Extending the OSP oral absorption toolbox: An end-to-end Physiology-Based Biopharmaceutics Modeling (PBBM) approach

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OSP Community Conference, Basel, October 7th, 2024

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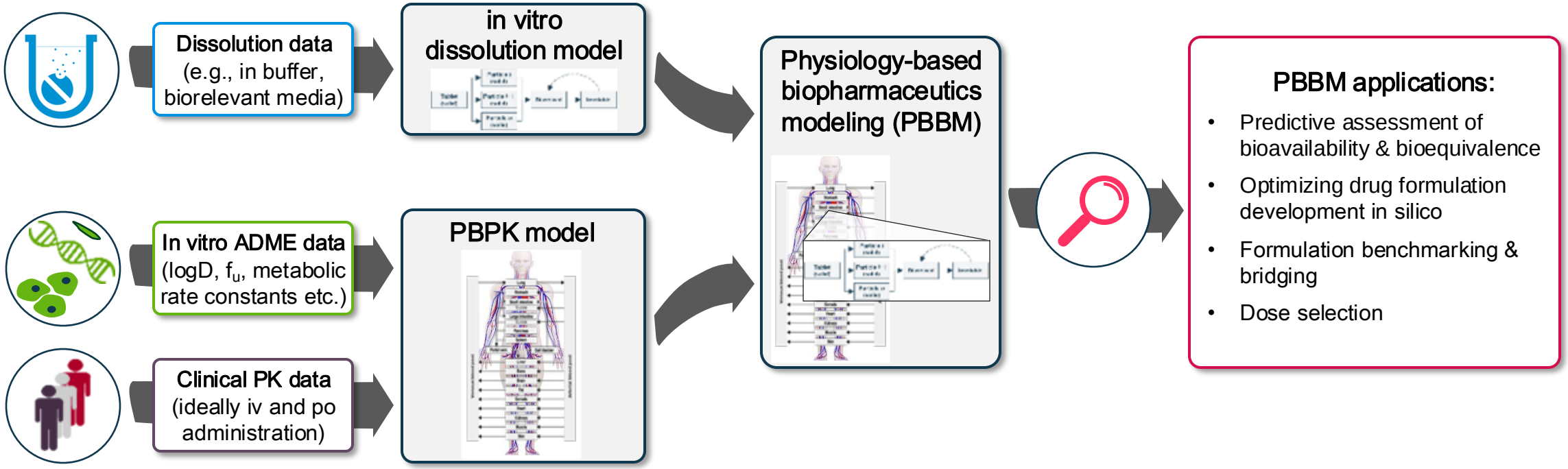
No conflicts of interest to declare

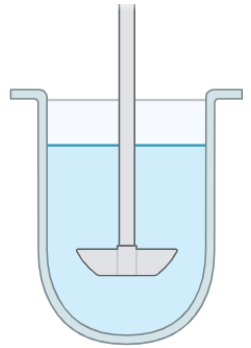
Physiology-based biopharmaceutics modeling (PBBM): Develop an OSP based approach for oral drug products

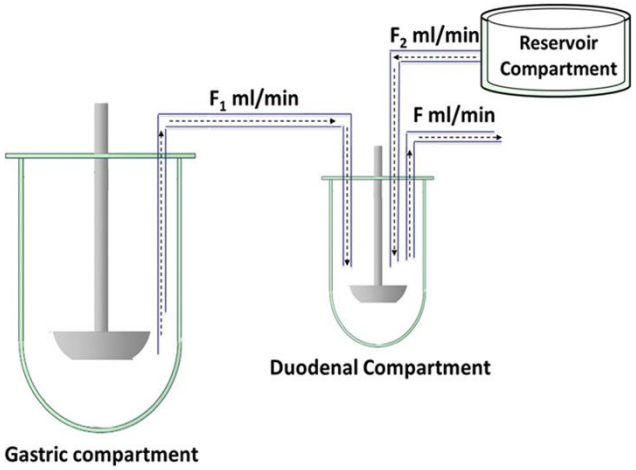


Abbreviations: ADME: absorption, distribution, metabolism, and excretion; fu: fraction unbound; PBBM: Physiology-based biopharmaceutics modeling; PBPK: Physiologically-based pharmacokinetics; PK: Pharmacokinetics

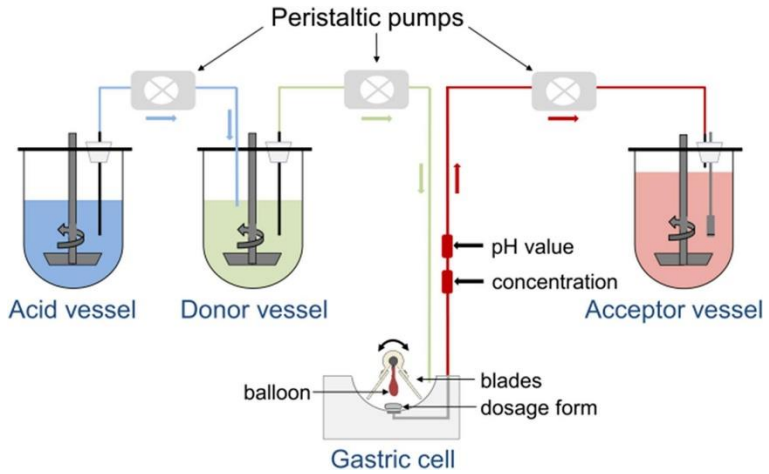
Approaches to PBBM, current mechanistic PK-Sim PBBM capabilities date back to 2012

- Mechanistic vs. Biomimetic approach:
  - Mechanistic modeling (compendial USP2 dissolution apparatus)
    - Inform drug and dosage form characteristics from simpler experiments
    - Make *in* vivo predictions, potential for extrapolation to untested scenarios
  - Biomimetic dissolution devices (e.g., BioGIT, GastroDuo, TIM-system)

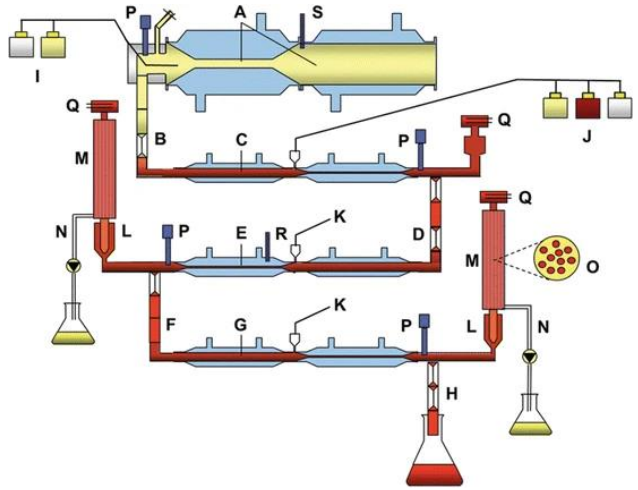




Kourentas et al., Eur. J. Pharm. Sci., 82, 2016



Schick et al., Mol. Pharm., 16, 2019



Minekus, 2015, The Impact of Food Bioactives on Health: in vitro and ex vivo models

