

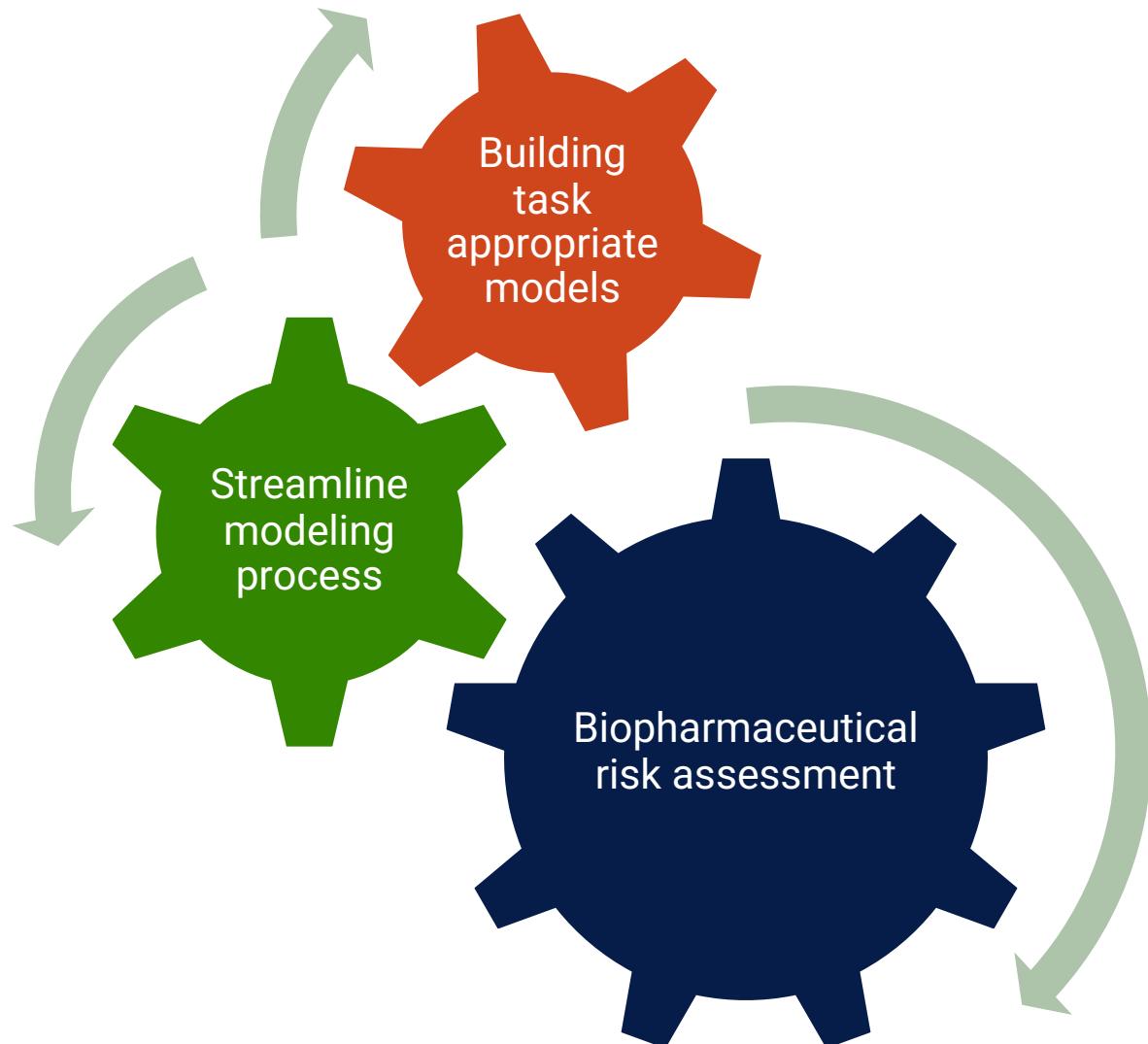
# Combination of in vitro and in silico tools for biopharmaceutical risk assessment in drug product development.

