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The Evolution of Biopharmaceutics:

Risk Assessment and Clinical Relevance

M-CERSI

MAS
Material and Analytical Sciences

"From Established to Essential: How TIM Systems are routinely replacing in-vivo assessments in industry to manage biopharmaceutical risk, and accelerate development"

Robert Schwabe

Biopharmaceutics group

Boehringer Ingelheim Pharmaceuticals (Ridgefield, CT)

Outline

- TIM Systems from perspective of Experts Working Group (EWG)
  - System overview
  - Application to Drug Development
  - Case Studies
  - Limitations

- Future:
  - Regulatory aspect -> Biowaivers

White Paper Publication: Expert's View on TIM Systems

molecular pharmaceutics

pubs.acs.org/molecularpharmaceutics

Perspective

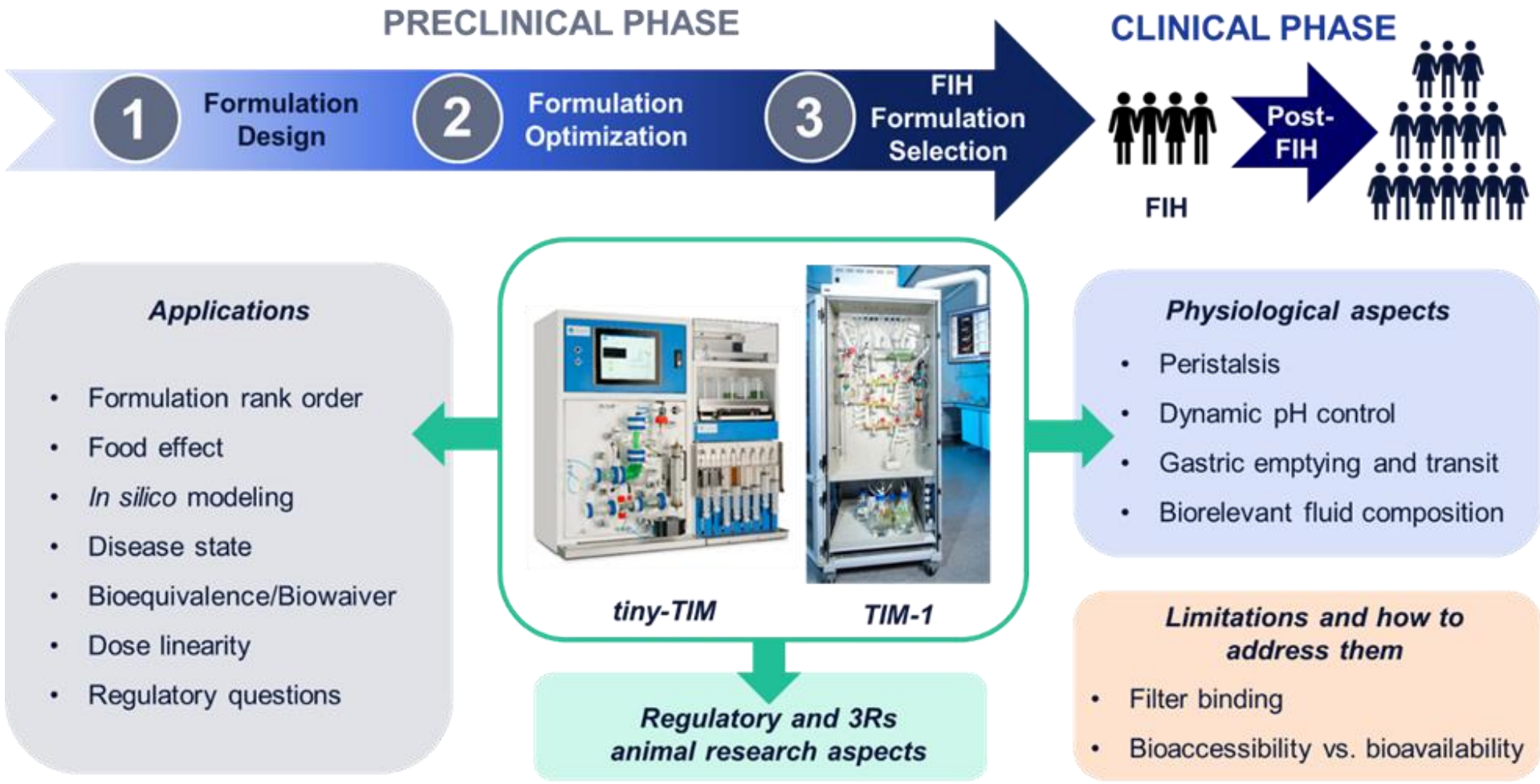
An Expert's View on the Application of TIM Technology in the Development of Oral Drug Products

Álvaro López Mármol,*,¶ Richard Barker,*,¶ Mirko Koziolek, Robert Schwabe, Bart Hens, Inese Sarcevica, James M. Butler, Mark McAllister, Edward Taylor, Po-Chang Chiang, Nick Stainforth, Eleanor Jones, and Hannah Batchelor

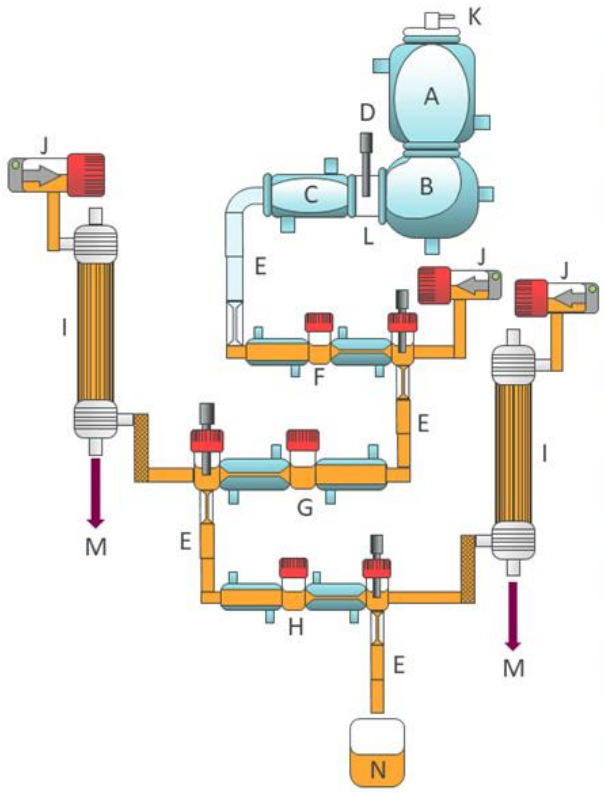
https://doi.org/10.1021/acs.molpharmaceut.5c01197