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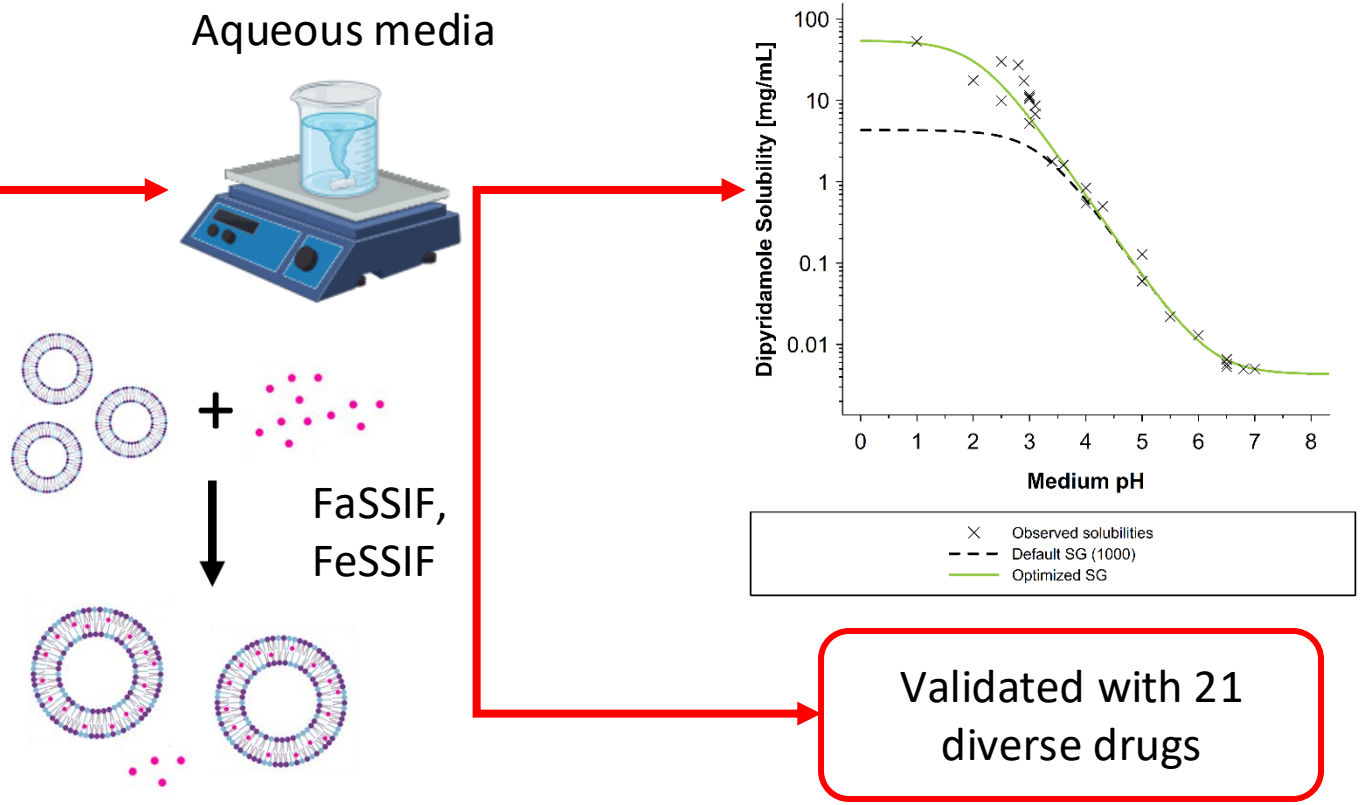


Validated with 21 diverse drugs

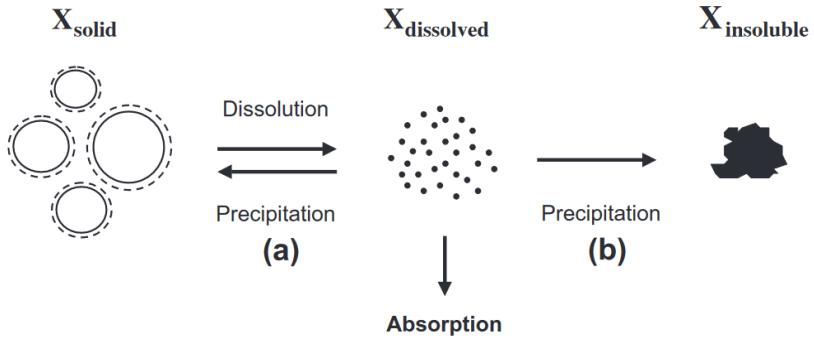
$$S_{br} = \left([BileSalt] \times \frac{S_0}{[H_2O]} \times K_{m:w,neutral} + S_0\right) + \left([BileSalt] \times \frac{S_i}{[H_2O]} \times K_{m:w,ionized} + S_i\right)$$

Sugano, Exp. Opinion drug Met. & Tox, 5, 2009

Abbreviations: SG: Solubility gain per charge; FaSSIF: fasted state simulating intestinal fluid; FeSSIF: fed state simulating intestinal fluid

Extending the PK-Sim Particle Dissolution model

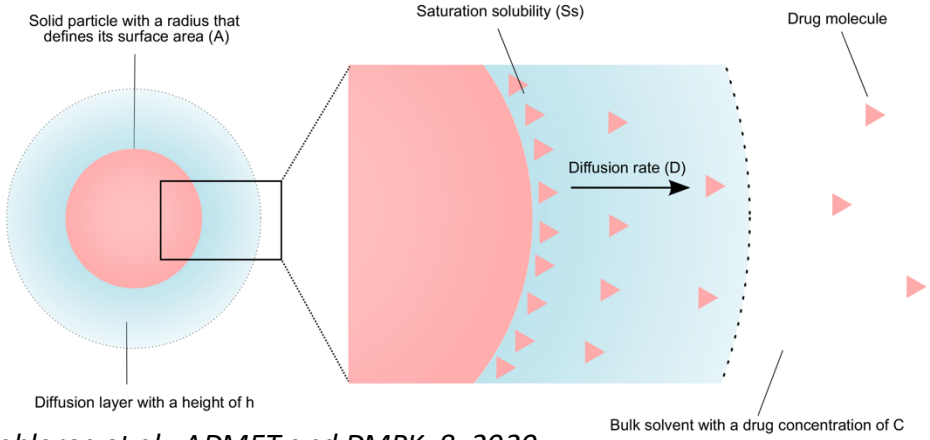
- Noyes-Whitney type equation
  - Film-theory of drug dissolution



$$\frac{dm_{solid}}{dt} = -A * \frac{D}{h} * (S - C)$$

Willmann et al., Eur. J. Parm. & Biopharm., 76, 2010

- Account for bile salt micellization
- Diffusion layer thickness
  - Hydrodynamics and particle size



Dahlgren et al., ADMET and DMPK, 8, 2020

Abbreviations:

- m_{solid}: Solid drug mass
- A: Surface area
- D: Diffusion coefficient
- h: Diffusion layer thickness
- S: solubility
- C: Concentration in the bulk fluid

