

Capturing Fasting Gastric Motility and pH Variability *In Vitro* to De-Risk Development of Oral Medicines

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What is important for de-risking IR formulation development?

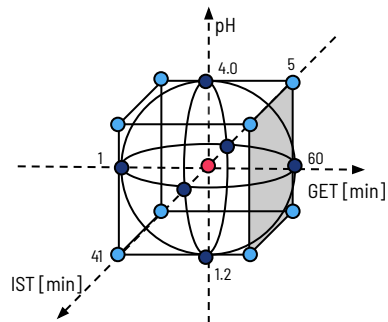
Identification of critical parameters

How to do it?

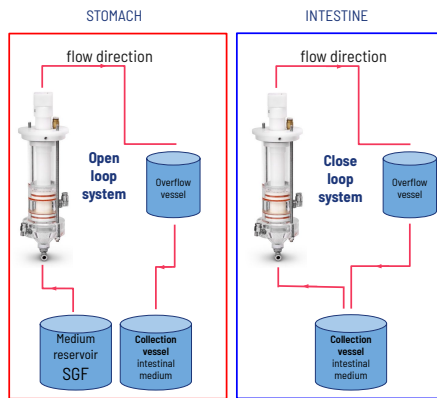


How to de-risk IR formulation development?

Rationally parametrized **variability of fasting** intake conditions

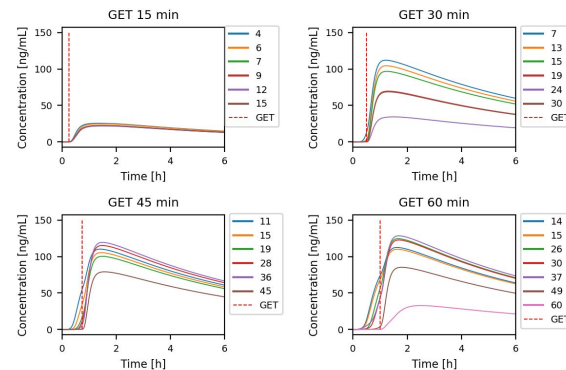


Reliable and straightforward biopredictive test



SGF - pH 1.2 - 4.0; Intestinal medium - 50 mM PB, pH = 6.5, 0.3% SLS

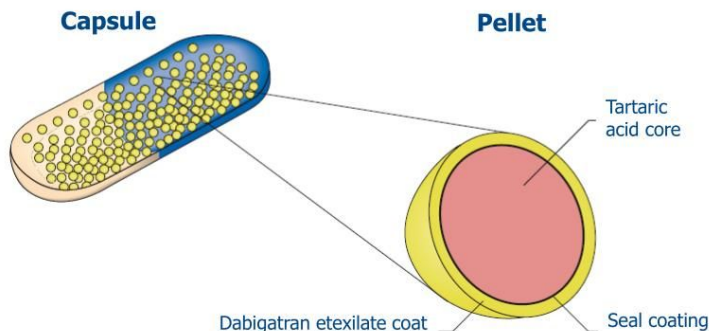
Understanding the **influence of GI physiology on dissolution** to predict *in vivo* performance.





Same drug - different PK

The capsule formulation of dabigatran etexilate



CAPSULES WITH PELLETS	vs	BARE PELLETS
↑ 3-fold greater variability		↑ 75% higher AUC_{0-inf}
↑ 25% longer T_{max}		↑ 86% higher C_{max}

- High solubility under gastric and low under intestinal conditions
- Weak base drug of pKa 4.0
- pH modifier in pellets

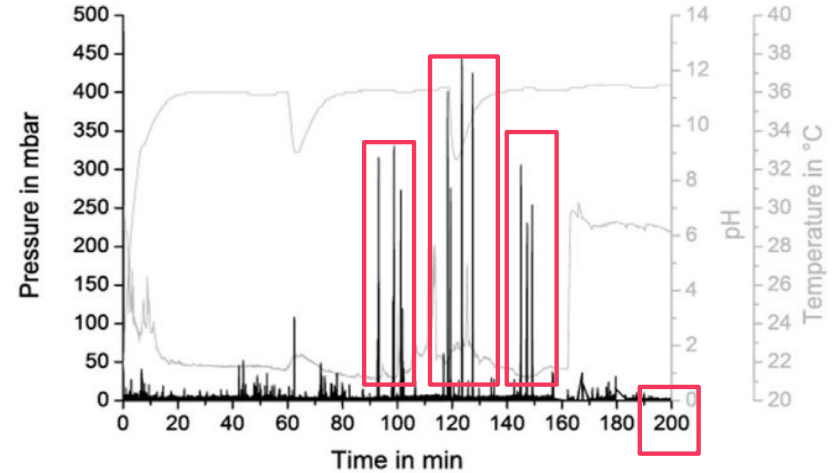
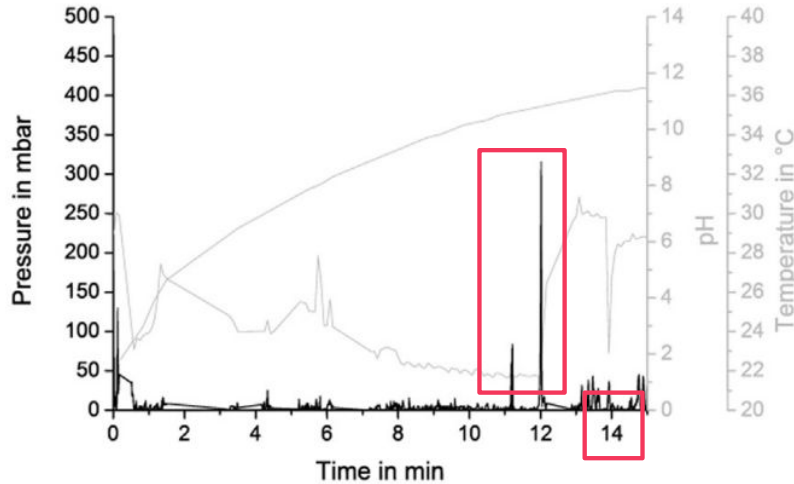
Are the variable gastric motility patterns the reason?



Physiological aspects of the fasted stomach

Variable gastric emptying residence times and intragastric pressures

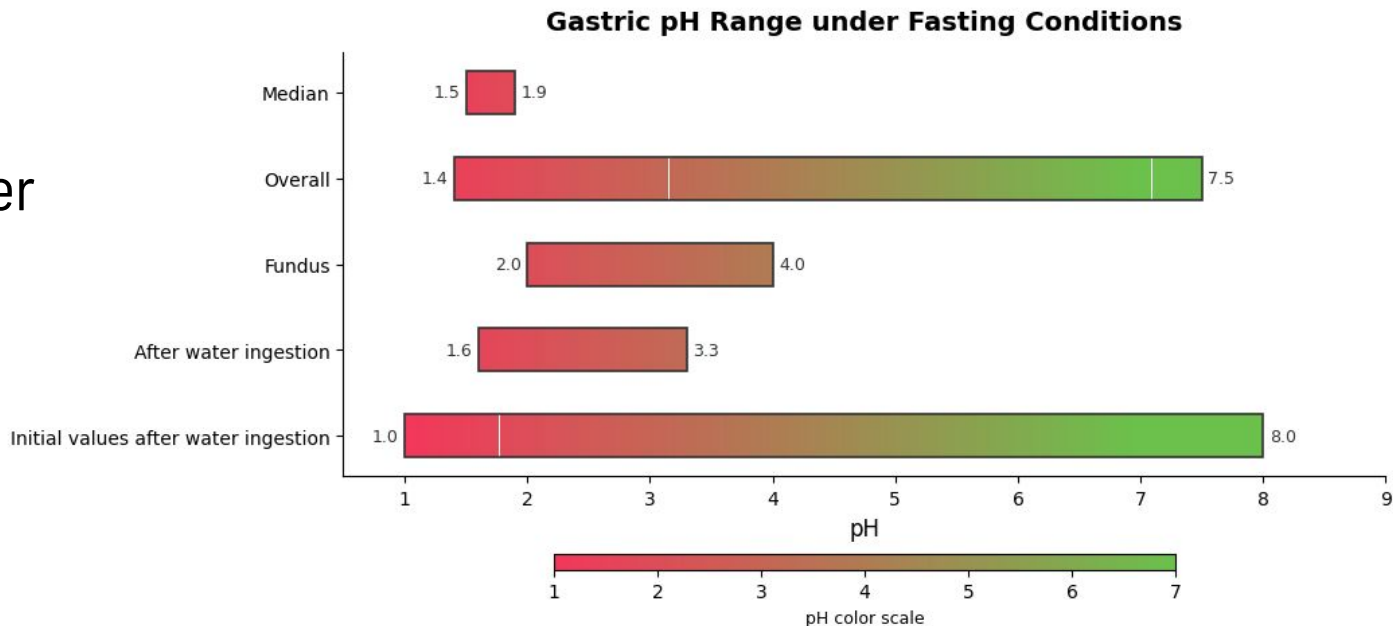
Gastric pressure profiles measured in vivo after fasted state ingestion of the SmartPill®





