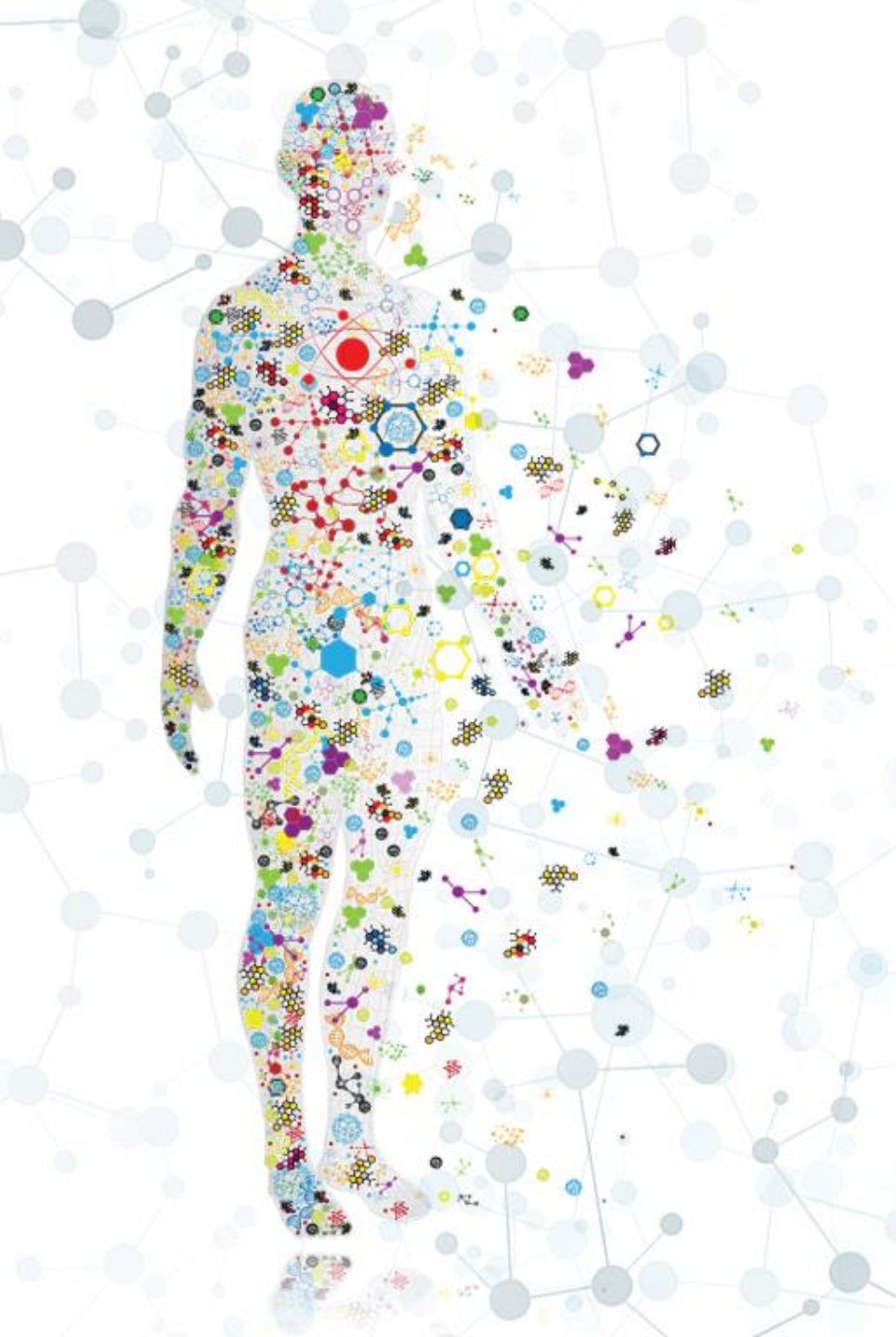


Updates to the Simcyp Simulator's ADAM / M-ADAM Models

David Turner

Jan 29th 2020

This webinar is being recorded and will be made available to view on the Certara website in due course

FDA Grant 1U01FD005865

Simcyp Industrial Consortium

Summary

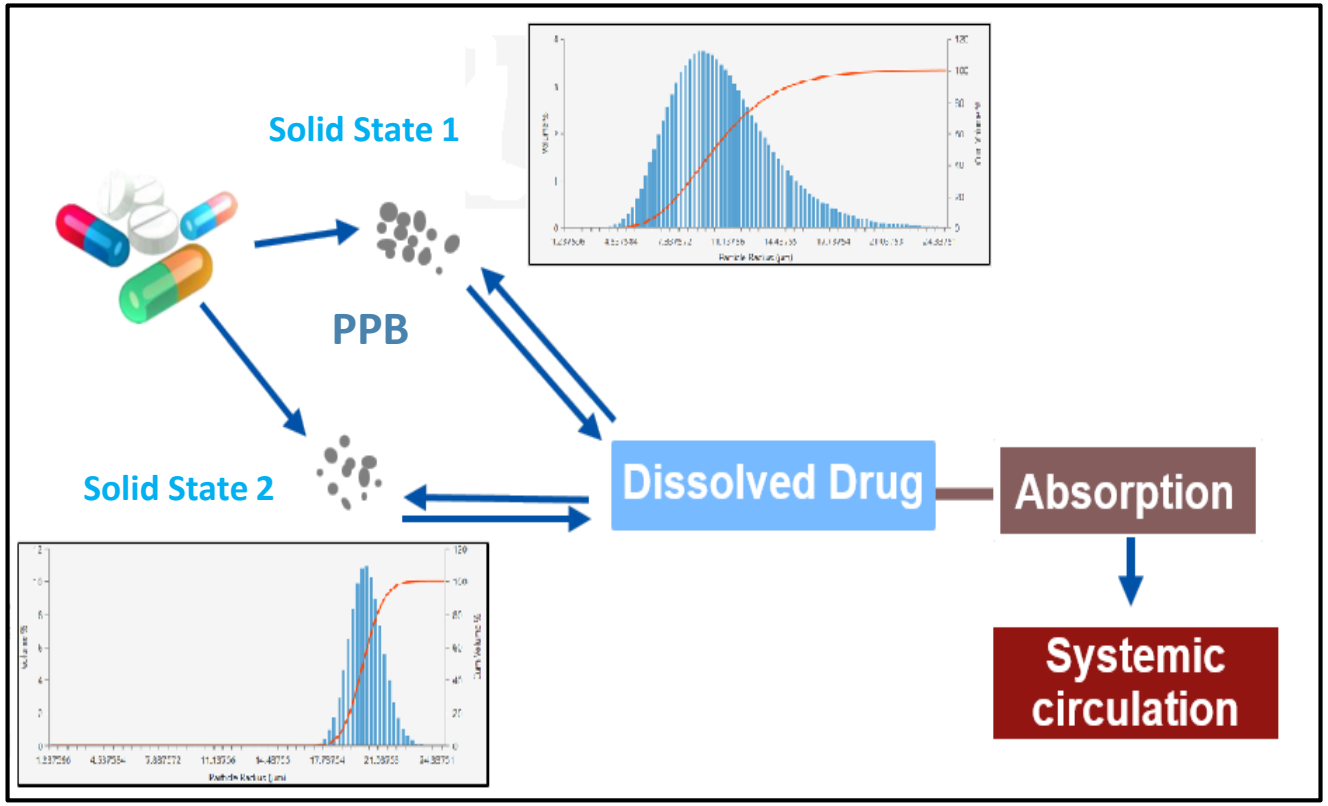
- Recent Additions
  - New Models
  - Tools – “Wrappers” – IVIVC, VBE, GSA (Global Sensitivity Analysis)

This webinar is being recorded and will be made available on the Certara website in due course

- Modelling Strategy – Coupling in vitro experiments to PBPK modelling
- Case Studies / Examples
  - Tacrolimus ASD Formulation – VBE
    - What extent of crystallisation leads to bioinequivalence?
  - Excipient Solubilisation
    - Why does formulating with a cyclodextrin reduce exposure?
    - Assess the optimal amount of cyclodextrin to use in a formulation
- Salt and Surface pH Models
- Summary
- QA

Major Additions to the Simcyp Oral Absorption Models

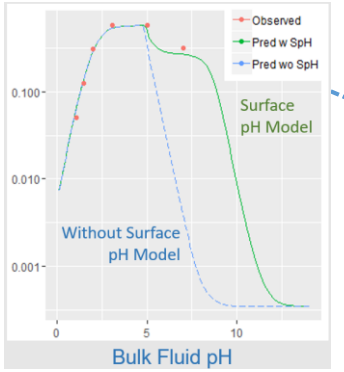
PPB – Particle Population Balance Model



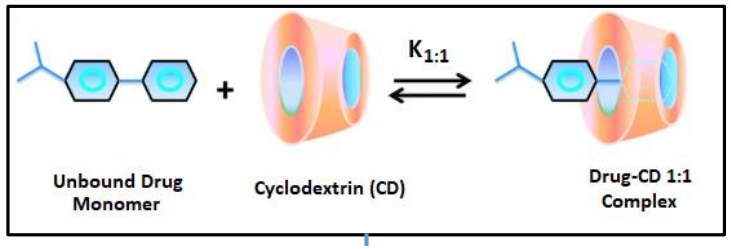
CERTARA

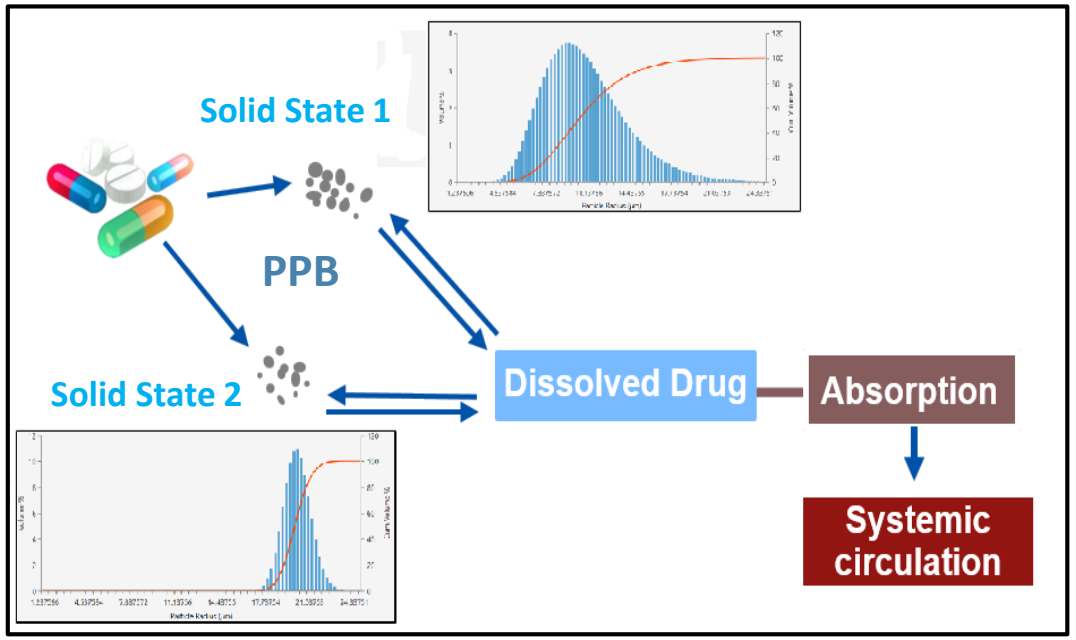
Major Additions to the Simcyp Oral Absorption Models