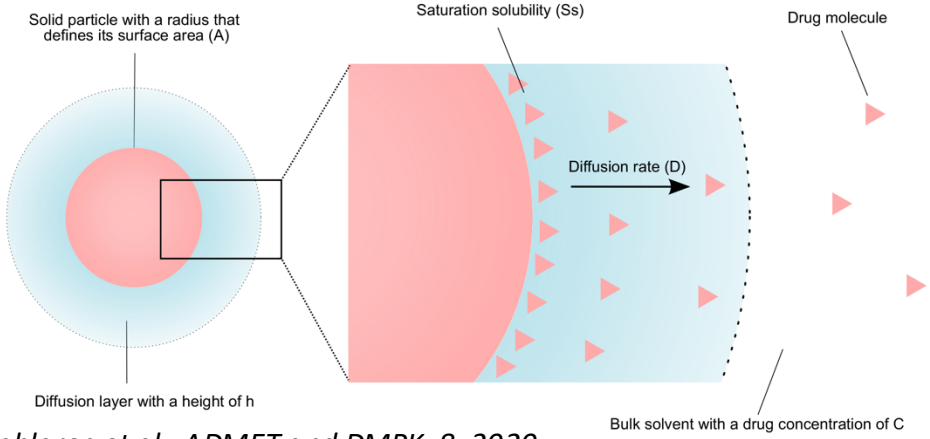
Implemented versatile Particle Dissolution equation

Sub-models can be switched on/off based on drug, available data and application

$$\frac{dm_{solid}}{dt} = -A * \left(\frac{D_u}{h_u} * \left(S_{u,surf} - C_u\right) + \frac{D_b}{h_b} * \left(S_{b,surf} - C_b\right) \right) * \Psi$$

Gamsiz et al., Pharm. Res., 27, 2010

u = unbound, b = micelle bound



Dahlgren et al., ADMET and DMPK, 8, 2020

Surface Area (*A*)

Particle Size
(Monodispersed or Distribution)

$$A = 4\pi r_t^2 N_0$$

$$N_0 = \frac{Amount_{bin,0}}{\left(\frac{rho}{MW} \times \frac{4}{3}\pi r_{bin,0}^3\right)}$$

Solubility (*S*)

OSP solubility toolbox:
- SG estimation tool for ionizable drugs
- Mechanistic bile salt micelle model ($S_{b,surf}$)
- Surface pH model (manual calculation)

Diffusion coefficient (*D*)

Molecularly dissolved unbound drug (*u*) and bile salt micelle bound (*b*)

- D_u: Measured value or OSP empirical eq.
- D_b: Stokes-Einstein eq.

Diff. layer thickness (*h*)

Constant *h*
- Default: 30 µm

Hintz-Johnson model:
- *h* = particle radius (Max *h* = 30 µm)

Hydrodynamic model:
- (semi)Mechanistic
- *In vitro* conditions

Surface integration factor (Ψ)
- Accounts for processes occurring at the particle surface that slow the precipitation rate

Sjögren et al., Eur. J. Pharm. Sci., 4, 2013

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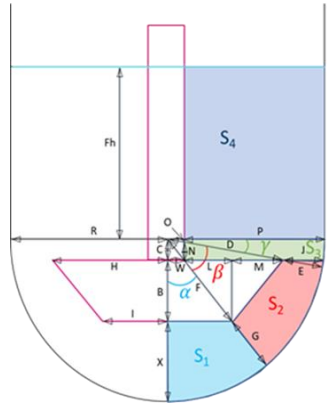
New versatile dissolution model was developed and enables extrapolations to different experimental conditions:

- Agitation rate
- Fluid volume
- Medium viscosity
- Effect of surfactants (e.g., solubility)
- Surface pH
  - Medium pH
  - Buffer capacity medium

Pepin et al., Pharm. Sci., 111, 2022



Benefits of the new model:

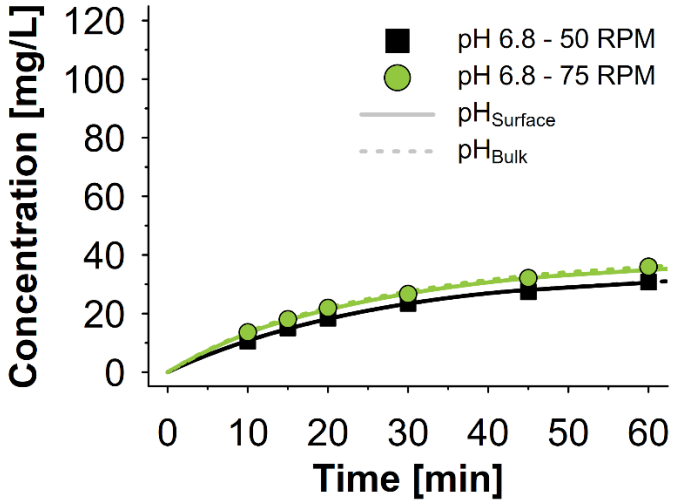
- Mechanistic understanding of *in vitro* dissolution kinetics
- Considers hydrodynamic differences between *in vitro* and *in vivo*, enables translation to a whole body PBPK-model

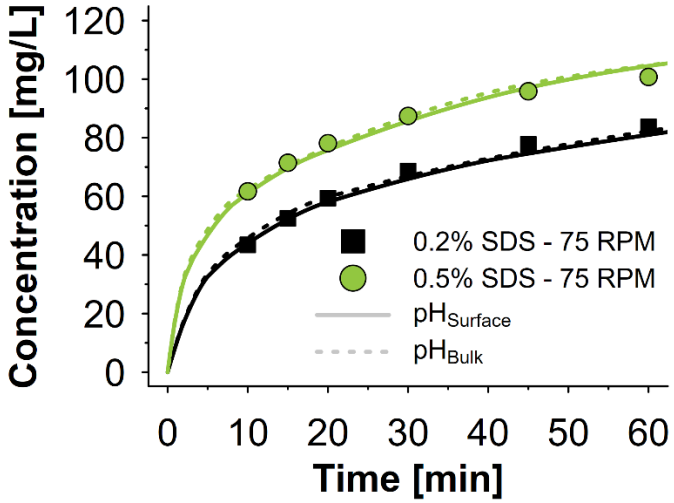
Product-Particle Size Distribution (P-PSD) approach:

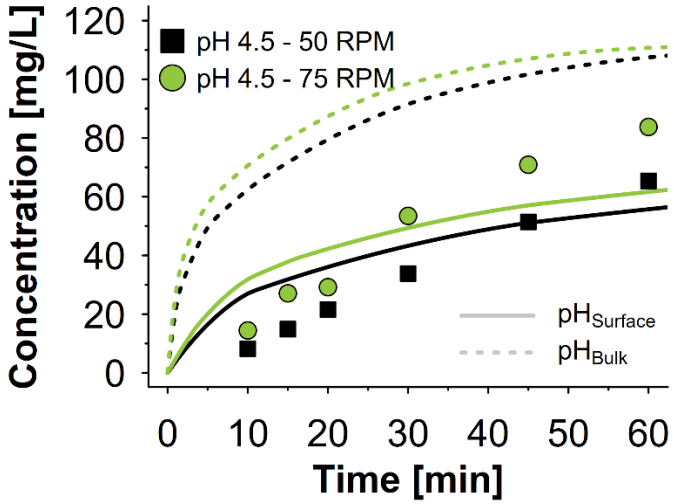
- Log-normal distribution or 1-10 sperate bins fitted to one or more dissolution condition(s)
- Confirm/reject in different in vitro dissolution conditions