Fabian Winter

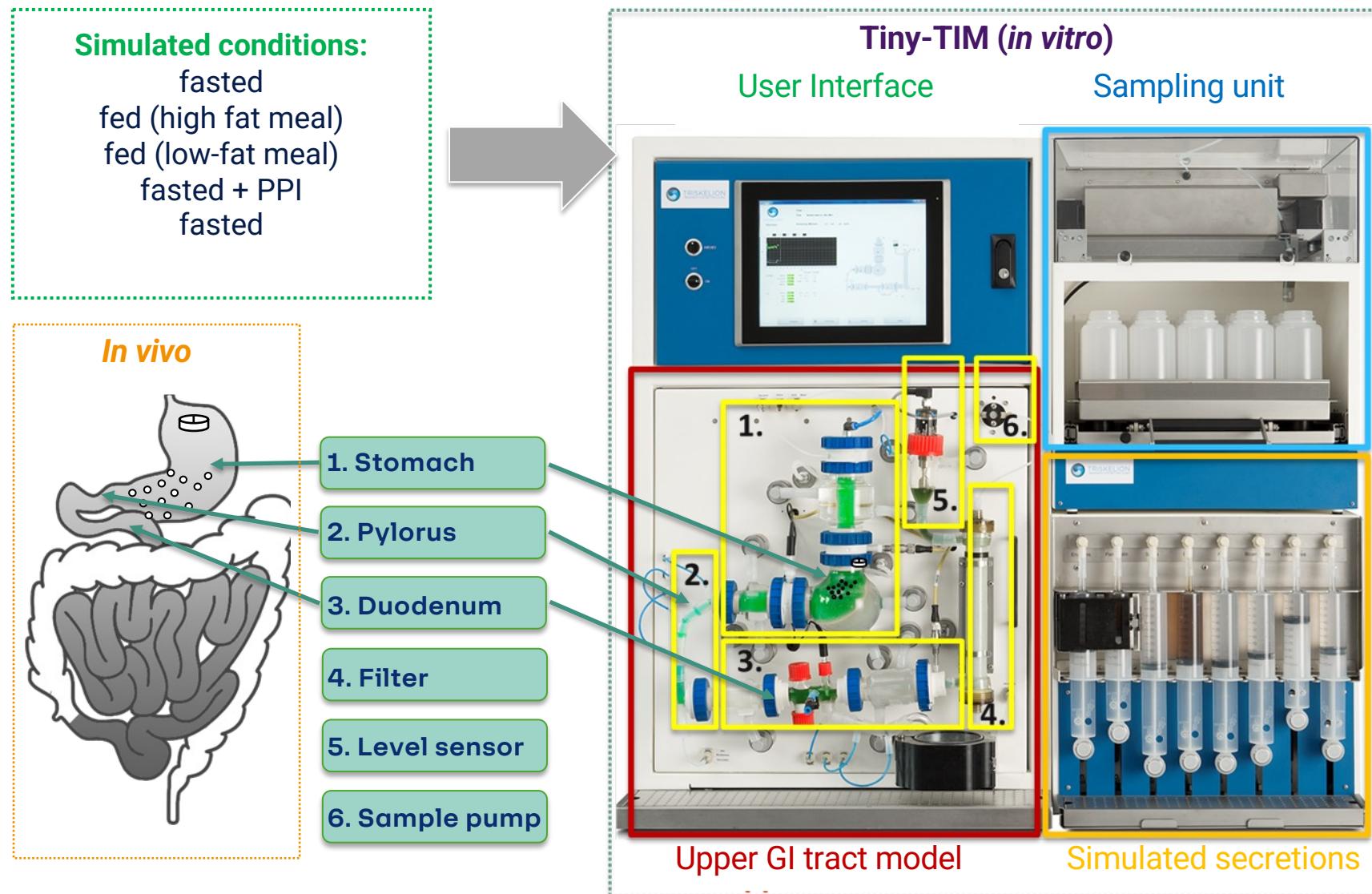
07. Oct. 2024



# Goals in biopharmaceutics modeling



# Tiny-TIM



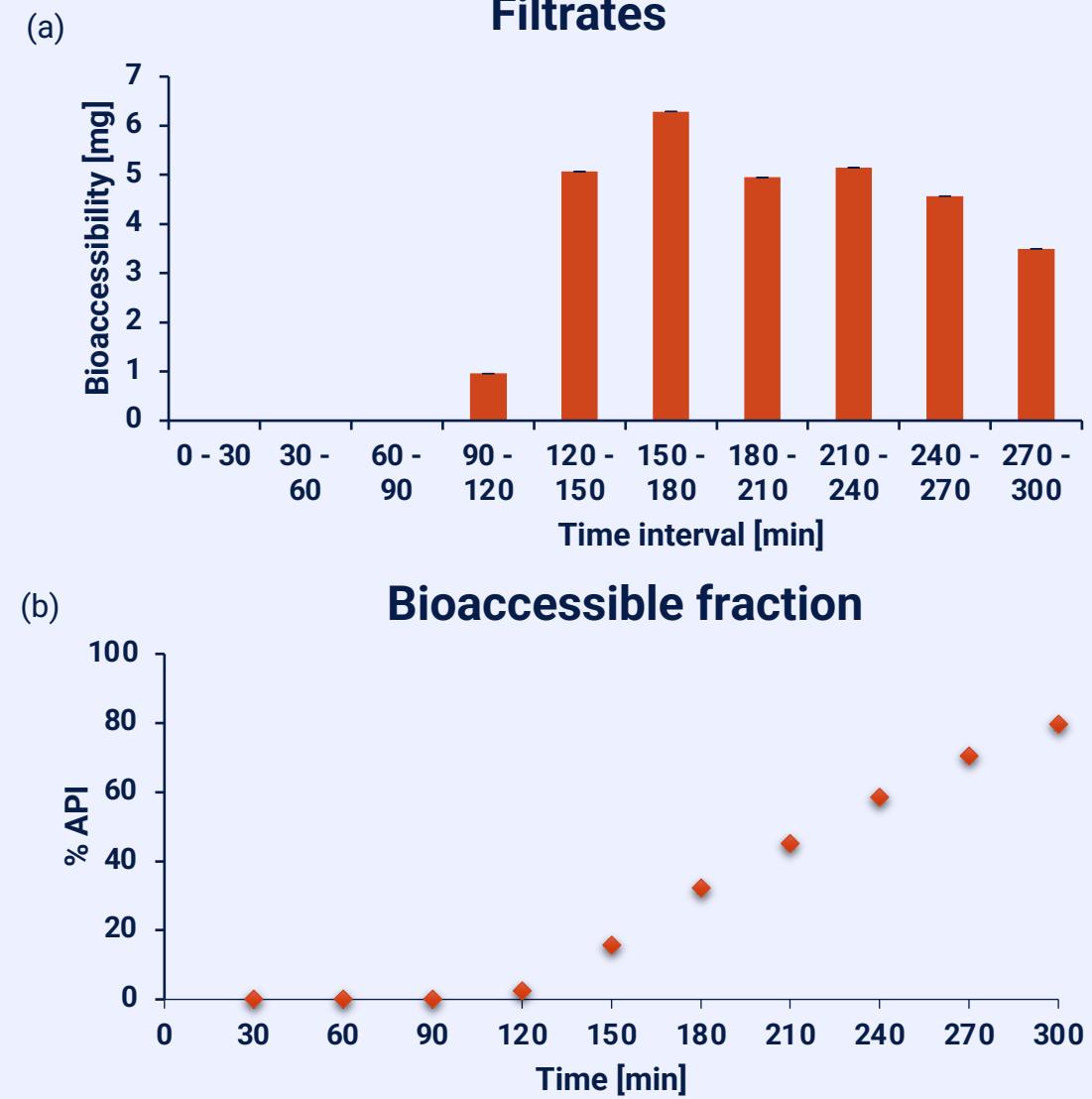
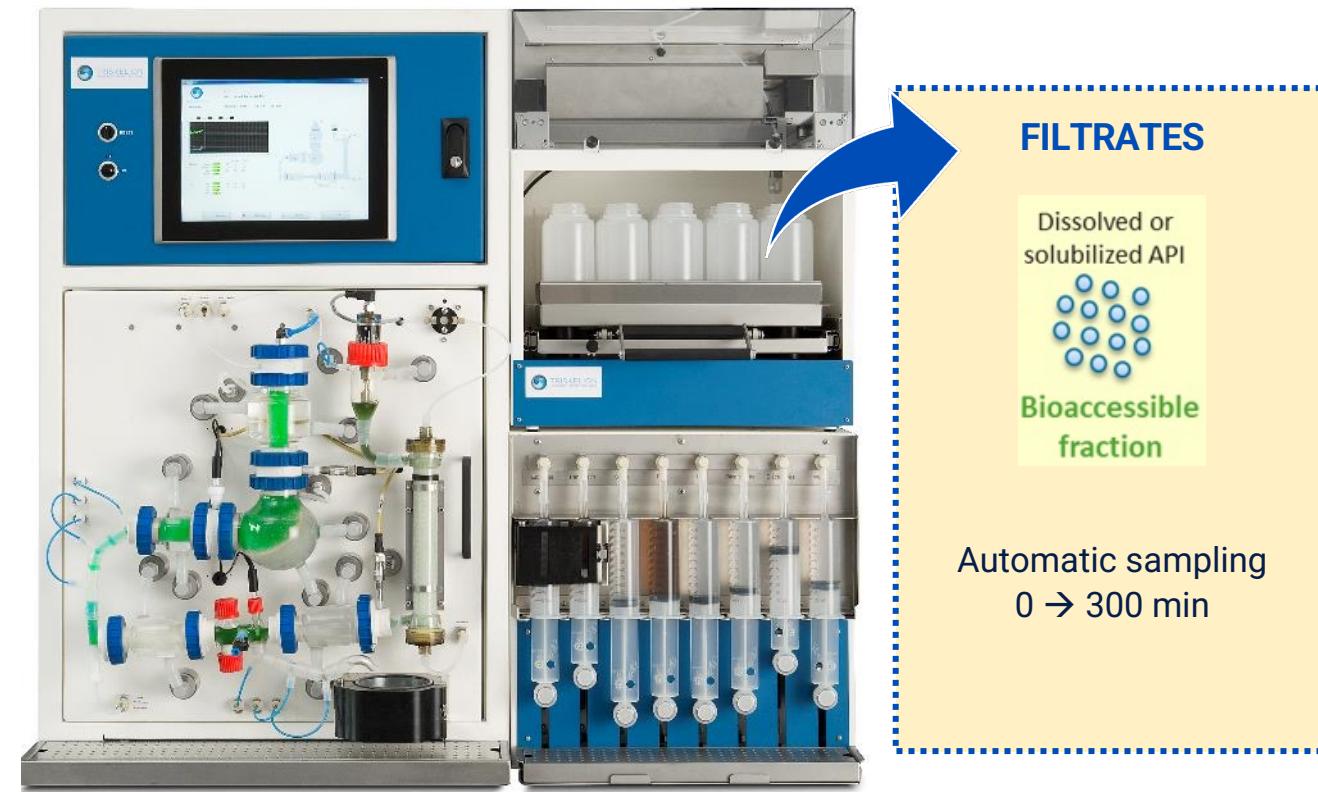
## Biorelevant simulation:

- GI fluid composition
- Dynamic changes caused by secretion and digestion
- Gastrointestinal motility (transit times)
- Gastric emptying as a function of the simulated prandial state

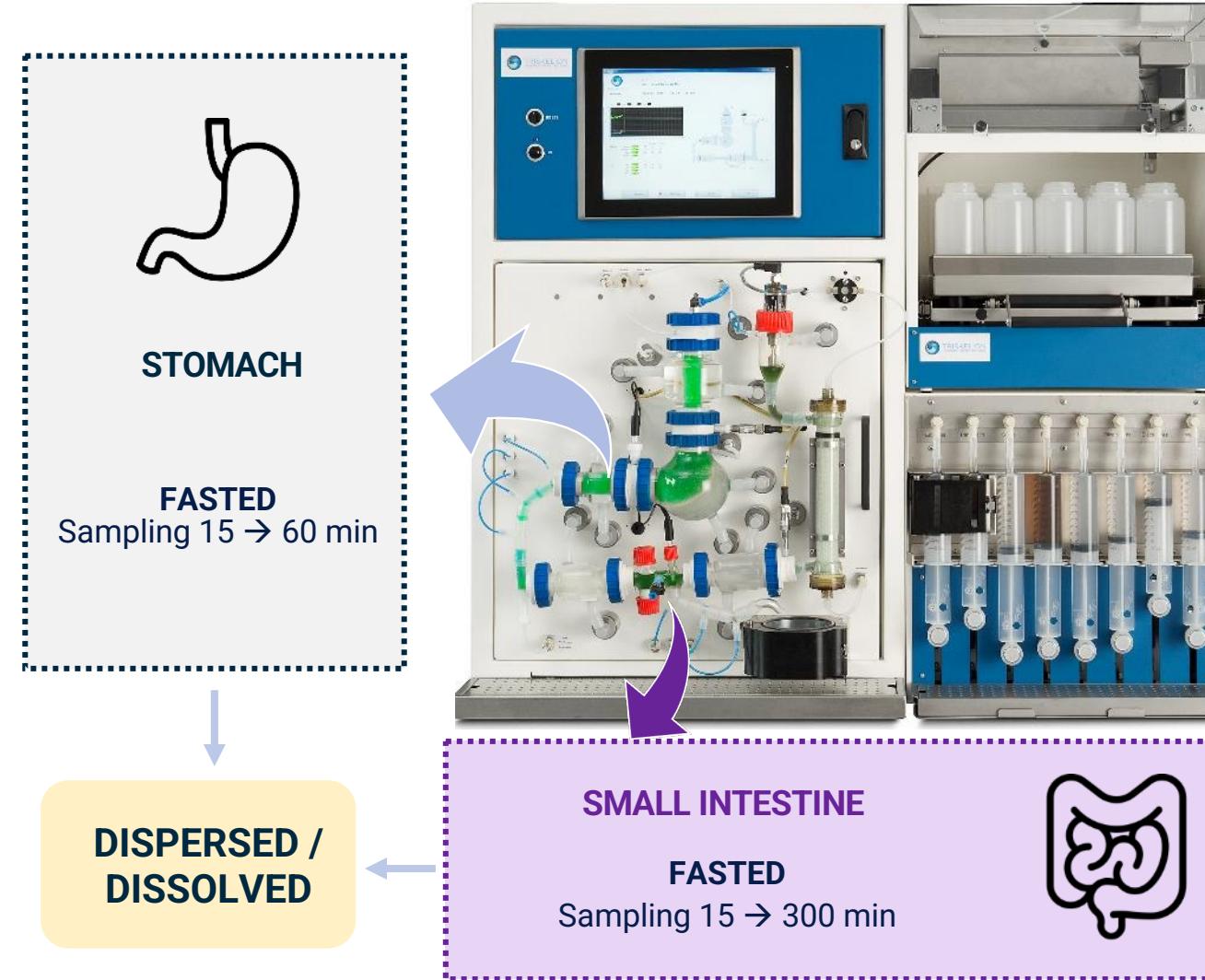
## Secretion:

