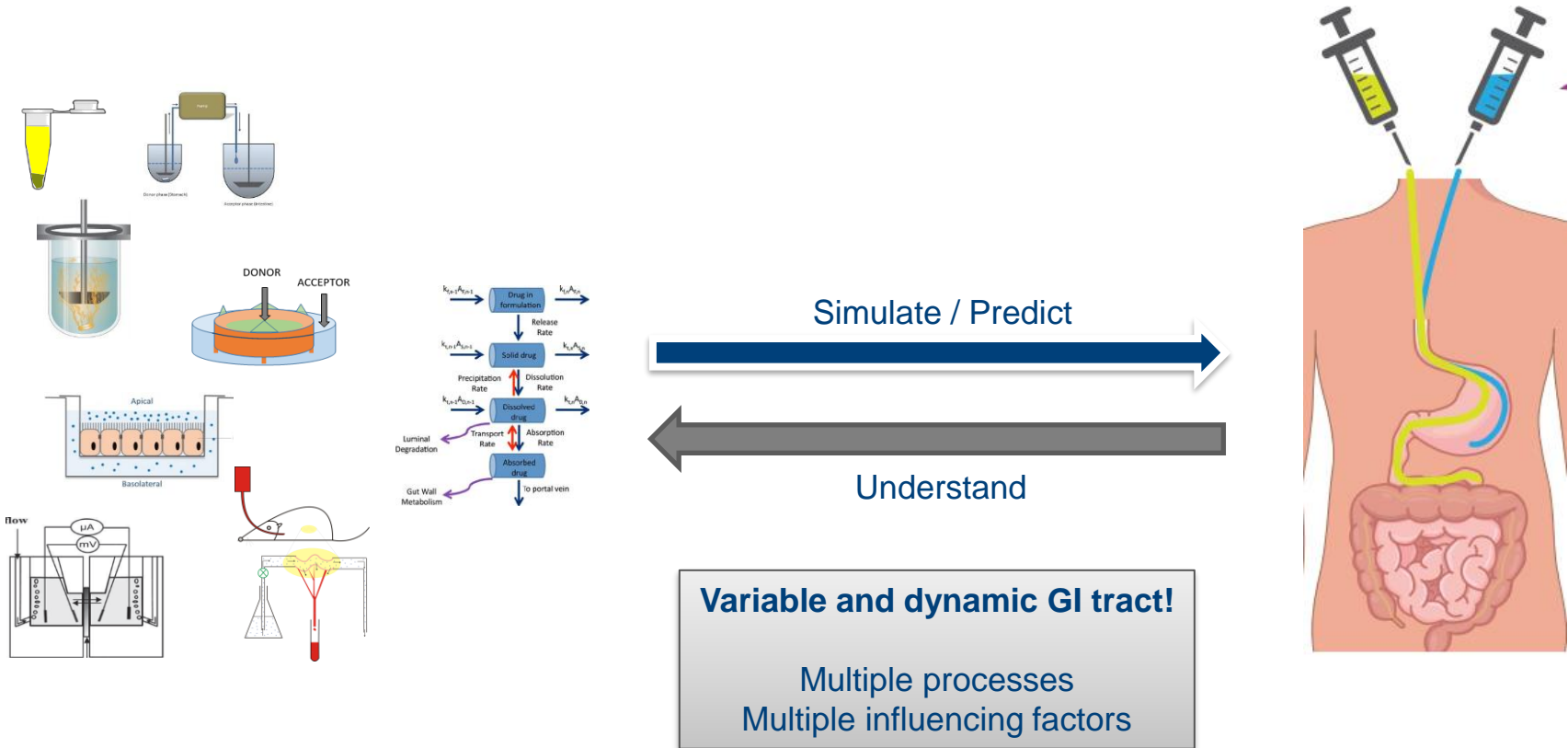
Understand

Variable and dynamic GI tract!

Multiple processes
Multiple influencing factors

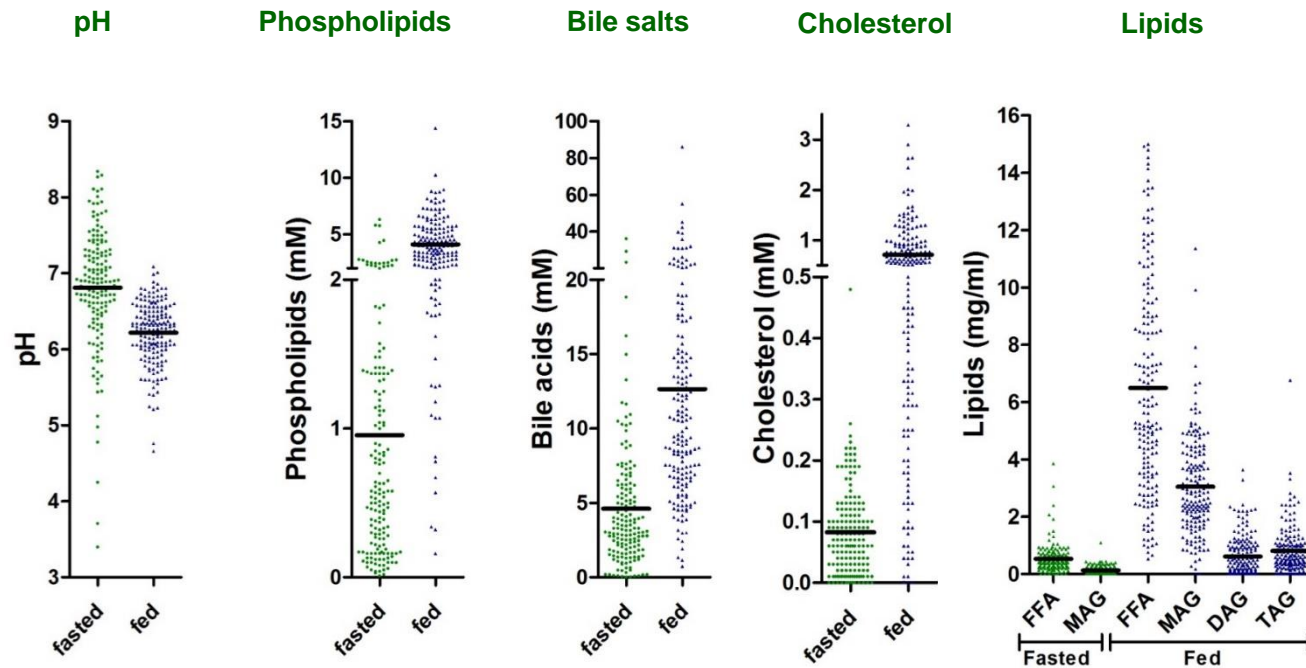


Drug behavior in the gastrointestinal tract

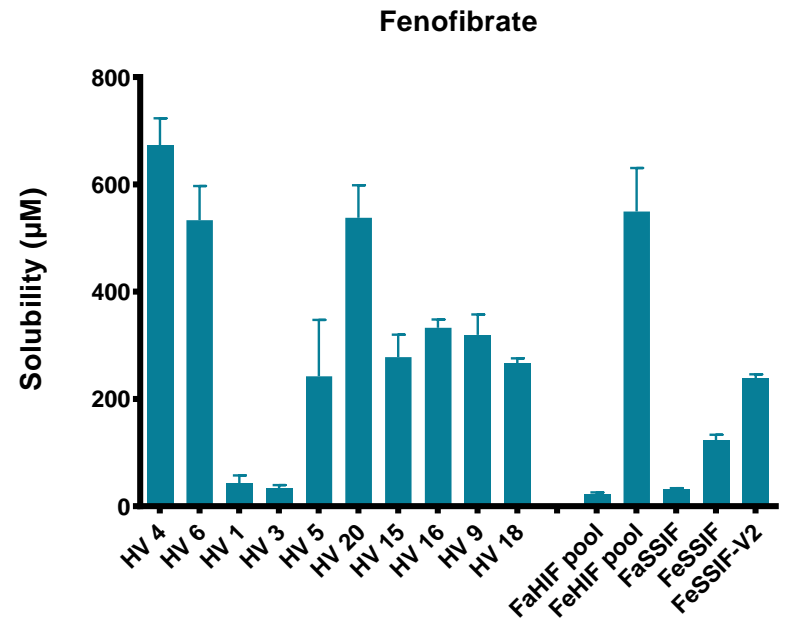
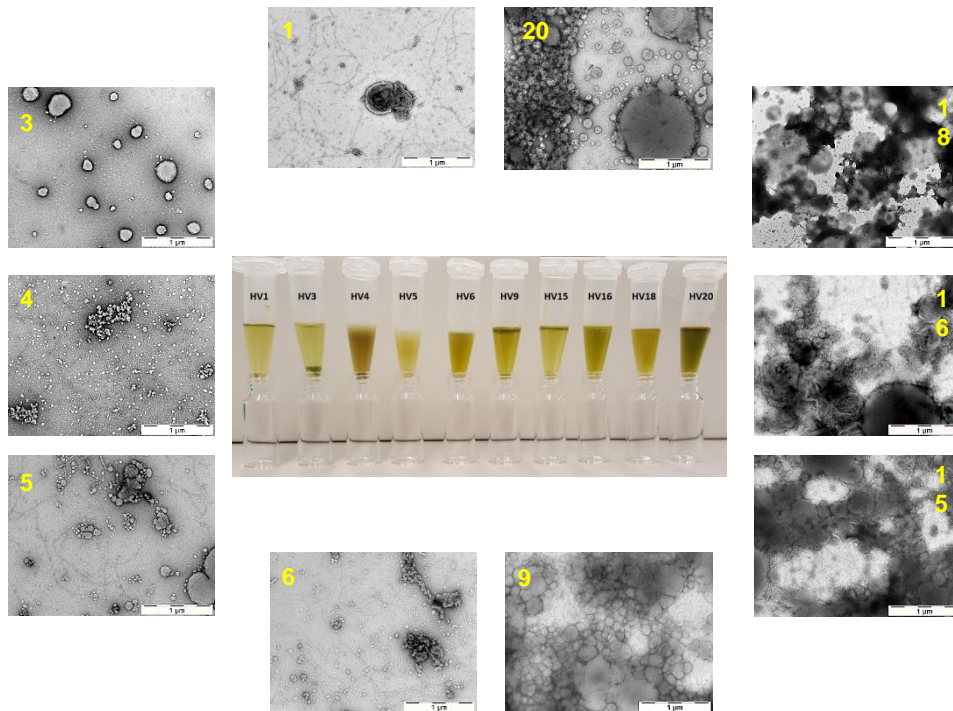


GI fluid characterization: composition

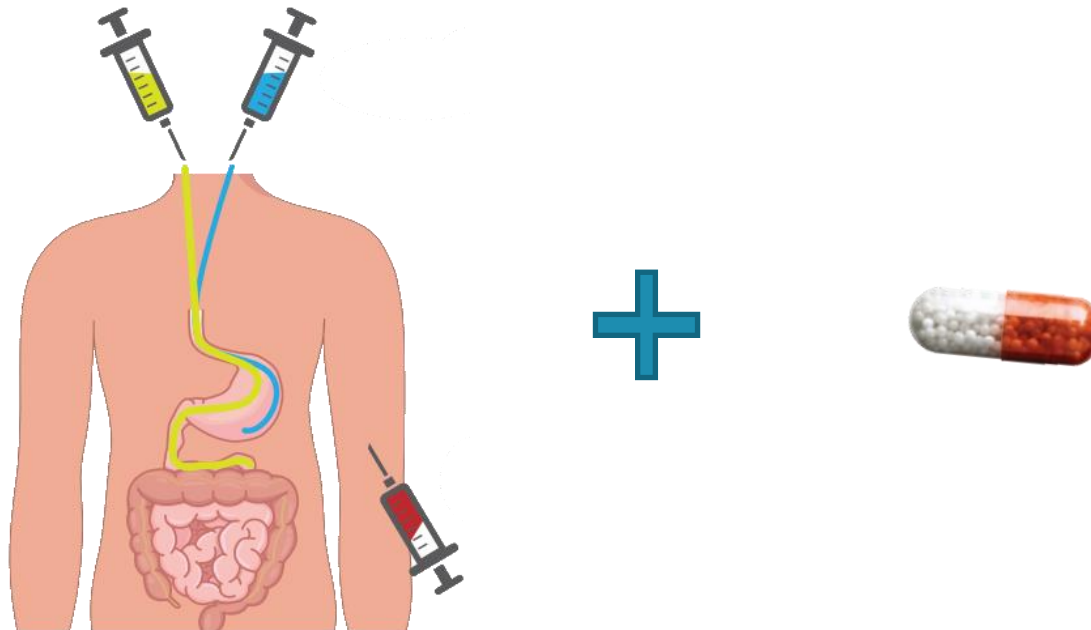
20 volunteers, time-dependent aspiration of duodenal fluids in fasted and fed state



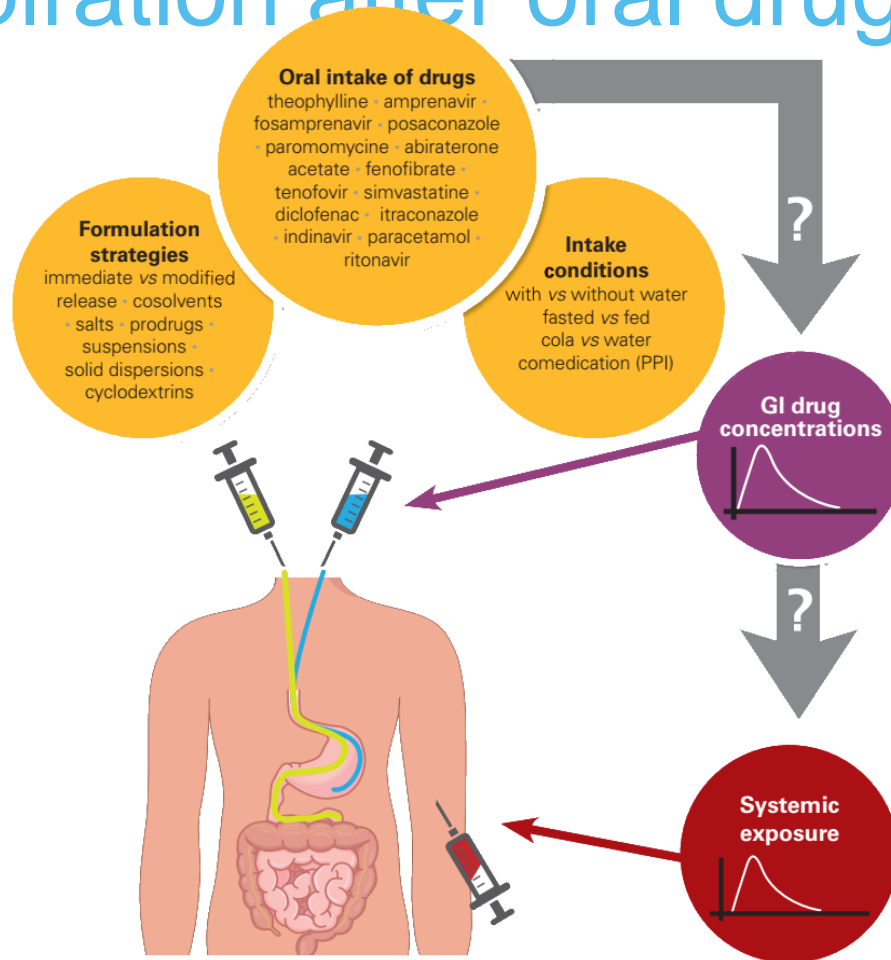
GI fluid characterization: ultrastructure & functionality