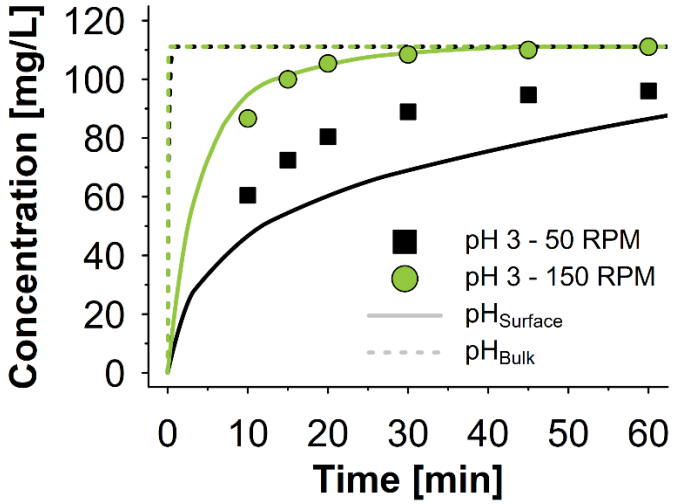
Pepin et al., Mol. Pharm., 13, 2016

Surface solubility required to capture dissolution in more acidic media for Acalabrutinib (diprotic base)









Pepin et al., Pharm. Sci., 111, 2022

Key observations

- P-PSD fitted to dissolution in pH 6.8 at agitation rate 50 RPM
- Effect of increasing agitation (to 75 RPM) well predicted
- Effect of surfactant (0.5 or 0.2 % SDS) captured
- When using the pH$_{Bulk}$ dissolution rate is overpredicted
- When using pH$_{Surface}$ dissolution kinetics are captured

Abbreviations: RPM: revolutions per minute; SDS: sodium dodecyl sulfate

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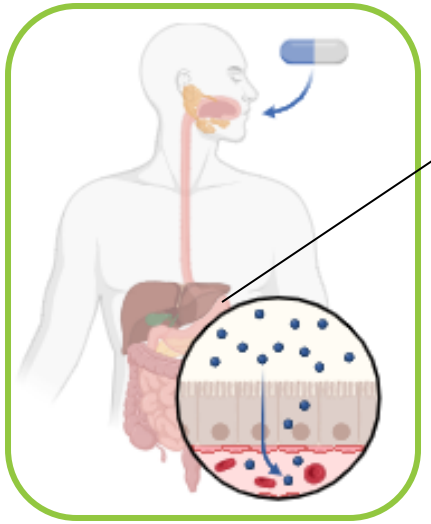

Luminal pH
- Population Variability
- Dynamic

Compartment	Old	New	SD	Difference
Stomach	2	1.82	0.51	-0.18
Duodenum	6	6.27	0.8	0.27
Upper jejunum	6.25	6.69	0.73	0.44
Lower jejunum	6.92	6.69	0.73	-0.23
Upper ileum	7.21	7.49	0.46	0.28
Lower ileum	7.46	8.08	0.52	0.62
Caecum	5.7	7.36	0.63	1.66
Colon A	5.6	7.66	0.56	2.06
Colon T	5.7	6.6	0.59	0.9
Colon D	6.6	6.6	0.59	0
Colon S	6.6	6.6	0.59	0
Rectum	6.6	6.6	0.59	0

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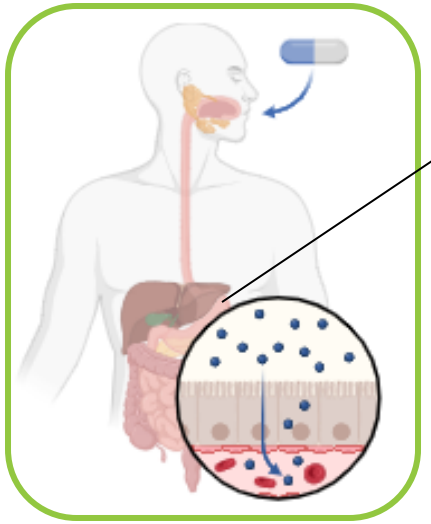

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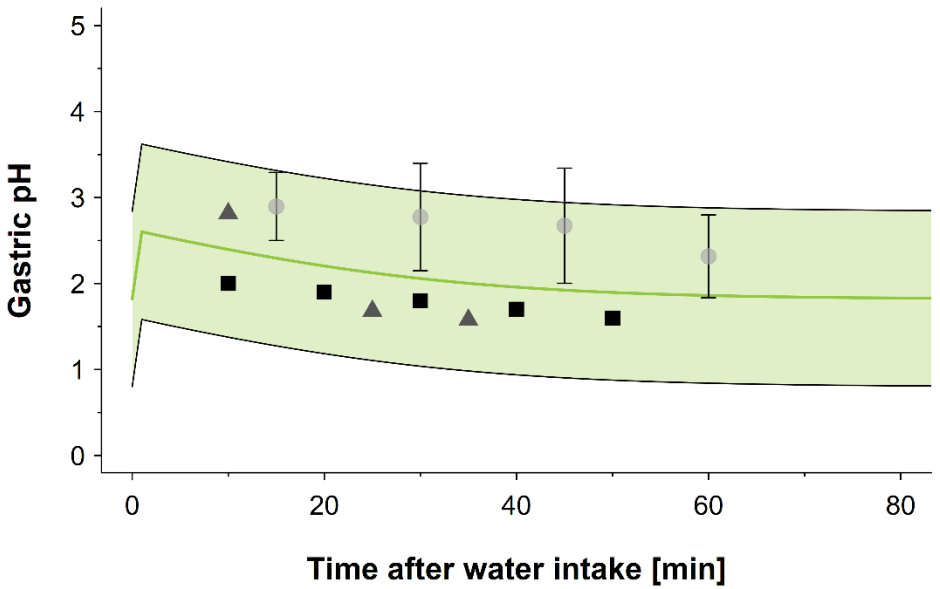

$$pH_{Sto,t} = -Log_{10}\left(10^{[-pH_{Basal}]} * \frac{V_{Sto,Basal}}{V_{Sto,t}}\right)$$

Petrakis et al., J. Pharm. Pharmacol., 67, 2015
Litou et al., Pharm. Res., 33, 2016
Koenigsknecht et al., Mol. Pharm., 14, 2017

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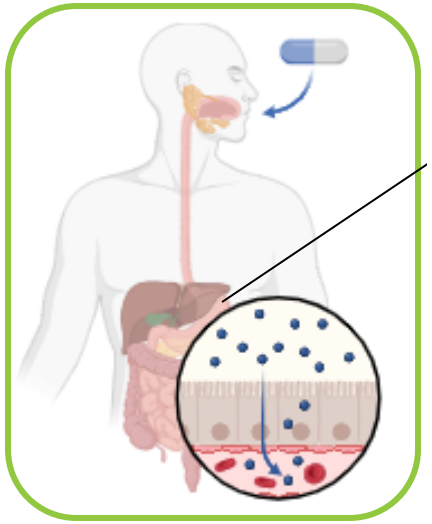

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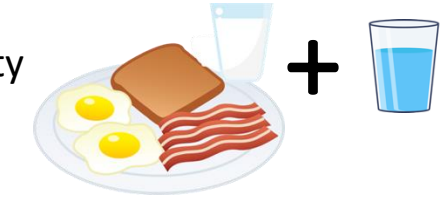