1. Salts / Surface pH

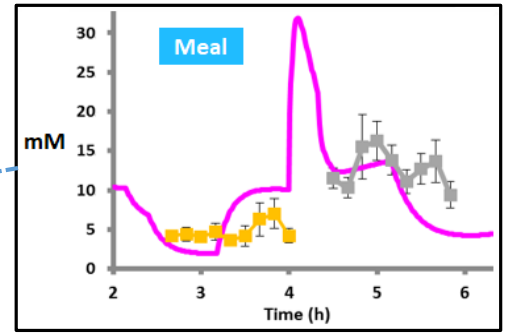


2. Cyclodextrin Binding Solubility-Permeability-Free Fraction Interplay



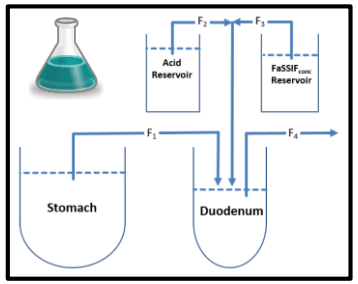


3. Dynamic Bile Salt Model*



Duodenum average subject

KU LEUVEN



Dynamic *In Vitro* Precipitation Experiments

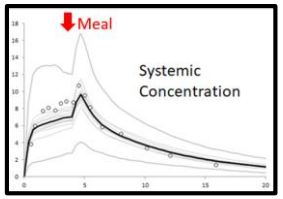
SIVA

5. Nucleation Model

Nucleation Rate ($1/s/m^3$)

$$J(t) = Z(t) \cdot f^* \cdot C^*(t)$$

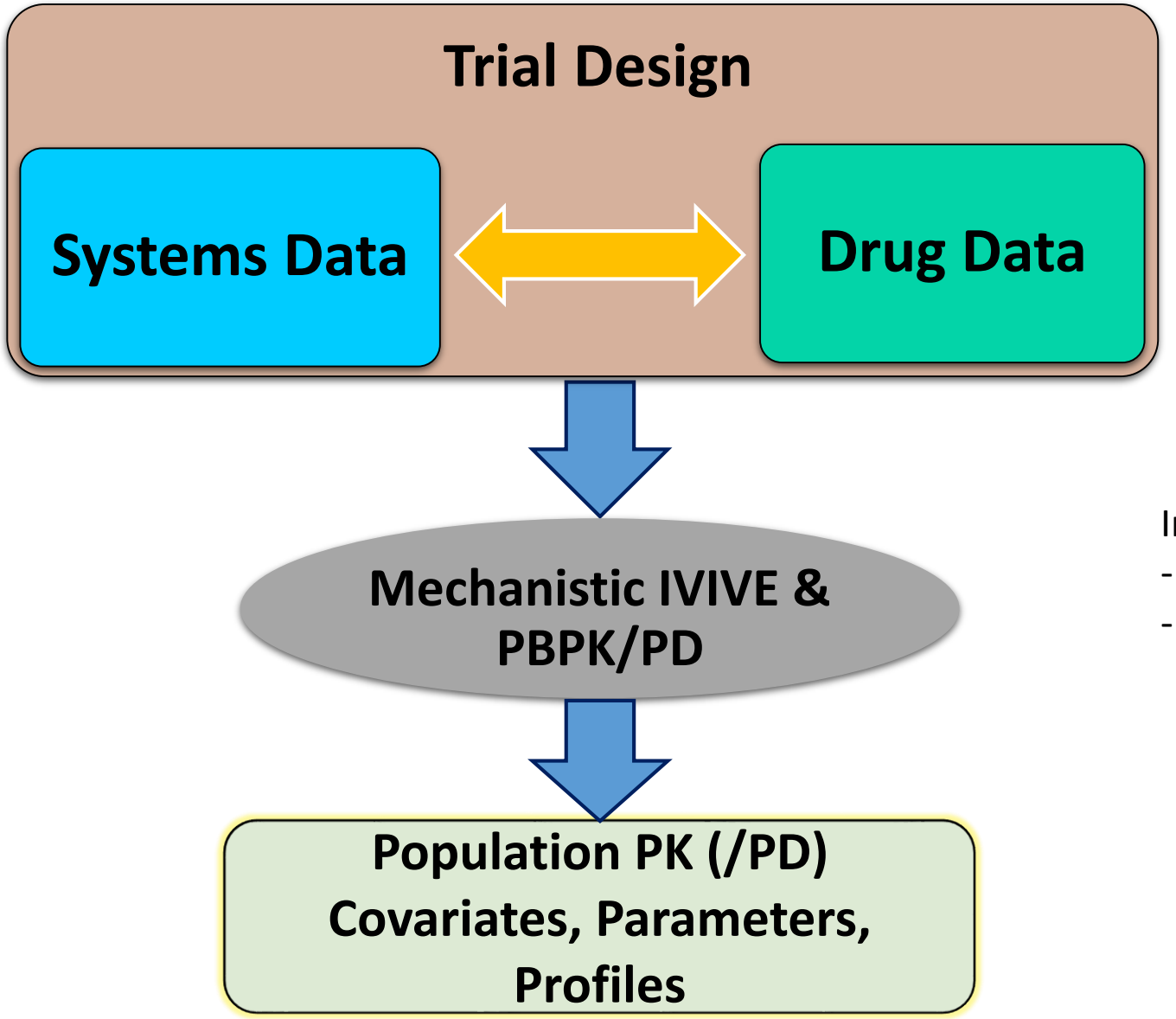
4. Food Staggering/Custom Trial Design



*ms. submitted

CERTARA

Systems Pharmacology - Separating Systems & Drug Information



Input data:
- Compound file
- Population library
- Project (workspace)

Integrated Models:
- Simulation environment
- Multi-dimensional models/algorithms

Output data:
- Raw output data
- Data analysis
- Post processing

CERTARA

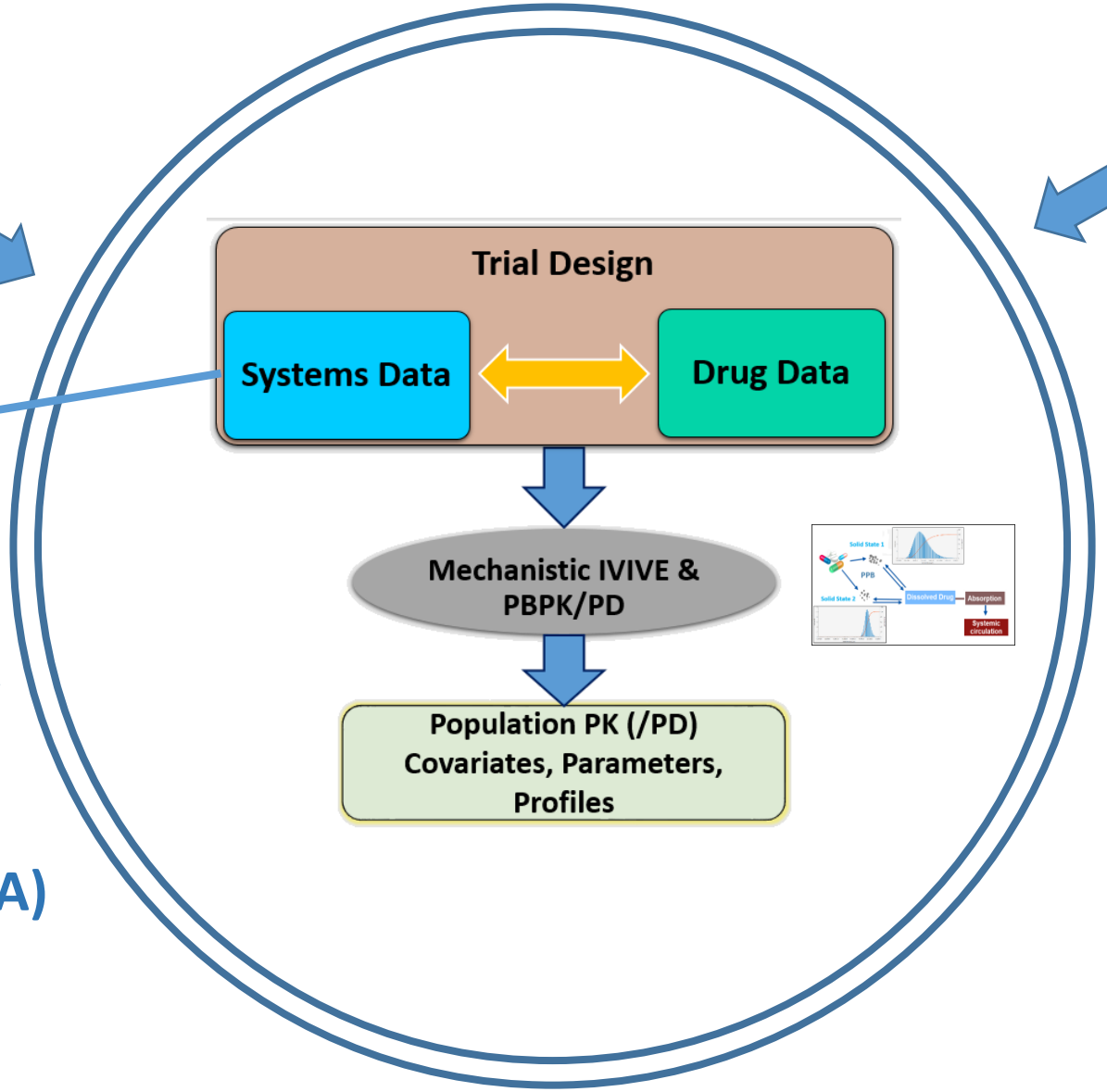
Mechanistic Models Form the Core – Various "Wrappers" are Available