Physiological aspects of the fasted stomach

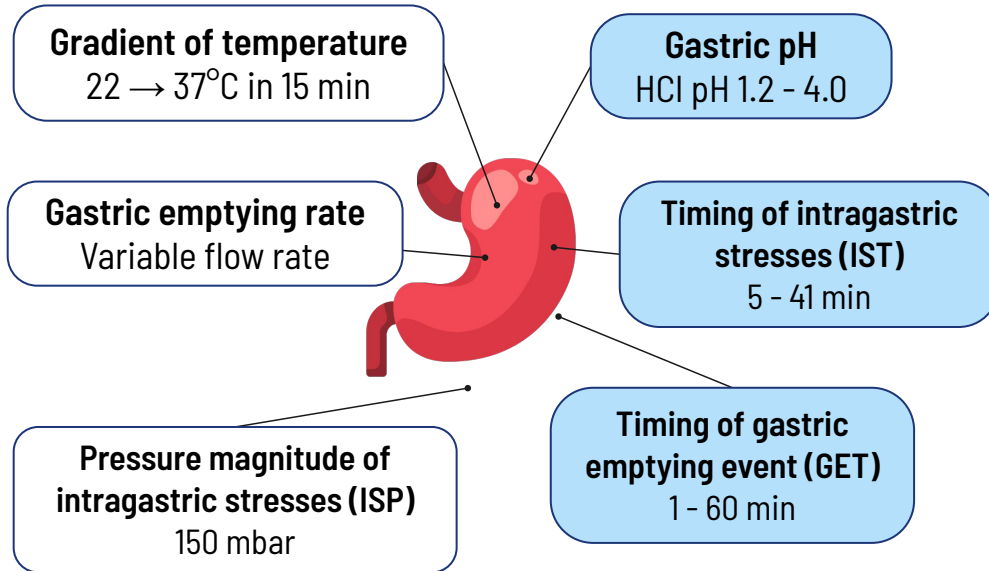
Variable pH,
especially after
water intake





Physiological parameters variability

*Physiological parameters
of interest*



Nearly endless number of
physiologically -relevant
parameter combinations

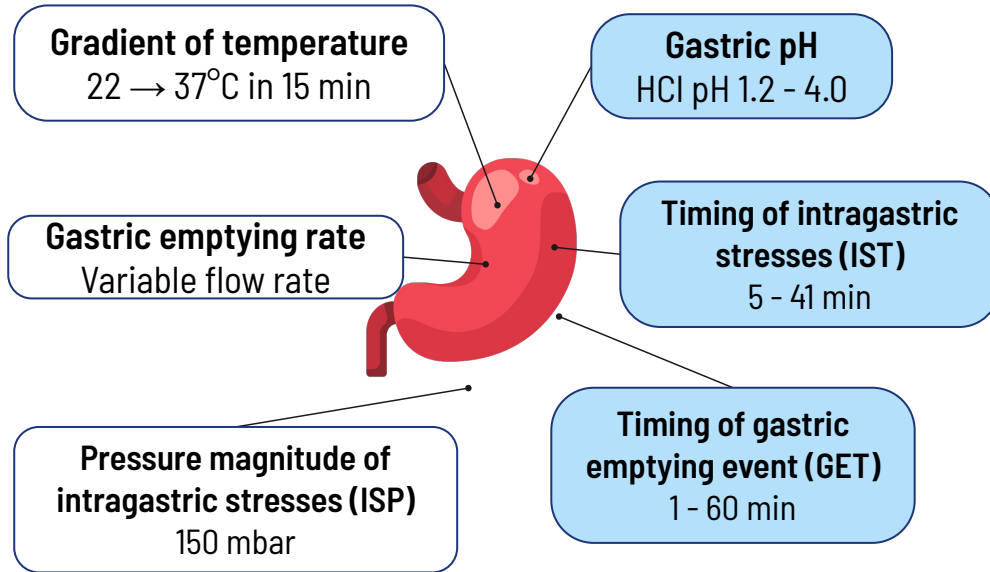


Finished number of
in vitro dissolution tests?