➢Internal and external awareness of TIM Systems

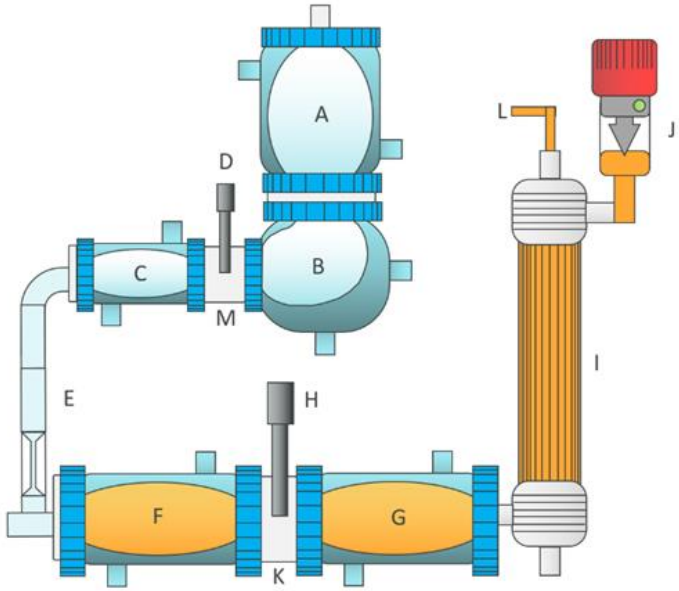
Graphical Outline



TIM Systems: Description of TIM-1 and tiny-TIM



TIM-1 AGC system schematic	
A	Stomach, corpus module
B	Stomach, bottom module
C	Stomach, antrum module
D	Gastric pH/temperature probe
E	PVP (peristaltic valve pump) train
F	Duodenum compartments/sampling port
G	Jejunum compartments/sampling port
H	Illeal compartments/sampling port
I	Hollow fibre filtration membrane
J	Level sensor
K	Stomach dosing port
L	Stomach sampling port
M	Bioaccessibility samples
N	Illeal effluent



TinyTIM system schematic	
A	Stomach, corpus module
B	Stomach, bottom module
C	Stomach, antrum module
D	Gastric pH/temperature probe
E	Gastric PVP (peristaltic valve pump) train
F	Small intestine module 1
G	Small intestine module 2
H	Small intestine pH/temperature probe
I	Hollow fibre filtration membrane
J	Small intestine level sensor
K	Small intestine sampling port
L	Small intestine absorption port
M	Stomach sampling port

TIM-1

tiny-TIM

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TIM Design

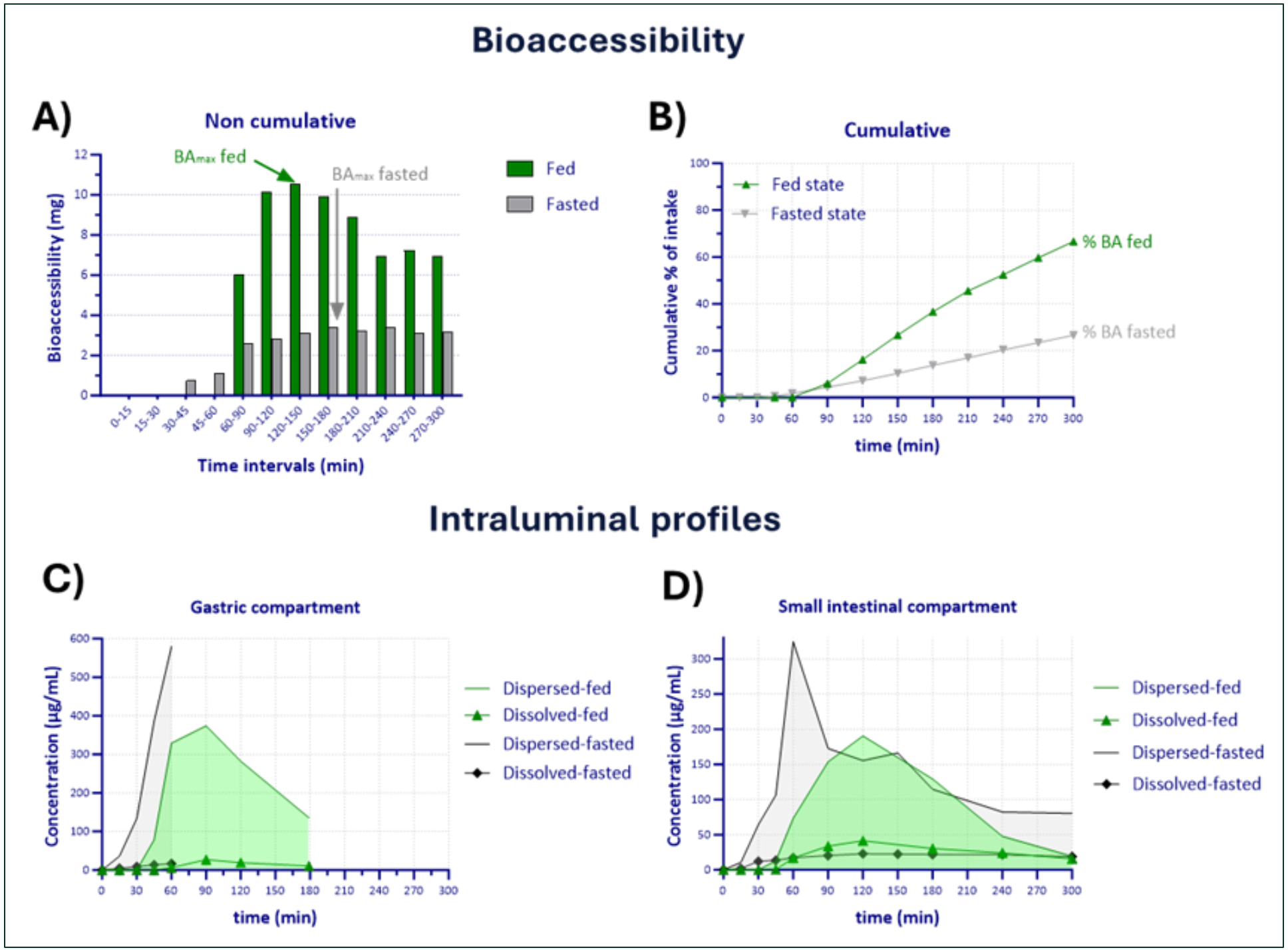
Physiological parameters simulated by TIM Systems	
Gastric	**Small Intestine**
Mastication	Intestinal fluid volume
Salivary secretion	Intestinal pH
Initial meal structure and viscosity	Intestinal fluid composition
Shape of gastric compartment	Intestinal residence time
Gastric fluid volumes	Absorption from small intestine
Gastric secretion	
Gastric pH	**Gastric & SI**
Gastric emptying of contents	Peristalsis
Gastric residence time	