- Bile
- Bicarbonat
- Saliva
- Water
- Enzymes
- Acid

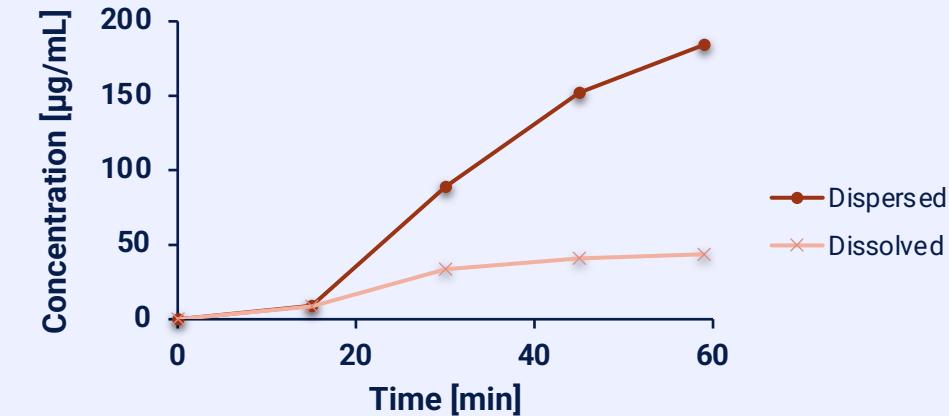
# Bioaccessibility



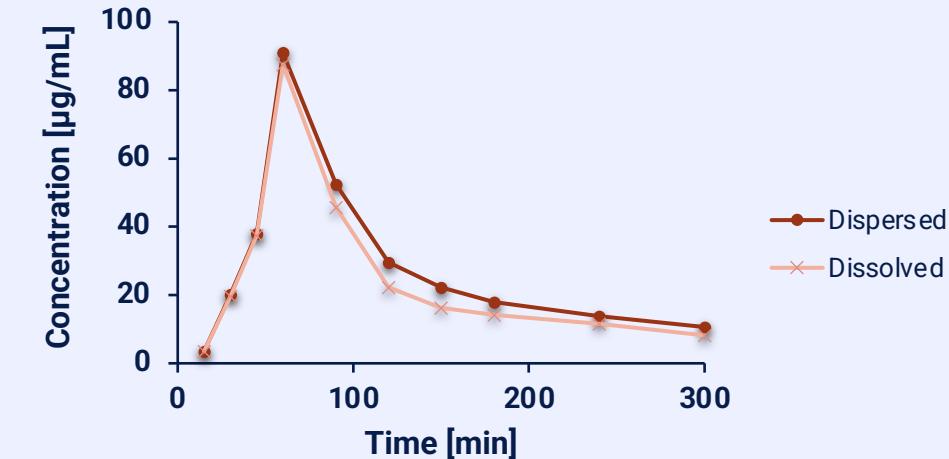
# Gastric and intestinal samples



## Gastric samples



## SI samples

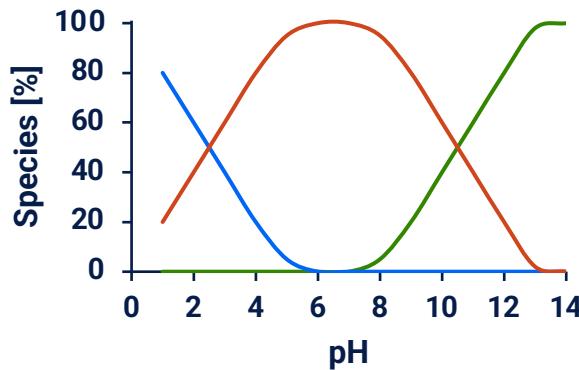


Drug concentration measured in gastric (a) and intestinal (b) TIM samples.

# Digital Tiny-TIM

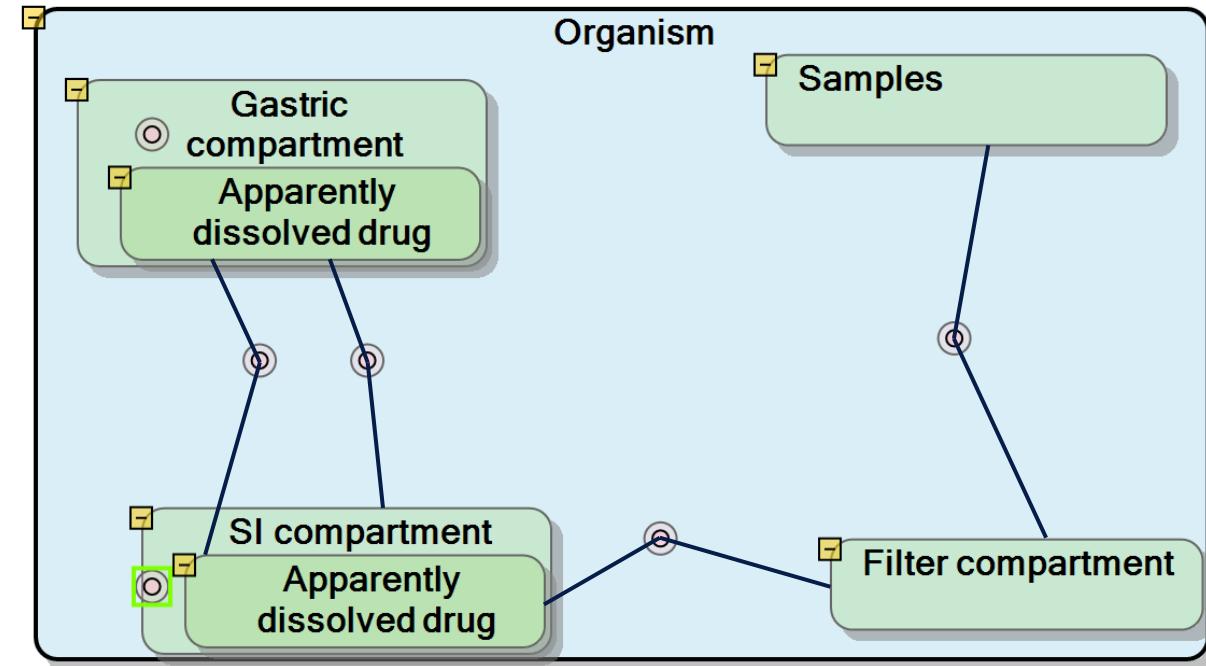
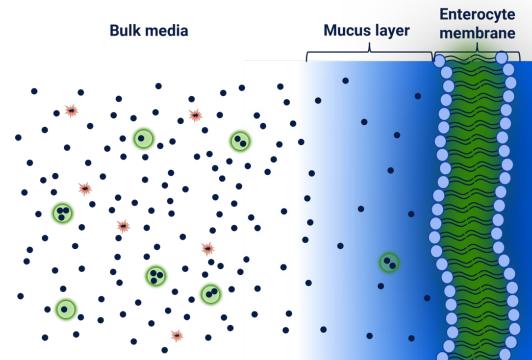
## Input:

- Solubility in buffer/TIM media
- Physicochemical characteristics ( $\log D$ ,  $pK_a$ )
- Measured concentration in gastric and SI samples
- pH
- Transfer rates



## Calculated/optimized parameters:

- Ionisation
- Micelle distribution
- Absorption rate
- Precipitation rate
- Volumes