VBE

WSV
(Within Subject Variability)

VBE Study Designs

Physiologically-Based IVIVC (PB-IVIVC)

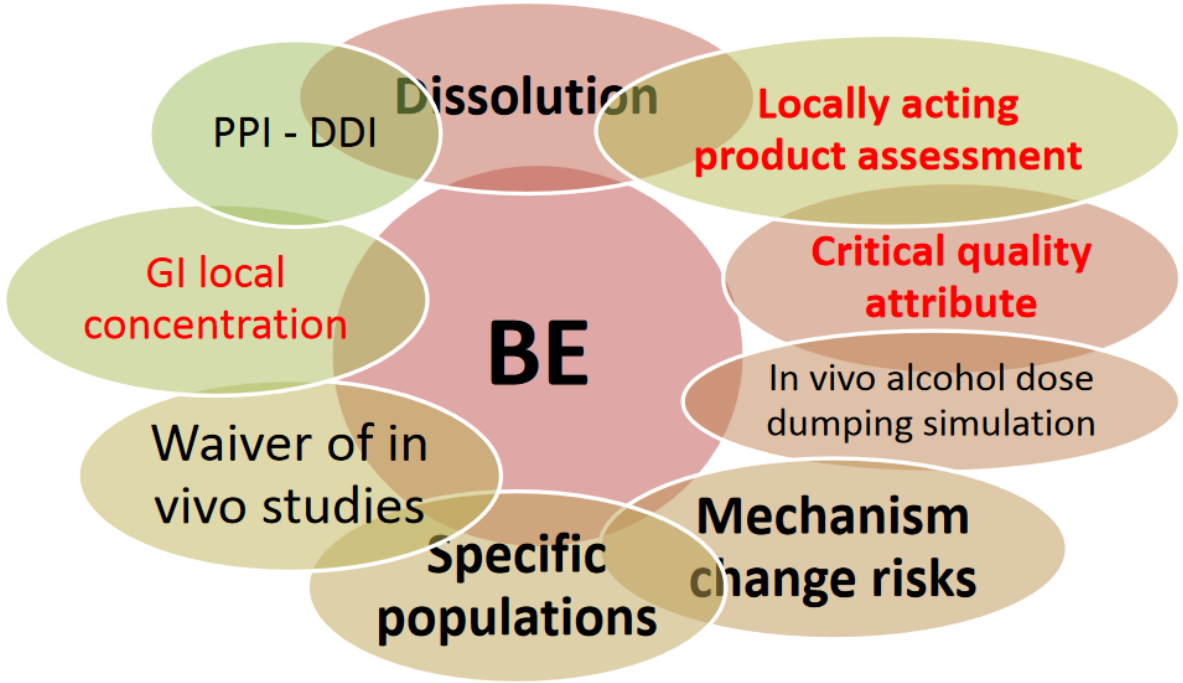


Sensitivity Analysis (SA)
Local SA &
Global SA

CERTARA

Virtual BE – Significant regulatory support and interest

General PBPK Model Applications for Generic Products



Increasing trends in using PBPK models to support regulatory decision making in the realm of generic drug development

BE: bioequivalence; PPI : proton pump inhibitor; GI: gastrointestinal ; DDI: drug-drug interaction

Zhao, Generic Drug Research Public Workshop May 2017, MD, USA

Virtual Bioequivalence Module – Simcyp Version 20

1) VBE Trial Design - Most common designs available plus custom option
   - Crossover 2 Treatment, 2 Period, 2 Sequence (typical crossover BE)
   - Crossover 2T, 2P and 4S
   - Crossover partial replicate (2T, 3P, 4S)
   - Crossover full replicate (2T, 4P, 2S)
   - Crossover full replicate (2T, 4P, 4S)
   - Parallel (up to four treatments) – different population allowed per treatment
   - Crossover custom design

2) Within Subject Variability is Added to Physiological Parameters

Parameters Selected for Within Subject Variability

Parameters

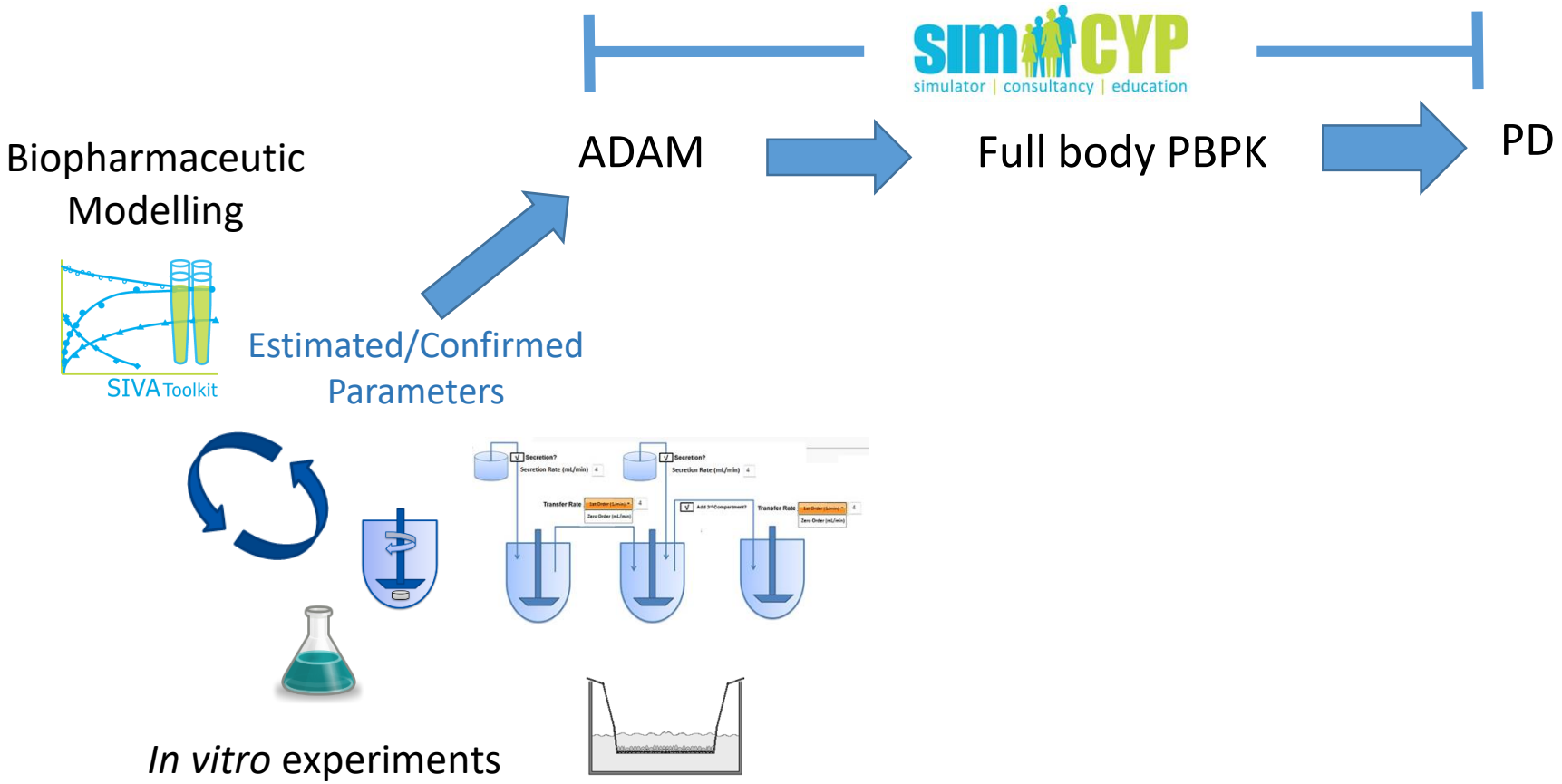
Selected Parameter	Distribution	Variation (CV%)	Minimum Limit	Parameter Value	Maximum Limit
Mean Gastric Emptying Time Fasted	LogNormal	35	0.07	0.4	0.45
Mean Small Intestinal Transit Time	LogNormal	23	1	3.3	5