Results

Bioaccessibility

≠

Bioavailability



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Application to Drug Development

- TIM models can be applied **before** & **after** **first-in-human** (FIH) studies
- Formulation robustness and reformulation activities.
- Drug Product performance **knowledge.**
- Clinical trial **success**.
- **Accelerate** drug product timeline.
- **Biowaiver.**
- **Bioequivalence.**

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Applications for Evaluating Drug Product Performance

Drug Substance and Drug Product –> same protocol		**Other**
Formulation Rank Order		Input for PBPK/PBBM
Formulation changes		Bioequivalence/ Biowaiver
Drug Substance Quality		
Solubility dependent dose linearity		
Physiology –> change TIM protocol		
Food Effect		
Acid Reducing Agent		
Disease modeling		
Pediatrics		

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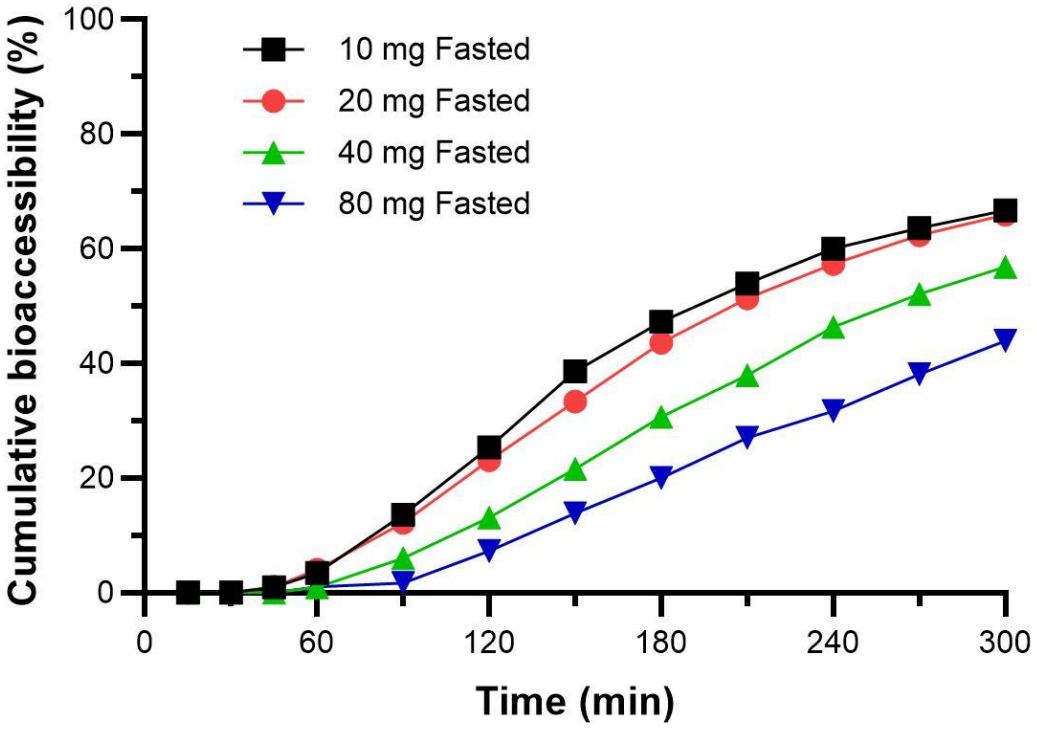
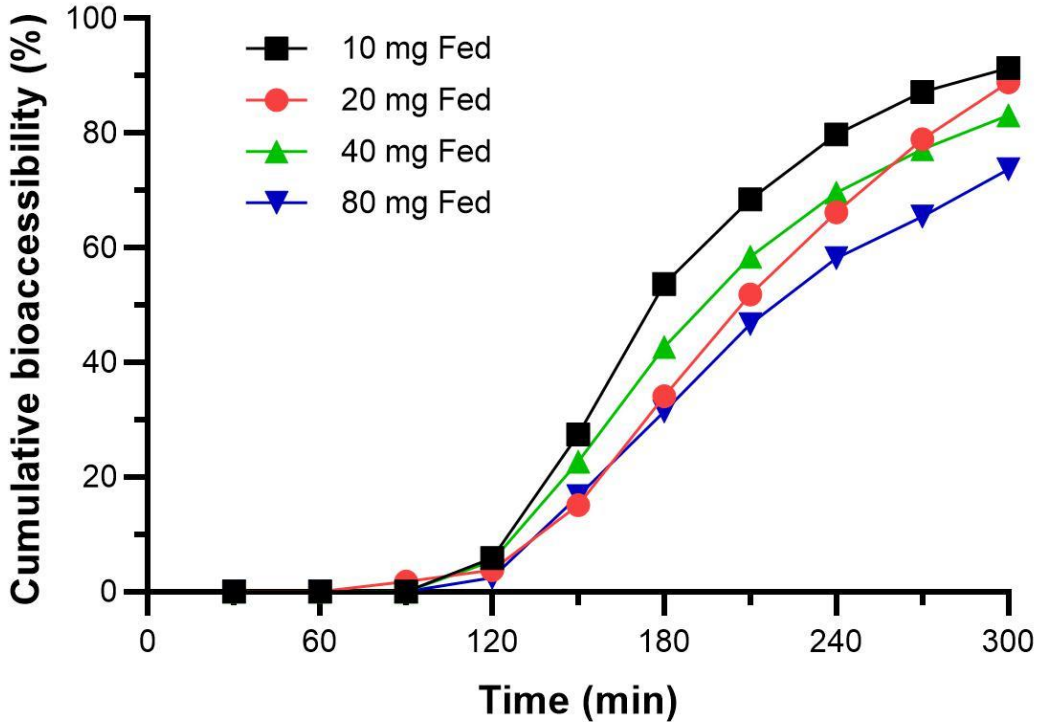
Case study 1 –
Goals: Food effect, dose linearity and input for *in silico* PBPK models