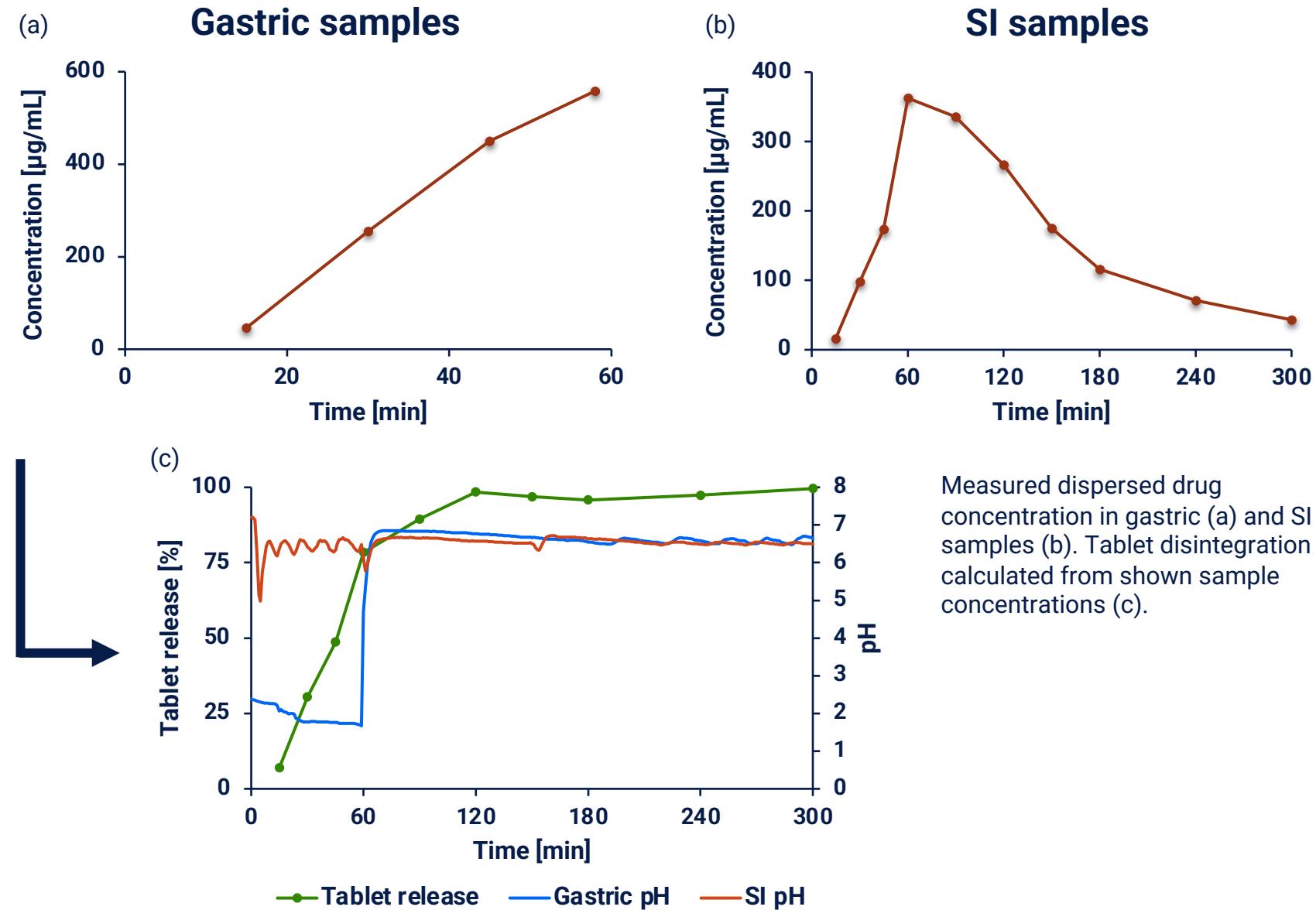


## Assumptions

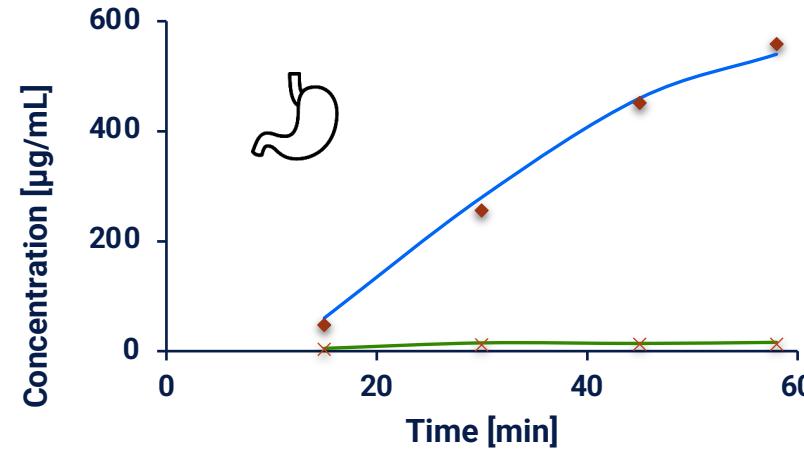
- Drug can only be transported to the same state (dissolved or undissolved)
- Within each compartment (gastric and SI) drug can precipitate or dissolve
- Only dissolved drug can be filtered
- Precipitation follows a first order rate process

# Tablet disintegration

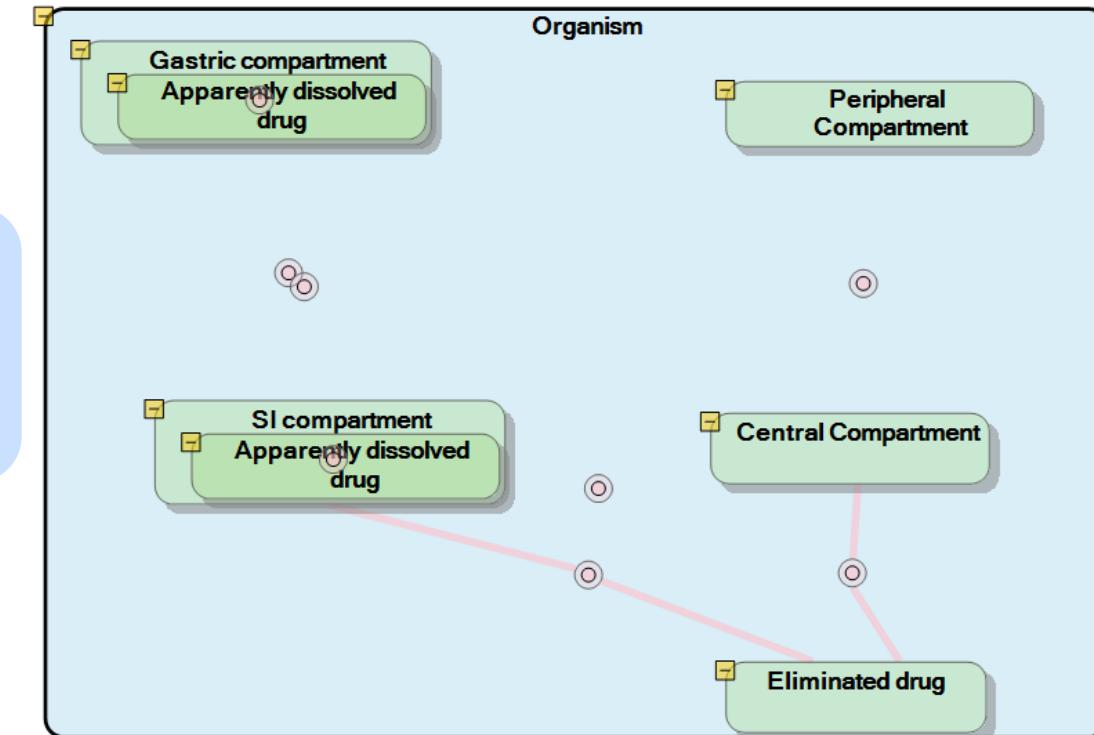
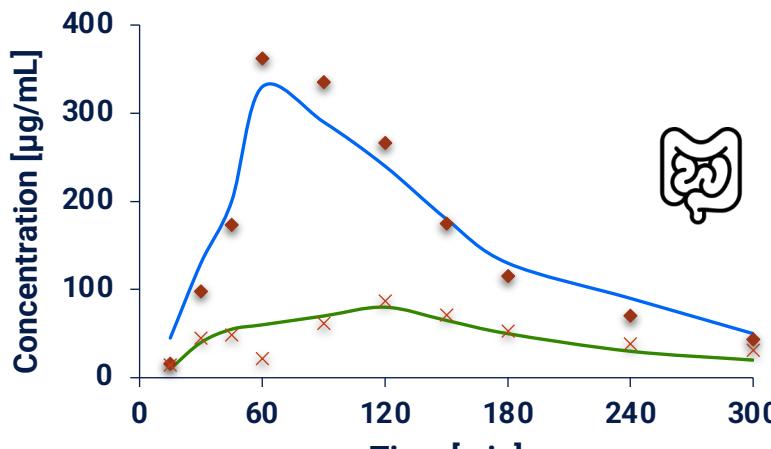
- Tablet release can be calculated from dispersed drug concentration in gastric and SI samples
- Effect of food and pH changes on tablet disintegration can be investigated
- Calculation considers drug transport and filtration
- Especially useful for eroding formulations