3) BE Analysis - Phoenix

CERTARA

Running Theme

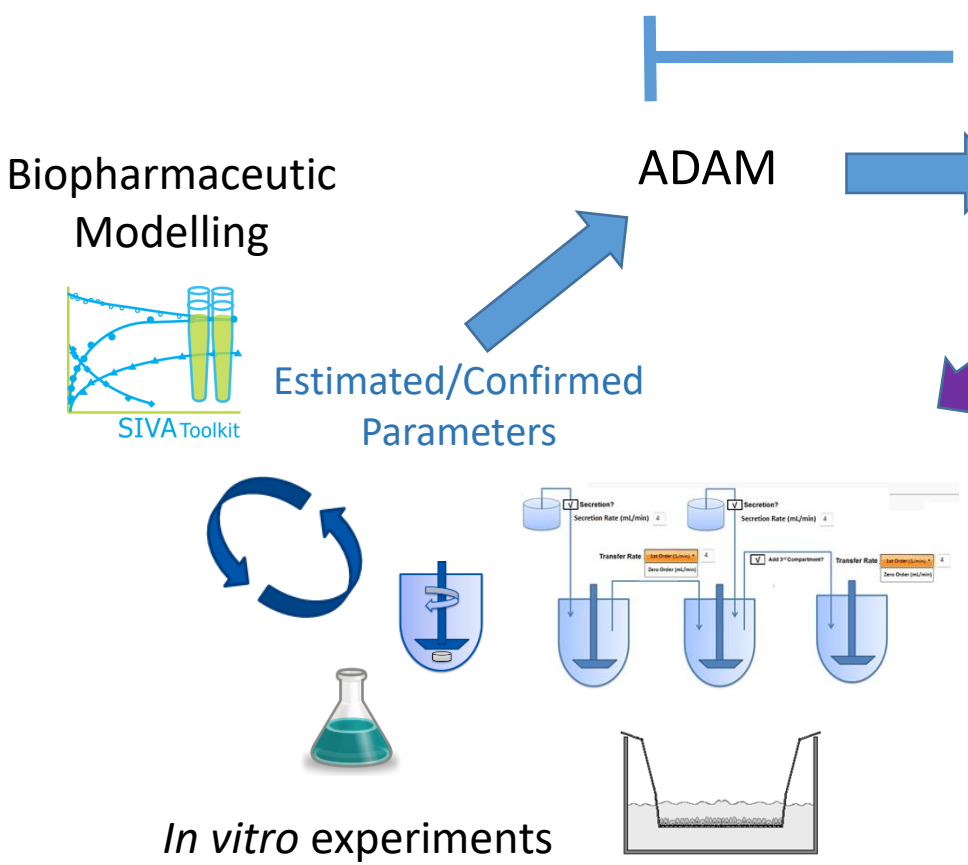
- PBPK / PBBM modelling
  - Informed by *in vitro* experiments



CERTARA

Running Theme

- PBPK / PBBM modelling
  - Informed by *in vitro* experiments



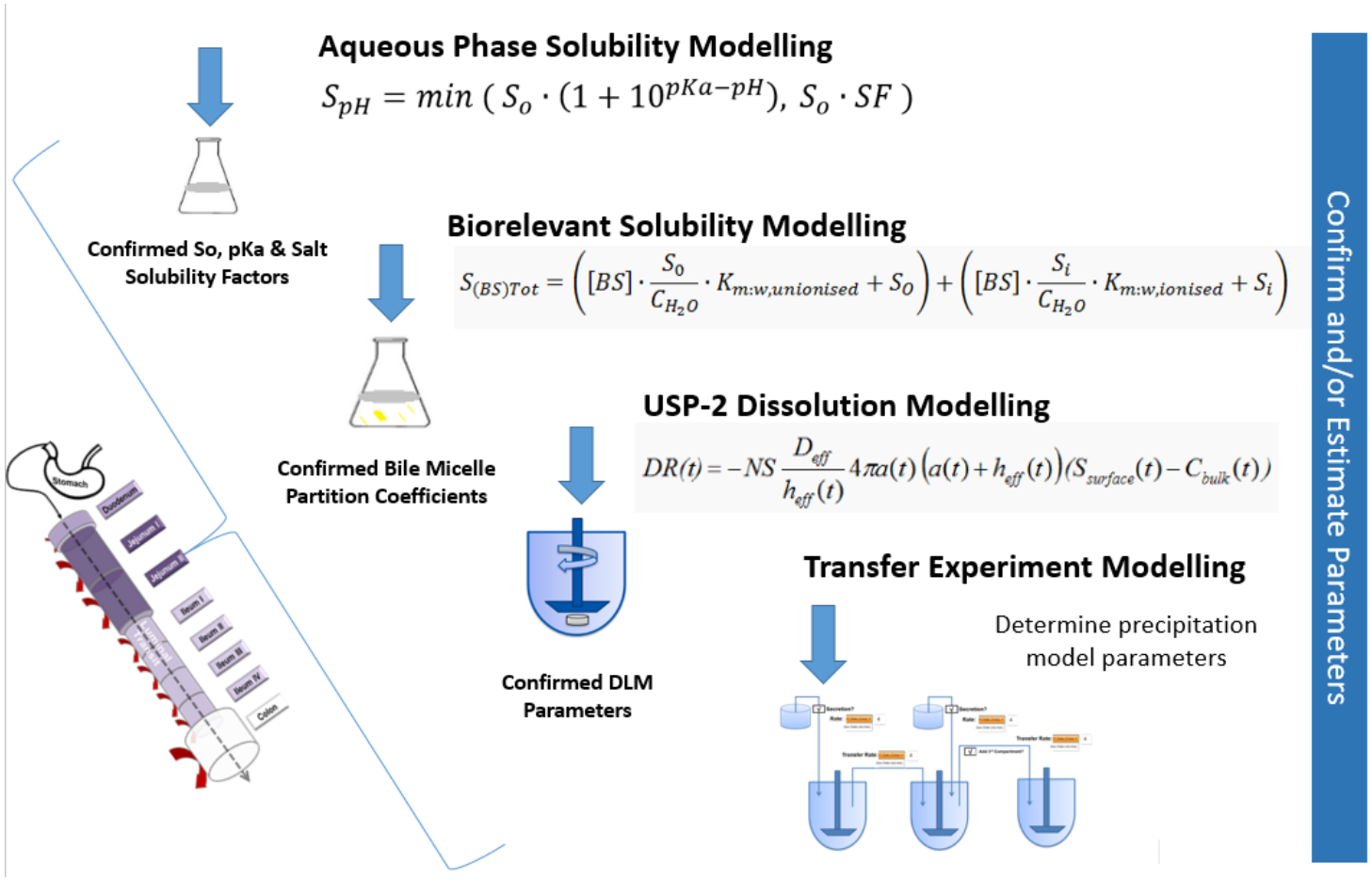
- Design of *In Vitro* Experiments
  - Informed by PBPK / PBBM modelling

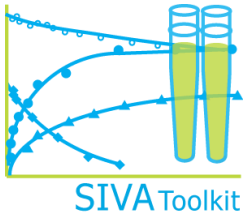
For example, what are the expected *in vivo* concentrations (max, min) of my drug and/or excipient?

CERTARA

Workflow SIVA-Simcyp

Modelling of *in vitro* experiments to inform PBPK simulations - learn confirm, QbD





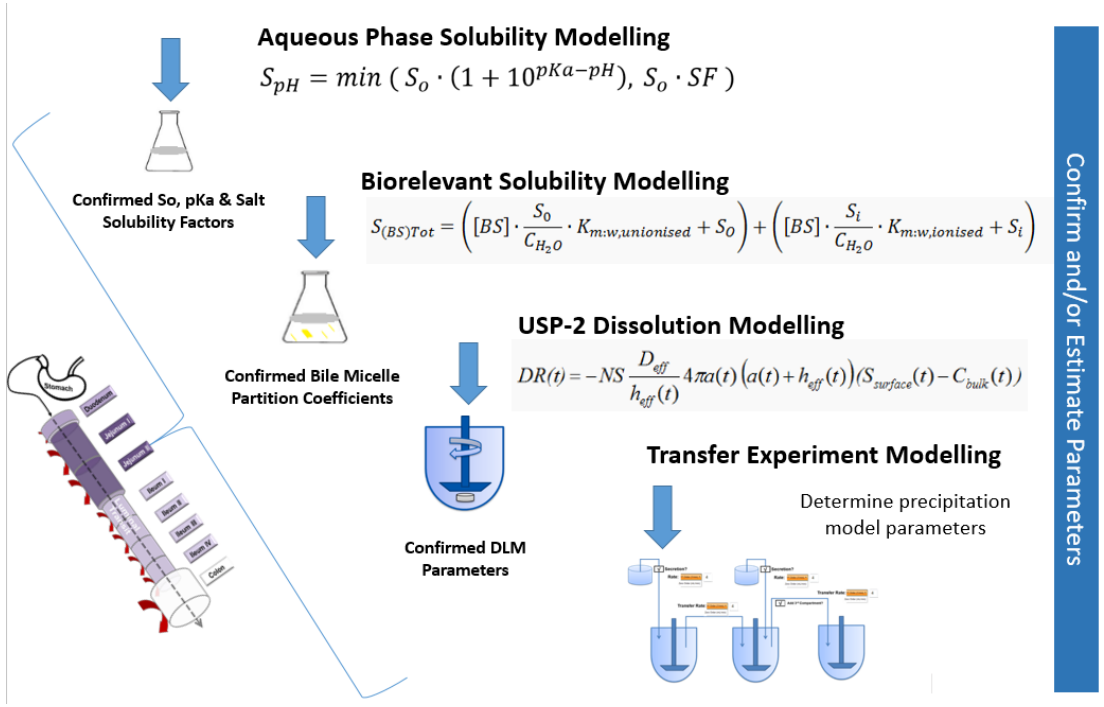
Simcyp **I**n **V**itro data **A**nalysis Toolkit
A standalone software for modelling *in vitro* experiments

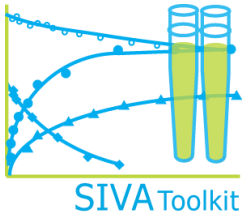
Pathak et al., 2017, 2019; Loisios-Konstantinidis et al., 2020; Hens et al., 2017.

CERTARA

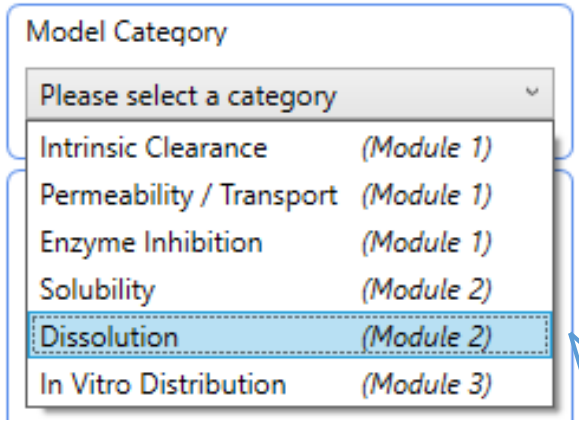
Workflow SIVA-Simcyp

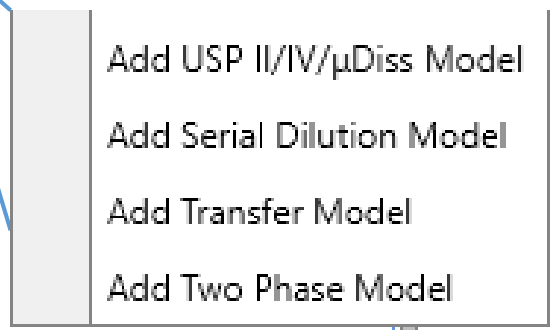
Modelling of *in vitro* experiments to inform PBPK simulations - learn confirm





Simcyp **I**n **V**itro data **A**nalysis Toolkit
A standalone software for modelling *in vitro* experiments





Pathak et al., 2017, 2019; Loisios-Konstantinidis et al., 2020; Hens et al., 2017.