GI aspiration after oral drug intake



GI aspiration after oral drug intake



Brouwers et al, 2018, AAPS Newsmagazine Dec 2018:16-22.

pH

Water intake

Volume

Food effects

Motility

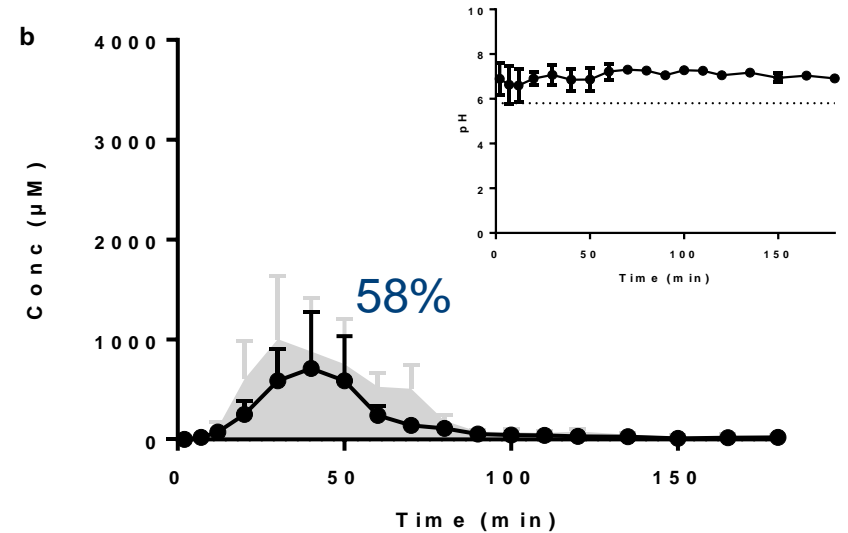
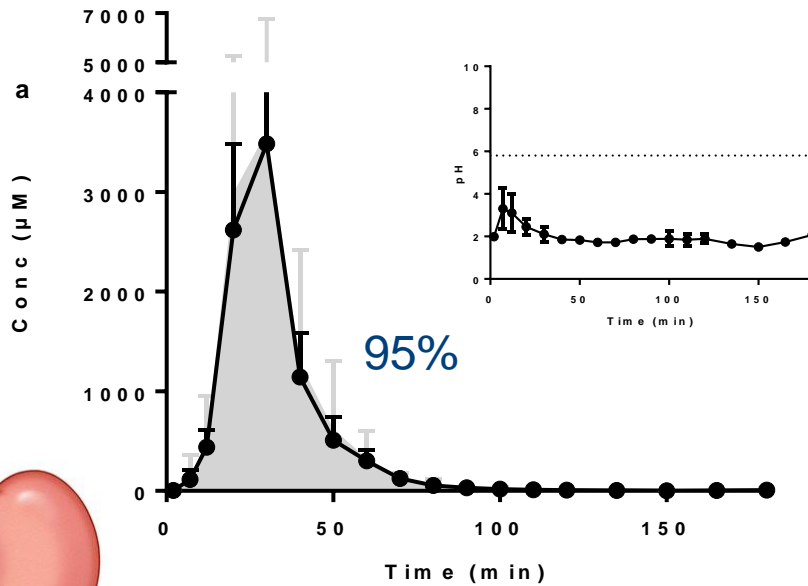
Bariatric surgery

INDINAVIR SULFATE (Stomach)



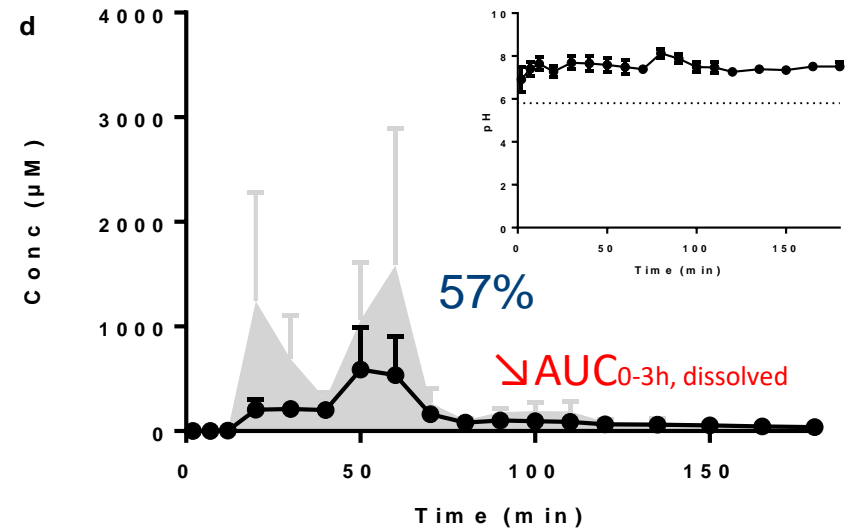
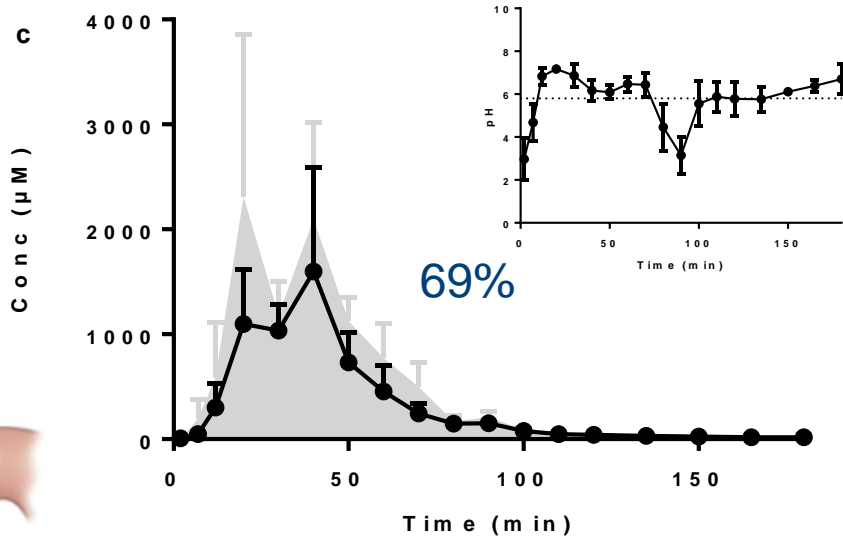
FASTED

FASTED + PPI



- Importance co-medication & stomach pH!

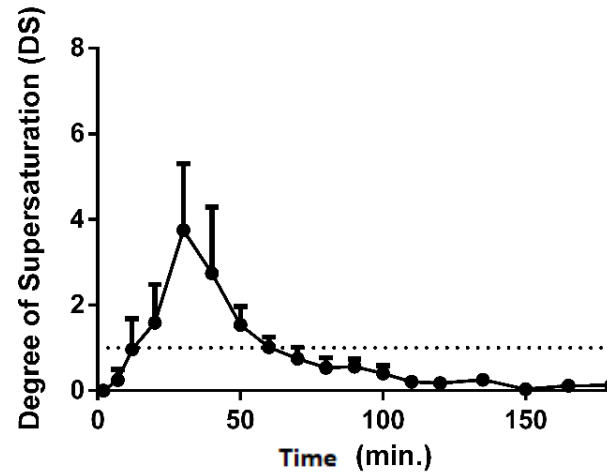
INDINAVIR SULFATE (Duodenum)



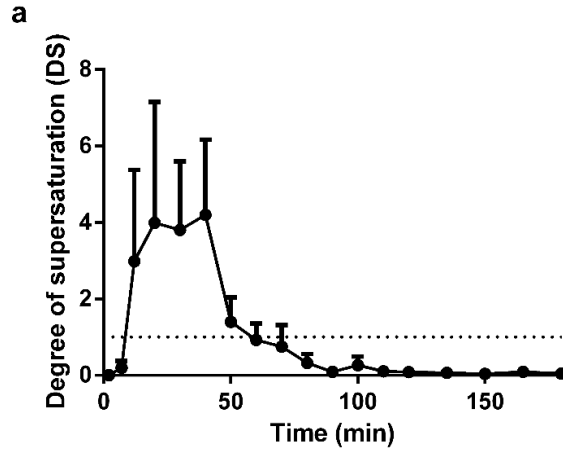
- Importance co-medication & stomach pH!

INDINAVIR SULFATE: degree of supersaturation

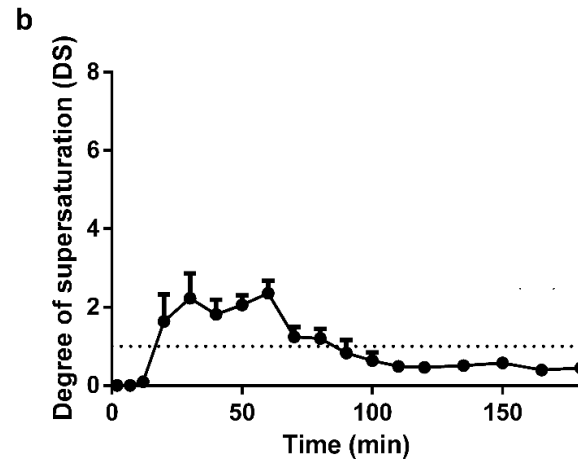
Fasted Stomach + PPI



Fasted Duodenum

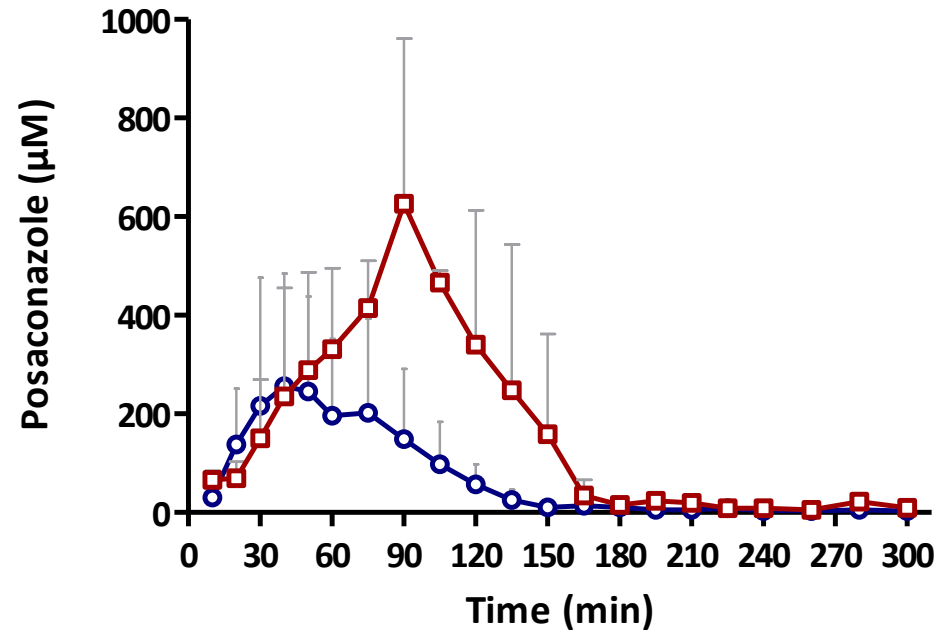
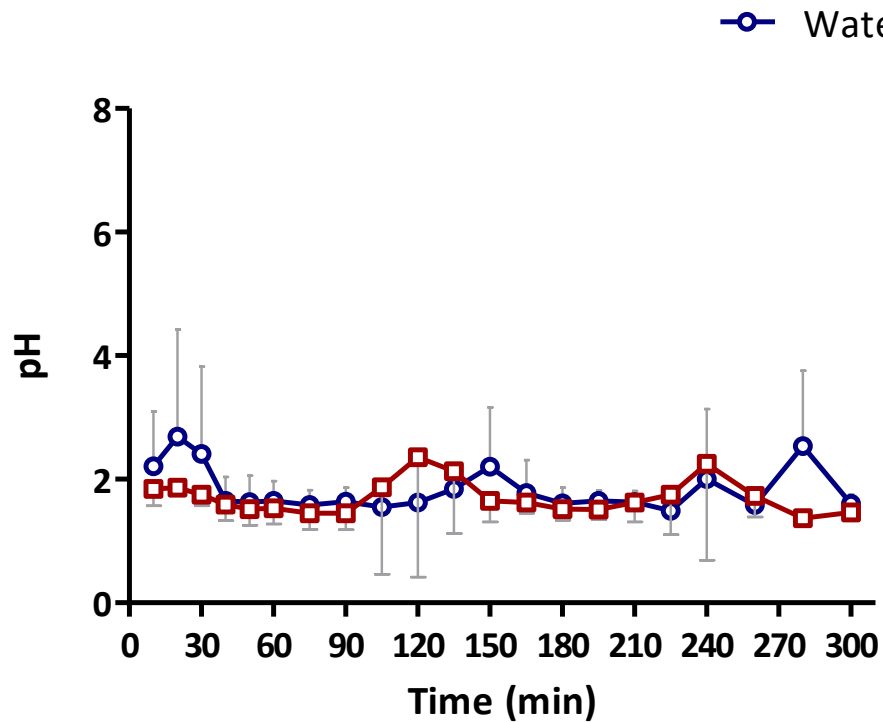