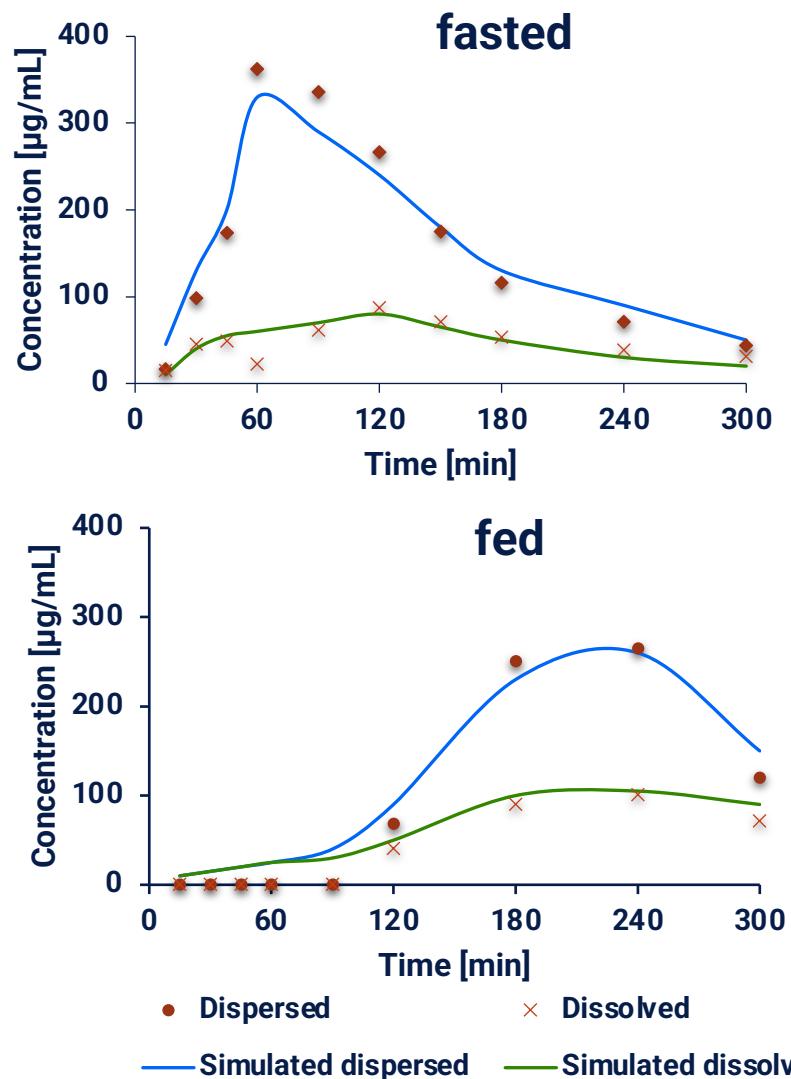
# Simulation and Optimization



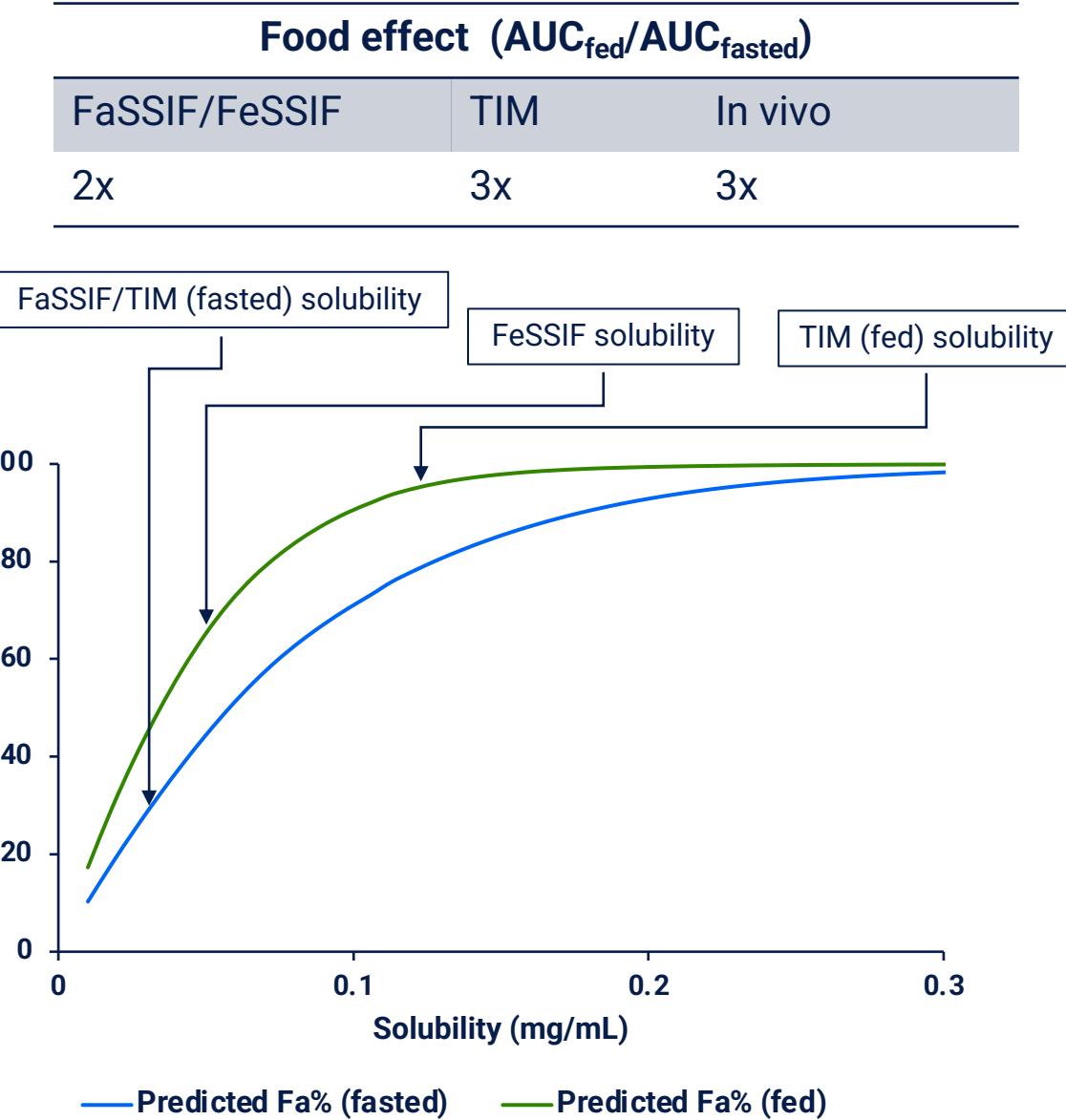
- ✓ Solubility
- ✓ Precipitation
- ✓ Micelle distribution
- ✓ Disintegration



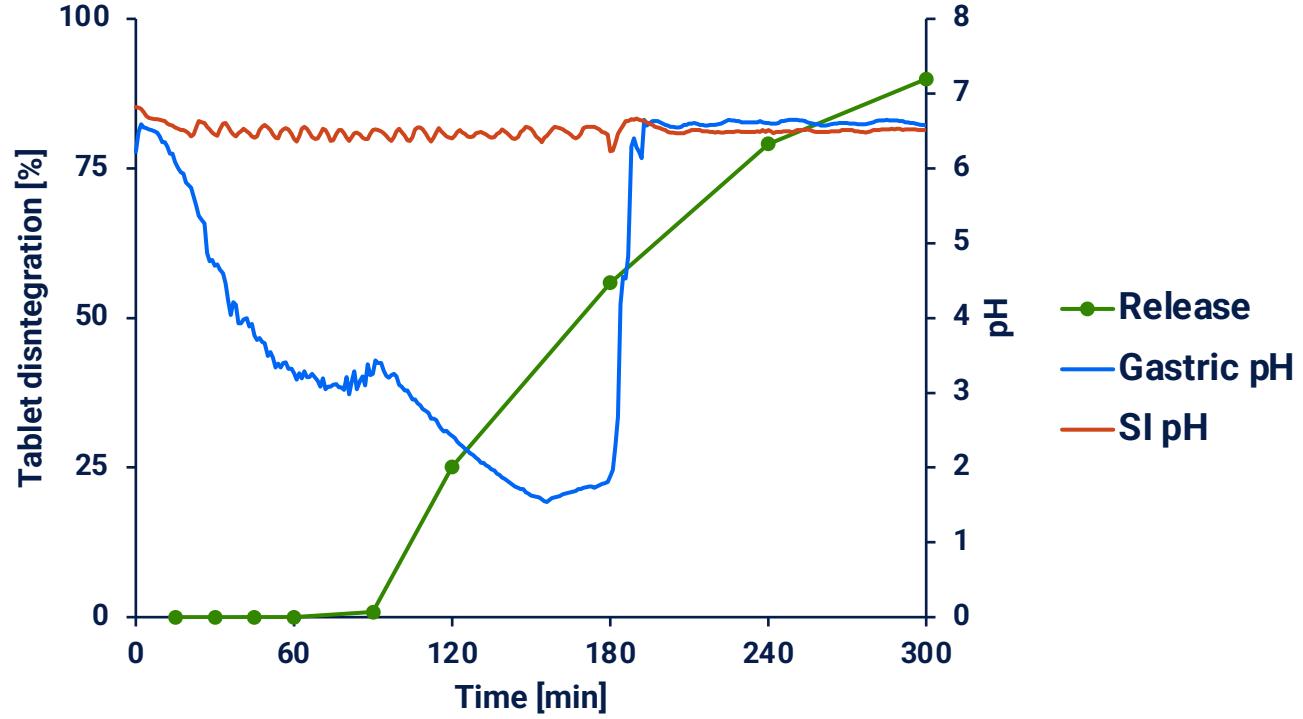
# Food effect prediction



✓ Food effect prediction using the input from the fasted and fed TIM



# Finding Outliers



Calculated disintegration of an eroding ASD in Tiny-TIM under fed state conditions.