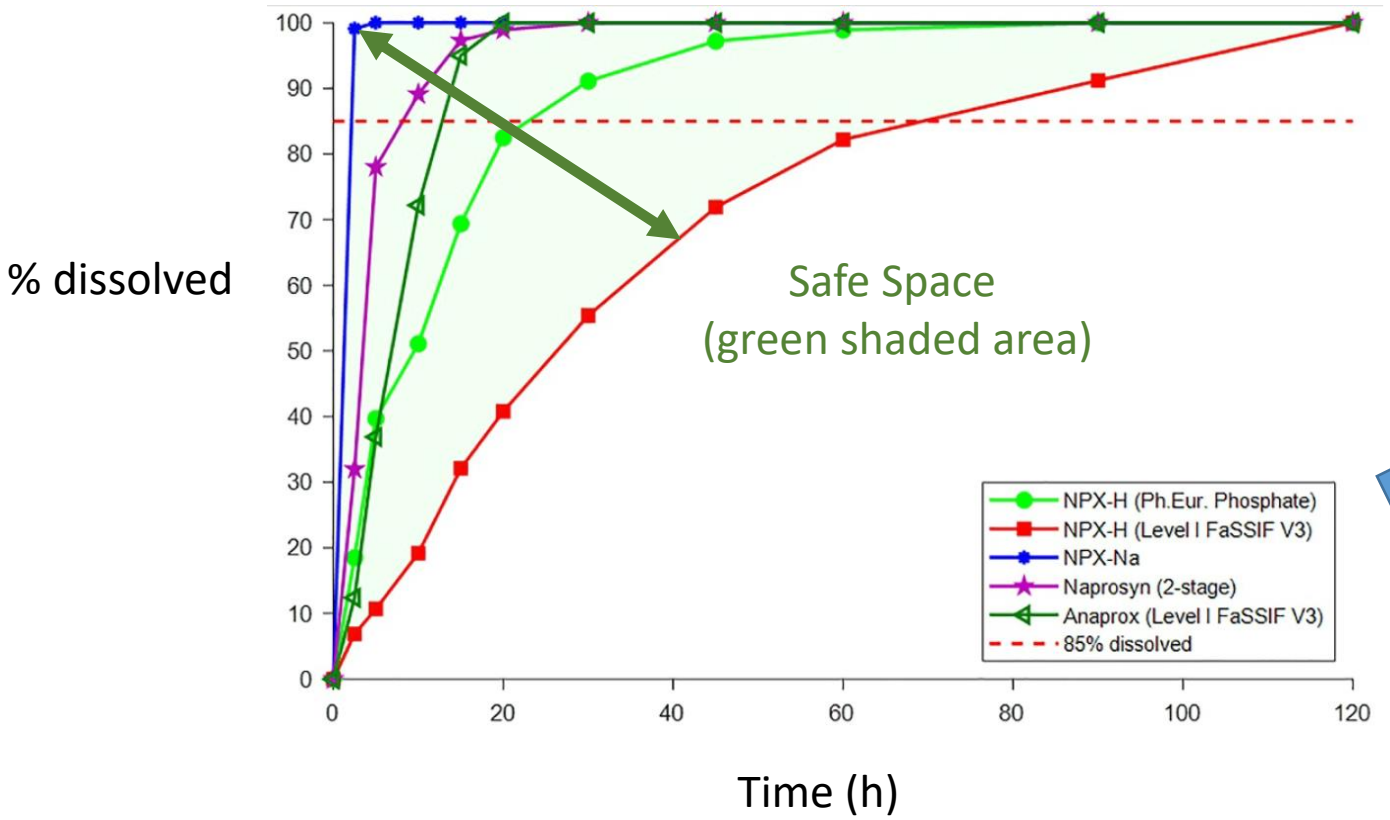
CERTARA

Application of SIVA-Simcyp for Safe Space Identification

Establishing virtual bioequivalence and clinically relevant specifications using *in vitro* biorelevant dissolution testing and physiologically-based population pharmacokinetic modeling. case example: Naproxen

Ioannis Loisios-Konstantinidis[a], Rodrigo Cristofoletti[b], Nikoletta Fotaki[c], David B. Turner[e], Jennifer Dressman[a,d,*]

2020 *Eur J Pharm Sci*



Naproxen PBPK Model built
Middle out approach*
Verified against clinical data*

Dissolution Scenarios
Model-based analysis of In Vitro Dissolution
Further Clinical trial simulations

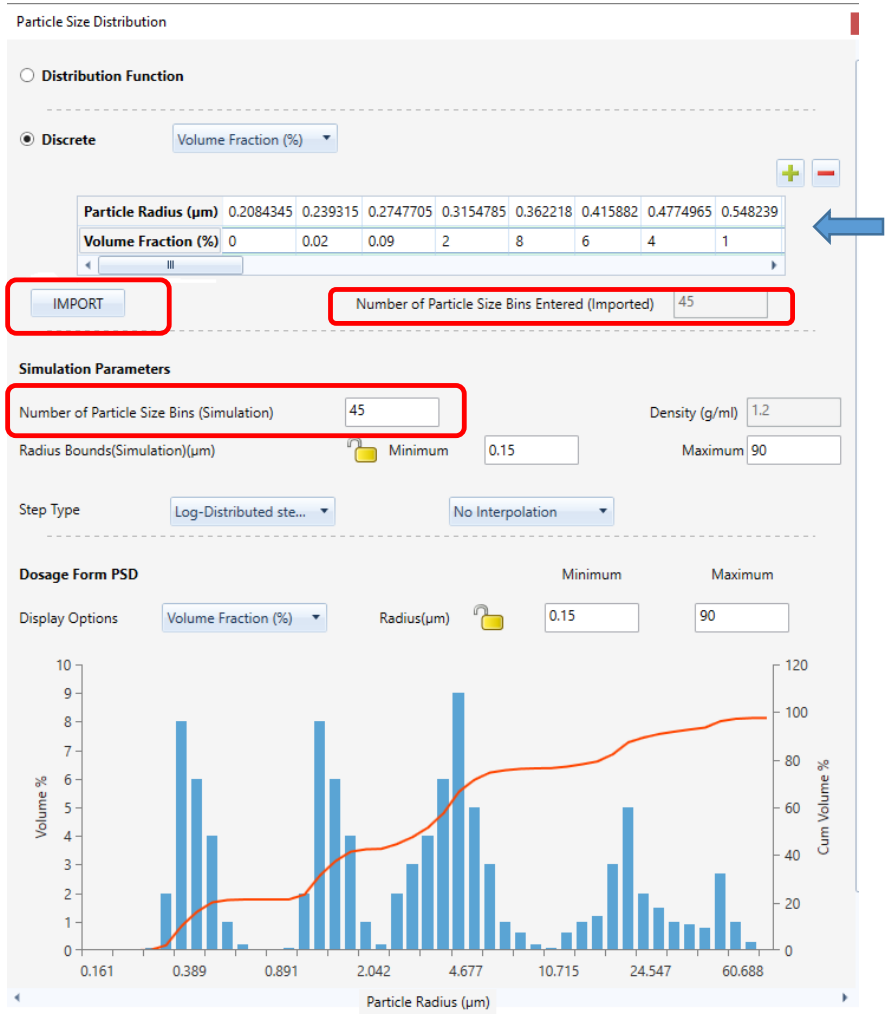
VBE Trials 2S 2T 2P Crossover
IOV added to Critical Physiological Parameters

* Shebley *et al.*, 2018 *CPT* 104 88-110

CERTARA

Particle Population Balance Model: PSD Import and Mapping Tools

- New PSD Tools including IMPORT from (e.g.) a Mastersizer instrument – no need for d10,d50,d90
- Automatically map from raw Mastersizer data to user-defined number of PSD bins