Fasted Duodenum + PPI



Posaconazole & Cola

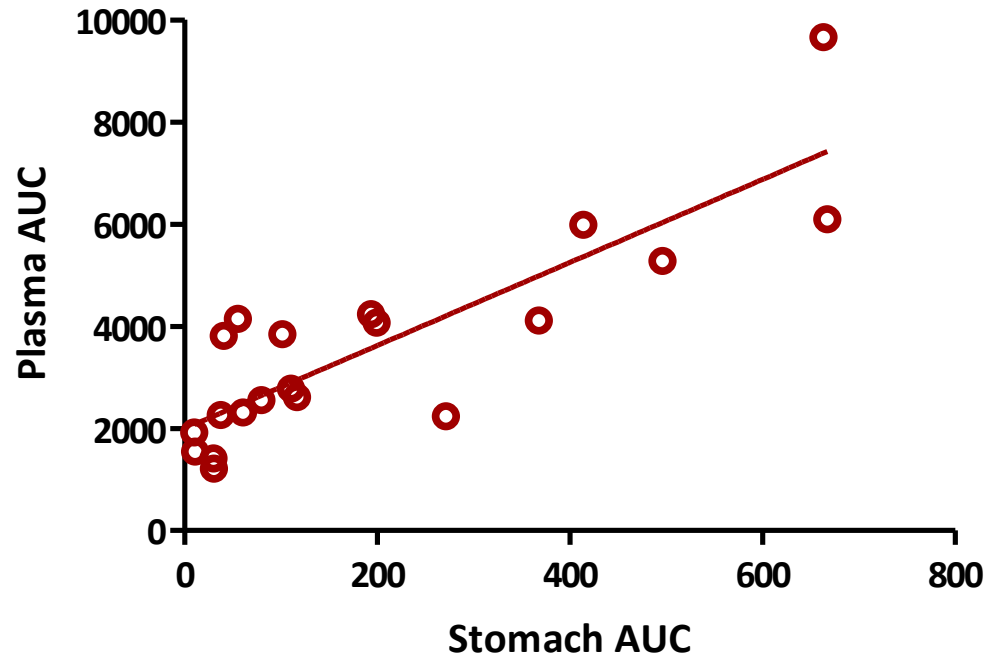
Stomach



Summary:

gastric conditions & posaconazole absorption

- Gastric dissolution affects posaconazole absorption



pH

Water intake

Volume

Food effects

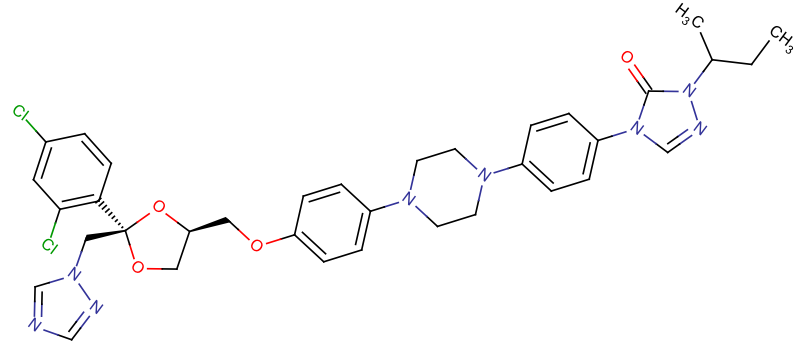
Motility

Bariatric surgery

Cyclodextrins to enable absorption

Itraconazole

- lipophilic, weak base
 - clogP 7.14
 - pKa 2.2 & 3.9
- low solubility in gastric (5 μM) and intestinal (0.5 μM) fluid
- available formulations (200 mg):
 - Sporanox capsules – solid dispersion in HPMC
 - Sporanox solution – HP- β -CD 40% (w/v)



Cyclodextrins to enable absorption

Impact of intraluminal dilution

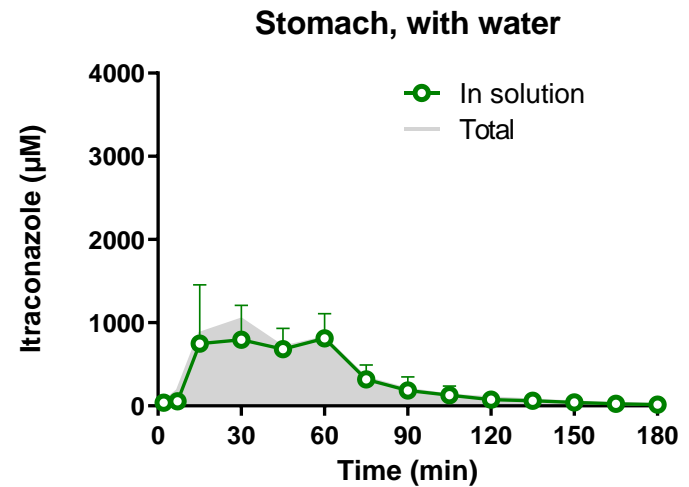
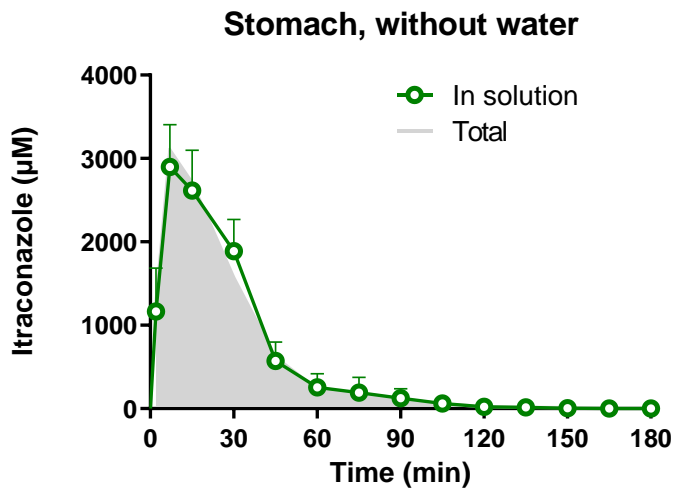
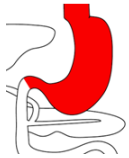


VS



Berben et al. 2017, Int J Pharm 526:235-243.

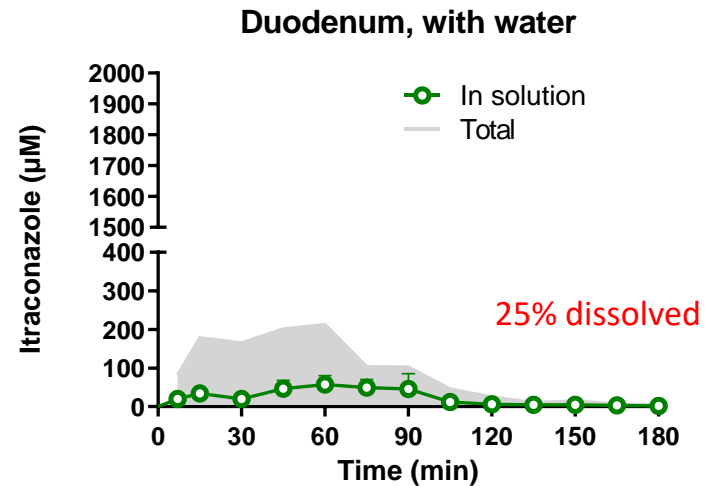
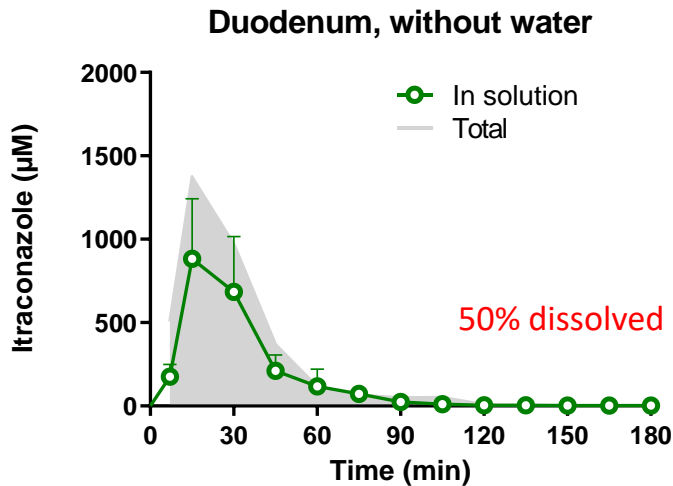
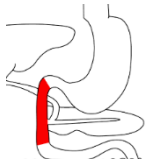
Impact of intraluminal dilution: gastric concentrations



dilution effect

Berben et al. 2017, Int J Pharm 526:235-243.

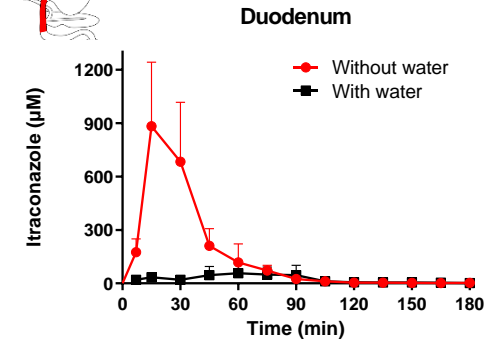
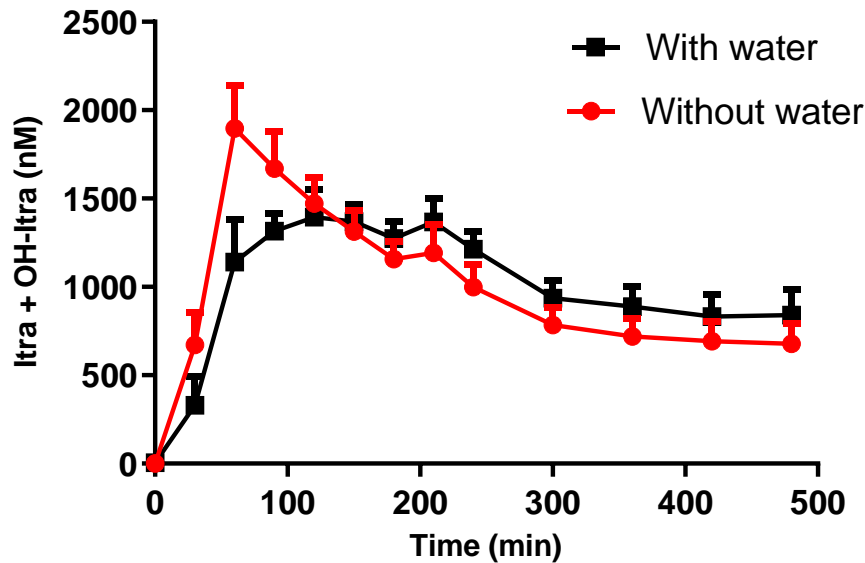
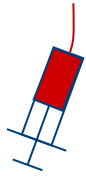
Impact of intraluminal dilution: duodenal concentrations



dilution effect
precipitation \uparrow

Berben et al. 2017, Int J Pharm 526:235-243.

Impact of intraluminal dilution: systemic exposure



Discrepancy between effect on intestinal vs systemic concentrations!

Berben et al. 2017, Int J Pharm 526:235-243.

pH

Water intake

GI Volume

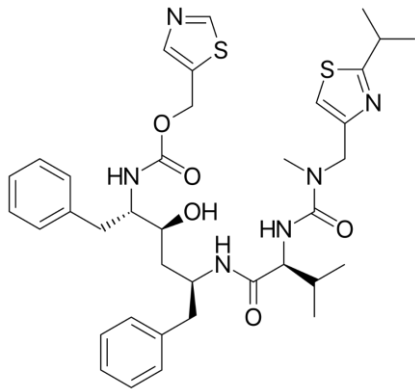
Food effects

Motility

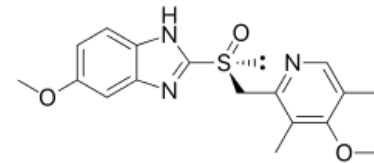
Bariatric surgery

Case study

The effects of proton-pump inhibitors on the disposition of ritonavir



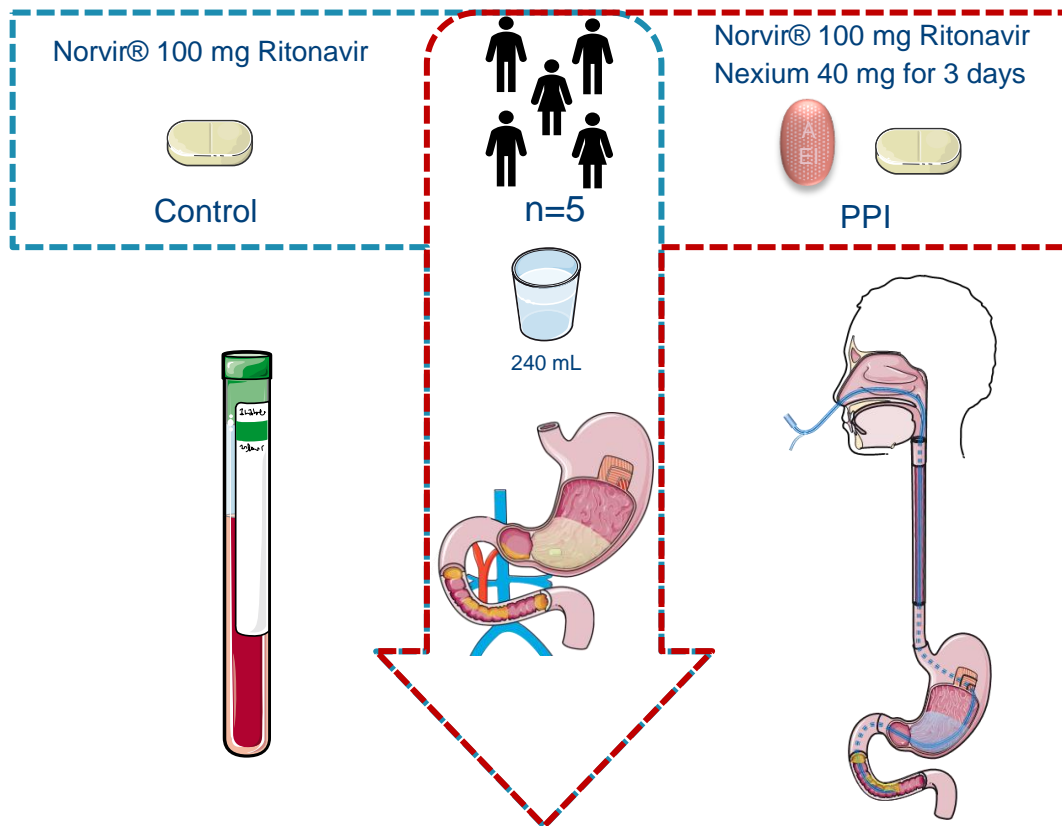
Norvir®; HIV-1 protease inhibitor
Dosage form: Amorphous Solid Dispersion
Solubility ~ 5µg/mL
pKa = 2,84 (conjugated acid)
LogP = 4,3



Nexium®; Proton-pump inhibitor
Dosage form: Gastro-resistant tablet
pKa = 4,77 (conjugated acid)
LogP = 2,43