# Food interaction

Tablet in Basket



Tablet



FaSSGF, pH 1.6

Milk 3.5% Fat, pH 6.5

High-Fat Meal, pH 5.0



Remaining rests  
of coating

High-Fat Meal

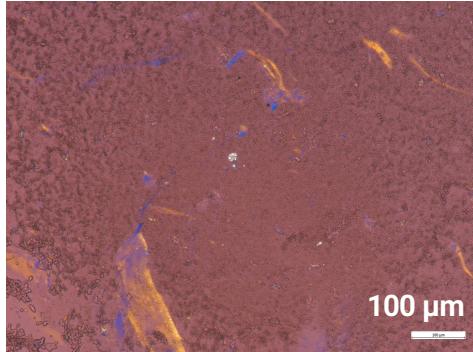
Remaining rests  
of coating

Tablet core

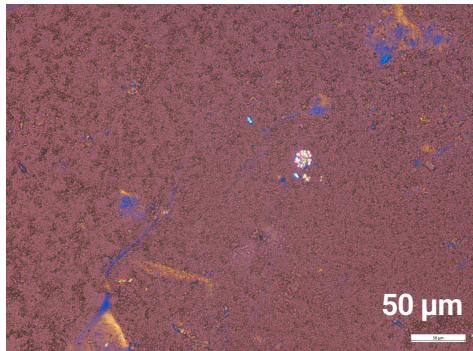
# Food interaction

FaSSGF, pH 1.6

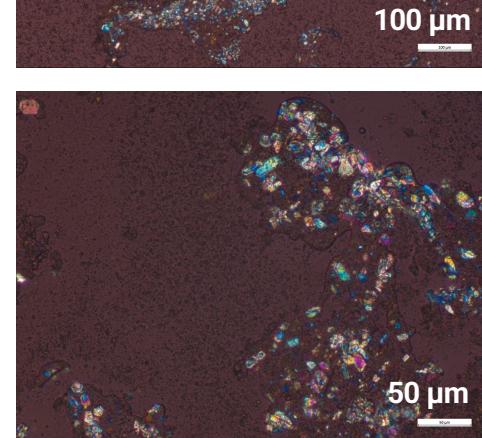
100x



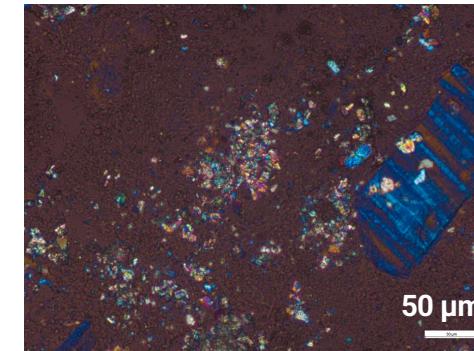
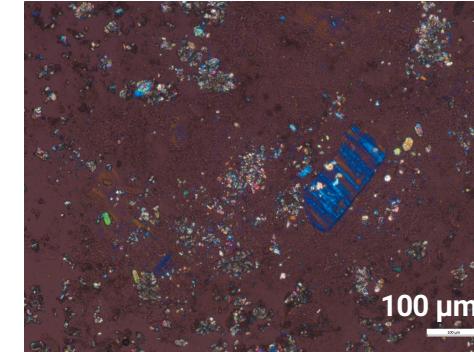
200x



Milk 3.5% Fat, pH 6.5



High-Fat Meal, pH 5.0

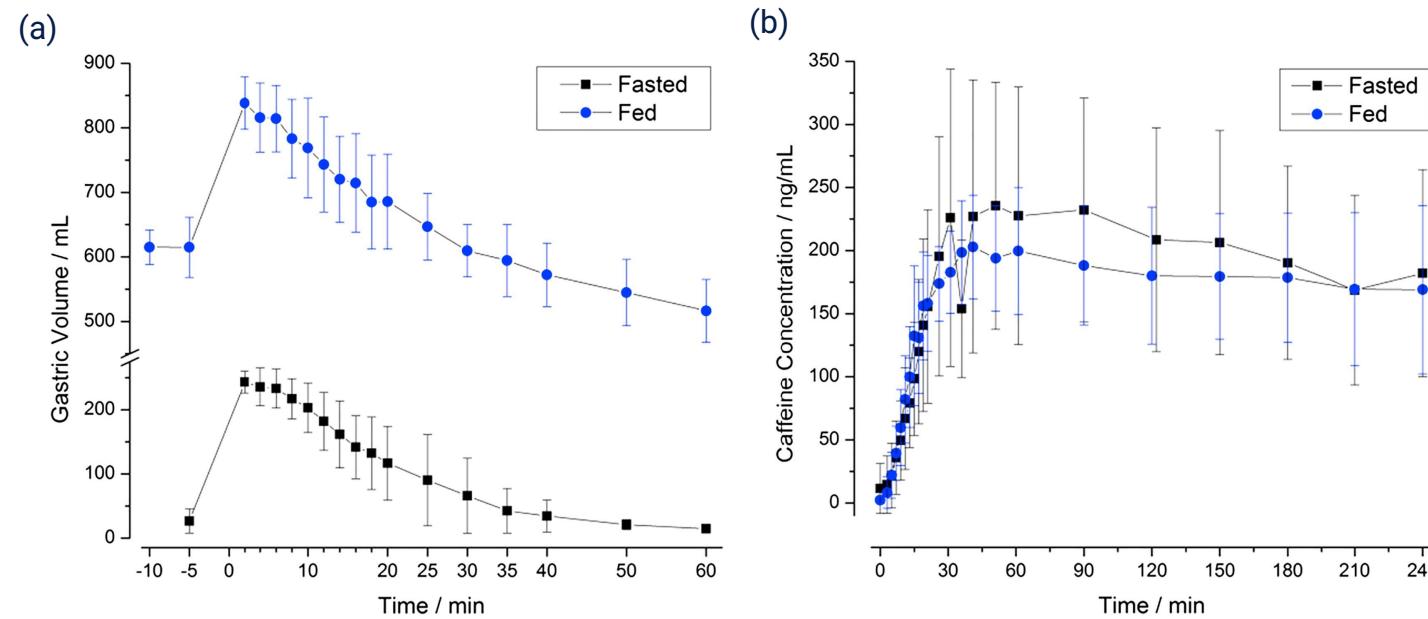
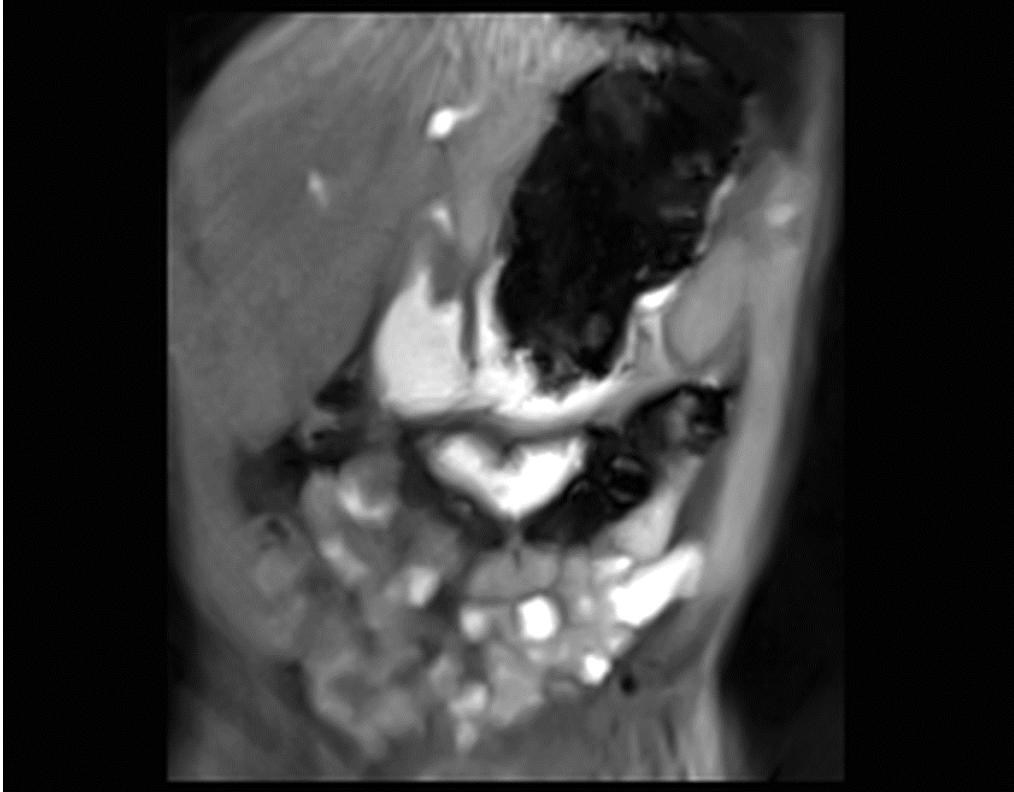


Polarized light microscopy taken after 60 min in different media.