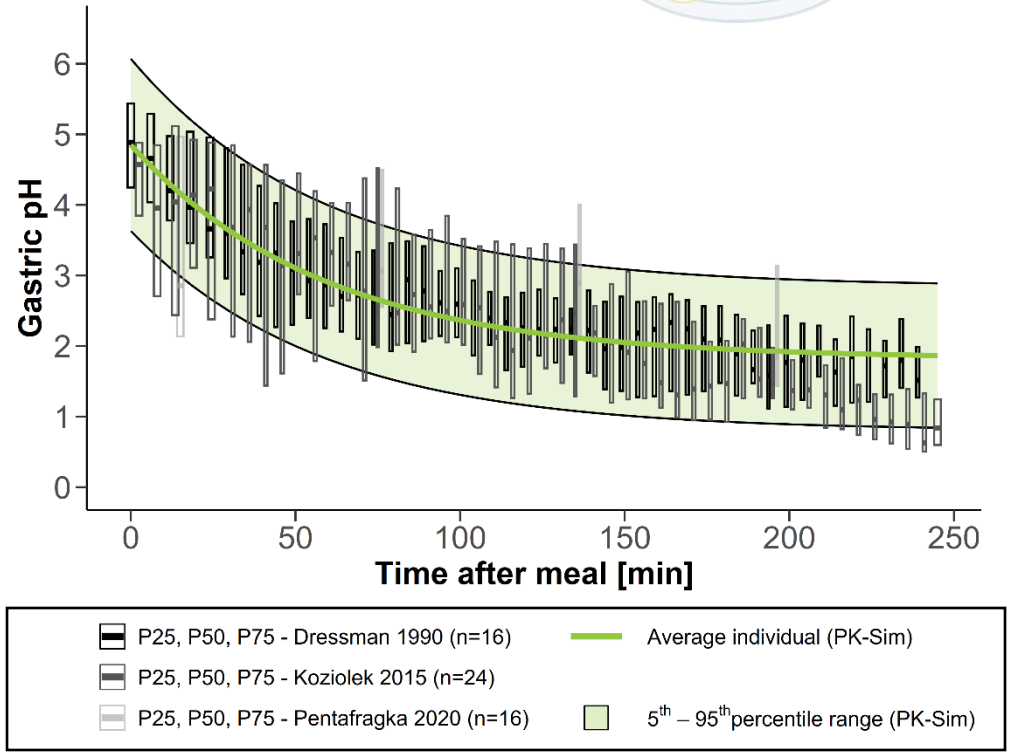

$$pH_{Sto,t} = pH_{Basal} + (pH_{Fed} - pH_{Basal}) \times e^{[-\alpha(t-t_{Meal})]}$$

Dressman et al., Pharm. Res., 7, 1990
Koziolek et al., J. Control. Release., 220, 2015
Pentafragka et al., Eur. J. Pharm. Sci., 155, 2020

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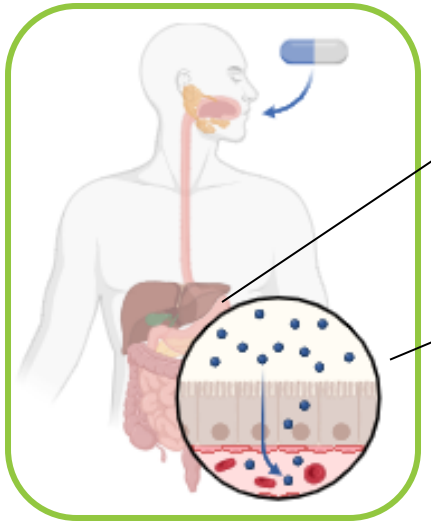

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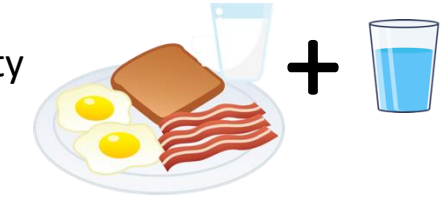
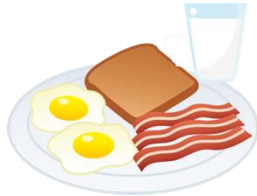
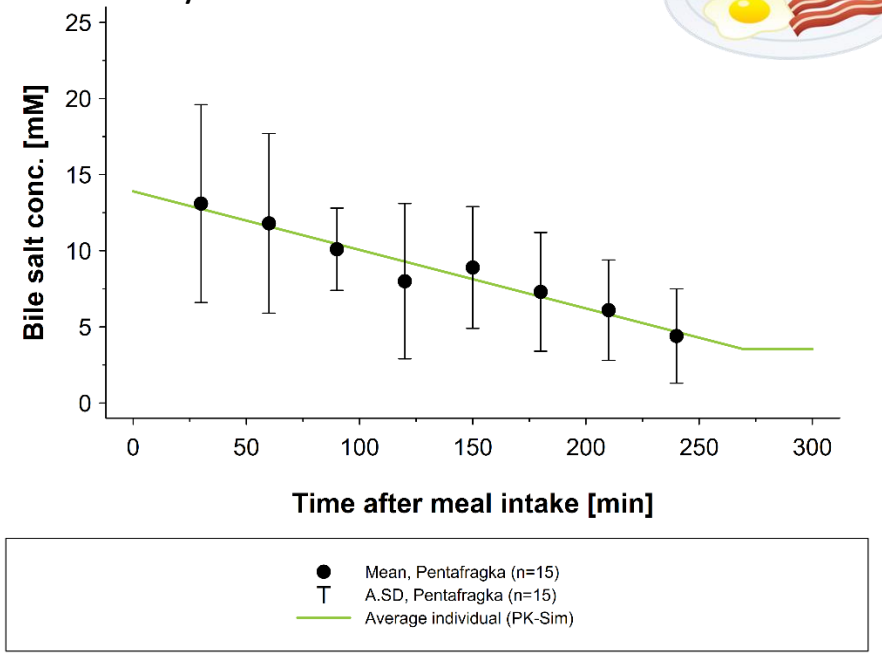


Bile salt concentrations
- Population Variability
- Dynamic





$$C_{bile,t} = max(C_{Fed} - a * t\ , C_{Fasted})$$

Pentafragka et al., Eur. J. Pharm. Sci., 155, 2020

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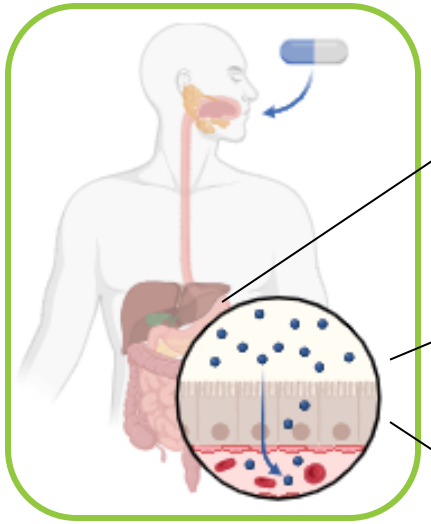

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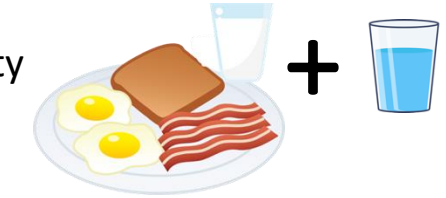

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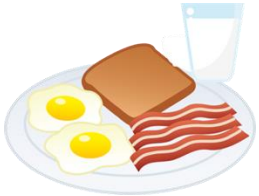