Case study

The effects of proton-pump inhibitors on the disposition of ritonavir



Case study

The effects of proton-pump inhibitors on the disposition of ritonavir

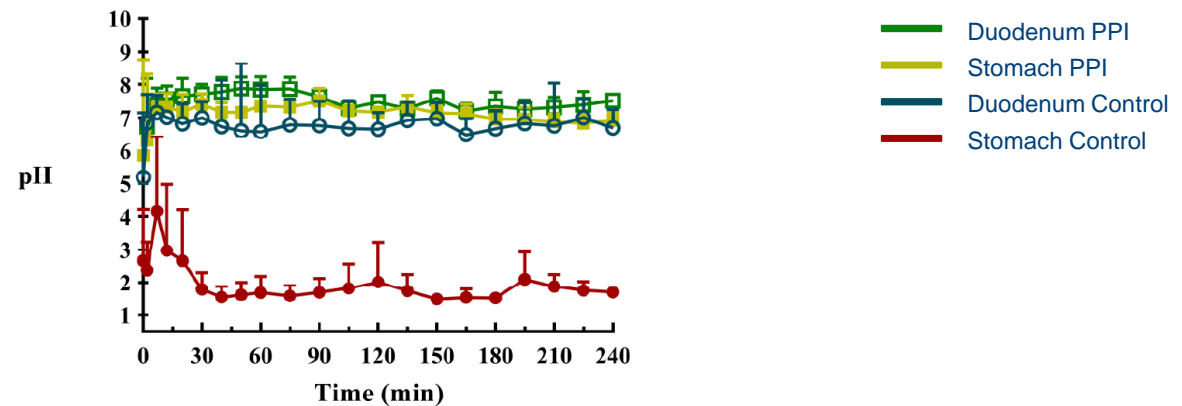
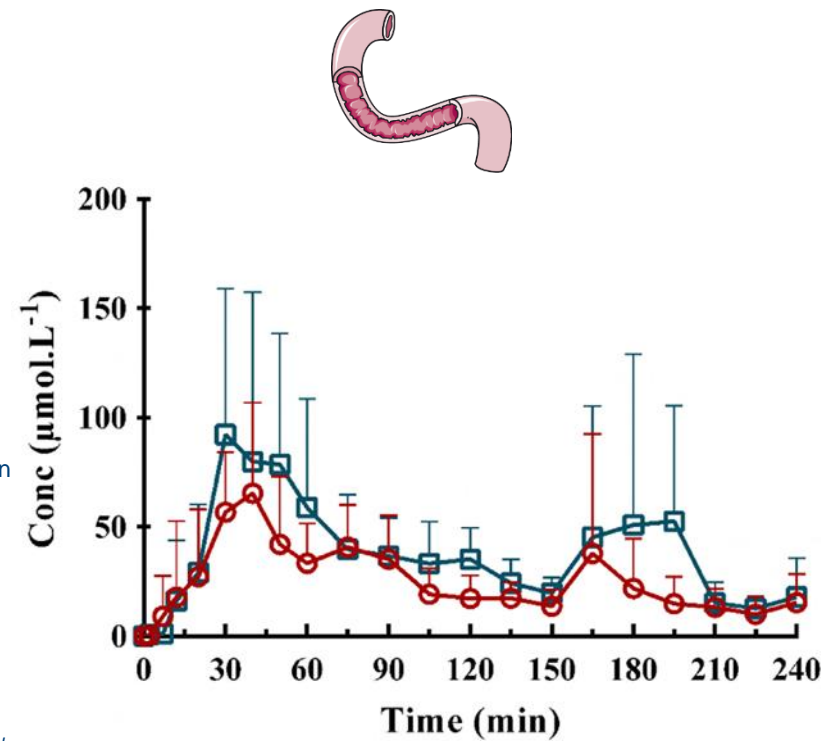
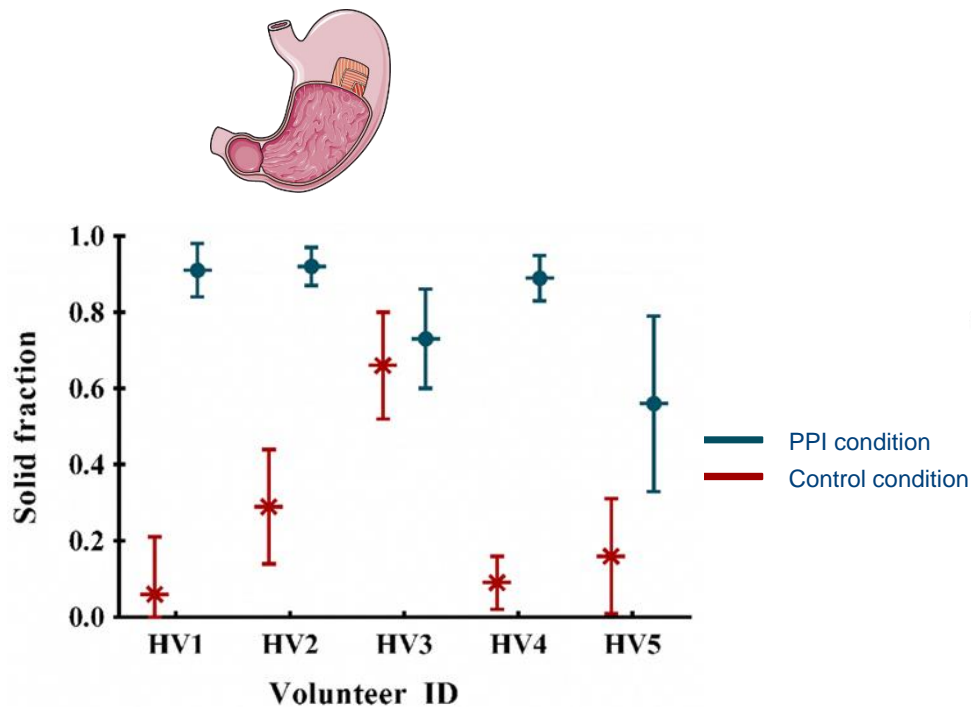


Figure 1. Mean (+ S.D., n = 5) pH of aspirates from stomach (closed symbols) and duodenum (open symbols) as a function of time after oral intake of one tablet of Norvir® (100 mg ritonavir) under fasted state conditions (bullets) or fasted + PPI conditions (squares).

Van Den Abeele, J. *et al.* (2020)

Case study

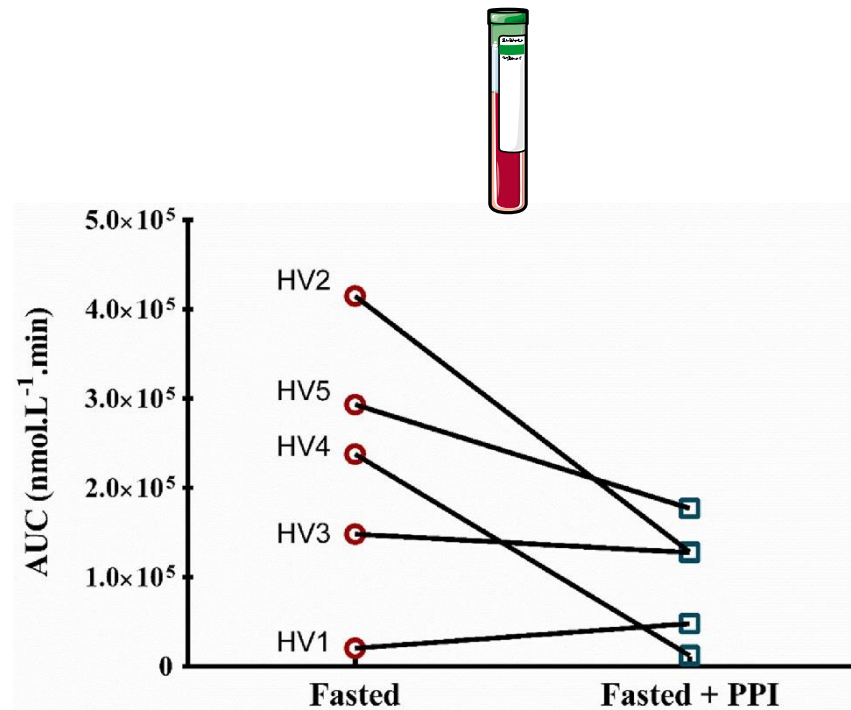
The effects of proton-pump inhibitors on the disposition of ritonavir



Van Den Abeele, J. *et al.* (2002)

Case study

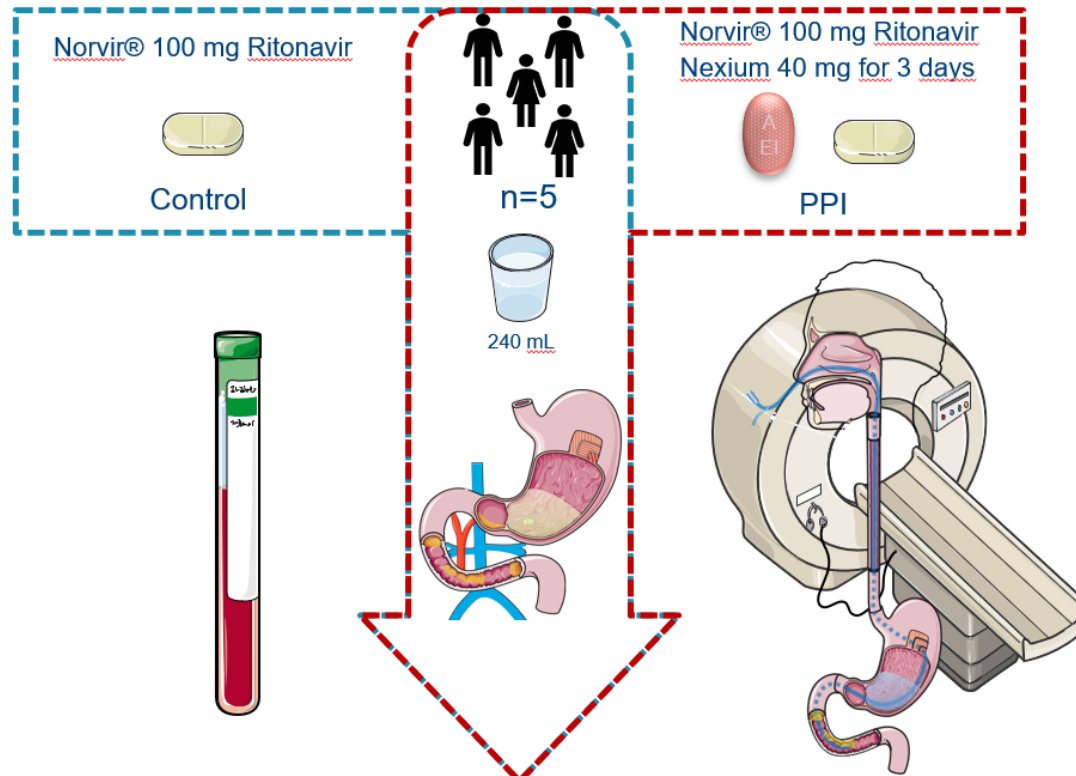
The effects of proton-pump inhibitors on the disposition of ritonavir



Van Den Abeele, J. *et al.* (2020)

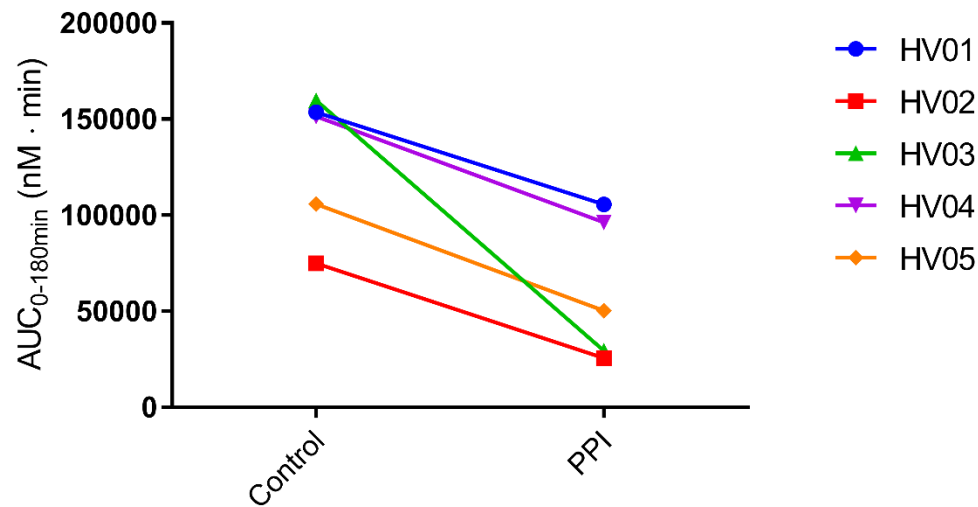
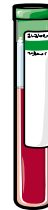
Case study

The effects of proton-pump inhibitors on the disposition of ritonavir



Case study

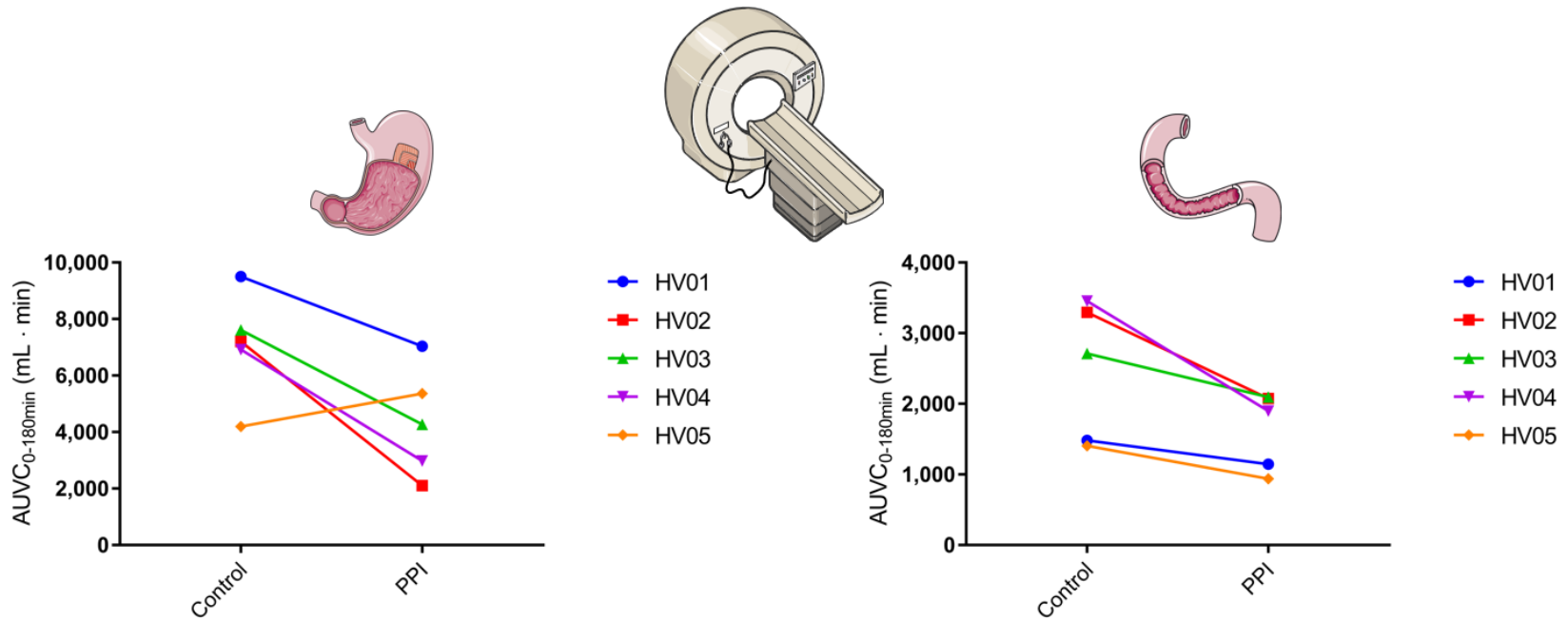
The effects of proton-pump inhibitors on the disposition of ritonavir