## Observations

- Tablet core nearly fully intact after simulated high-fat meal conditions
- Tablet core completely eroded after 120 min in FaSSGF and milk
- Large crystalline clusters observed on tablet surface in milk and high-fat meal

# Rapid gastric emptying via the stomach road

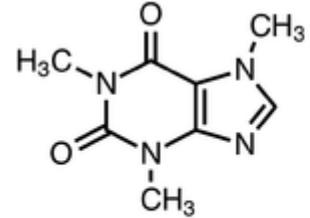


Gastric content volume (a) and caffeine salivary concentration (b) after intake of 25 mg caffeine in fed and fasted state ( $n = 6$ )

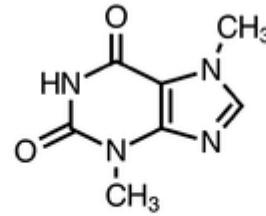
## Observations

- Water and dissolved drug can empty the stomach
- Drug has to dissolve rapidly to be able to empty with the ingested water

# Gastric emptying in PK-Sim



caffeine



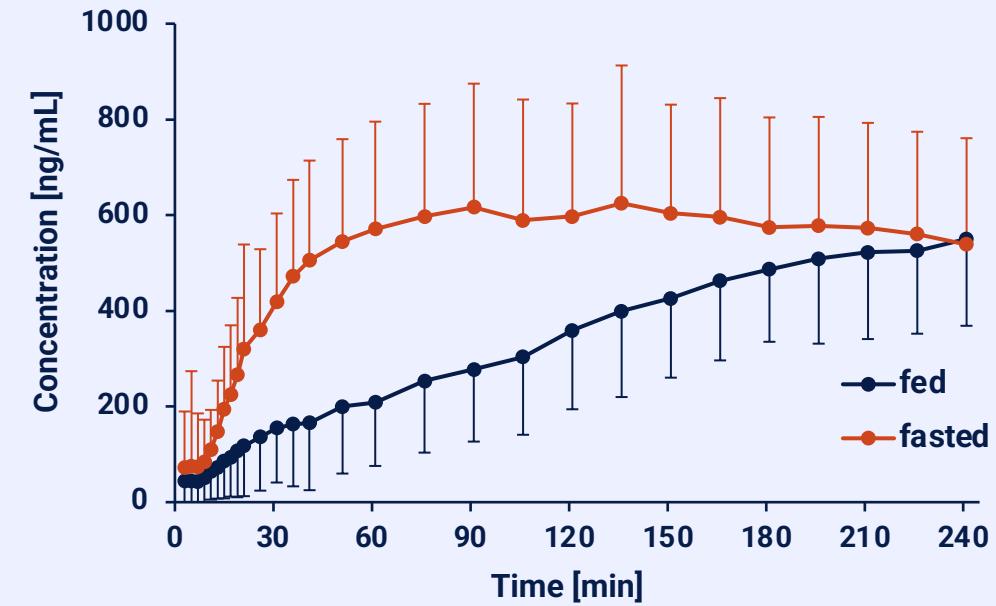
theobromine

## Observations



In comparison to caffeine, theobromine can not empty the stomach rapidly in fed state

Both are rapidly absorbed in fasting conditions

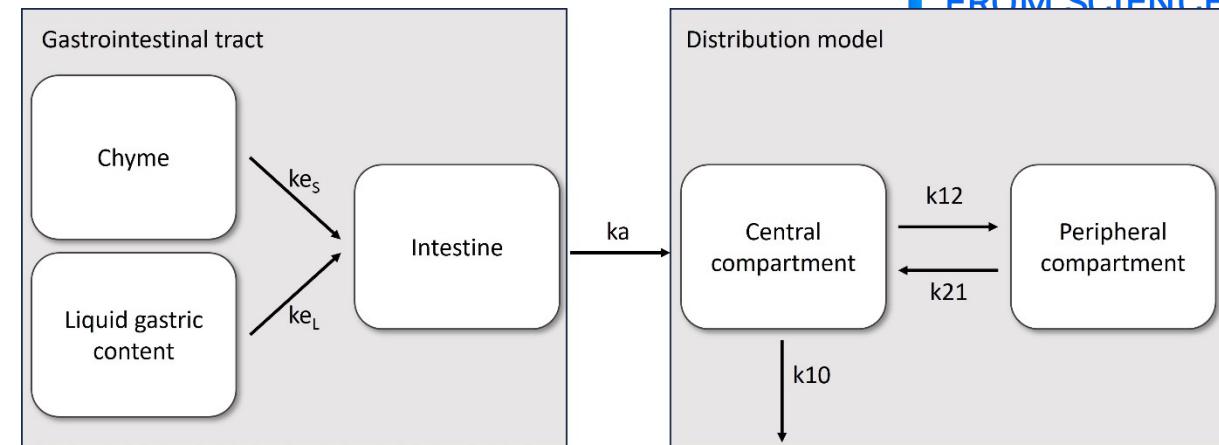


Salivary concentration of theobromine after intake in fasted and fed state.

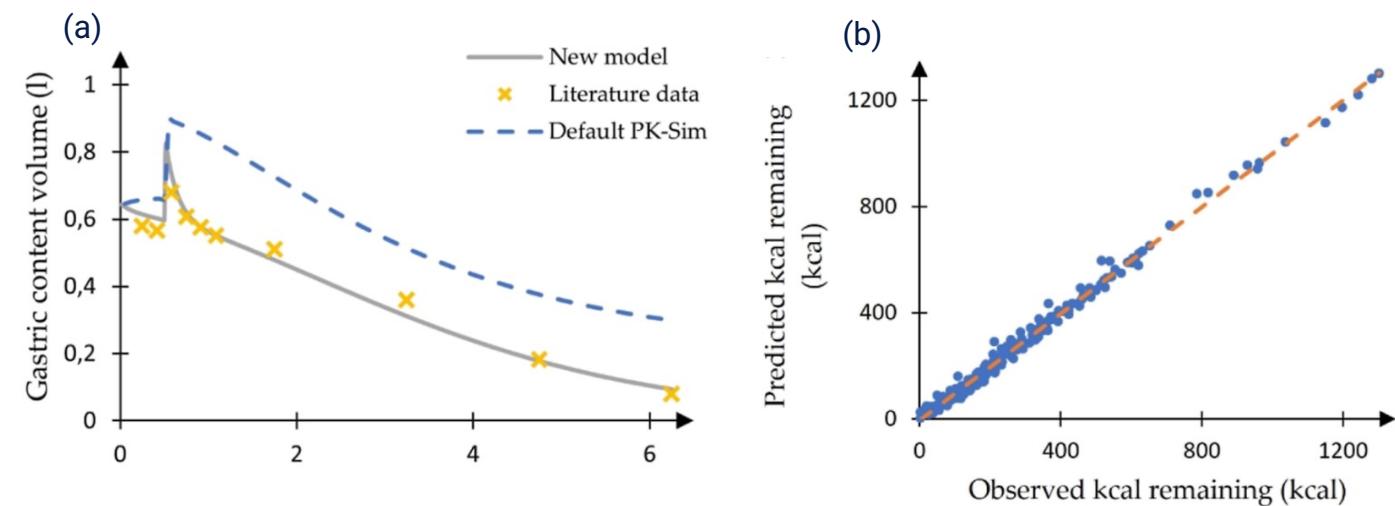
# Gastric emptying model

$$\frac{d(w)}{d(t)} = w \cdot \frac{k \cdot t_{50\%} \cdot \left( \frac{t}{t_{50\%}} \right)^{2 \cdot k \cdot t_{50\%} / \ln(2) \cdot V_0} \cdot 2^{1 - \left( \frac{t}{t_{50\%}} \right)^{2 \cdot k \cdot t_{50\%} / \ln(2) \cdot V_0}}}{t \cdot V_0}$$

- Multiple linear regression model
- Predict gastric content volume and gastric emptying rate based on meal calories and fat content
- Gastric emptying rate calculated as derivative of gastric content volume + secretion rate
- Biphase process
- Simulation of the stomach road

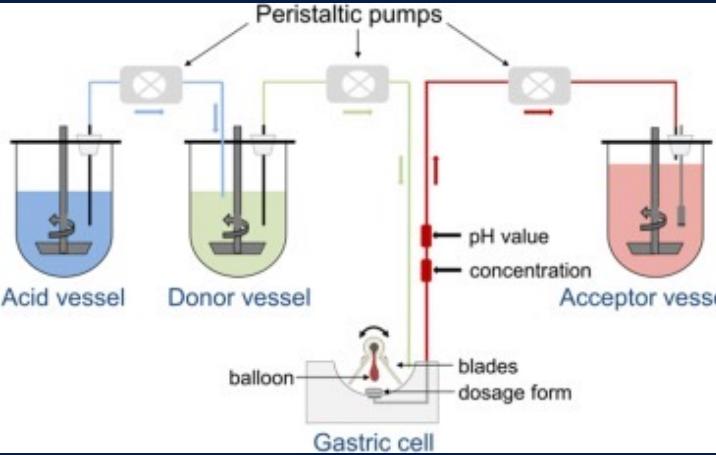


Schematic representation of mechanistic gastric emptying model incorporated in PK-SIM