Hydrodynamic model options:
- Simplified hydrodynamic model
  - Assuming laminar flow
  - Inbuild liquid transfer velocity
- Addition of Hintz-Johnson model

$$\frac{dm_{solid}}{dt} = -A * \left(\frac{D_u}{h_u} * \left(S_{u,surf} - C_u \right) + \frac{D_b}{h_b} * \left(S_{b,surf} - C_b \right) \right) * \Psi$$

Gamsiz et al., Pharm. Res., 27, 2010

u = unbound, b = micelle bound

Conclusions

- **Free and open-source PBBM framework:**
  - **R-shiny solubility toolbox** for characterizing drug solubility
  - **MoBi® in vitro dissolution model** for characterizing dissolution kinetics in vitro
  - **PK-Sim® whole body PBPK model** for predicting *in vivo* pharmacokinetics
- **Successful application:** The developed PBBM framework accurately predicted human pharmacokinetics of weakly basic drug in fasted and fed state and after antacid intake
  - Papers published soon
  - Complete PBBM framework will be made available on the OSP GitHub
- New features planned to be **included in future PK-Sim® versions**
  - **Support formulation strategies** and mitigate poor performance of oral drug products early
  - **Alignment with regulatory requirements:** The framework was designed to meet regulatory requirements for biopharmaceutics modeling (including a mechanistic dissolution model, validation with clinical data, and comprehensive documentation)

Acknowledgements

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- Dr. Juri Solodenko

Academic supervisor:
- Dr. Maria Vertzoni

Thank you!


InPharma

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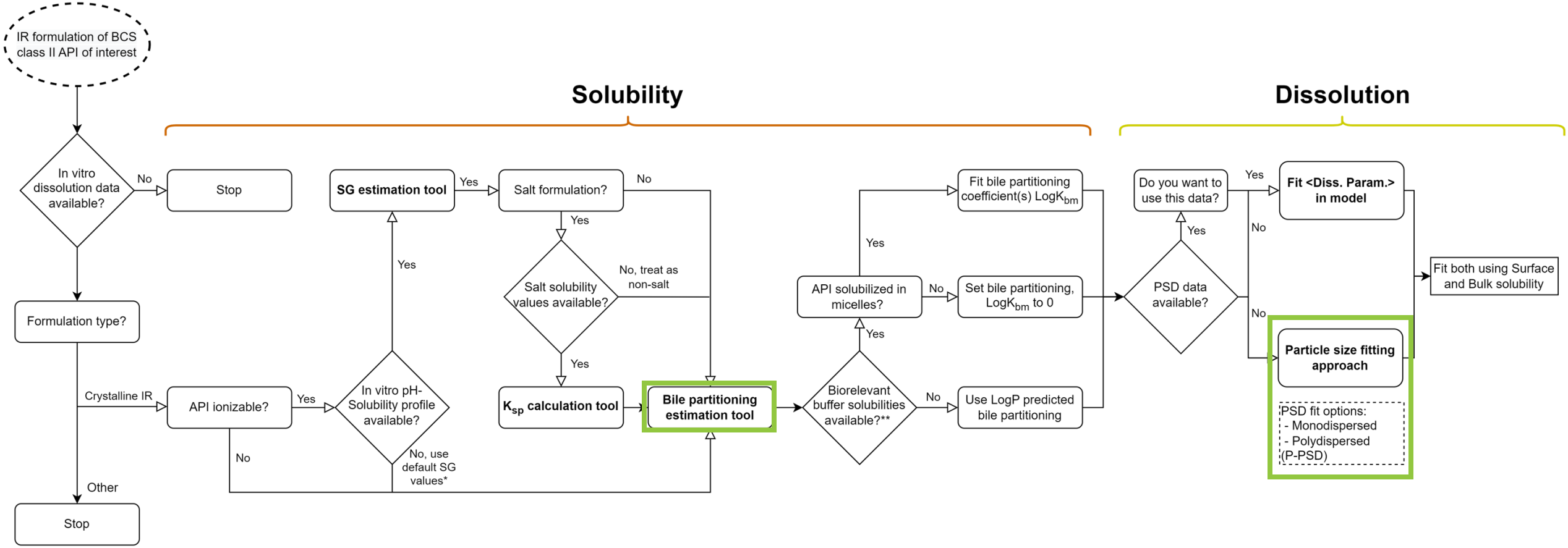
In Vitro In Vivo Translational (IVIVT) workflow for poorly soluble APIs

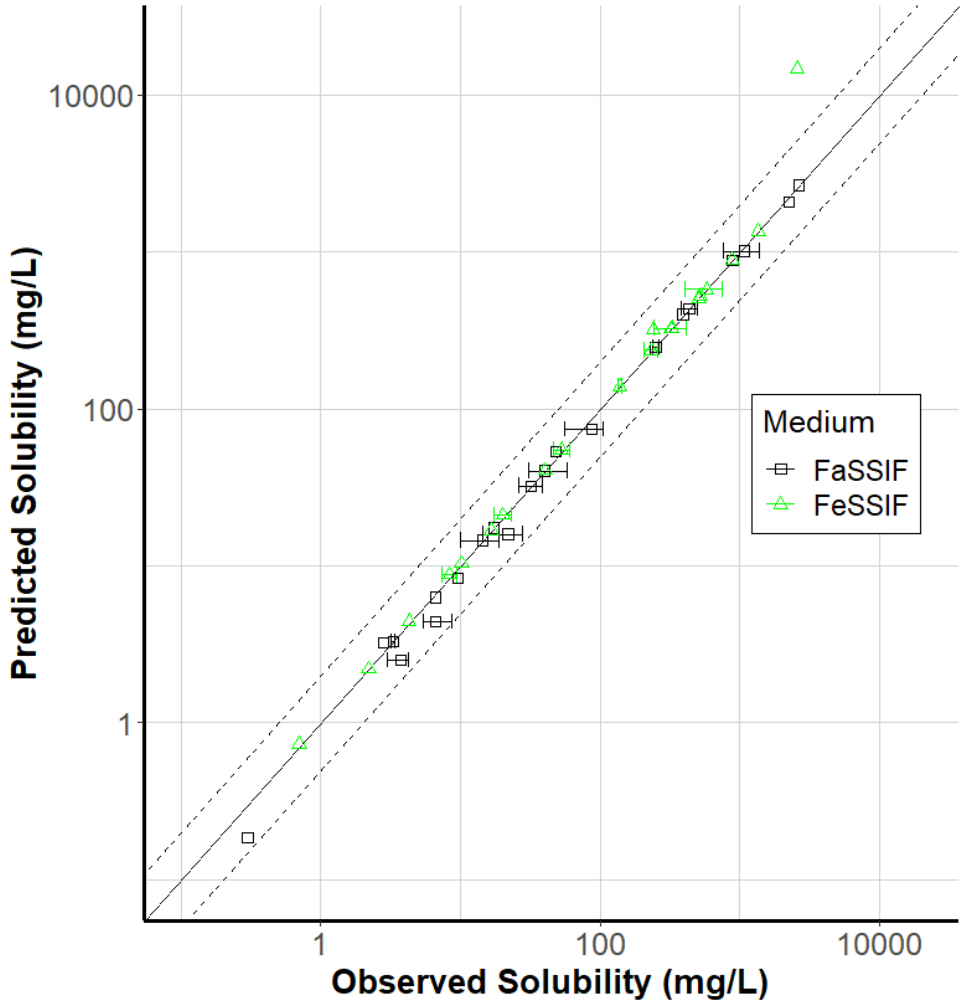


Validation: Adequate predictions of solubility in biorelevant media

- 21 APIs selected (8 neutral, 6 acidic, 7 basic):
  - Available biorelevant solubility data (both FaSSIF & FeSSIF)
  - Blank aqueous buffer solubilities as baseline reference (from literature)
  - API properties (from literature; MW, Log P and pKa(s))
- Intrinsic solubility ionizable APIs back-calculated
  - Aqueous reference solubility, pKa(s) and default OSP Solubility Gain due to ionization