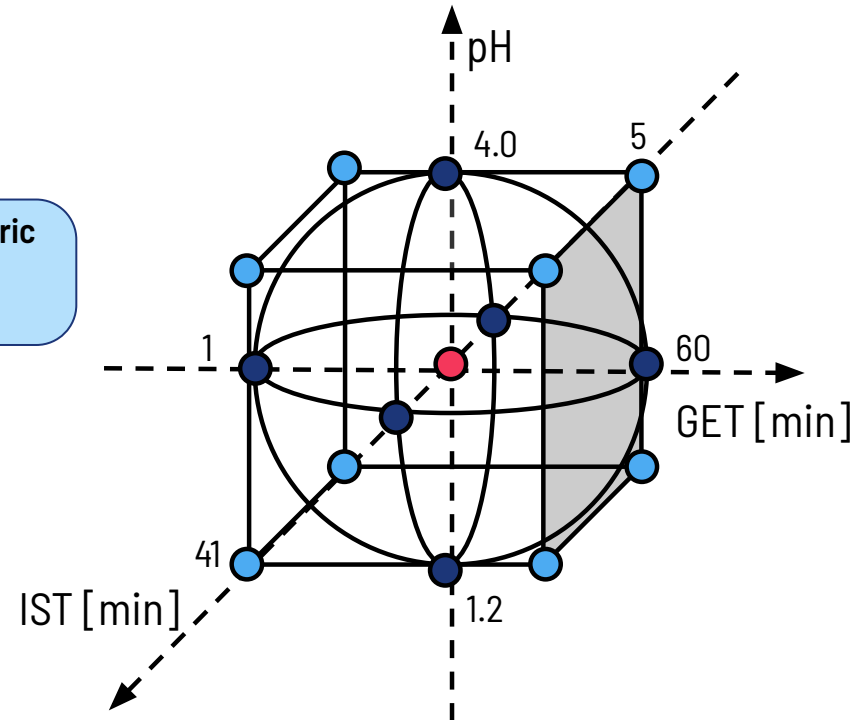


DoE - finite number of tests with full variability coverage

*Physiological parameters
of interest*



*3D physiological test space
designed with DoE*

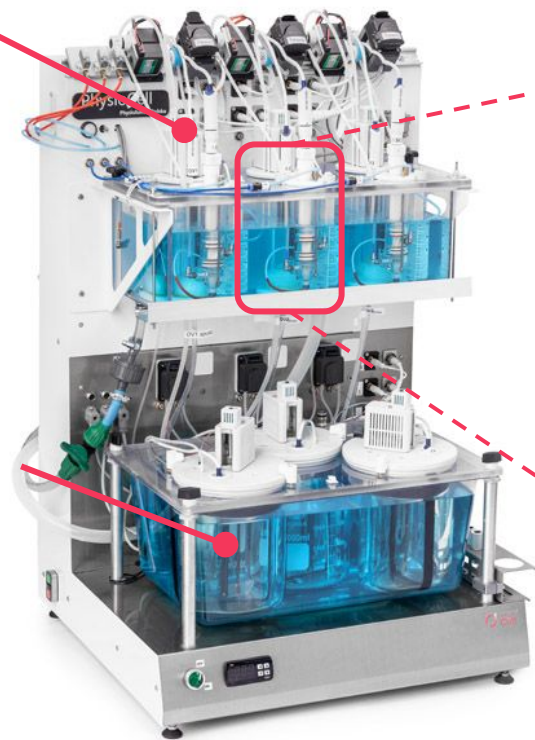




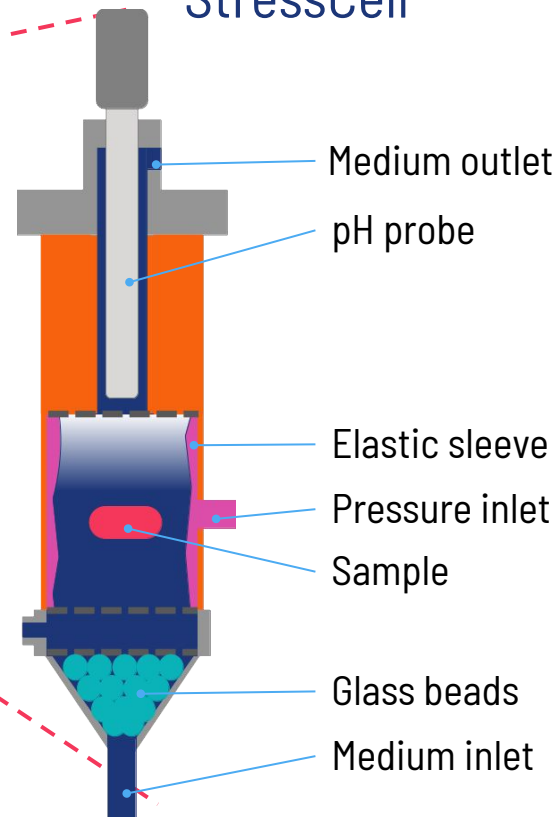
Dissolution apparatus - PhysioCell

Overflow Vessel

Collection Vessel



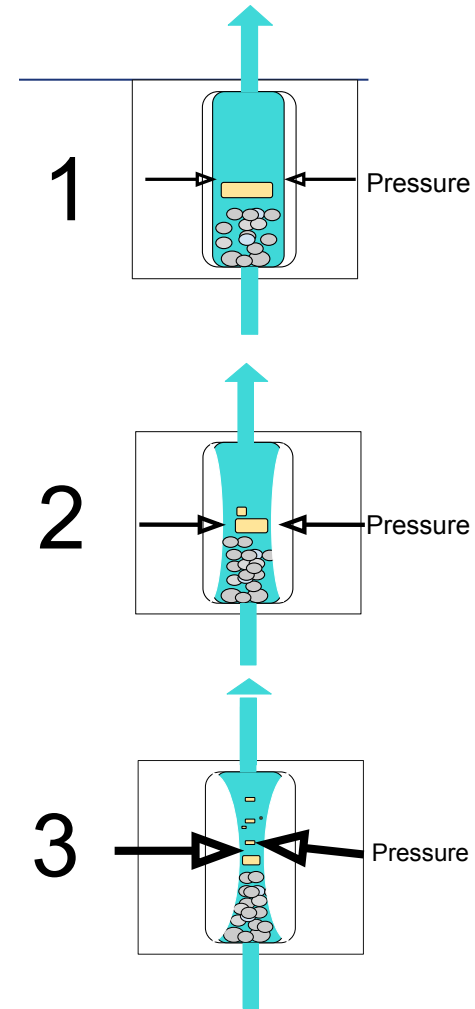
StressCell



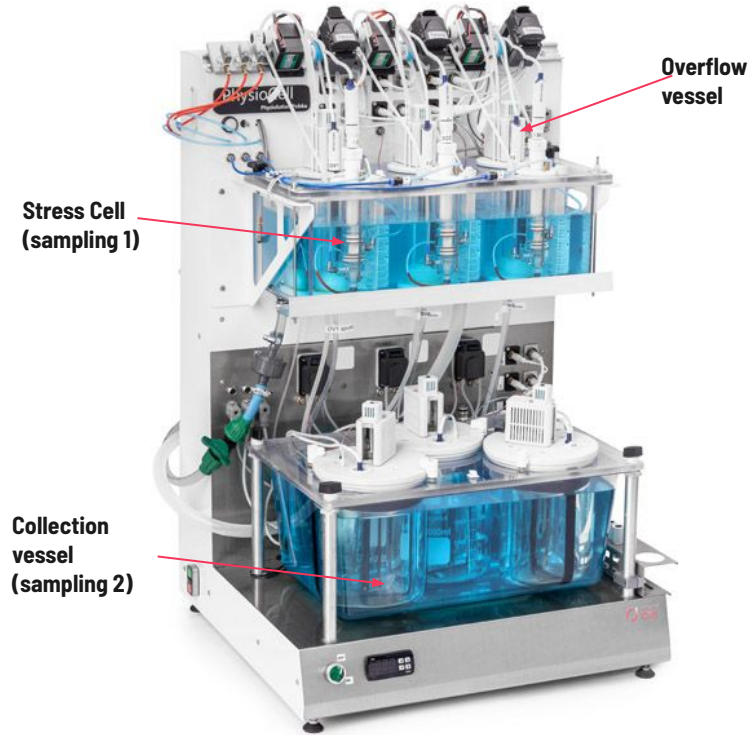


StressCell

- **Flow-through cell**
- **Small volume** (ca. 30 mL) of the dissolution medium in the probe chamber
- Simulation of **motility forces**
- pH and temperature measurement
- **Temperature gradients:** temperature increase from about 25 up to 37 °C within 10 - 15 min
- **Variable kinetics of gastric emptying** of non caloric liquids