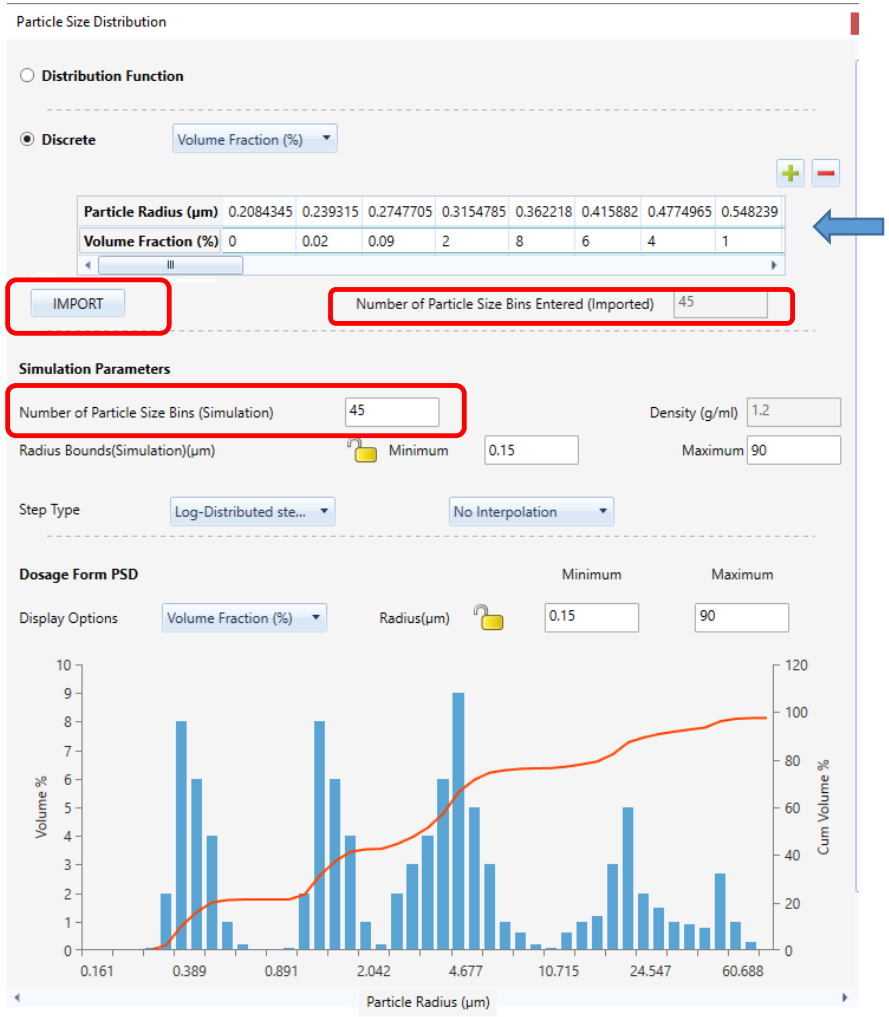
IMPORTED
Raw Data

- Switch between %volume and %count
- Interpolate or without interpolation

CERTARA

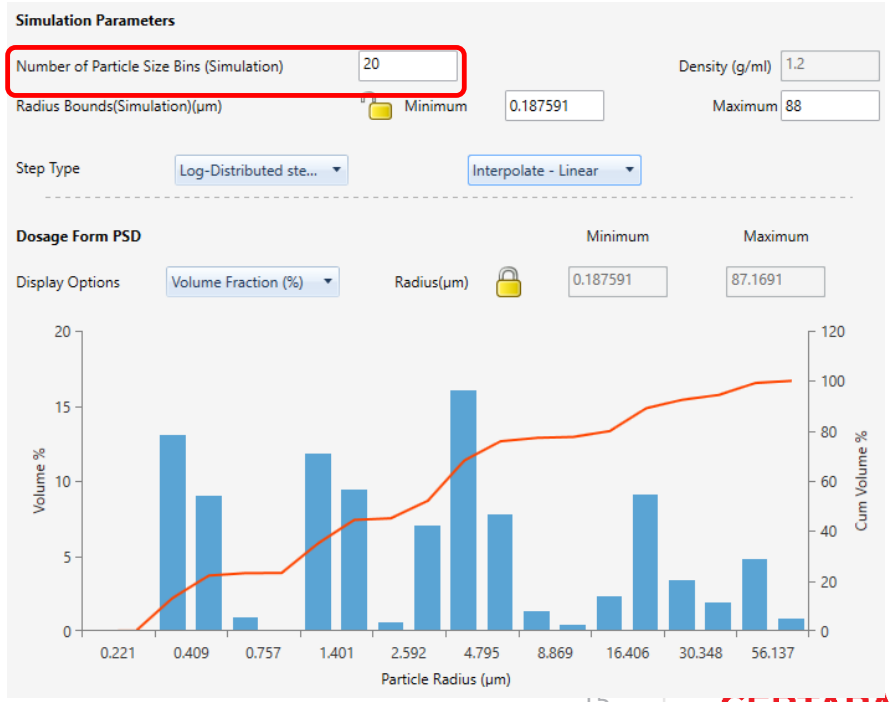
PSD Import Tools

- New PSD Tools including IMPORT from (e.g.) a Mastersizer instrument
- Automatically map from raw Mastersizer data to user-defined number of PSD bins



IMPORTED
Raw Data

- Switch between %volume and %count
- Interpolate or without interpolation



CERTARA

PPB: Two Solid State Tools

Dissolution Rate

$$DR(t) = \sum_{SS2}^{SS1} \sum_{NBINs}^{i=1} -N_i \, S_{DR} \frac{D_{eff}(t)}{h_{eff,i}(t)} 4\pi a_i(t) \left(a_i(t) + h_{eff,i}(t)\right) \left(S_{surface}(t) - C_{bulk}(t)\right)$$

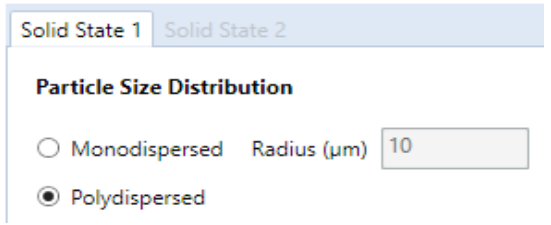
PSD

Separate PSD specification for each solid state

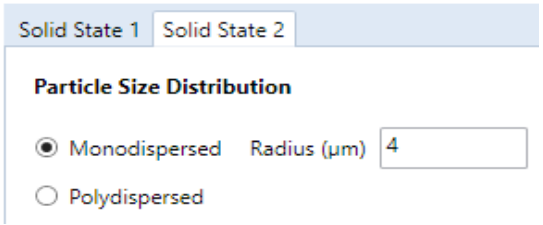
CERTARA

PPB: Two Solid State Tools

$$DR(t) = \sum_{SS2}^{SS1} \sum_{NBINs}^{i=1} -N_i \, S_{DR} \frac{D_{eff}(t)}{h_{eff,i}(t)} 4\pi a_i(t) \left(a_i(t) + h_{eff,i}(t)\right) \left(S_{surface}(t) - C_{bulk}(t)\right)$$

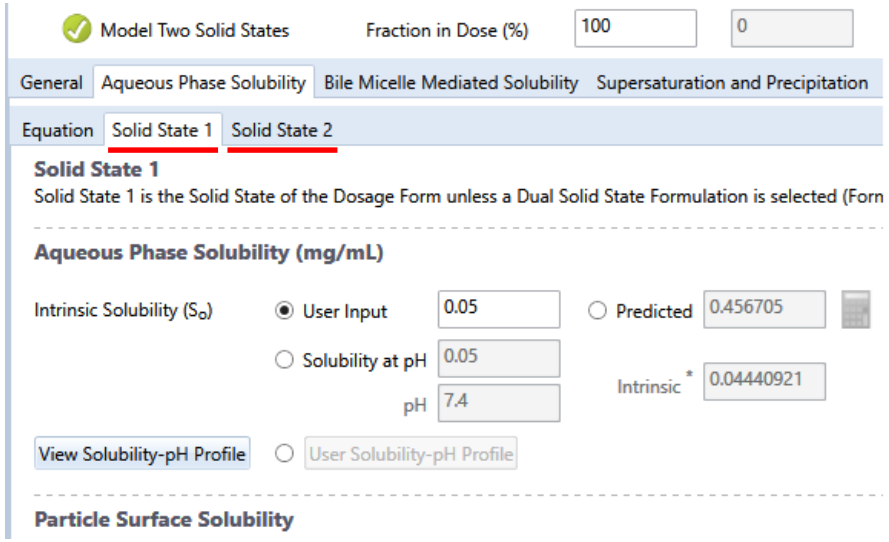


PSD

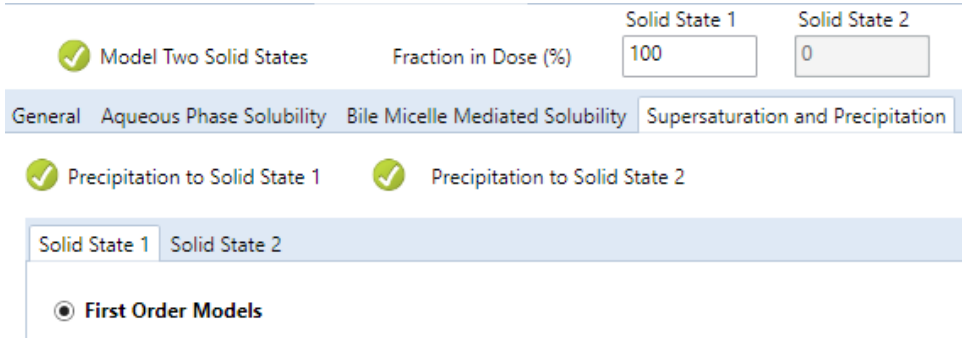


Separate PSD specification and dissolution (precipitation) modelling for each solid state

Solubility



Precipitation



CERTARA

An Application of the PPB/Two Solid State Models

Tacrolimus an immunosuppressant was first approved in 1994

– Innovator Product Prograf®

Tacrolimus is a poorly water-soluble, neutral (non-ionizing) BCS 2 compound

Commercially formulated as an Amorphous Solid Dispersion (ASD)

An Application of the PPB/Two Solid State Models

Tacrolimus an immunosuppressant was first approved in 1994

– Innovator Product Prograf®

Tacrolimus is a poorly water-soluble, neutral (non-ionizing) BCS 2 compound

Commercially formulated as an Amorphous Solid Dispersion (ASD)

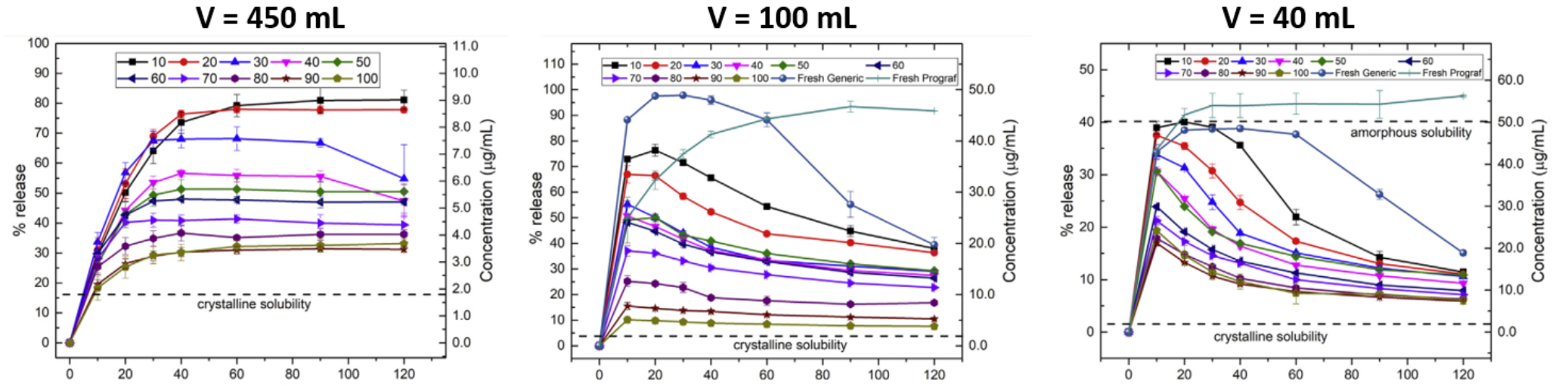
There are a number of generic formulations containing amorphous drug

The Accord formulation is susceptible to crystallisation over time during storage under stress conditions.