- Same formulation
- Dose range study in fasted and fed conditions
- Fasted: Dose proportionality decreases at 40 mg.
- Fed: Dose proportionality decreases at 80 mg.
- Dose dependent food effect

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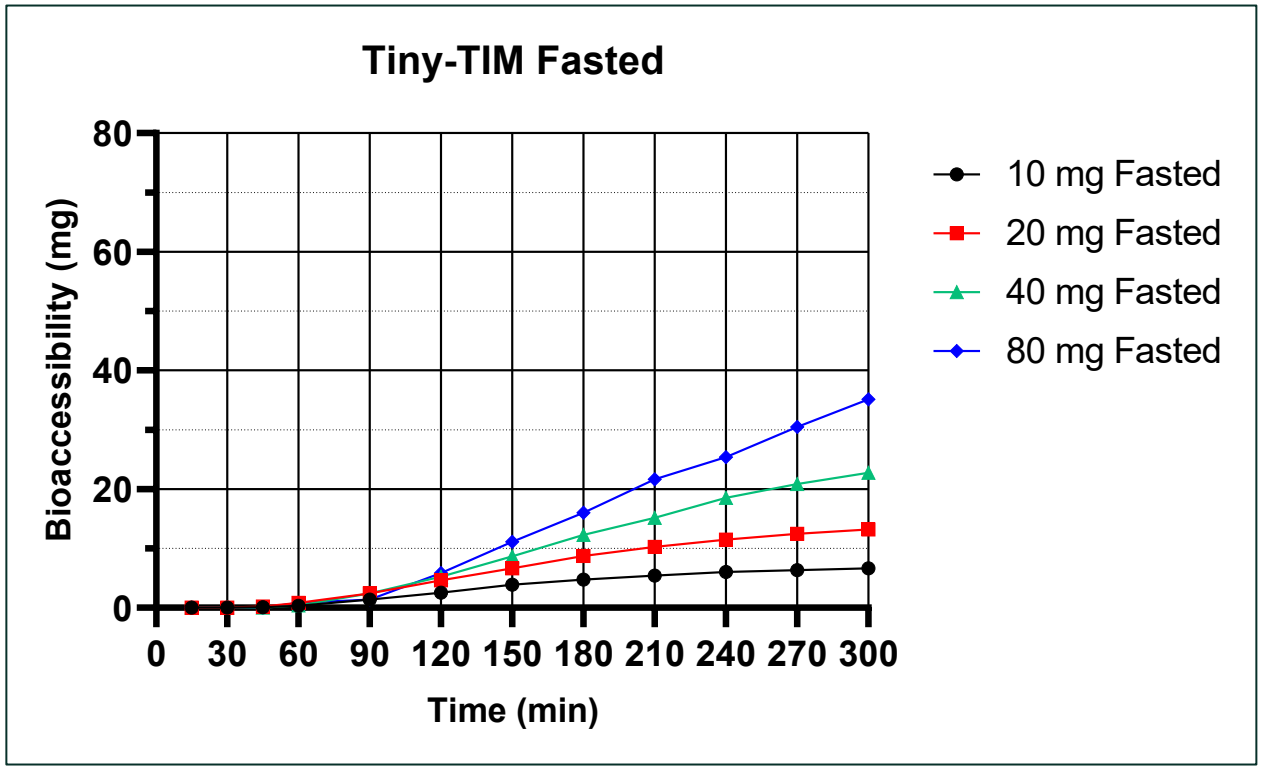
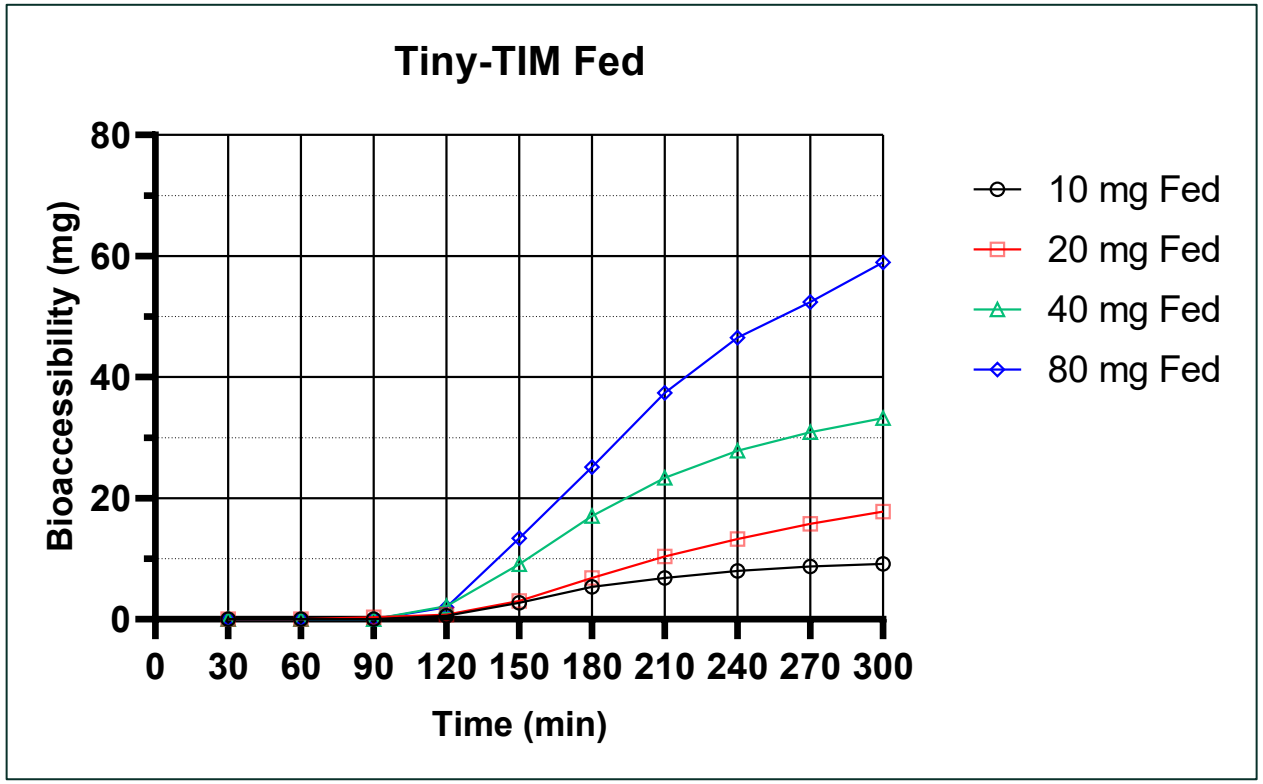
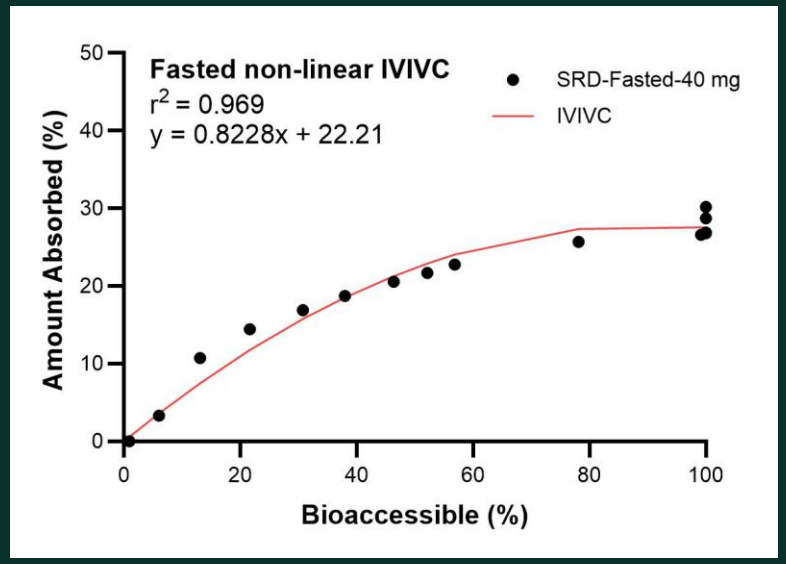
Case study 1 –
Goals: Food effect, dose linearity and input for *in silico* PBPK models