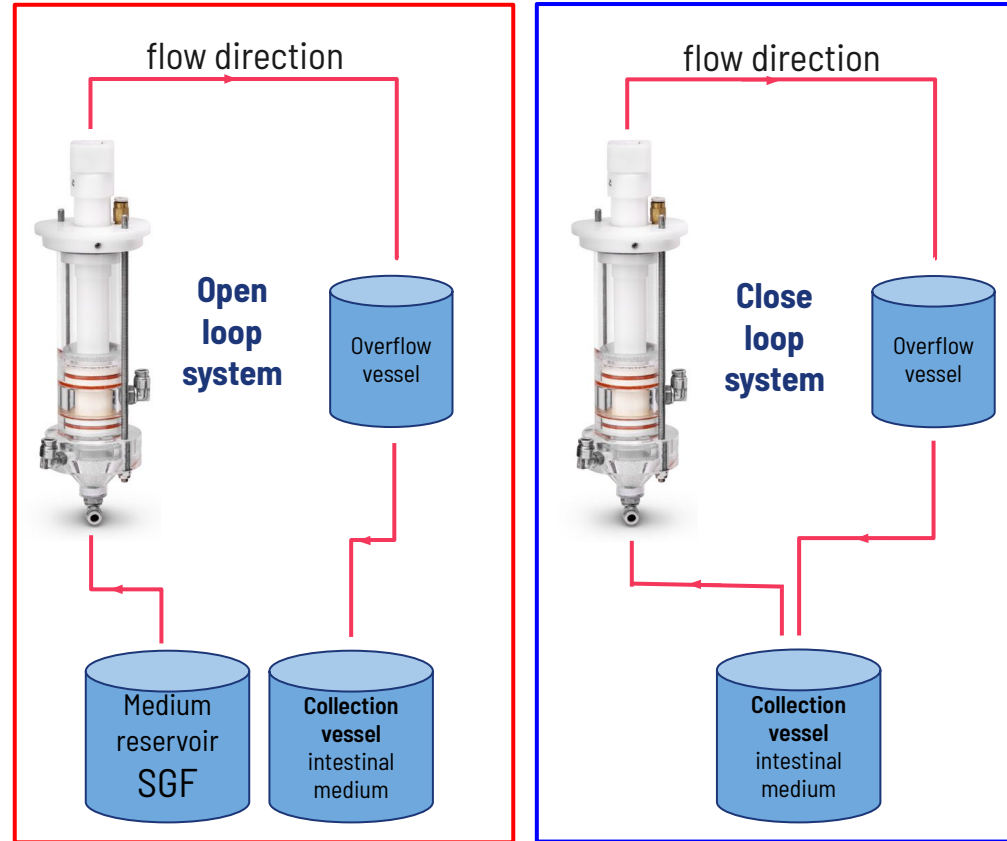


PhysioCell compartments



STOMACH

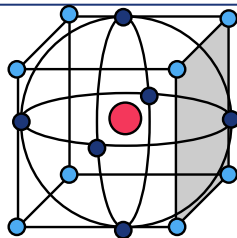
INTESTINE



SGF - pH 1.2 - 4.0; Intestinal medium - 50 mM PB, pH = 6.5, 0.3% SLS

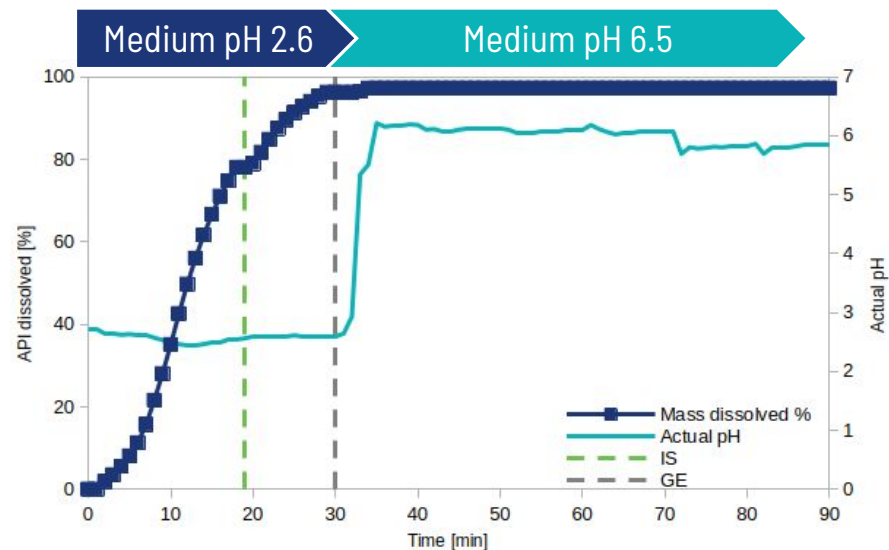
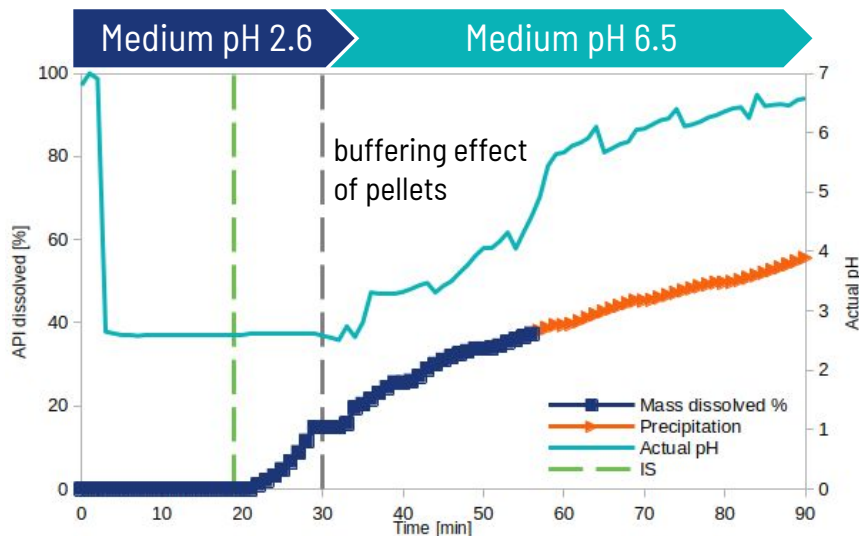


DoE central point dissolution results



Capsules in the StressCell

Pellets in the StressCell



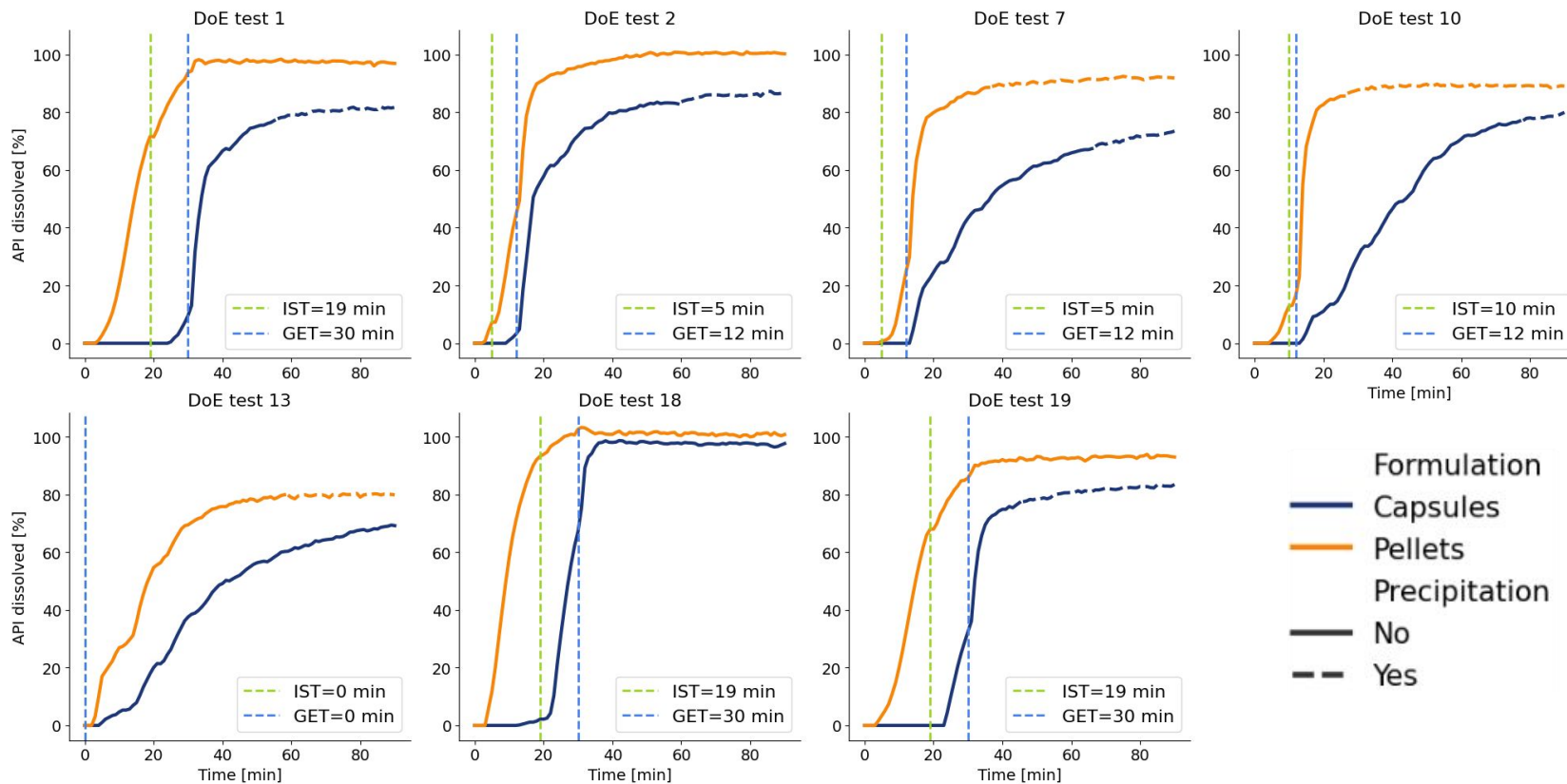
- Precipitation correlated with the pH increase.
- Disintegration triggered by the stress event.
- Incomplete dissolution due to the precipitation.

- Fast dissolution onset.
- Complete dissolution before GE, no precipitation.



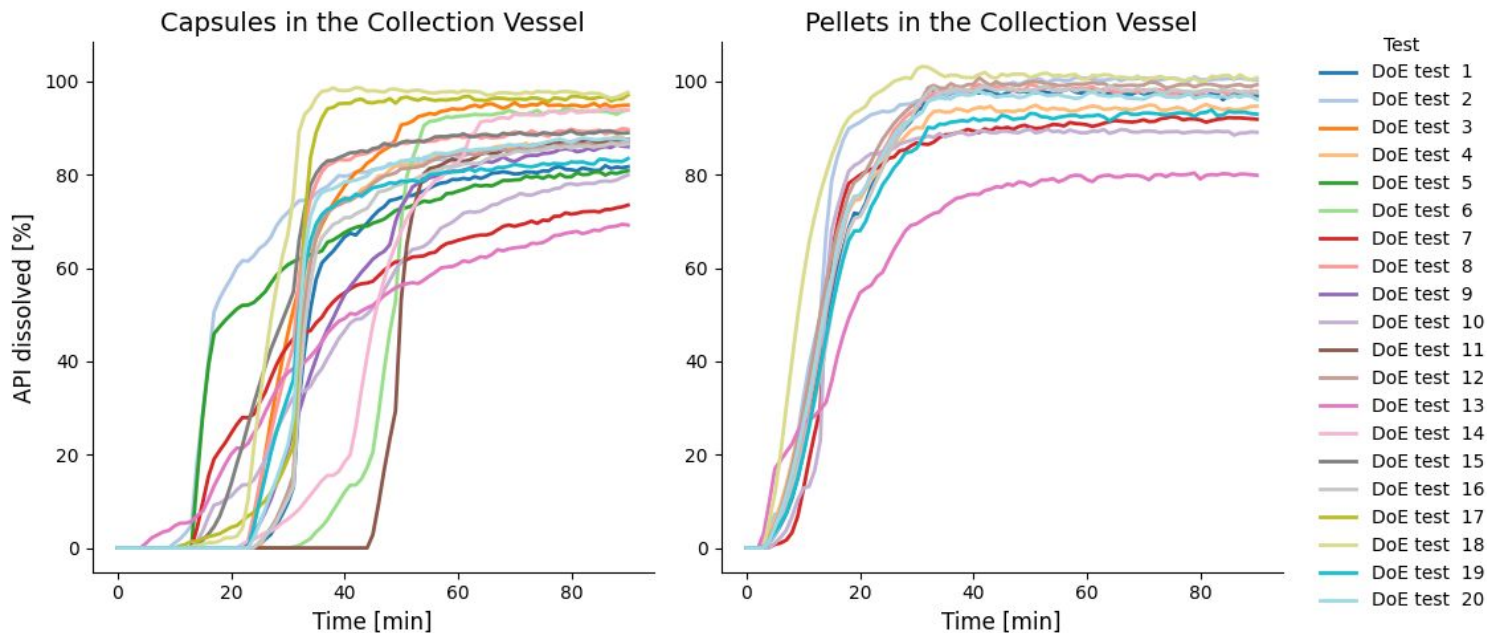
Dissolution of pellets in capsules vs loose pellets

Higher and faster dissolution of **pellets** in comparison to **capsules**.