De Waal, T. *et al.* (2020)

Case study

The effects of proton-pump inhibitors on the disposition of ritonavir



De Waal, T. *et al.* (2020)

pH

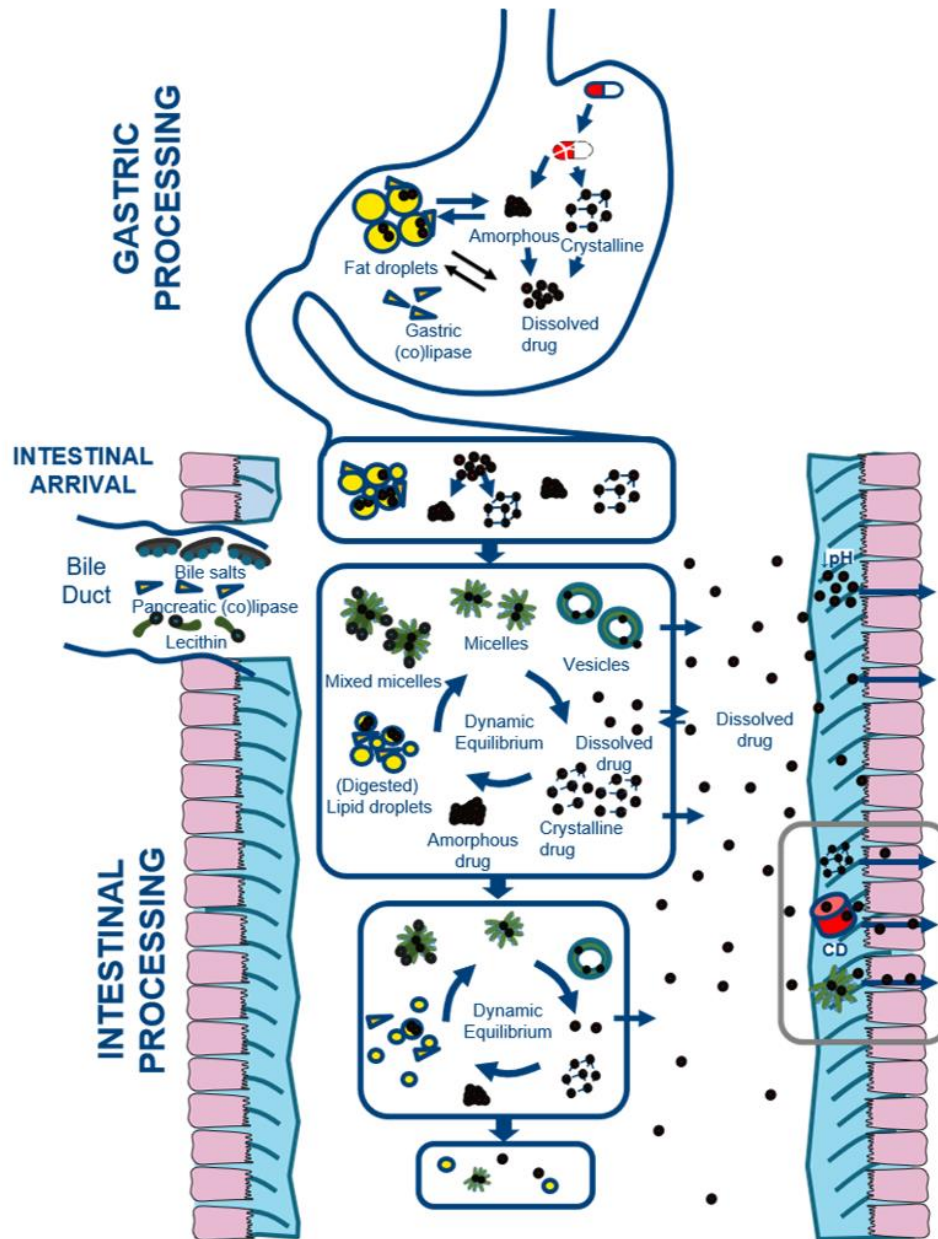
Water intake

Volume

Food effects

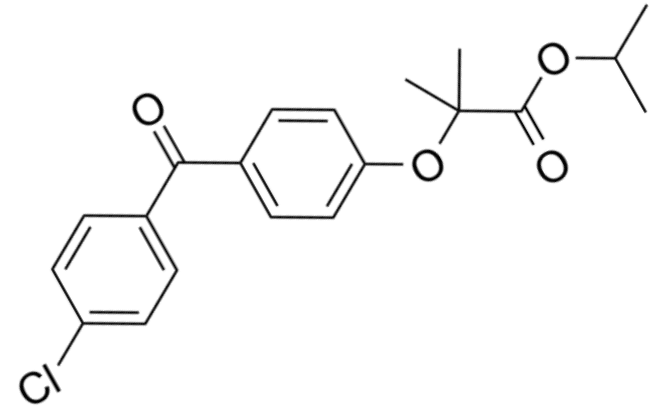
Motility

Bariatric surgery



Fenofibrate

- lipophilic, neutral
 - clogP 5.3
- multiple formulations available, for instance:
 - microsized particles
 - nanosized particles
 - ...
 - **lipid-based formulation: Fenogal Lidose**
 - fenofibrate dispersed in semi-solid lipid excipient Gelucire 44/14
 - micro-emulsion upon contact with water in GI tract
 - has to be taken with food!



How important is lipolysis for drug absorption?



Fenofibrate

- Log P = 5.2
- BCS II
- Lipid based formulation

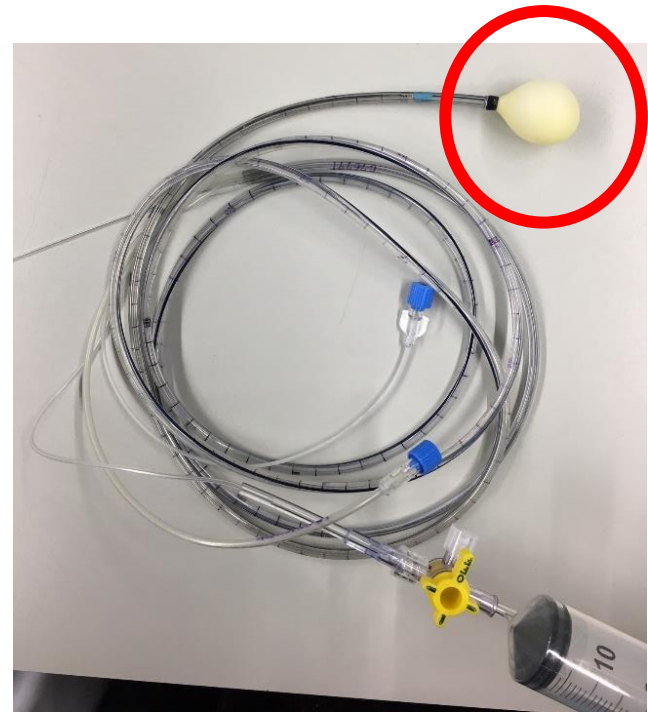
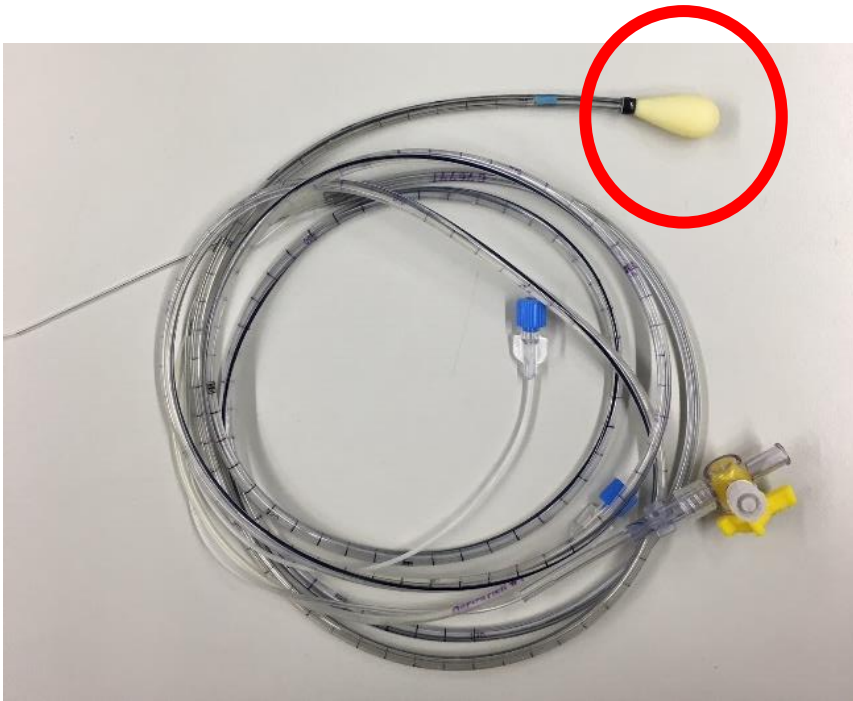
+/-



Orlistat

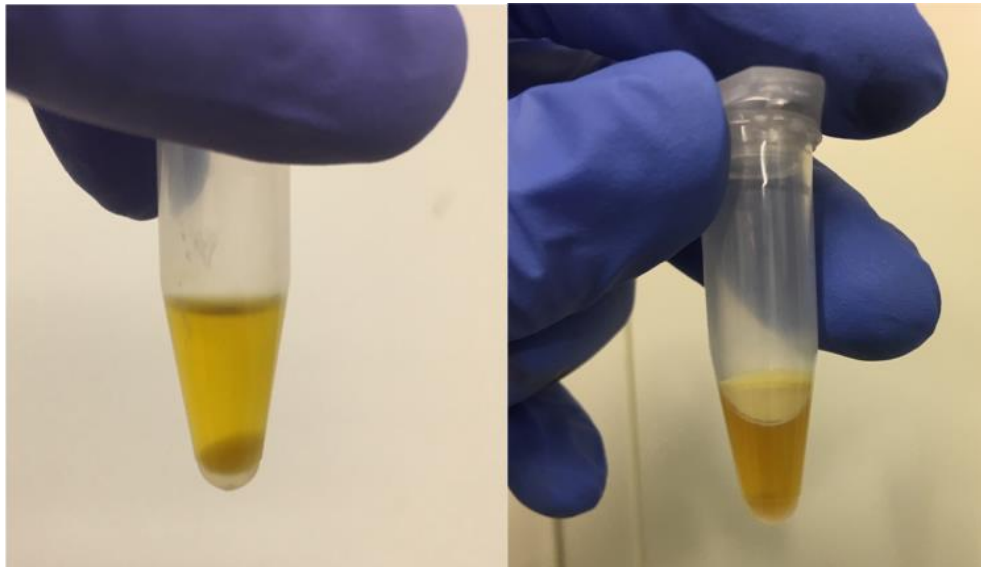
- Log P = 8.6
- Lipase inhibitor





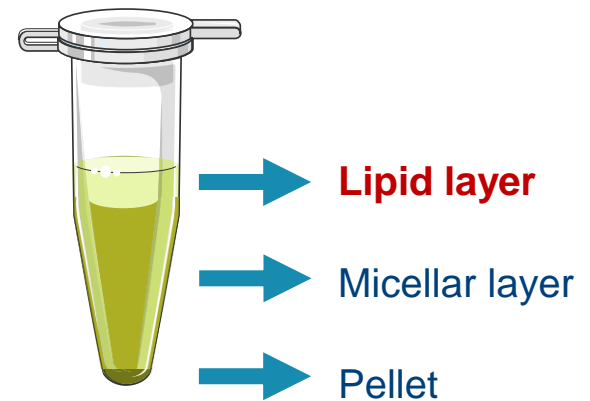
Balloon inflation when positioned in duodenum

Impact of orlistat: undigested lipids in jejunal fluids

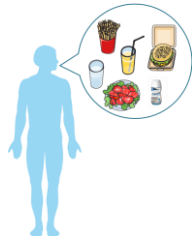


-
orlistat

+ orlistat



Braeckmans et al, 2022, Pharmaceutics 14: 119..

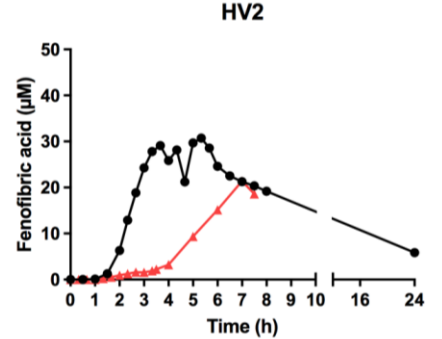
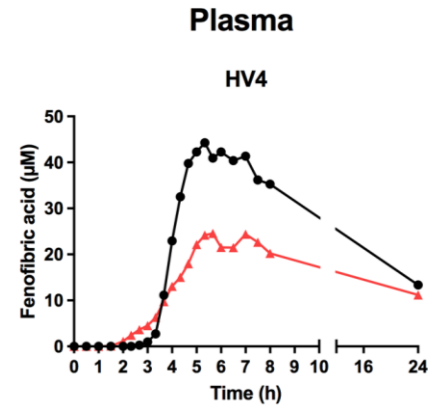
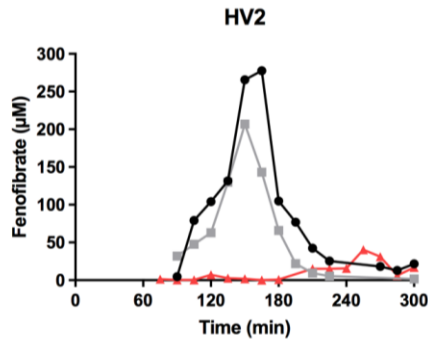
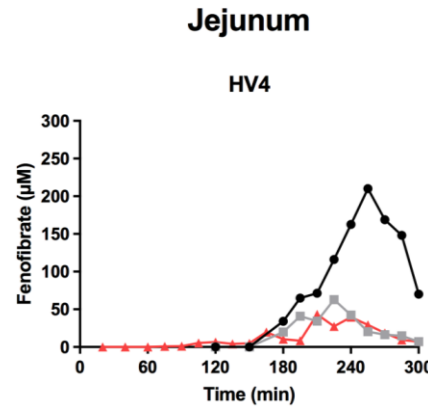


Fenofibrate

Orlistat co-administration sustained fenofibrate solubilisation for a longer period