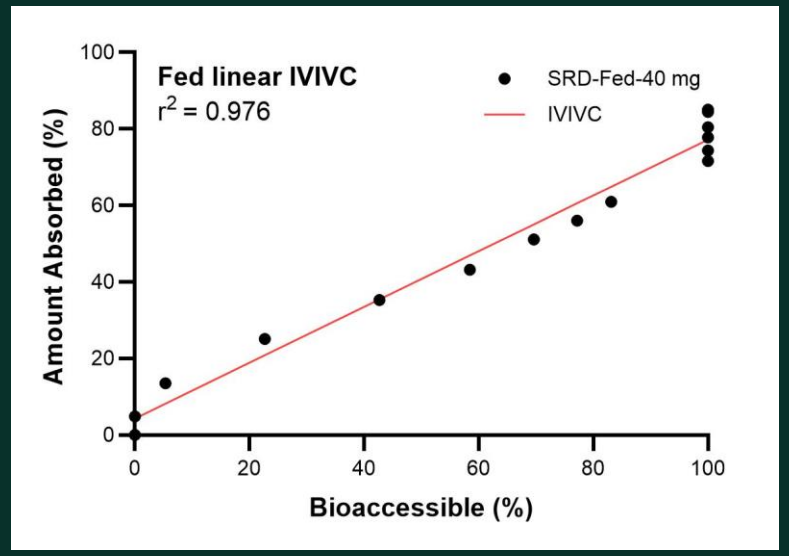


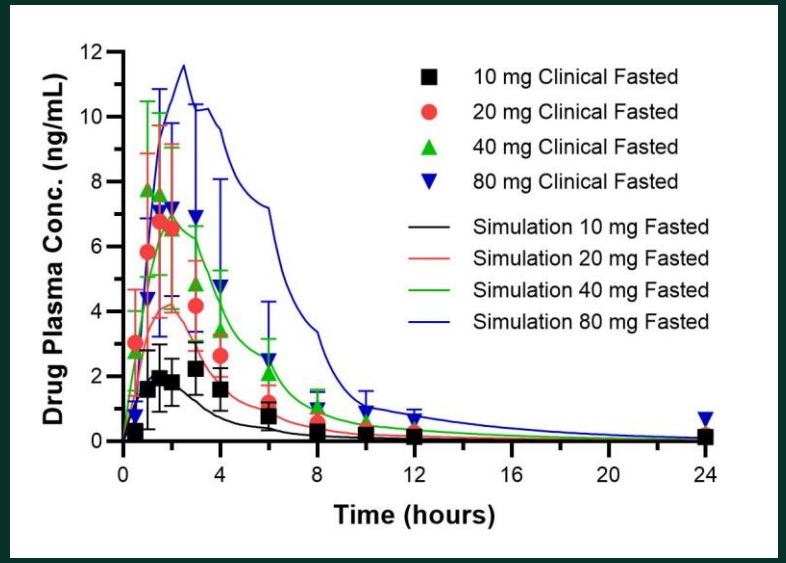


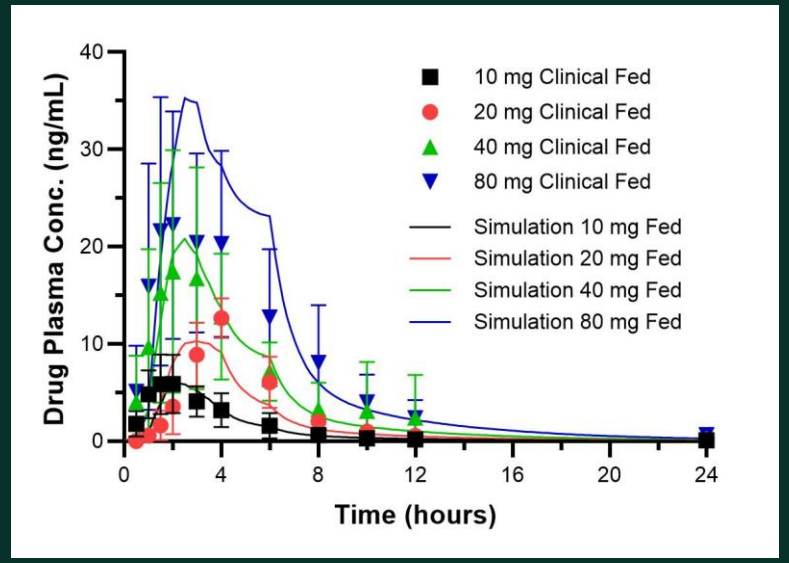
➢ Same data expressed in mg vs time, cumulative