Higher variability of capsules vs pellets



	Capsules 150 mg	Pellets 150 mg
AUC_{0-inf} [ng · h/mL]	599	1050
Geom. CoV [%]	93.3	33.8
T_{max} [h]	2.0	1.5



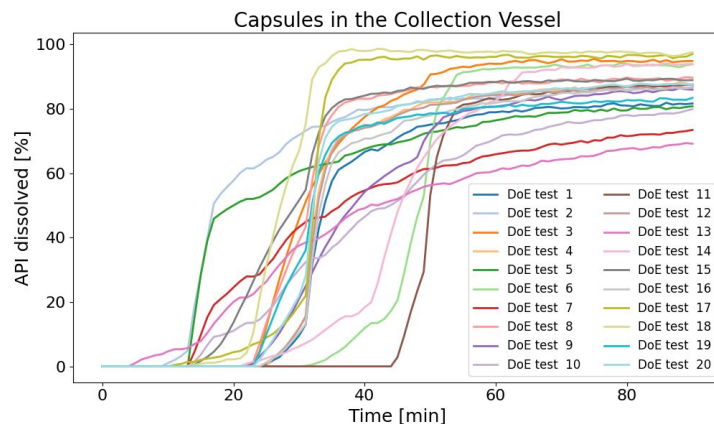
How to interpolate the conditions?

DoE matrix - 20 tests only

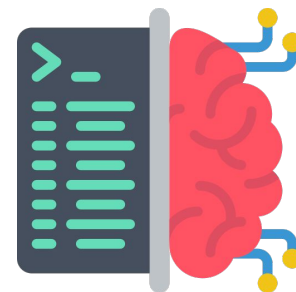
No.	IST [min]	GET [min]	pH
1	19	30	2.6
2	5	12	1.8
3	19	48	1.8



Dissolution experiments



Neural Networks / Random Forest algorithms

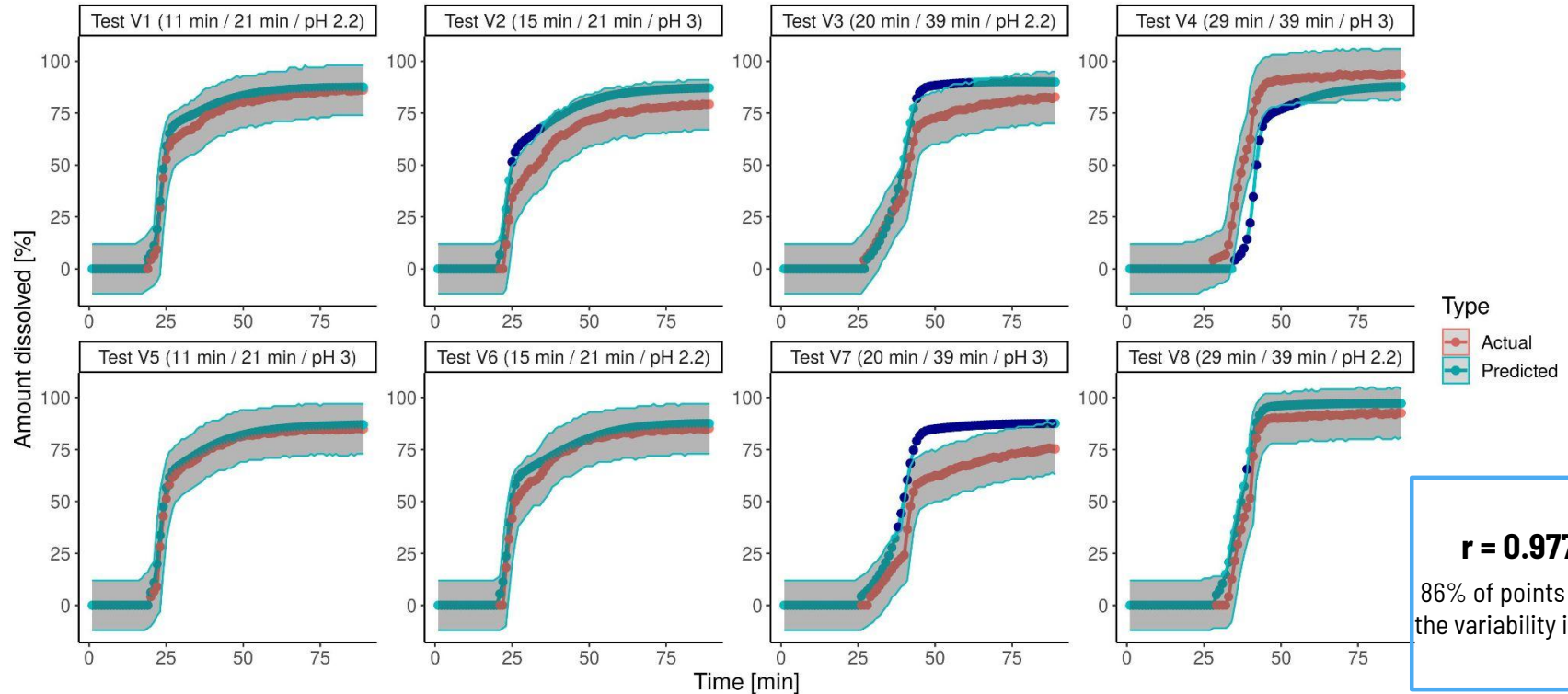


Validation



Model-predicted dissolution profiles of capsules

Verification tests

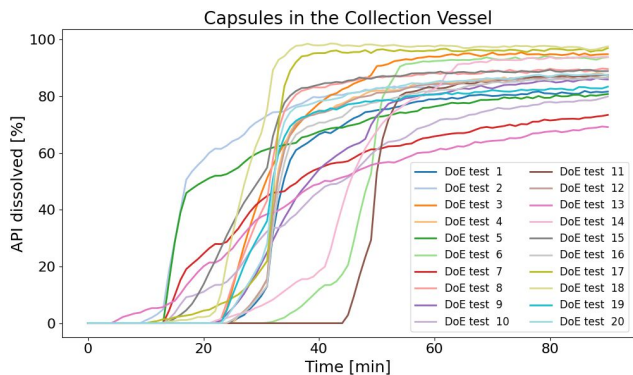




Performing dissolution tests *in silico*

Complete understanding of the formulation performance
in the defined physiological space