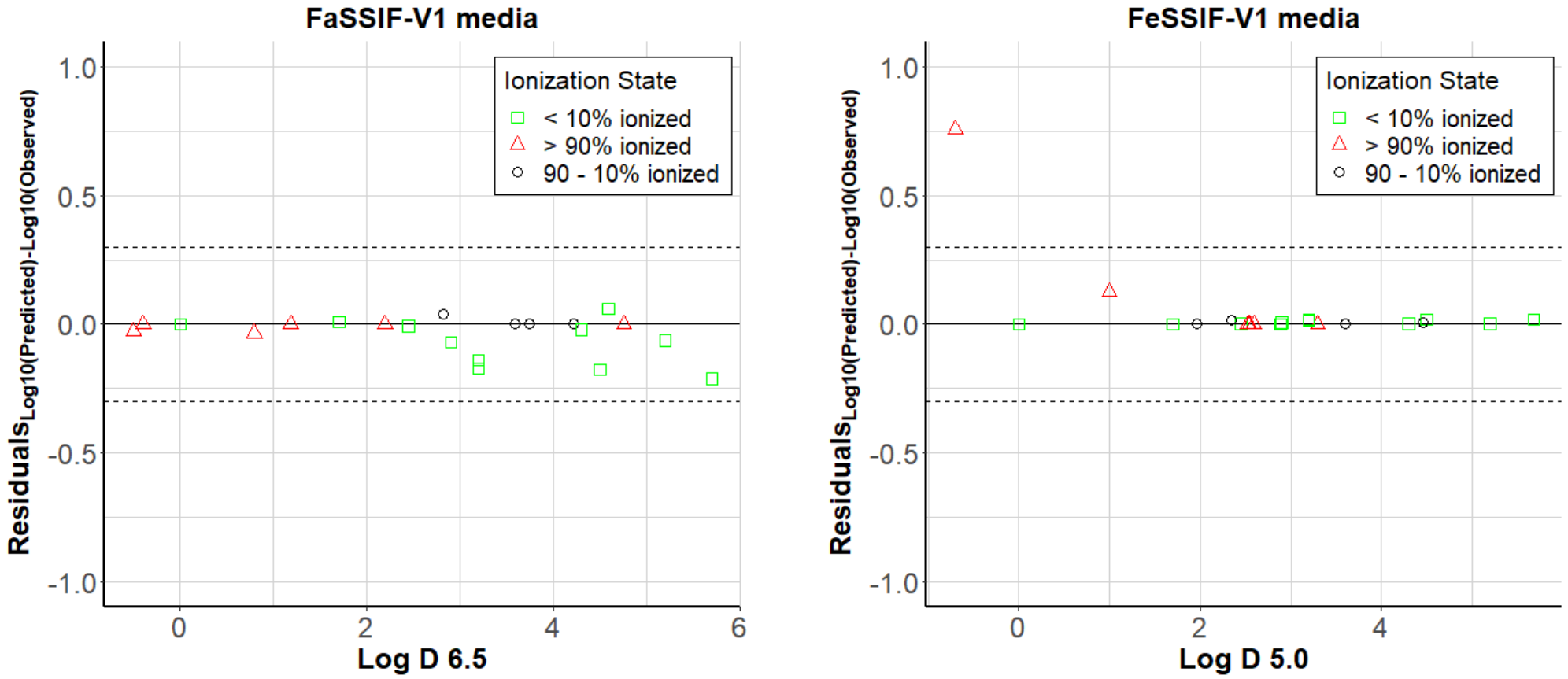
$$S_{br} = \left([BileSalt] \times \frac{S_0}{[H_2O]} \times K_{m:w,neutral} + S_0\right) + \left([BileSalt] \times \frac{S_i}{[H_2O]} \times K_{m:w,ionized} + S_i\right)$$

Sugano 2009, Exp. Opinion drug Met. & Tox, 5 (3), 2009



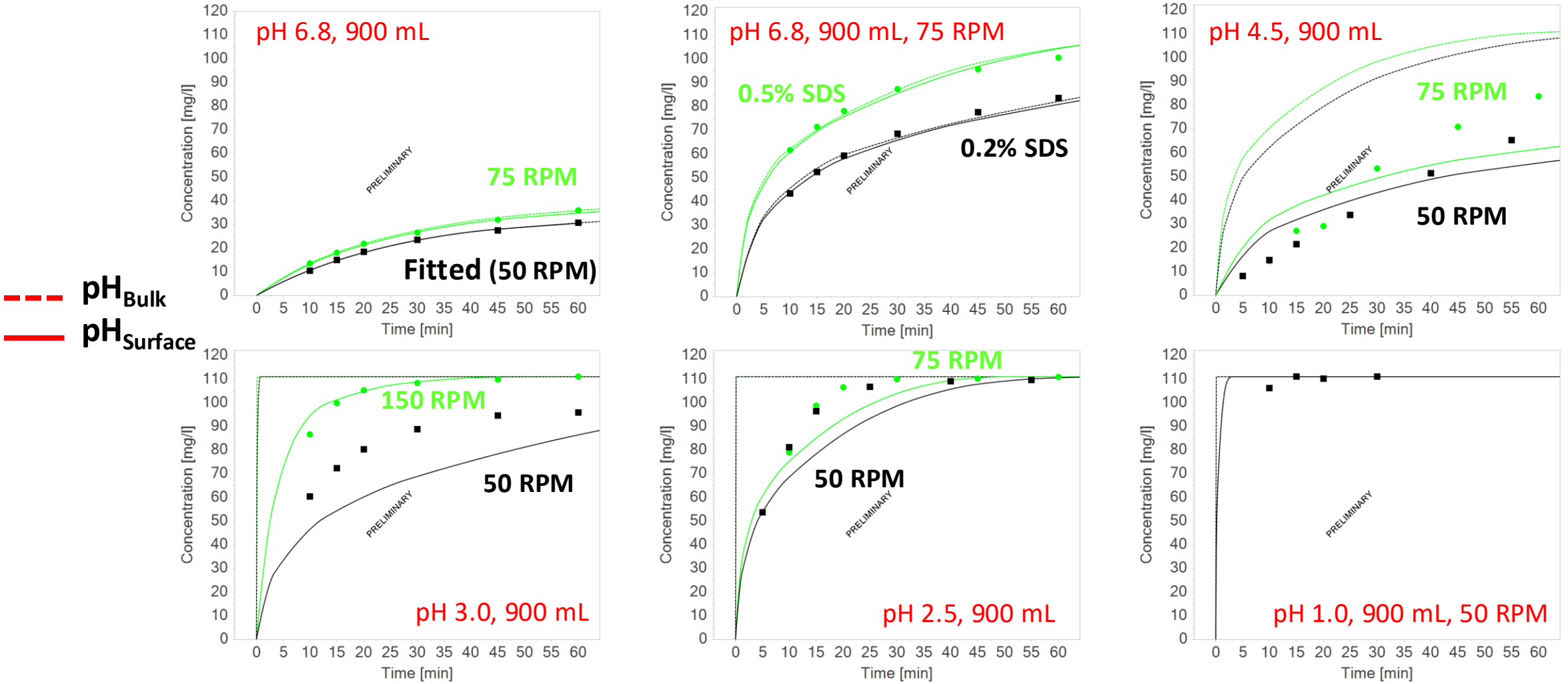
Data from: Clarysse et al. (2009, 2011), Annaert et al. (2010), Soderlind et al. (2010), Bevernage et al. (2010)