Case study 1 – Food effect, dose linearity, and input for *in silico* PBPK models









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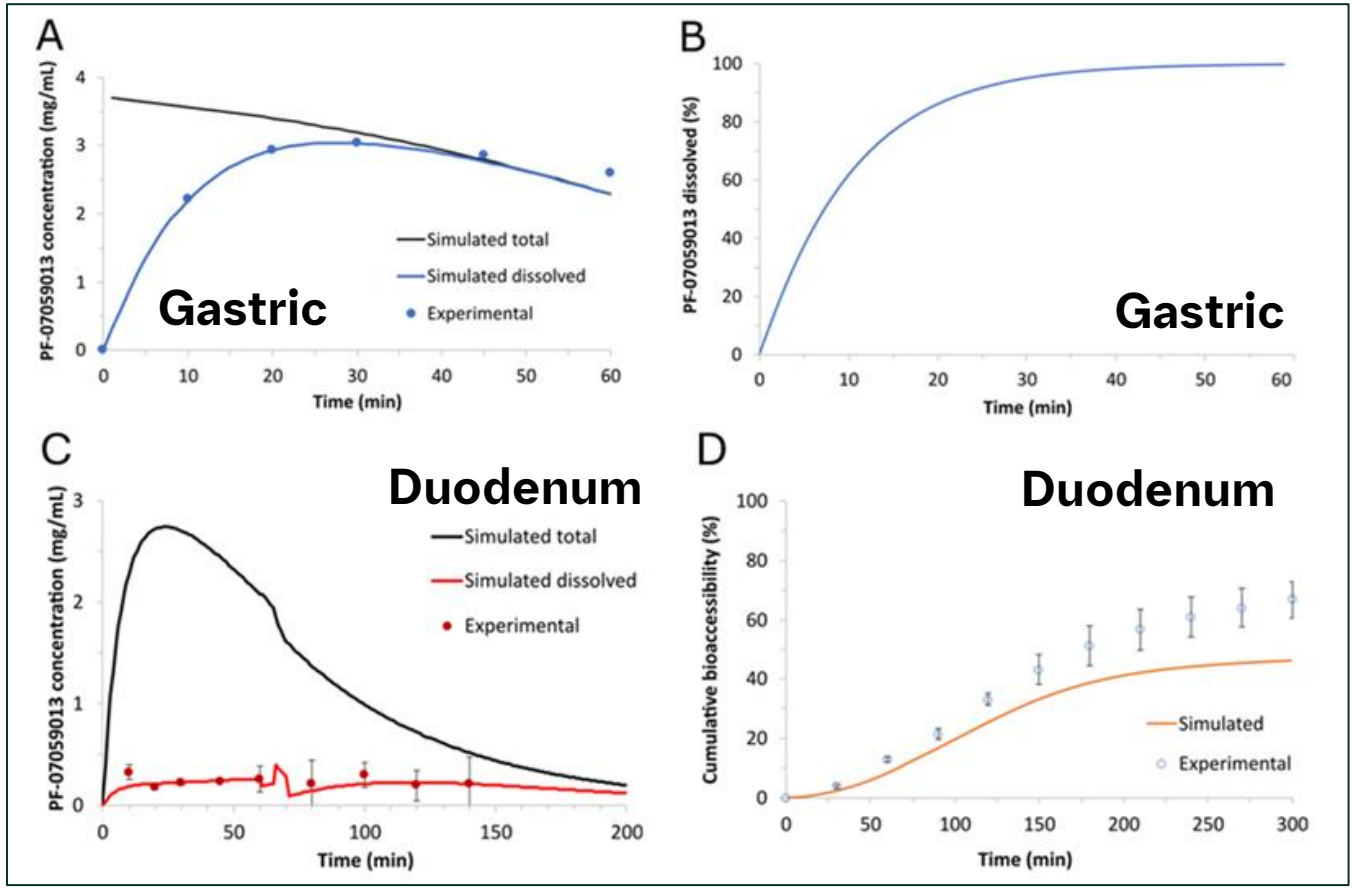
- IVIVC acceptable for fasted and fed states
- Can analyze prototypes and DS quality before heading to clinic

Case study 2 – Digital TIM-1 models

Goal: Understand Drug Product Performance

TIM-1 Data Explorer

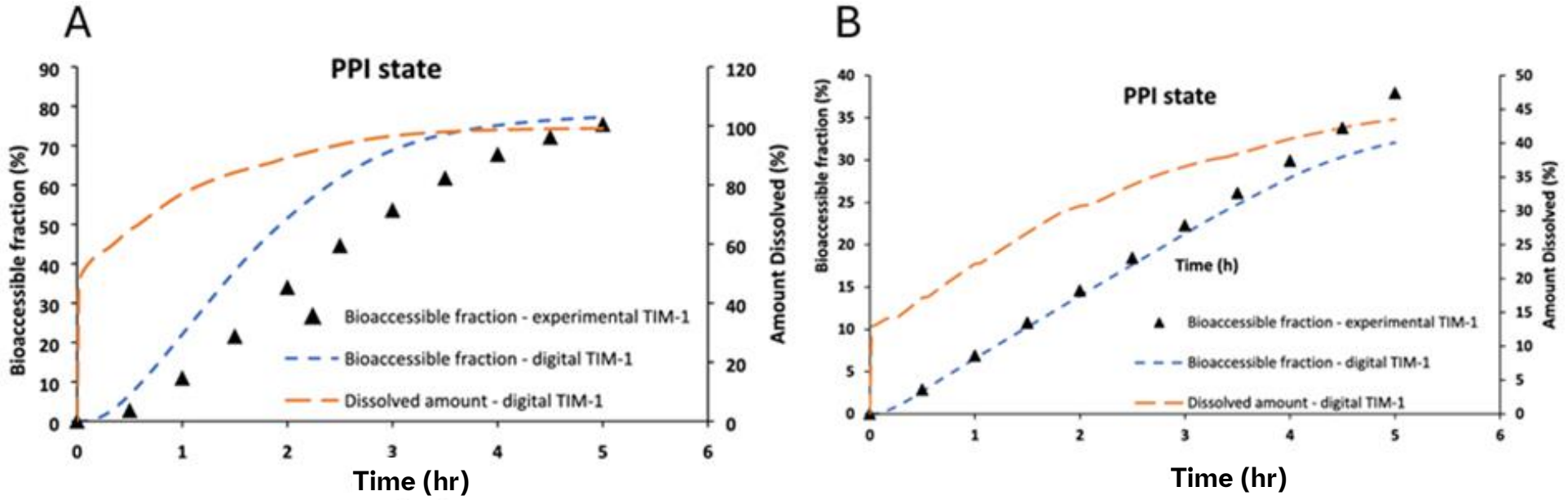


Understanding drug dissolution, precipitation, and bioaccessibility under physiologically relevant GI conditions is critical for oral drug development