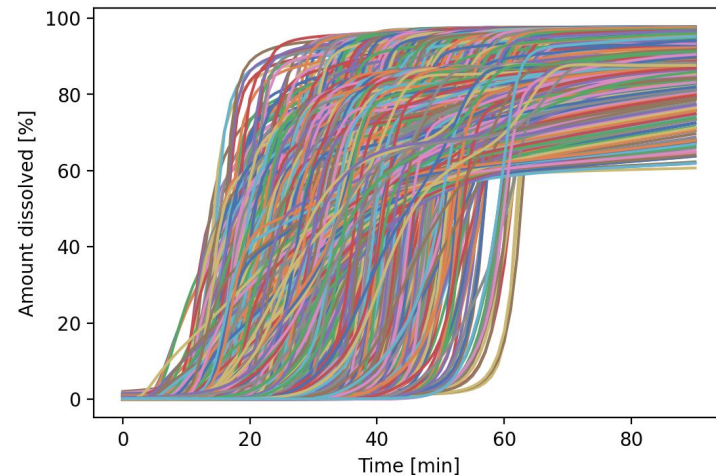
20 experimental dissolution profiles



ML model

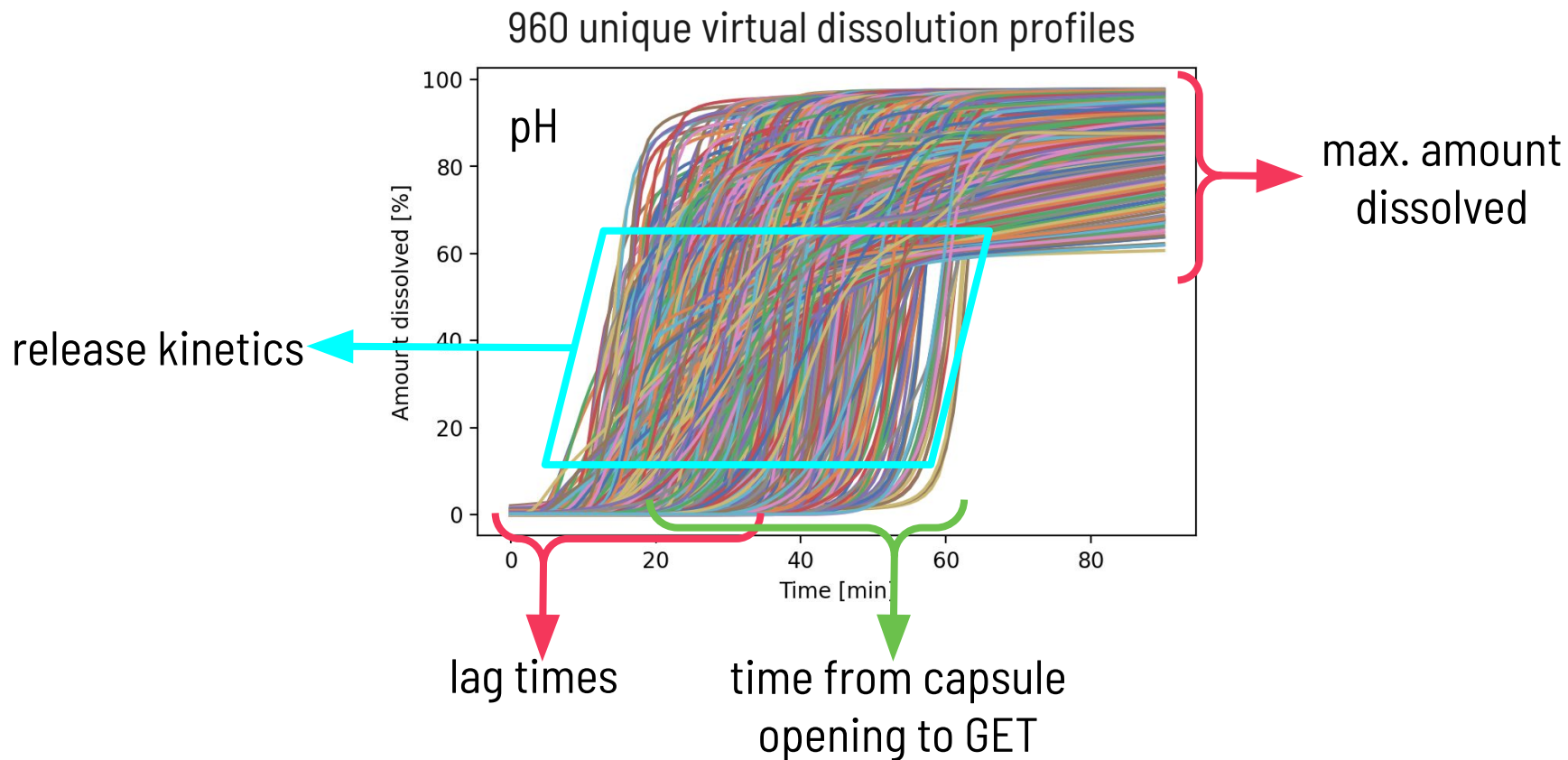


960 unique virtual dissolution profiles





Where is the variability?





How are these test results useful?

How to de-risk development?

**Which parameters are critical for the
in vivo performance?**

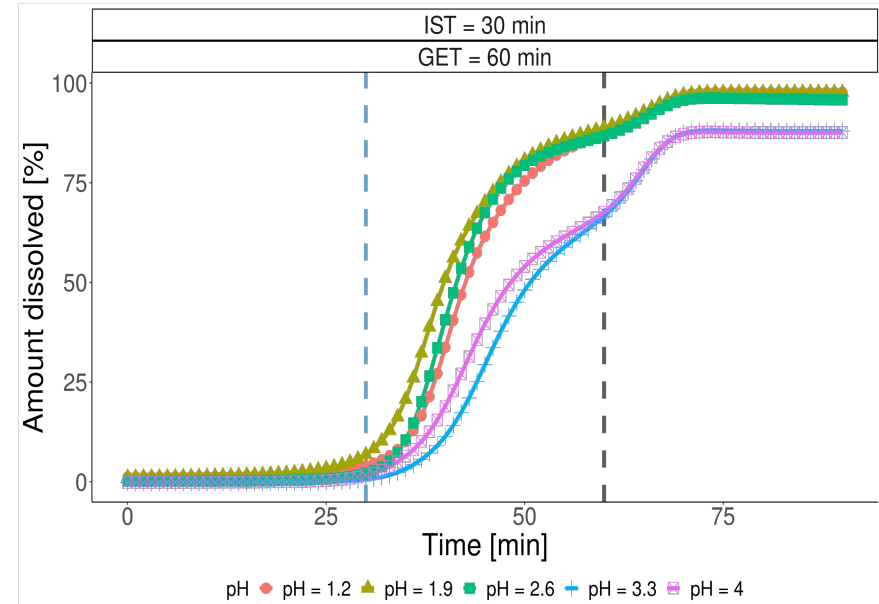


“What if” scenarios - factor pH

Modify one parameter, while keeping the others constant

When IST and GET are constant, **only high pH values (3.3 and 4.0)** cause slower dissolution before the simulated gastric emptying.

Various pH



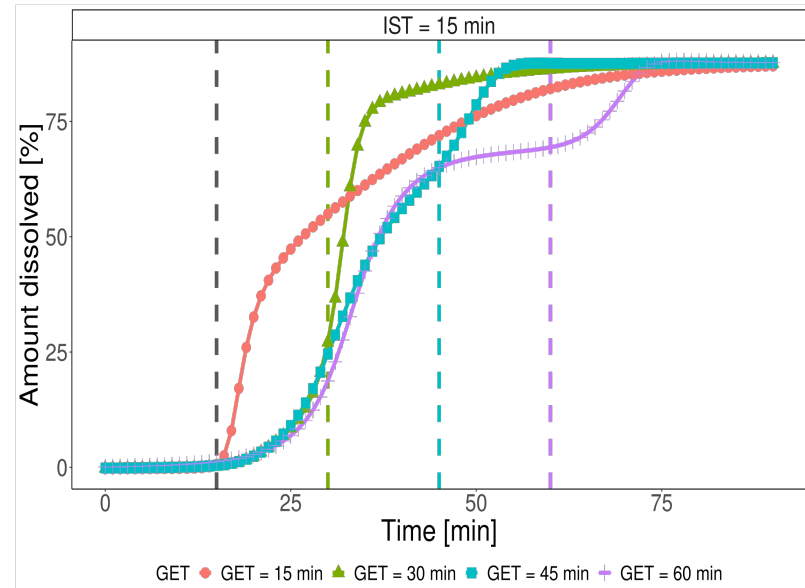


“What if” scenarios - factor GET

Modify one parameter, while keeping the others constant

When GET is early, the dissolution rate increases, but the post-GET courses of the dissolution curves differ.

Various GET



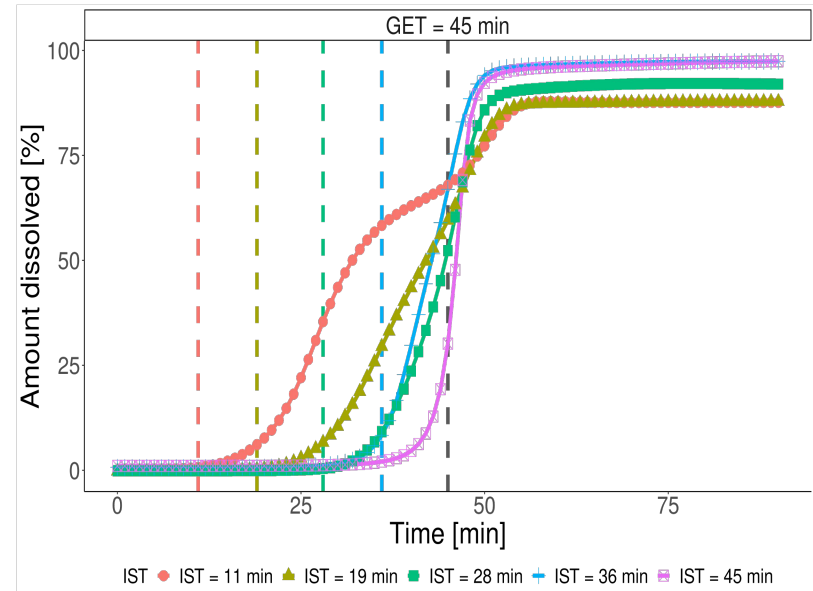


“What if” scenarios - factor IST

Modify one parameter, while keeping the others constant

Intragastric stress before GET **triggers capsule opening** and marks the dissolution onset in the majority of cases.