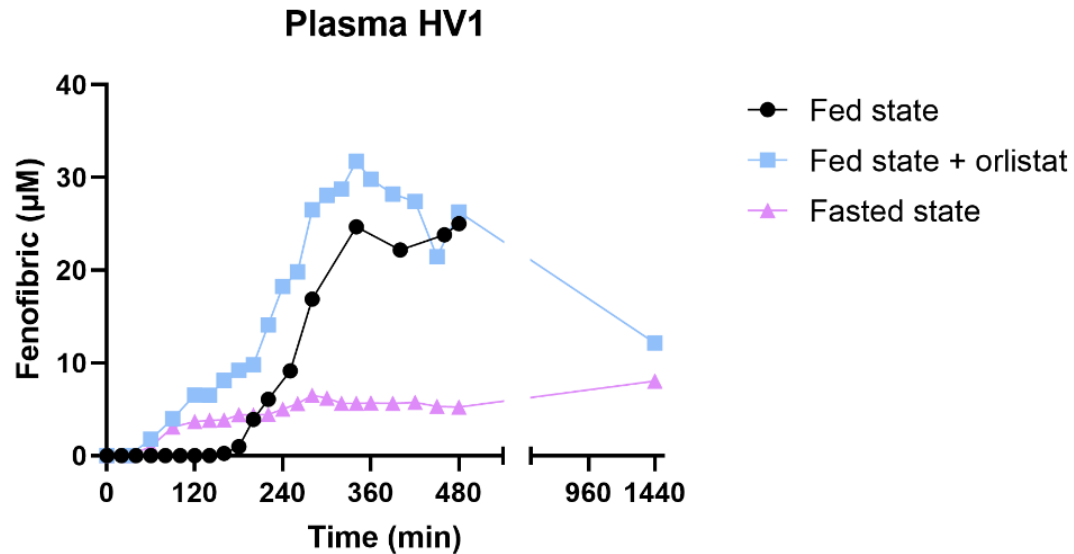
→ higher intraluminal fenofibrate concentrations

→ improved absorption in 5 out of 6 volunteers



Jejunum: ▲ Fed state ● Fed state + orlistat (total) ■ Fed state + orlistat (micellar)
 Plasma: ▲ Fed state ● Fed state + orlistat

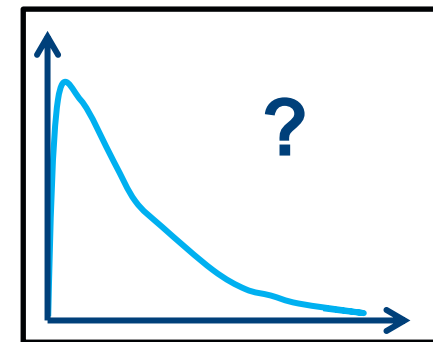
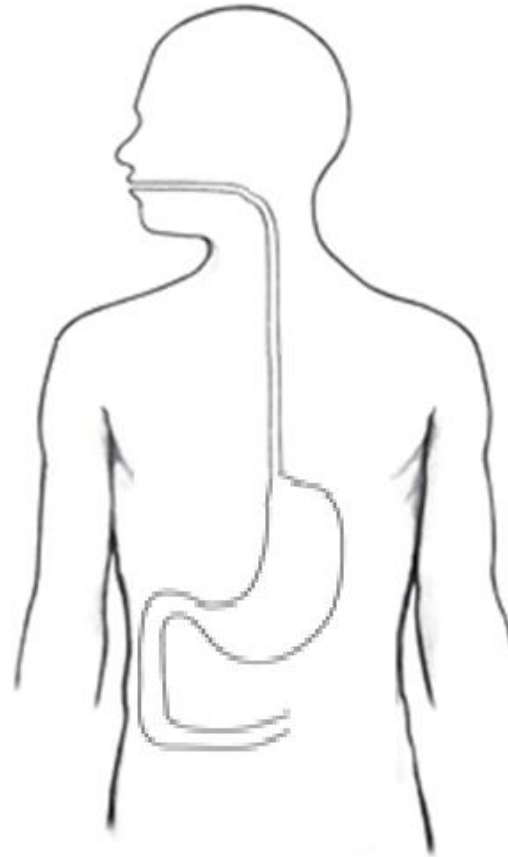
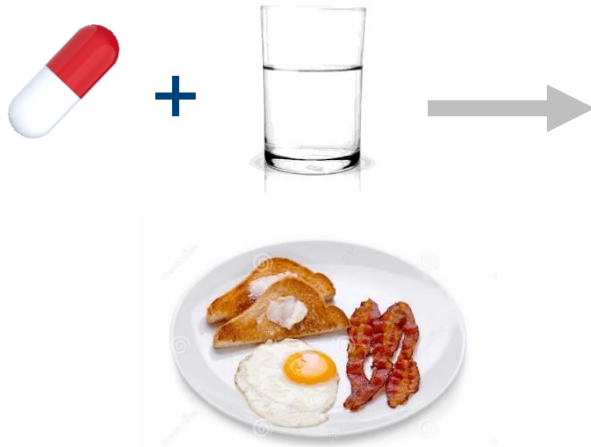
Results - plasma



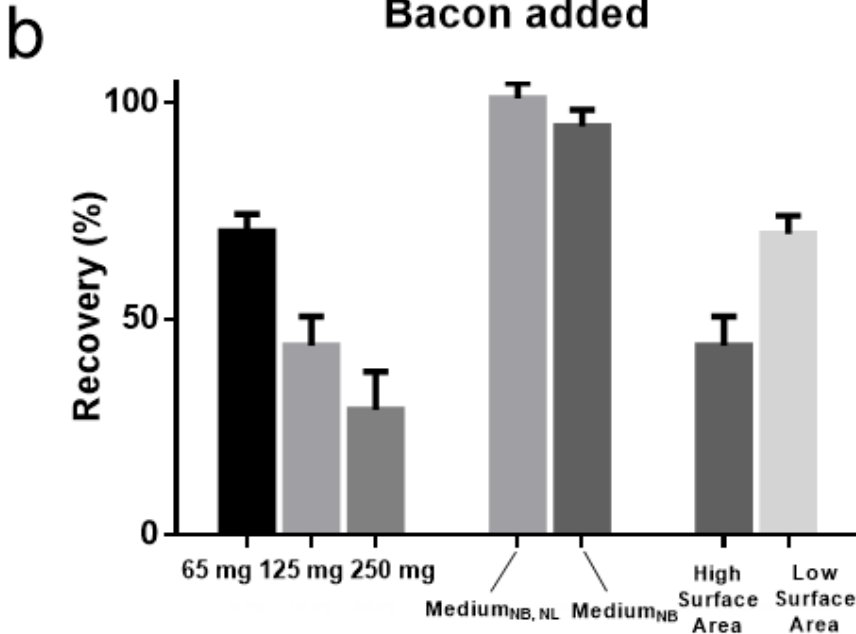
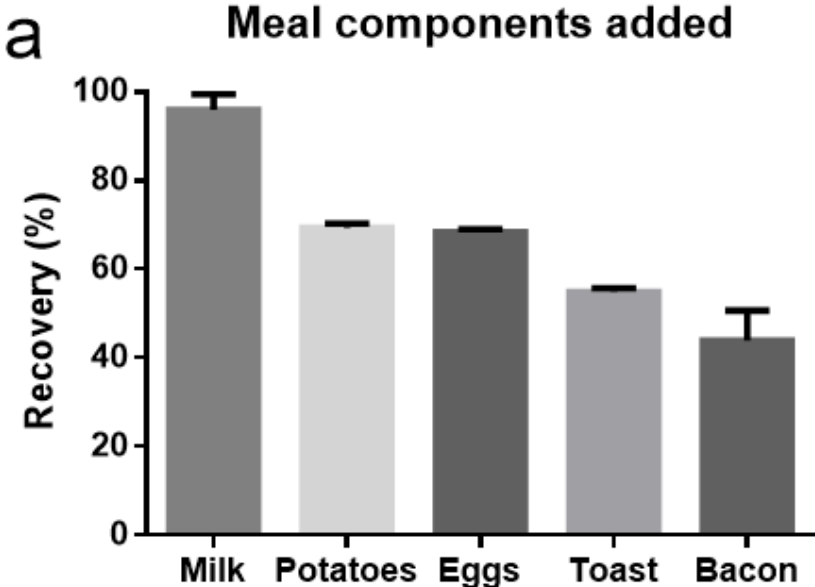
- Faster and higher absorption if administered with orlistat
- Systemic uptake fed state >> fasted state

Gastrointestinal drug behavior in real-life dosing conditions.

Weakly acidic drug
Diclofenac



Gastrointestinal drug behavior in real-life dosing conditions.



pH

Water intake

Volume

Food effects

Motility

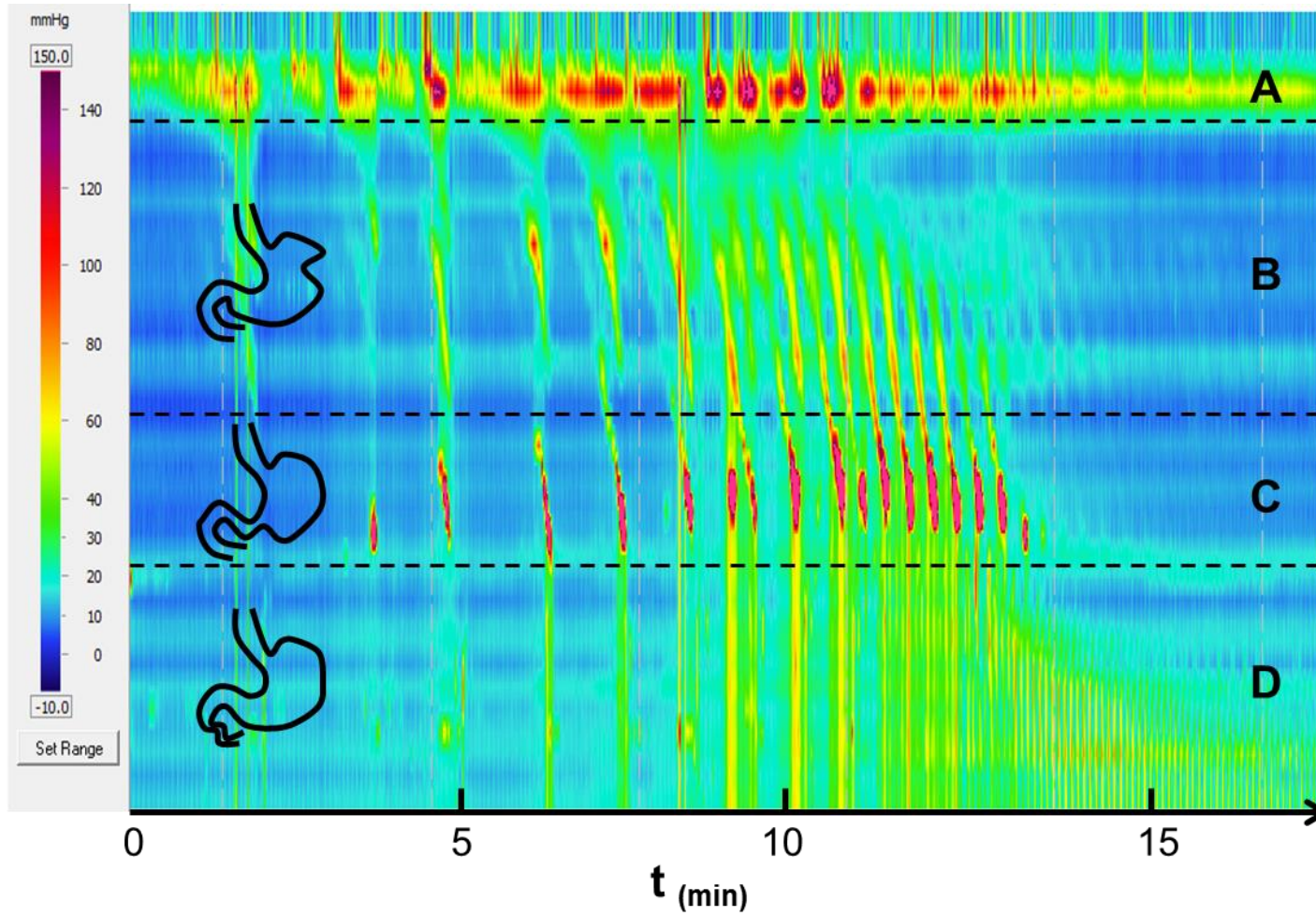
Bariatric surgery



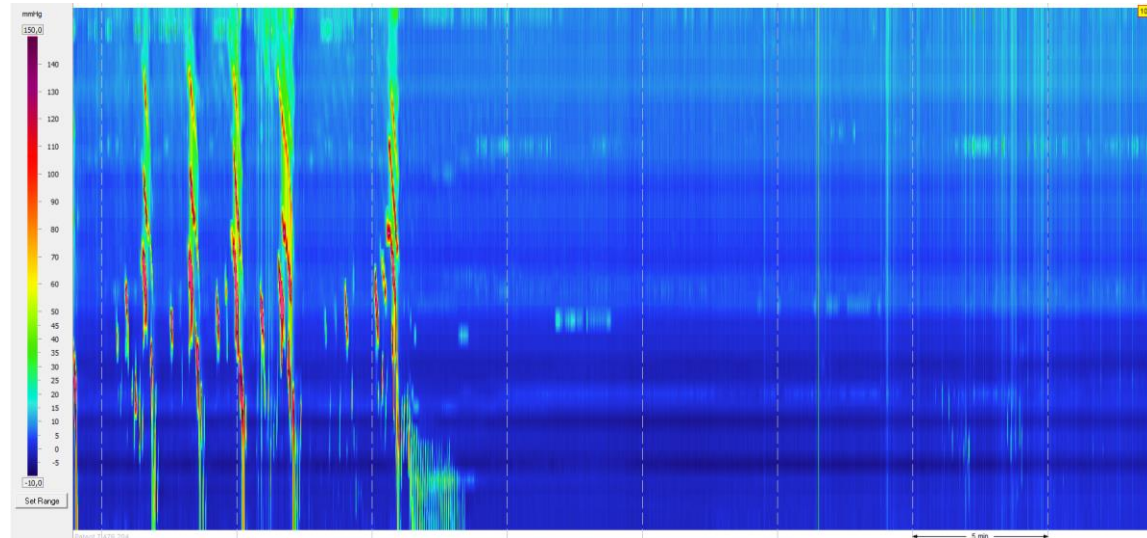
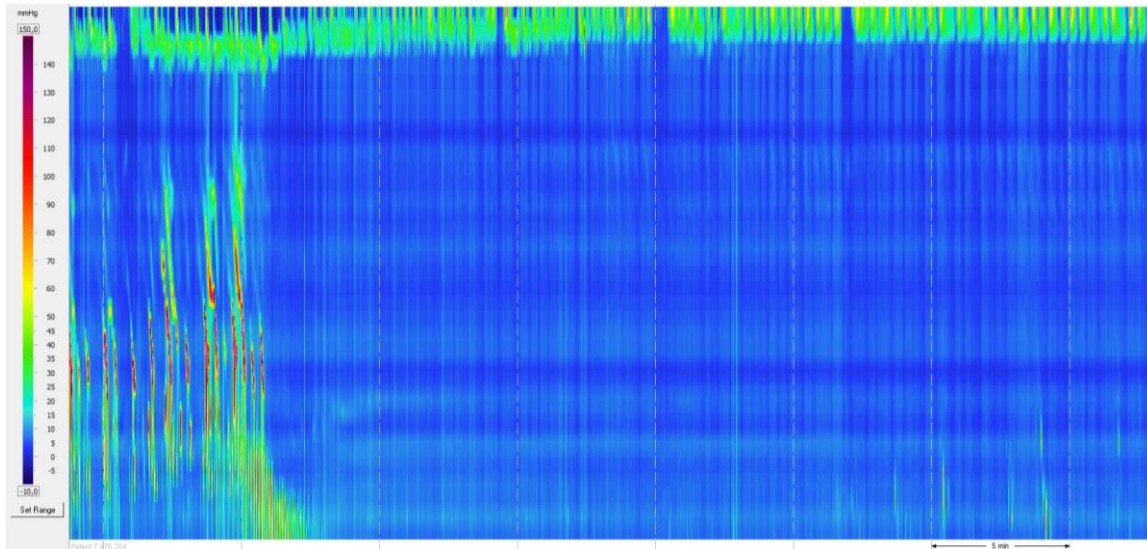
METHODOLOGY: High resolution manometry