Q: What degree of crystallinity renders the formulation bioinequivalent to the fully amorphous (intended) formulation?

Is Precipitation Expected *In Vivo?*

Tacrolimus *In Vitro* Dissolution Data



Increasing extent of crystallinity in formulation

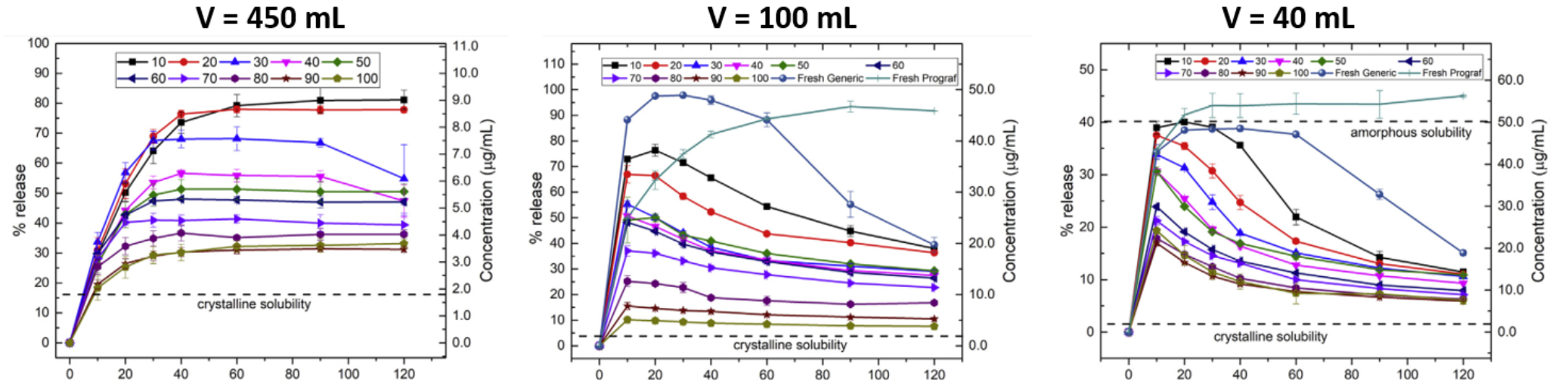
USP 1, Non-micellar buffer

In Vitro data: Purohit et al, 2018

CERTARA

Is Precipitation Expected *In Vivo?*

Tacrolimus *In Vitro* Dissolution Data



Increasing extent of crystallinity in formulation

USP 1, Non-micellar buffer

In Vitro data: Purohit et al, 2018

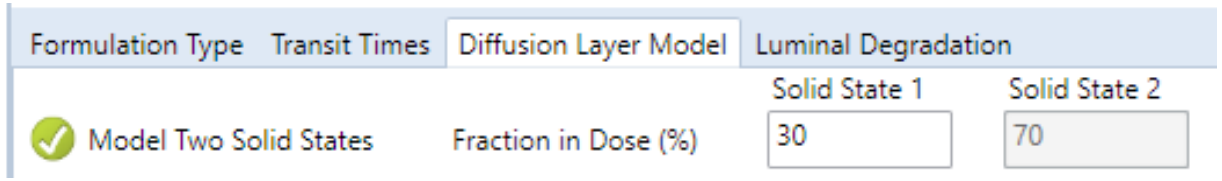
Which *in vitro* experiment (condition) is relevant to *in vivo*?

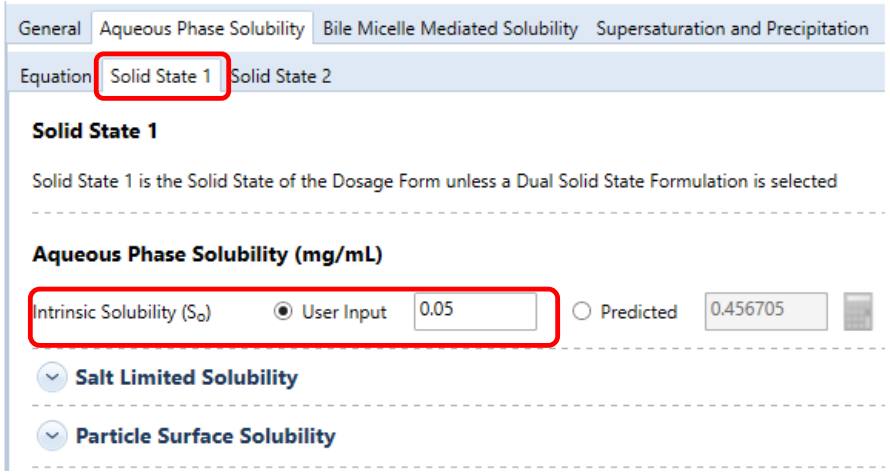
Which *in vitro* dissolution profiles should be directly input to a PBPK model?

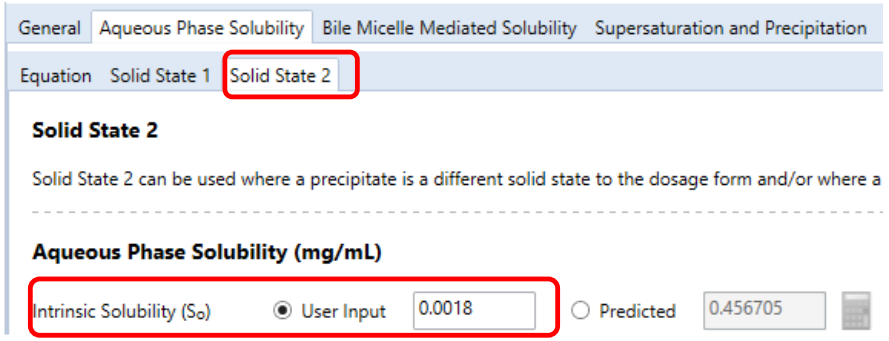
Is there an alternative approach?

CERTARA

Tacrolimus ASD – Potential Impact of Crystallisation During Storage







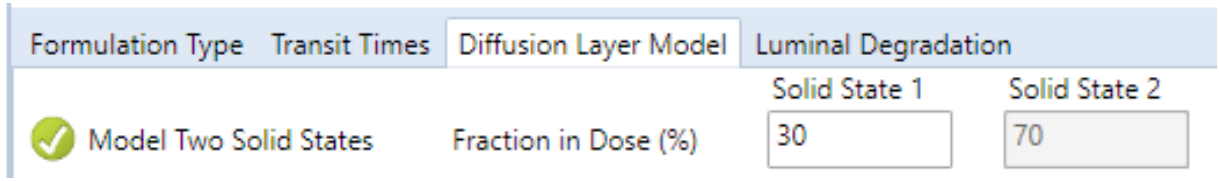
Intrinsic Solubility, So (µg/mL)

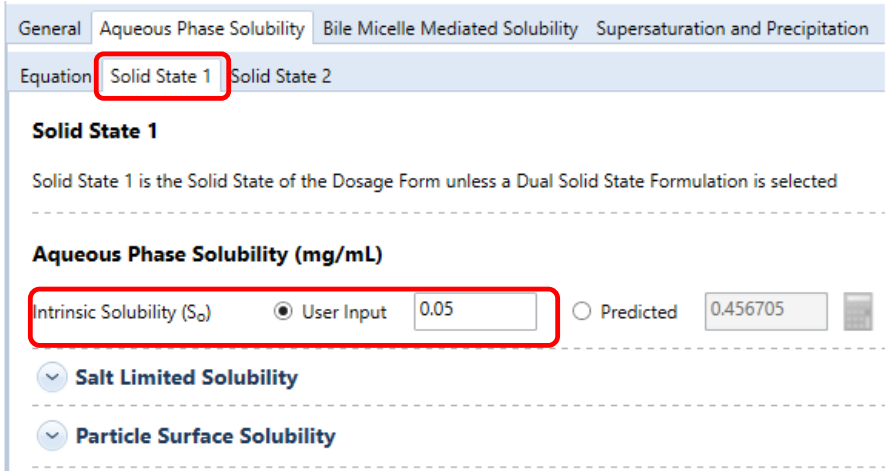
Amorphous form	50	Solid State 1
Crystalline (monohydrate)	1.8	Solid State 2

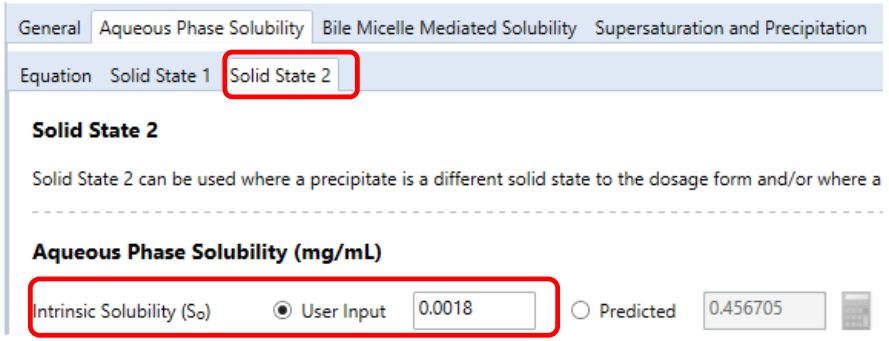
Formulated with 5.5 mg HPMC

CERTARA

Tacrolimus ASD – Potential Impact of Crystallisation During Storage







Intrinsic Solubility, So (µg/mL)		
Amorphous form	50	"Solid State 1"
Crystalline (monohydrate)	1.8	"Solid State 2"

Formulated with 5.5 mg HPMC

Stepwise Building of PBPK Model

- IV data are available
  - Very high, conc-dependent red blood cell binding
- Oral solution clinical study available to verify models prior to application to ASD modelling
  - High first pass GUT metabolism, Fg ~ 0.4
  - Mechanistic dissolution model (DLM) applied