Various IST

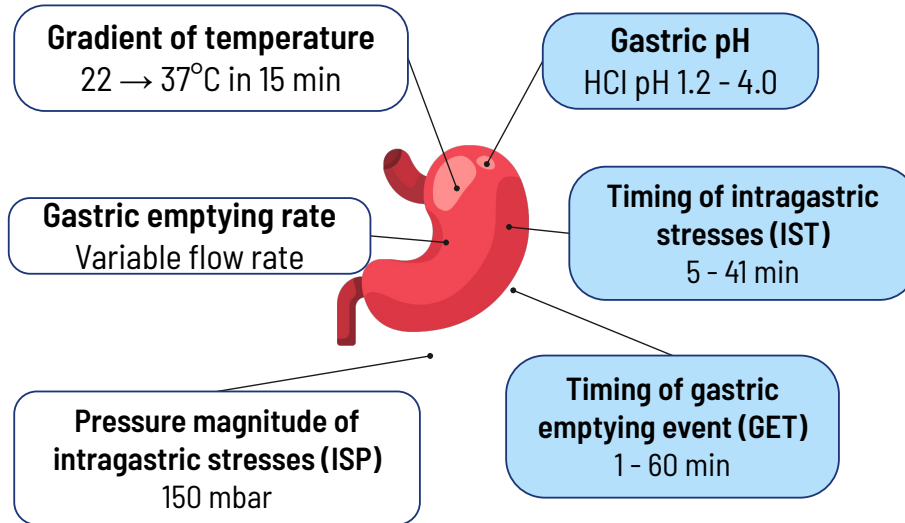




Fishing for the critical parameters

In vivo, parameters may change **independently**, without constraints.

Multiple and independent parameters



Understanding the impact of isolated factors

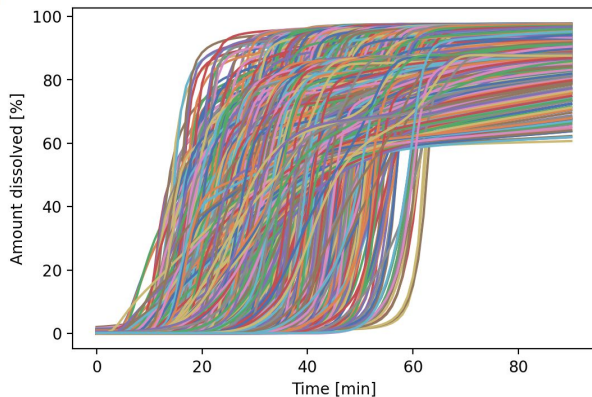


Identification of the most critical factors



More advanced modeling approach

960 unique virtual dissolution profiles



Parametrize the
dissolution curves

PhysioCell
virtual model

Include pharmacokinetics
(LADME)

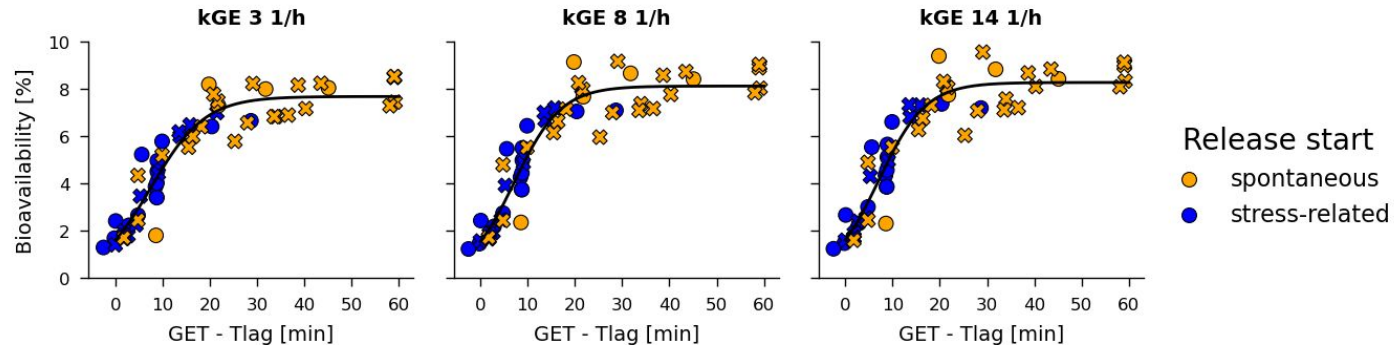
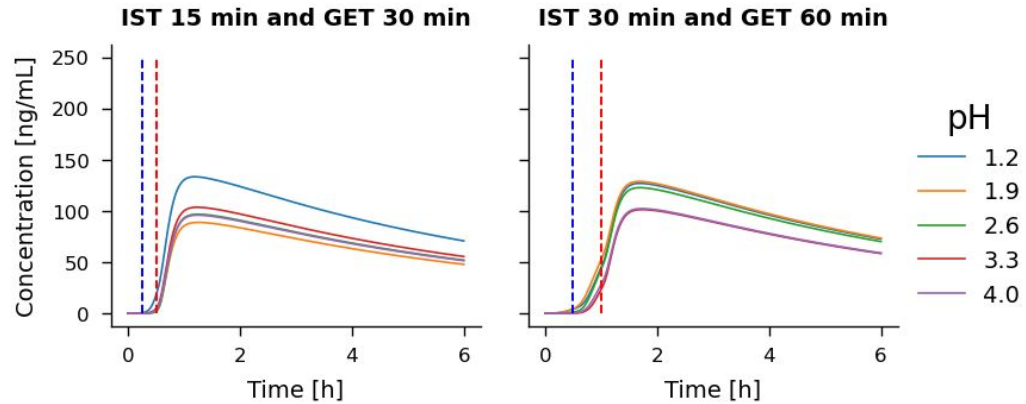
Physiologically-Based
Biopharmaceutics
Model

Identification of the critical parameters
influencing the drug plasma concentrations



Is pH a critical parameter?

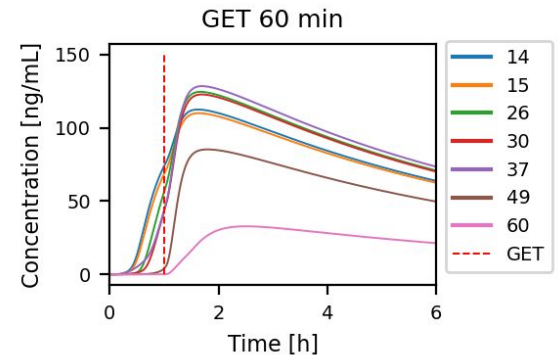
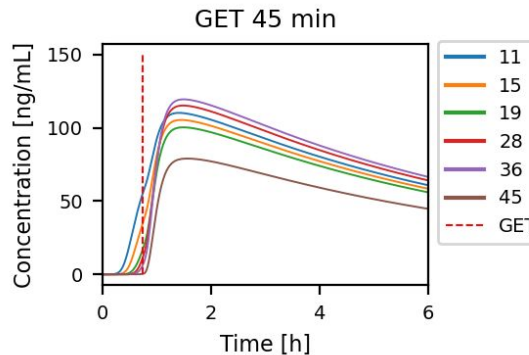
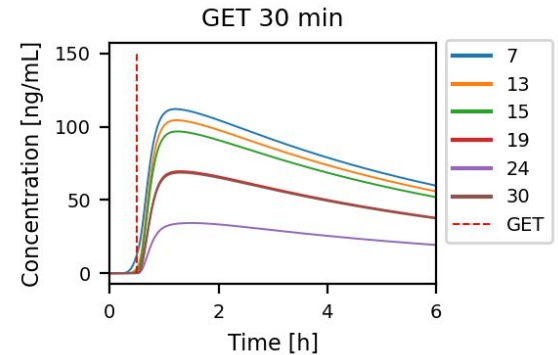
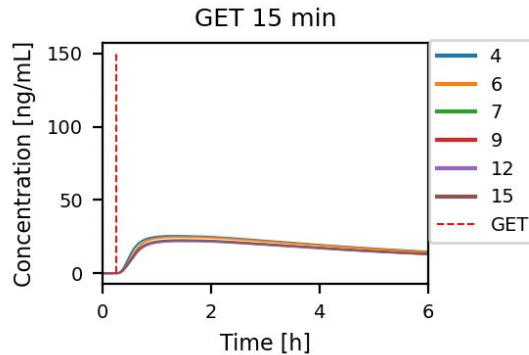
Gastric residence time has **greater influence** on the predicted BA than **intra-gastric pH**





Are GET and IST critical? Catching the interplay.