Case study 2 – Digital TIM-1 models

Goal: Higher Predictive Power

Digital TIM-1 model in GastroPlus™

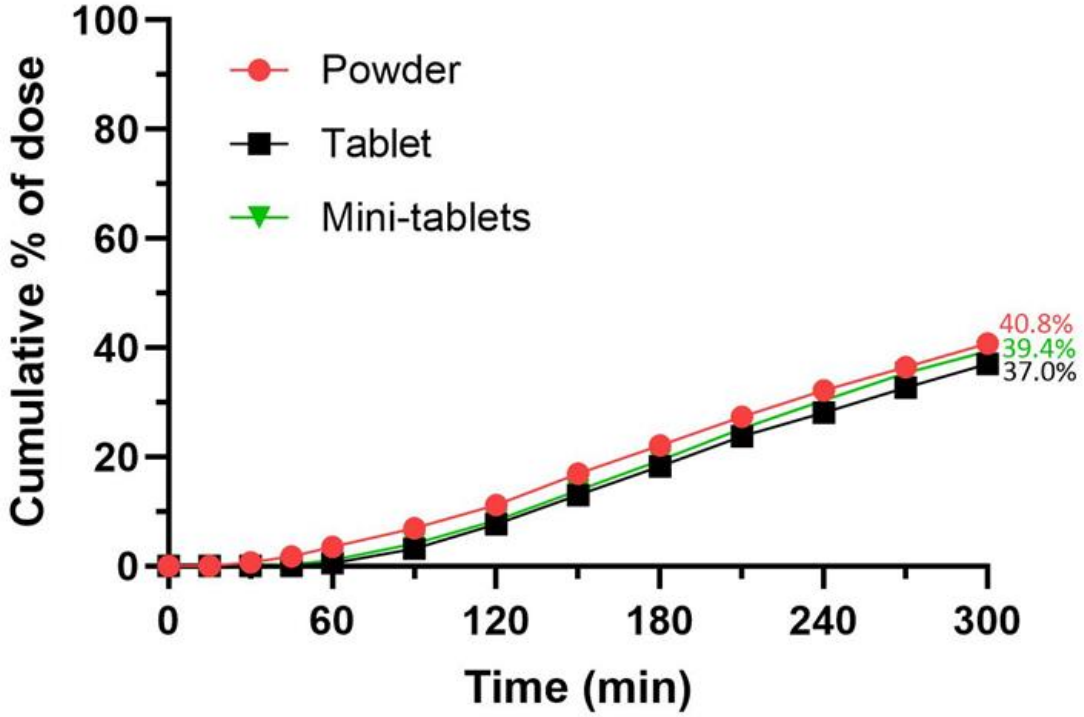


A digital twin of the TIM-1 model implemented within a commercial PBPK framework enables sensitivity analyses, formulation optimization, and absorption scaling to account for the non-absorptive characteristics.

As the models evolve to incorporate more realistic GI dynamics and patient populations, they will play a central role in establishing reliable IVIVC and supporting regulatory PBPK submissions.

Case study 3 – Development of ASD and Pediatric Formulations

- tiny-TIM assessment of amorphous solid dispersion (ASD) formulations of Ritonavir presented as a powder, minitablet and tablet.



Ritonavir is classified as a BCS Class IV compound, meaning its low permeability may further limit oral bioavailability.

Case study 3 – Development of ASD and Pediatric Formulations

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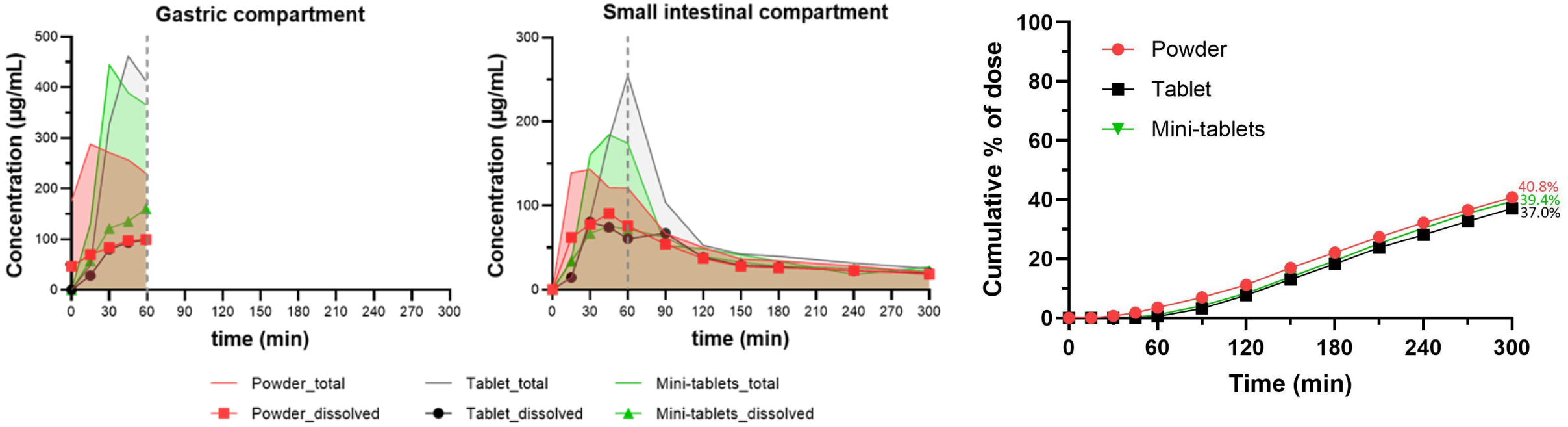

tiny-TIM demonstrated its value in supporting the development of ASD-based pediatric formulations and formed a key component of the structured protocol for biorelevant dissolution testing.