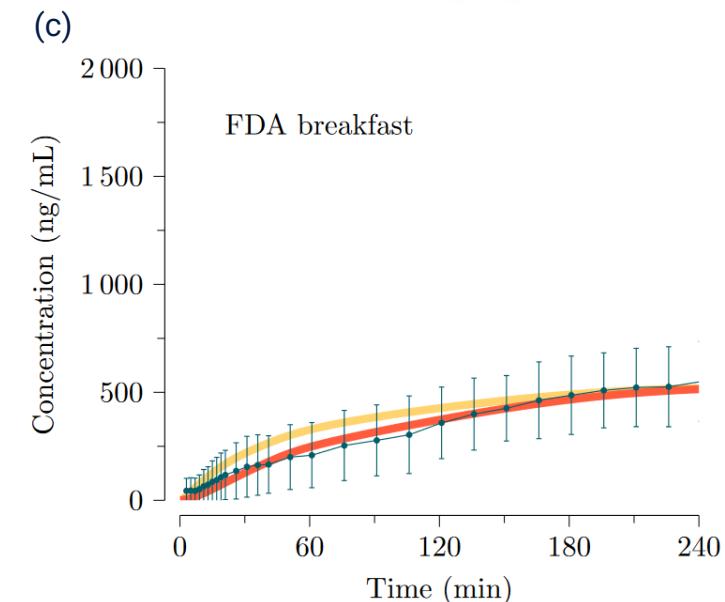
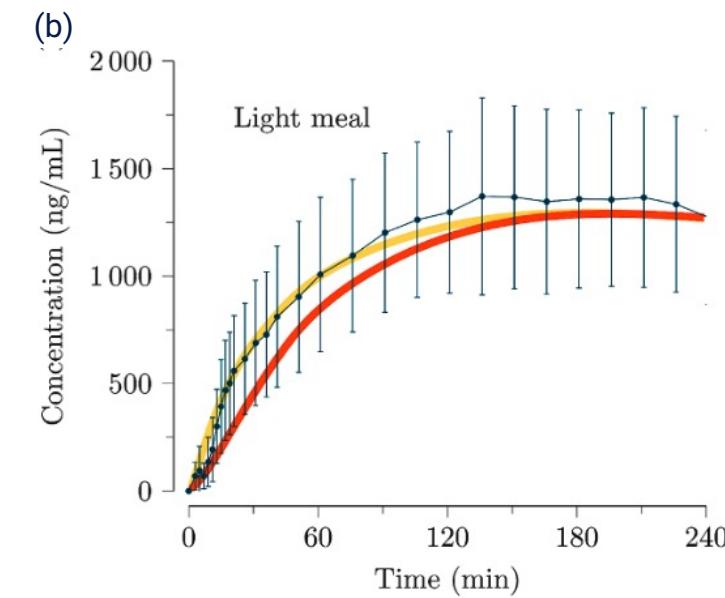
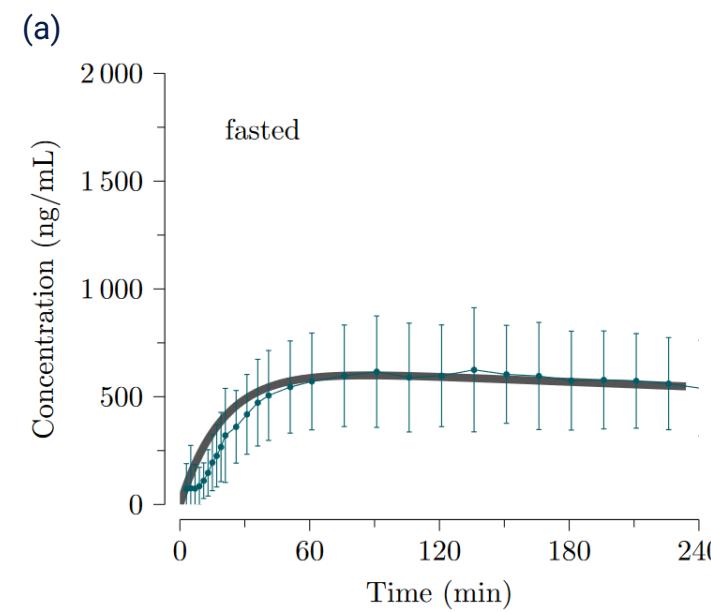
Comparison of the new gastric emptying model with default PK-Sim in simulating gastric content volume after ingestion of high-calorie high-fat meal (a) and predicted vs. observed plot for all data points for different meals

# Using *in vitro* Input



## GastroDuo

- Biorelevant dissolution test device that allows the simulation of certain
- Construction is based on the fed stomach model and the dynamic open flow-through test apparatus



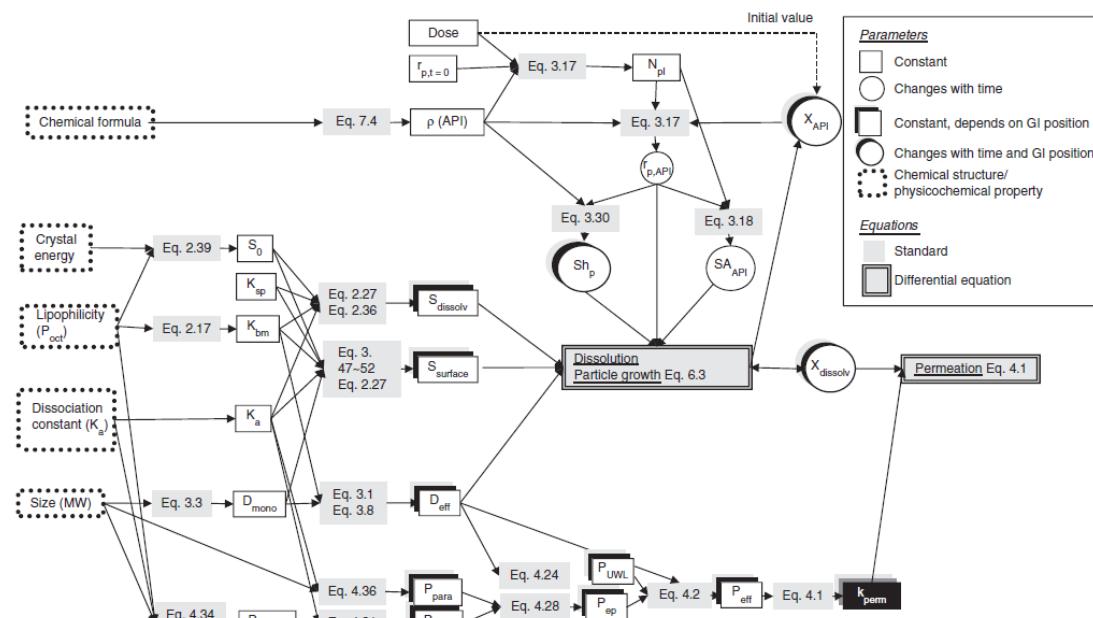
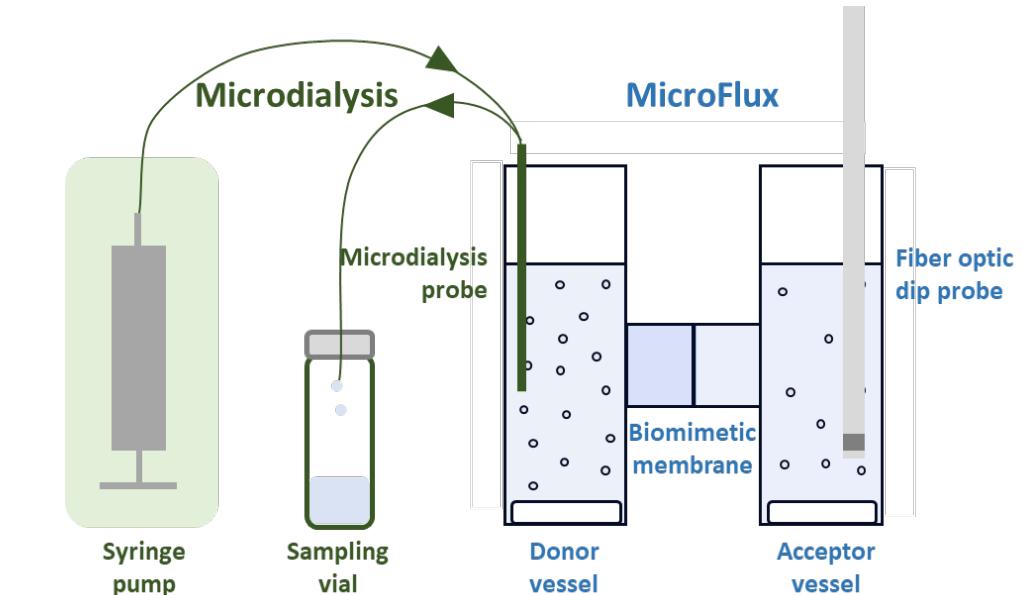
- Gastric emptying is rate limiting step for high absorption drugs in immediate release formulations
- Integration of results from GastroDuo in presented gastric emptying model.

25 mg theobromine dosed in fasted (a) and high-fat conditions (b). 75 mg dosed after intake of light meal (500 kcal). Integration of results from GastroDuo in presented gastric emptying model.

# Streamline simulation efforts



- MicroFlux integration build on the gut framework presented by Sugano et al.
- Calculation of  $P_{eff}$  considering  $P_{ep}$  and  $P_{WUL}$
- Used for preclinical formulations



# Thank You

abbvie