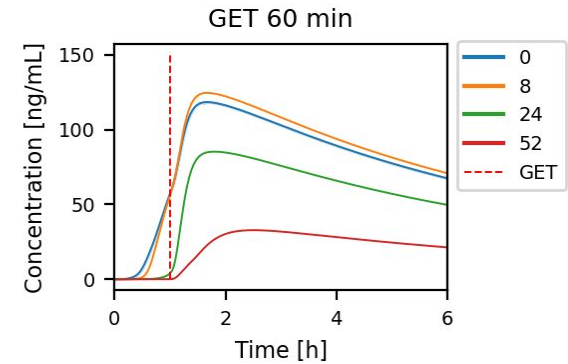
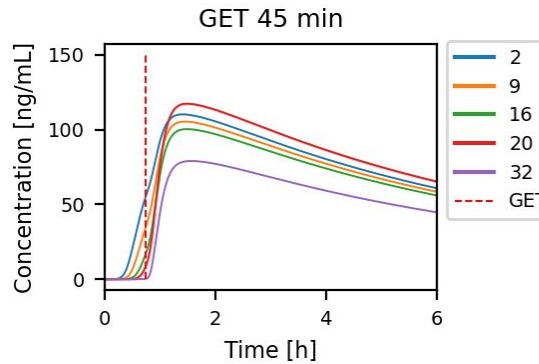
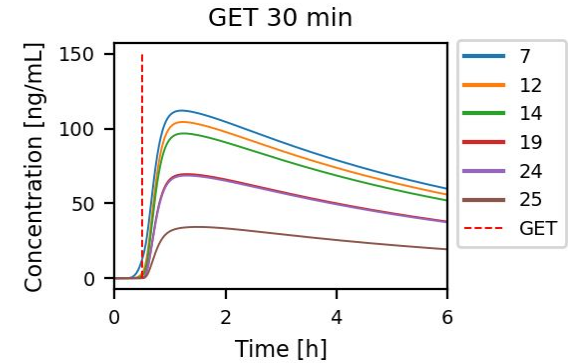
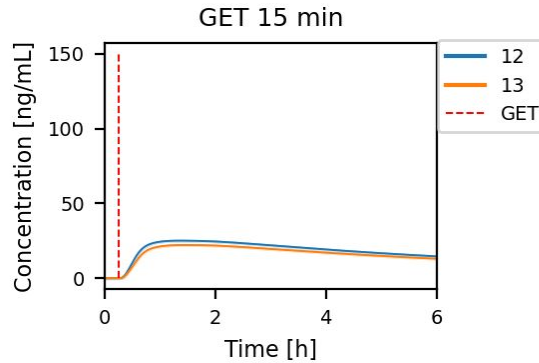
The longer the interval between **IST and GET**, the higher the predicted DAB exposure





Are GET and T_{lag} critical? Catching the interplay.

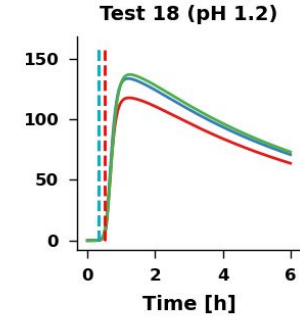
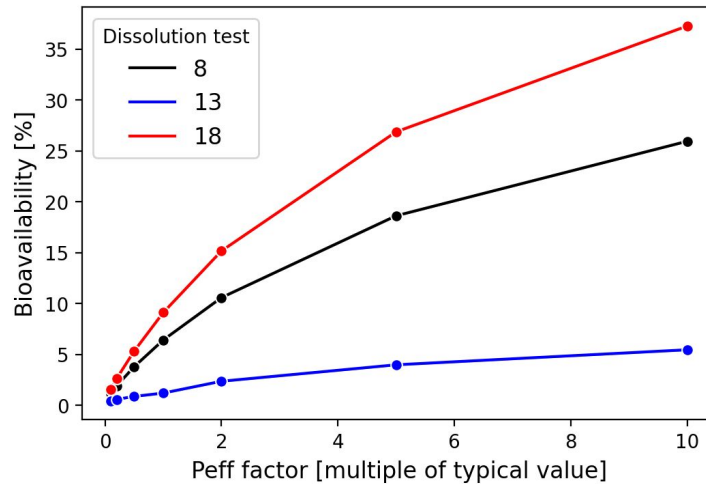
The longer the interval between T_{lag} and GET, the higher the predicted DAB exposure



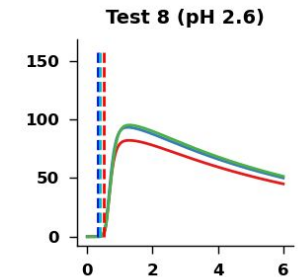


How important is the effective permeability?

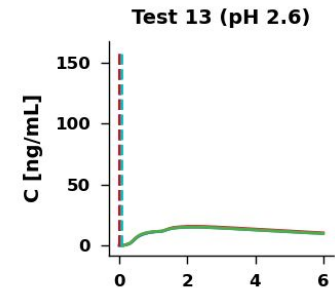
Predicted BA changes nonlinearly with P_{eff}



longer GE



typical GE

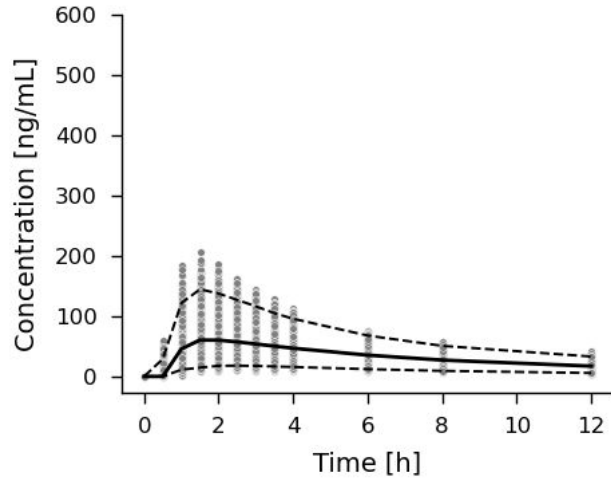


early GE



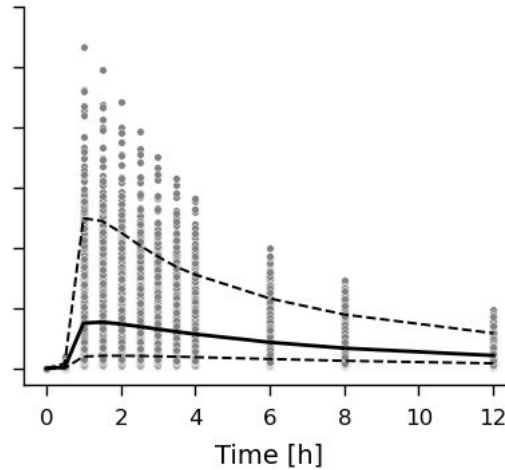
Which one has the greater impact - GE or P_{eff} ?

Variable gastric emptying



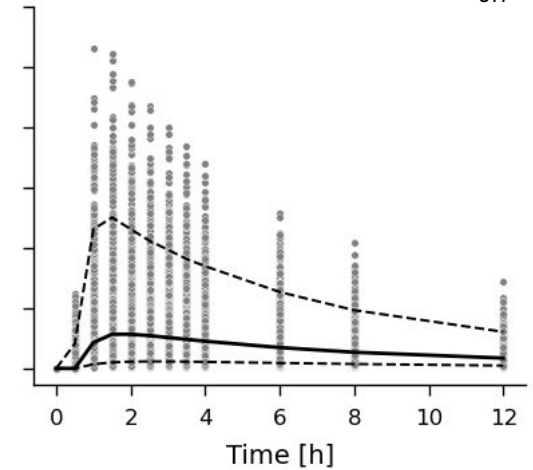
Best alignment with clinical data

Variable P_{eff}



Overpredicted exposure

Variable both gastric emptying & P_{eff}



Overpredicted exposure and variability

grey dots - simulated DAB plasma concentrations
solid line - geometric mean, dashed lines - 10 and 90% PI

Conclusions - **variability** is the key!

- Physiological design space rationally parametrizes **variability** of fasting intake conditions,
- Biopredictive tests straightforwardly simulate **variability** of physiological factors (pH, IST, GET),
- Well-designed dissolution tests adequately describe **variable** drug delivery performance,
- ML-based models identify critical parameters and predict **variable** *in vivo* performance.