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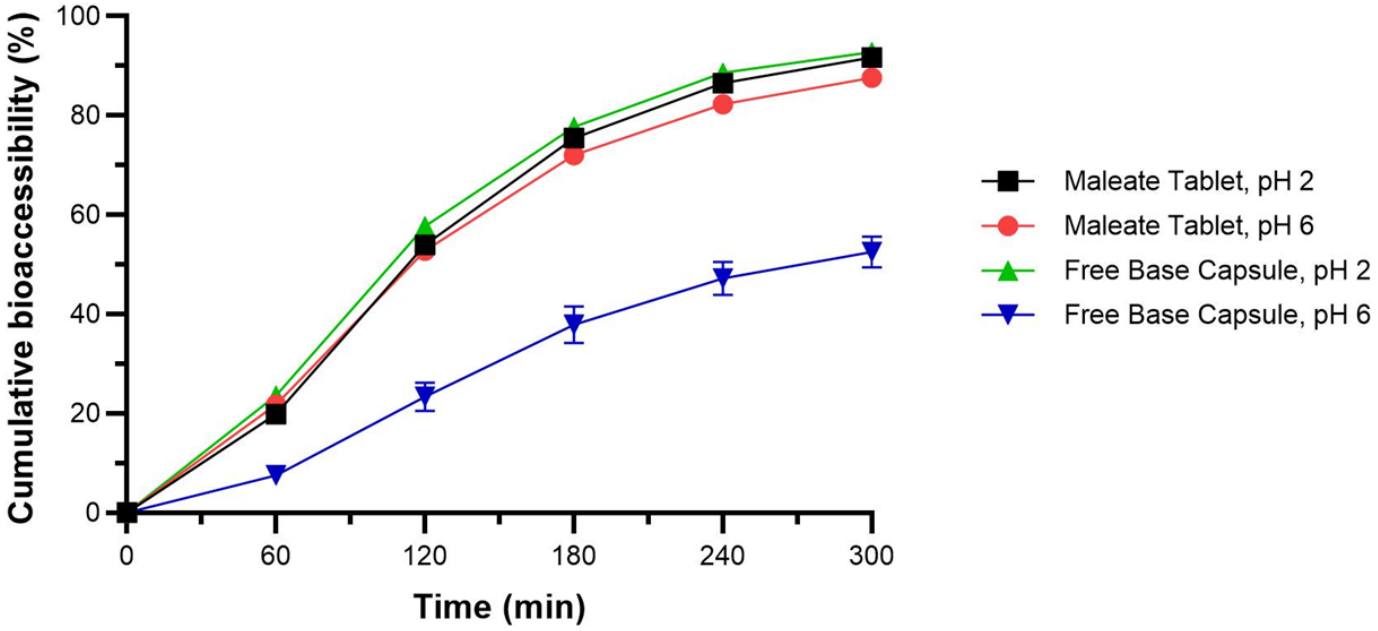
Case study 4 – Support of regulatory submissions

DS Form Switch and impact on ARA performance.

- **Issue:** CALQUENCE® capsules recommends avoiding co-administration with gastric acid reducing agents (ARAs)
- **Solution:** TIM data was used to support a regulatory submission regarding the switch from a free base capsule formulation of acalabrutinib to a maleate salt tablet of acalabrutinib, thereby removing an ARA restriction from the label due to low solubility of the free base above pH 4.



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Case study 4 – Support of regulatory submissions
Clinical trials

- *Study 1: Initial BE Assessment (Tablet (DS Salt) vs Capsule (DS Free Base)*
  - **Similar *in vivo* PK profiles** were observed for both formulations in Fasted state ->BE.
- *Study 2: Formal BE Study (Tablet vs Capsule)*
  - All PK parameters **met the BE criteria** in fasted state.
- *Study 3: Impact of Proton-Pump Inhibitors (PPIs)*
  - The results indicated that the **C_{max} of the tablet decreased by ~24% with PPI**. At the same time, a **slight increase (~14–17%) in the AUC was observed** with the PPI coadministration.

Conclusion:

- Maleate tablet provides **comparable biological efficacy** to the free base capsule.
- Advanced *in-vitro* tools, such as the TIM system, can be used to simplify the drug development process by **replacing, reducing or avoiding the need for *in-vivo* studies** (such as dog studies traditionally used for product development), and **shortening timelines to patients**.

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Regulatory aspects

Validation and Qualification proportional to risk:

- Supportive data in conjunction with *in silico* data for *in vitro* release method → **low risk**.
- TIM systems are employed as a surrogate for a human PK study → **thoroughly validated**.

Standardization of methods:

- Consistency and comparability across different studies.

Correlation with Clinical Outcomes:

- Demonstrate that the TIM Systems are valid models for the intended application.

Regulatory Guidance:

- High level
- Engage with Regulators and Submission of a Robust Dossier
- White Paper
- Post-approval commitments

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3R - Reduce, replace and refine animal testing

- **Reduction of Animal Testing:** The TIM Systems provide an alternative to animal testing and ethical concerns. Dog data to predict human data has been questioned, supporting the use of predictive *in vitro* testing.

- **Replacement of Animal Testing:** The FDA modernization act 2.0 additionally recommends the use of nonclinical testing before any clinical testing of a new drug is undertaken.

- **Refinement - Accuracy and Reproducibility:** The TIM systems offer a controlled and reproducible environment for studying GI processes, for applications discussed, to a level that is not possible in *in vivo* studies (either animal or human studies).

Limitations

- Lack of absorption simulation.
  - Bioaccessible - ‘available to be absorbed’
  - Absorption rate
  - Mechanism of absorption
- Filter binding
- Time and resources
- Risk mitigation – proprietary technology


BACK
TO THE FUTURE
Of
Dissolution

The Future of Dissolution

Physiological Data :

- Collaboration between RA and Pharma to study various human physiological parameters
- **Goal:** better understanding of physiological parameters for inputs to *in vitro* and *in silico* models

Biorelevant Dissolution Tools:

- Future advancements should aim to incorporate features that better mimic human biological processes
- Integration of Process Analytical Technology
- Emulate specific patient types and disease states, such as infant and elderly models
- Tools to encompass **full understanding of absorption process**

The Future of Dissolution

***In silico* models:**

- Digital Twins
- Digital Twins
- Utilize physiological parameter data to optimize models (DS, DP, in vivo parameters, physiology, etc).

Drug Product development:

- Pre-clinical Phase I → robustness of drug product performance
- Post-clinical → feedback to build validated *in vitro – in silico* models

Regulatory:

- **Collaboration with RA.**
- **Biowaivers** → work towards acceptability.
- Condensed clinical trial design → accelerated development → **faster to approval and patients**