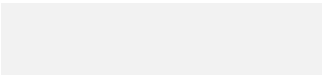
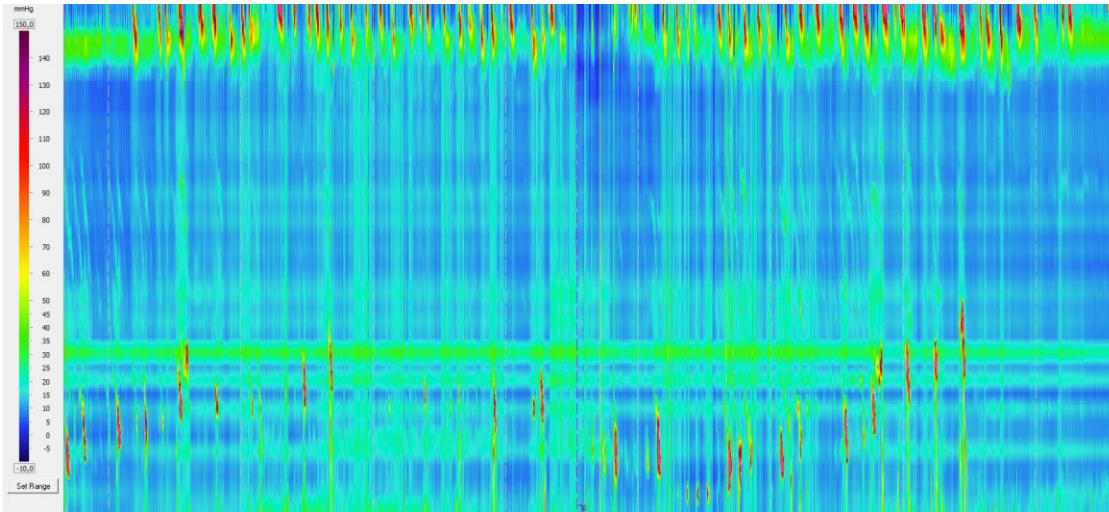
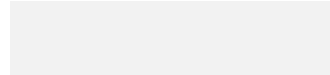
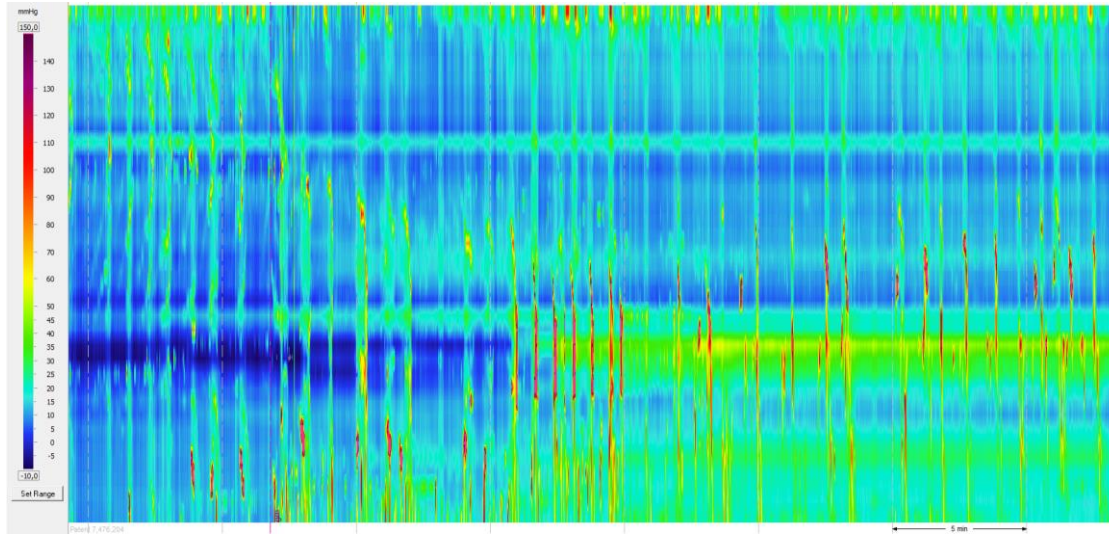
METHODOLOGY: High resolution manometry



Phase 1

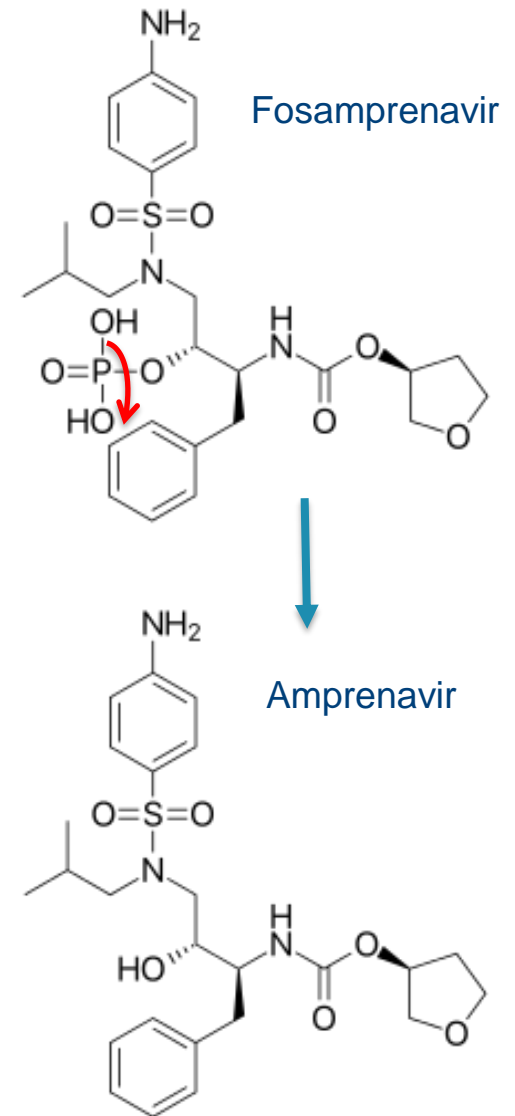


Phase 2



Fosamprenavir (Telzir[®])

- Phosphate ester prodrug of amprenavir
- BCS class 2
- HIV protease inhibitor
- Immediate release tablet

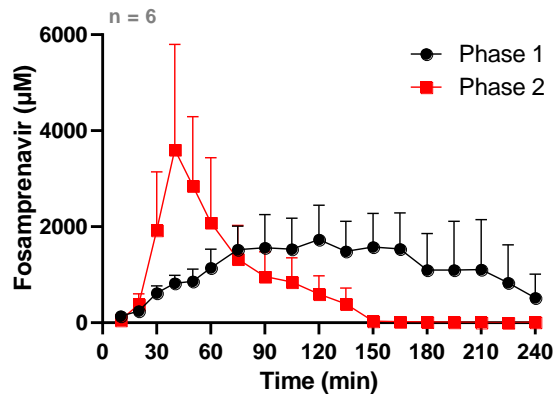


GI motility as a source of variability

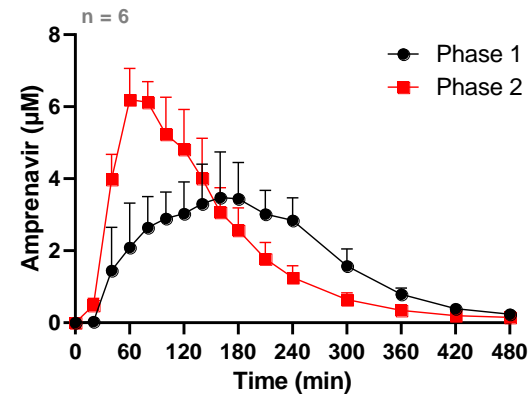
Drug administration in MMC phase 1 versus MMC phase 2

Example: fosamprenavir

Stomach



Plasma



Braeckmans et al. 2020, Eur J Pharm Sci 142:105-117.

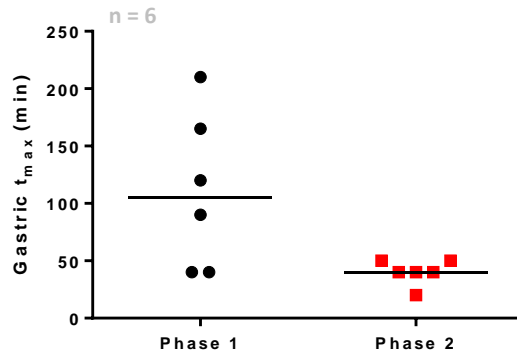
GI motility as a source of variability

Drug administration in MMC phase 1 versus MMC phase 2

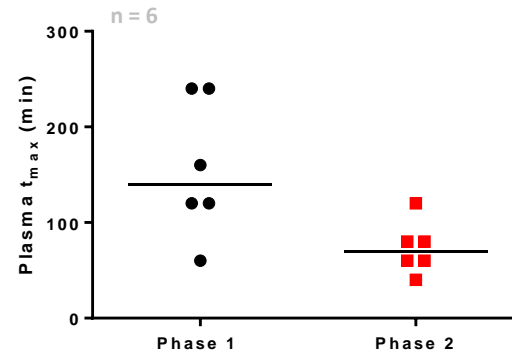
Example: fosamprenavir



Stomach



Plasma



Phase 1 intake
increased variability
risk for delayed release / absorption

Braeckmans et al. 2020, Eur J Pharm Sci 142:105-117.