Lipophilicity and ionization state in FaSSIF media might be factors to be considered



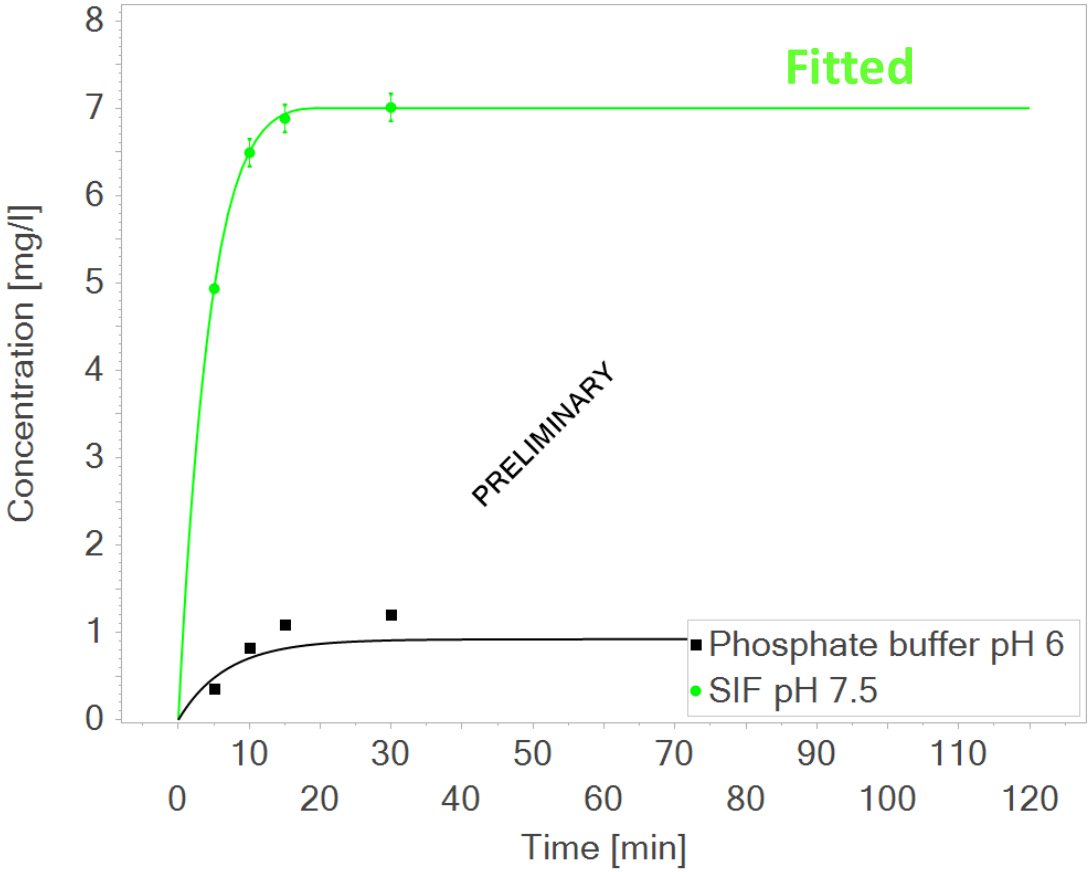
Data from: Clarysse et al. (2009, 2011), Annaert et al. (2010), Soderlind et al. (2010), Bevernage et al. (2010)

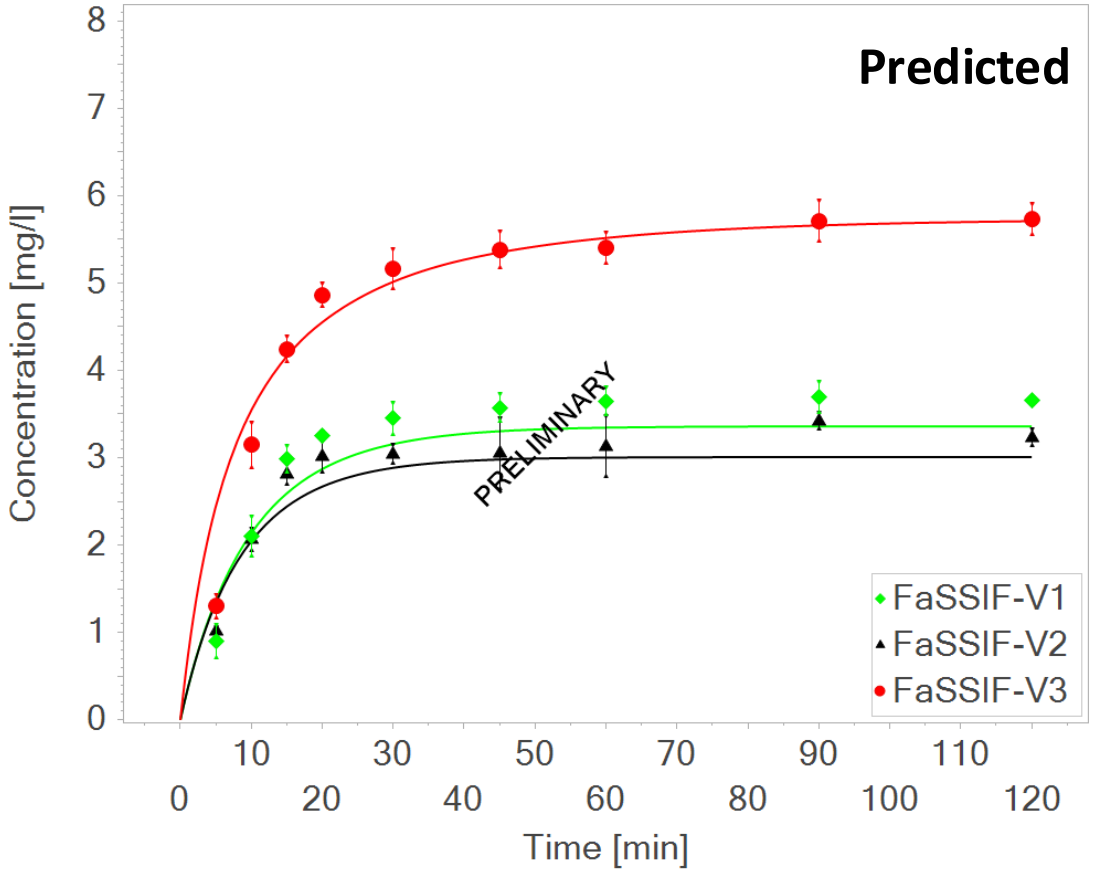
Surface solubility required to capture dissolution in more acidic media for Acalabrutinib



Pepin et al., Pharm. Sci., 111, 2022

Dissolution of Glibenclamide is captured well in biorelevant media





Löbenberg et al., Pharm. Res., 17, 2000

Klumpp et al., EJPS, 142, 2020