pH

Water intake

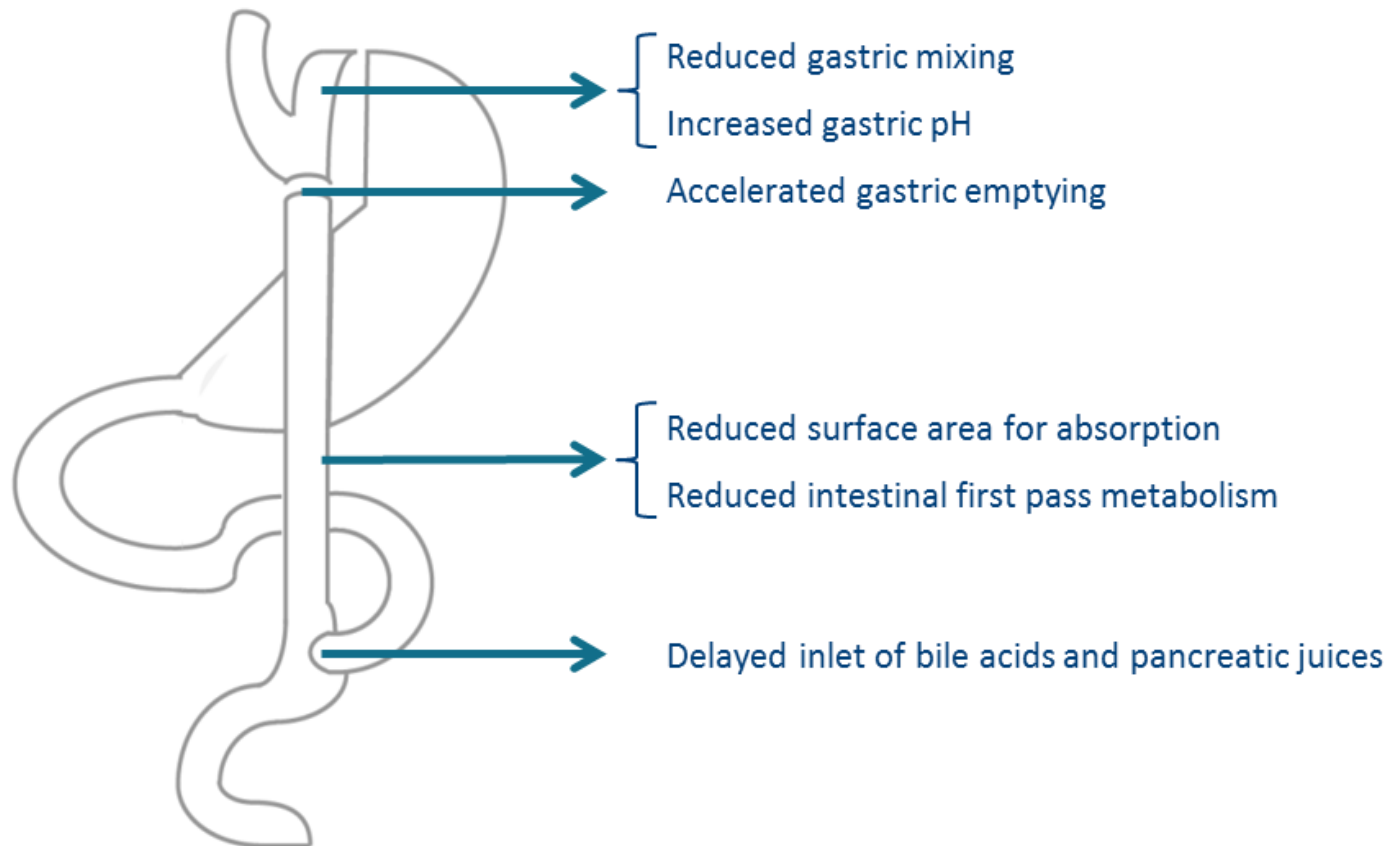
Volume




Food effects

Motility

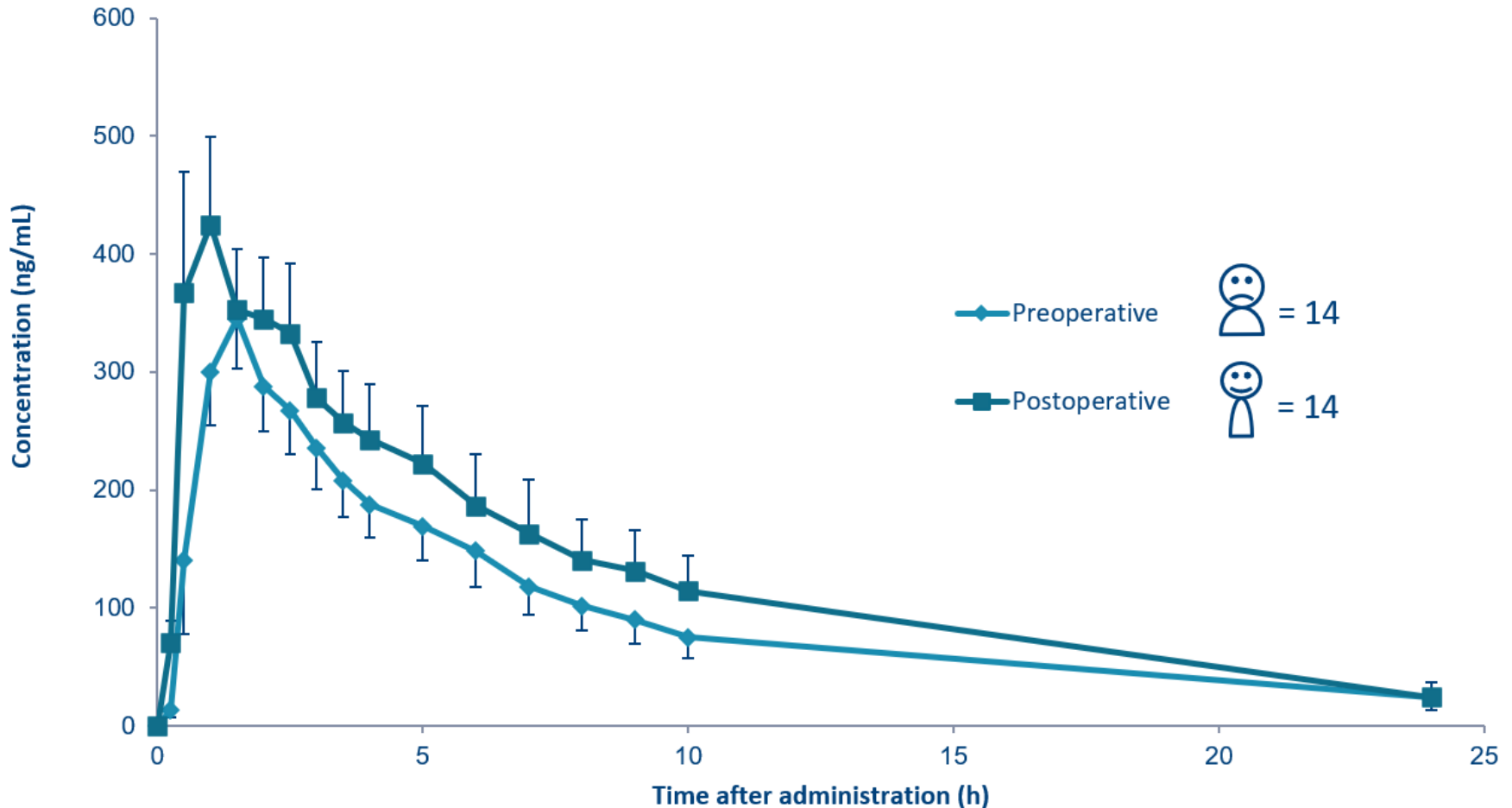
Bariatric surgery

RYGB changes physiological factors influencing drug disposition

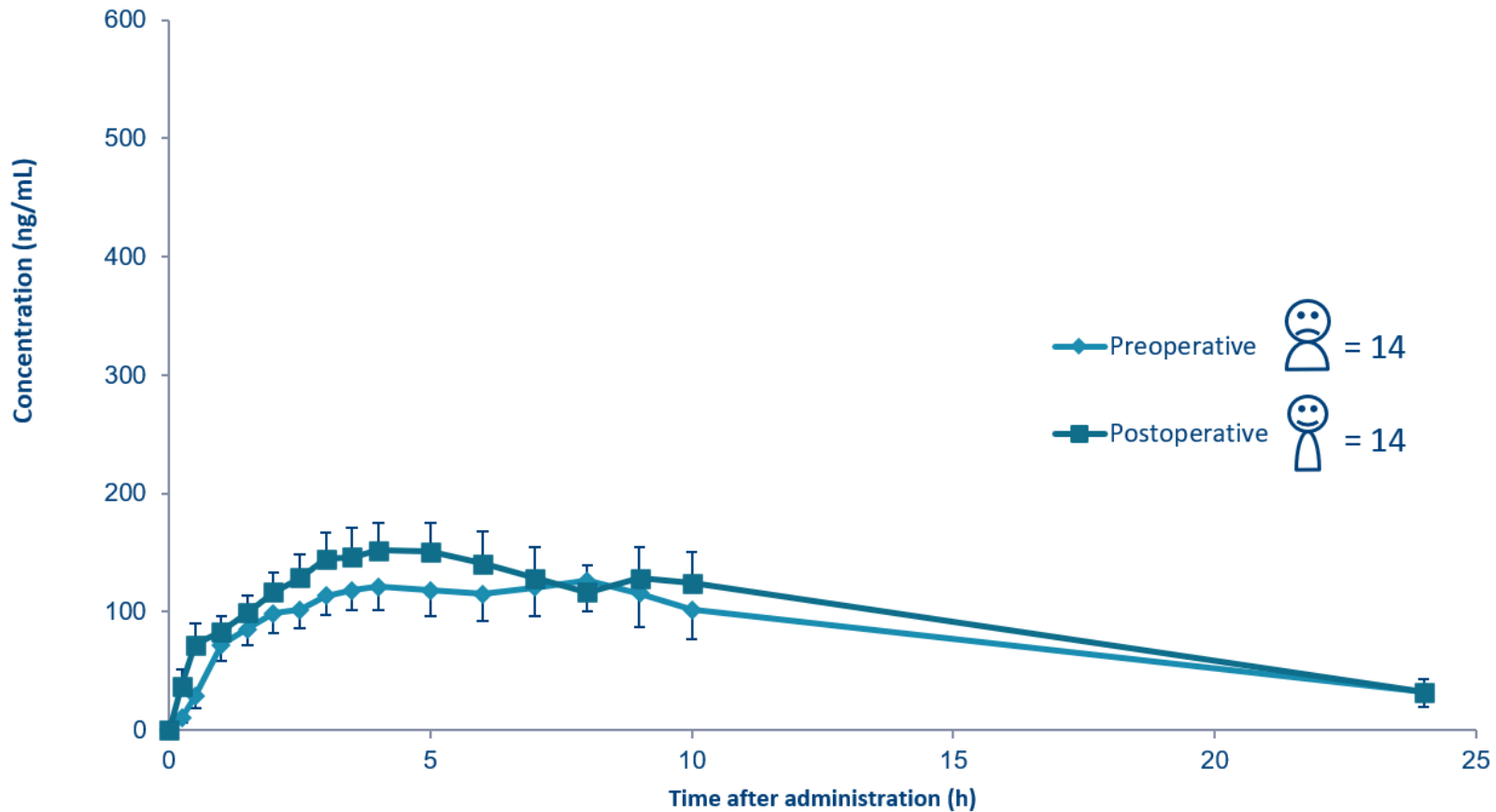


Studied compounds	BCS class	Active ingredient	Indication
	I	Metoprolol tartrate	Cardiovascular drug
	II	Fenofibrate	Lipid lowering agent
	II	Posaconazole	Anti-fungal drug

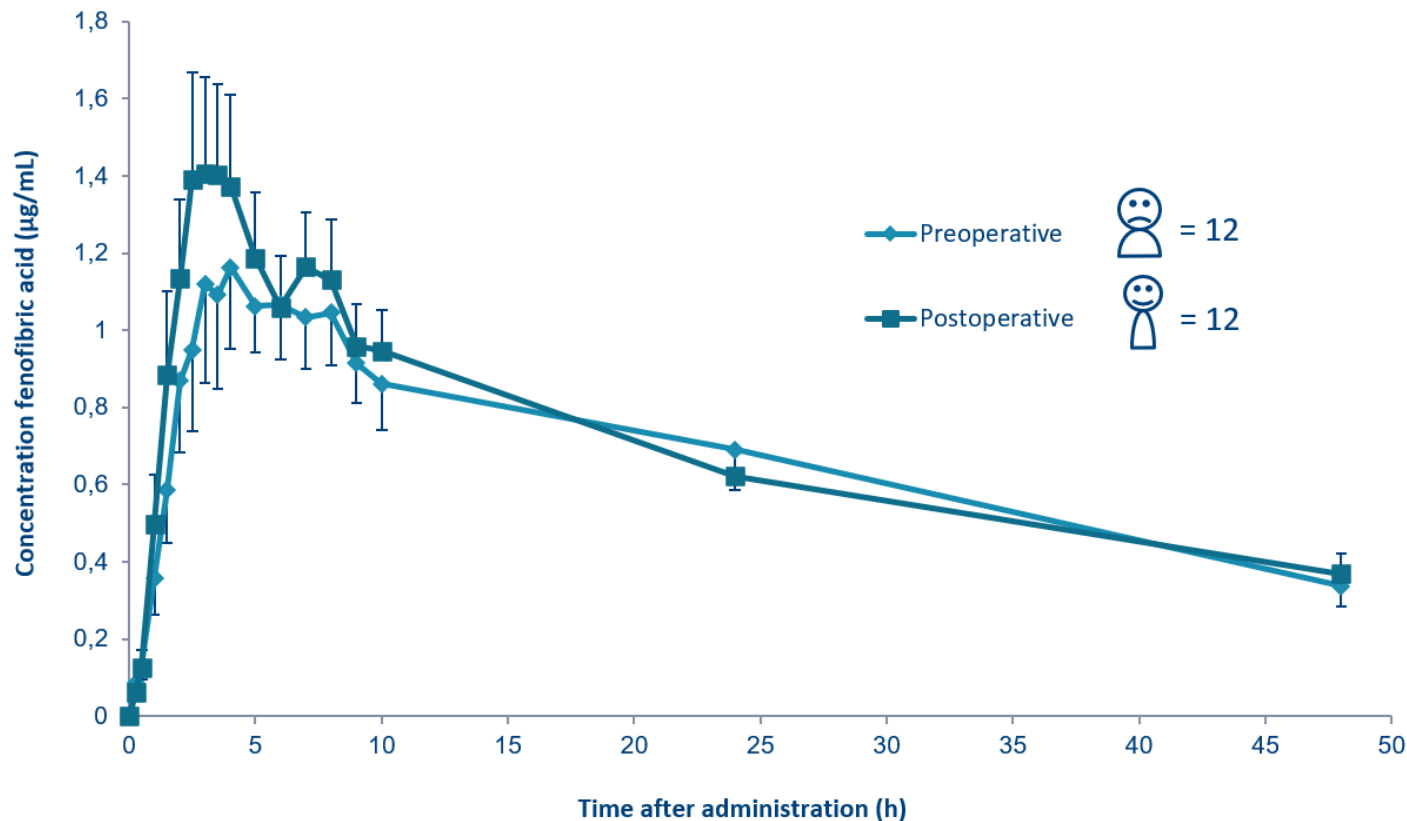
Metoprolol immediate release: no significant influence of RYGB



Metoprolol controlled release: no significant influence of RYGB

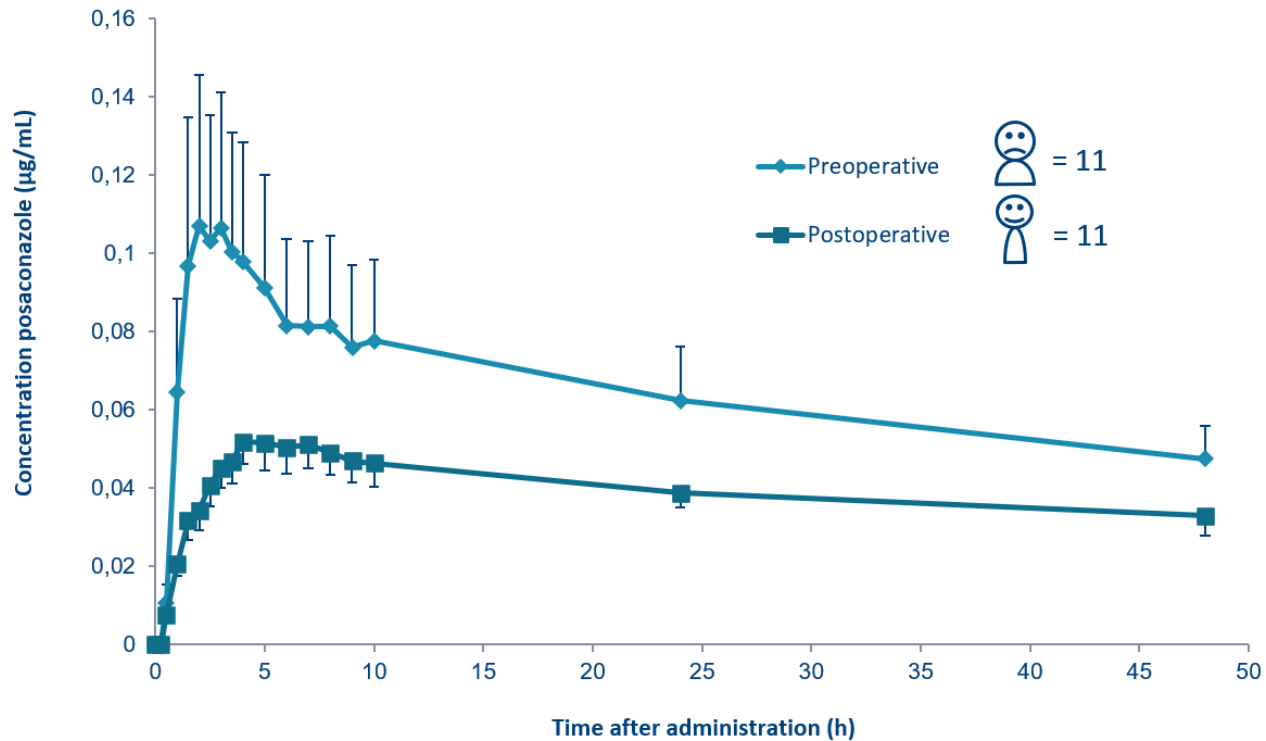


No significant difference in disposition of fenofibrate before and after RYGB



Shown as mean (95 % CI)

Significant reduction in disposition of posaconazole after RYGB



Data are shown as mean \pm sem

pH

Water intake

Volume

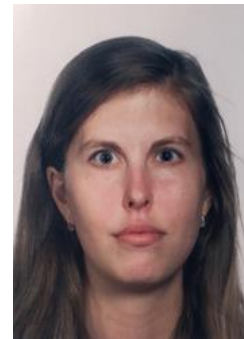
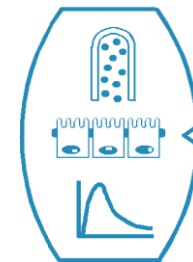
Food effects

Motility

Bariatric surgery

Acknowledgements

Drug Delivery and Disposition



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