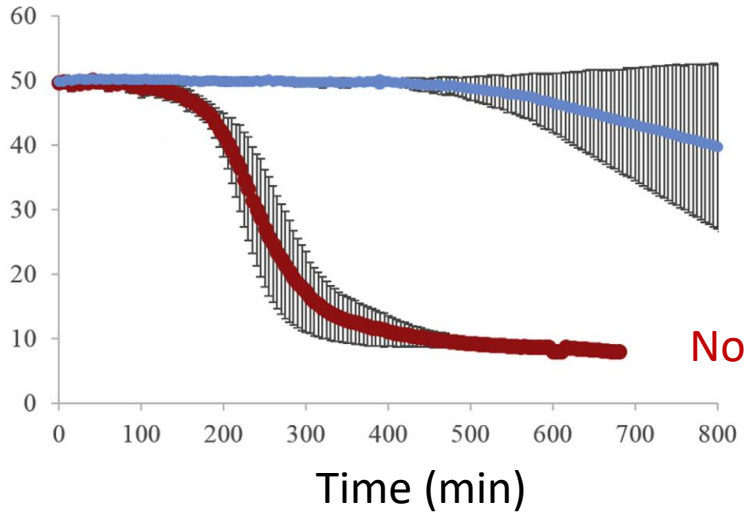
CERTARA

HPMC Impact and Anticipated HPMC In Vivo Concentrations

Induction Time for Tacrolimus Crystallisation

So,amorphous
= 50 µg/mL

Conc.
(µg/mL)



With HPMC
[HPMC] = 50 µg/mL

No HPMC

Trasi et al., 2017 *J Pharm Sci*

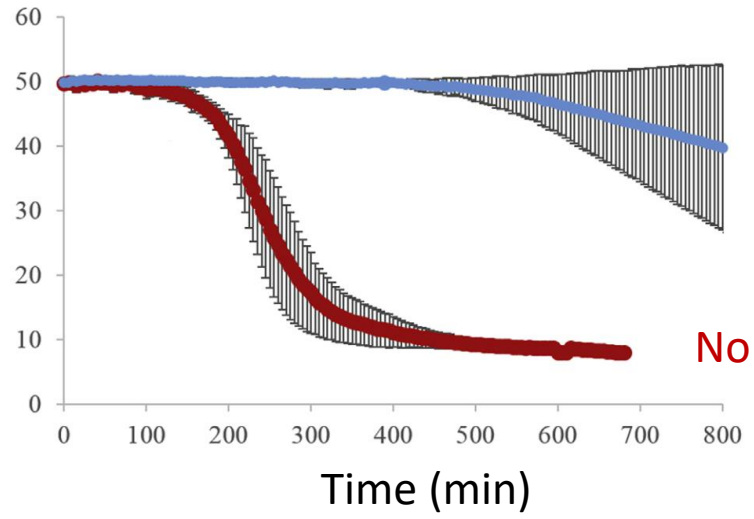
CERTARA

HPMC Impact and Anticipated HPMC In Vivo Concentrations

In Vitro Induction Time for Tacrolimus Crystallisation

So,amorphous = 50 µg/mL

Conc. (µg/mL)



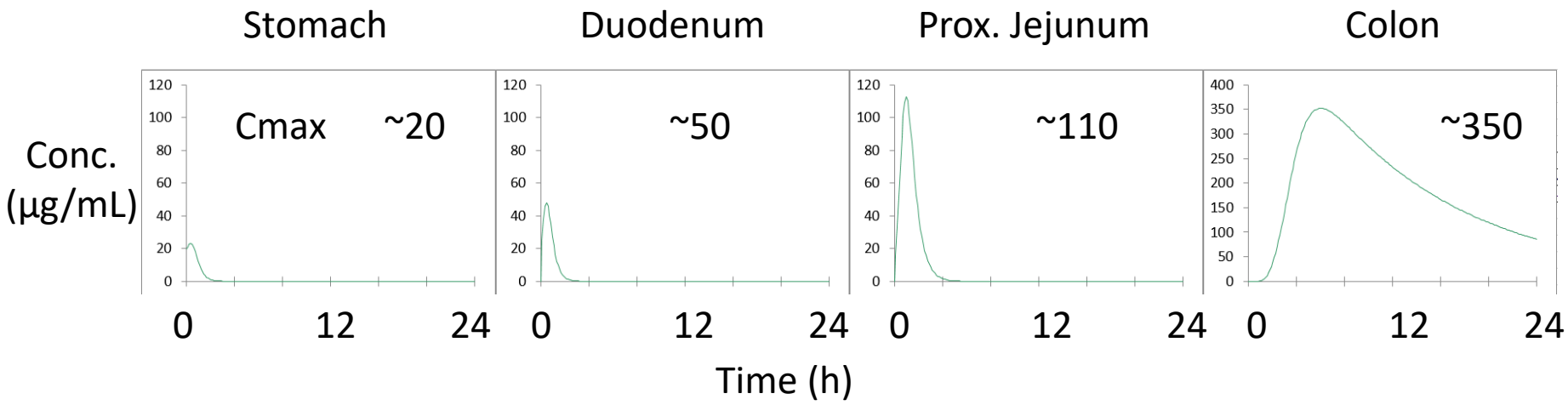
With HPMC
[HPMC] = 50 µg/mL

No HPMC

Trasi et al., 2017 *J Pharm Sci*

In vivo, precipitation is not expected

PBPK Simulated In Vivo HPMC Concentrations – 5.5 mg HPMC, 240 mL drink

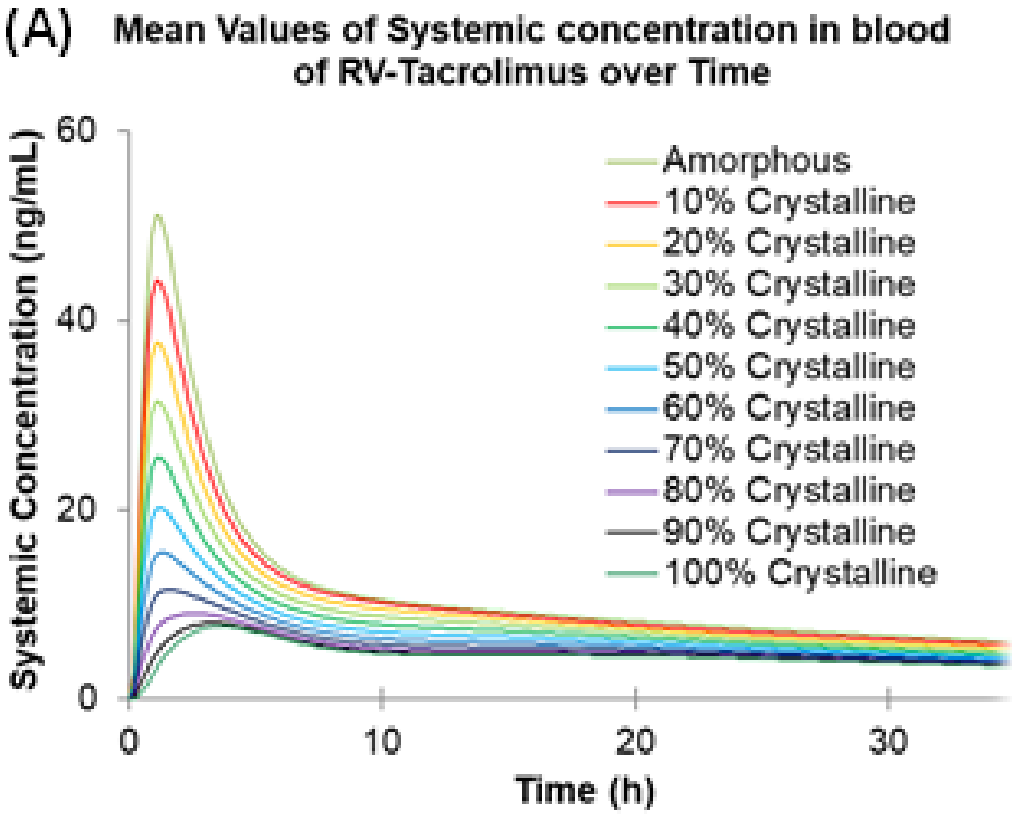


CERTARA

Tacrolimus ASD – Potential Impact of Crystallisation During Storage

Mechanistic dissolution model with two solid states applied

PBPK Simulation Results 50 subjects HVs, NEC Mean Profiles



Degree of crystallinity has significant impact on simulated PK

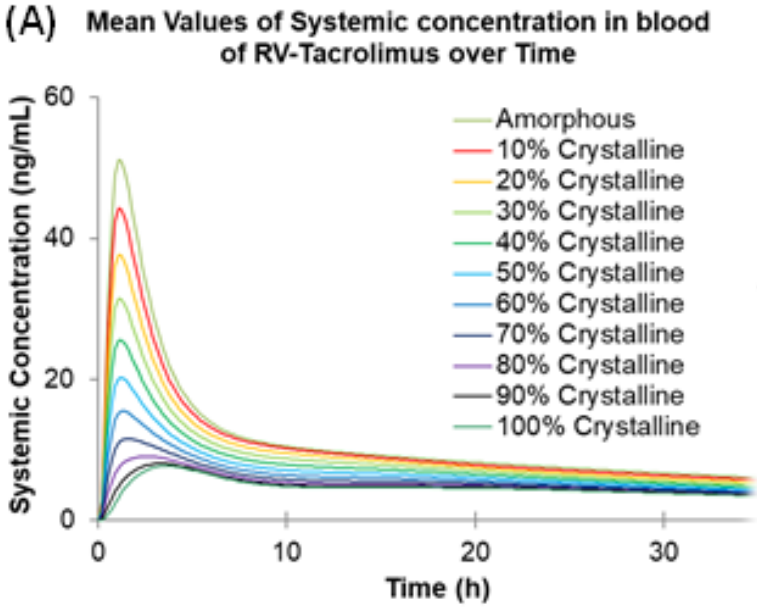
CERTARA

Tacrolimus ASD – Potential Impact of Crystallisation During Storage

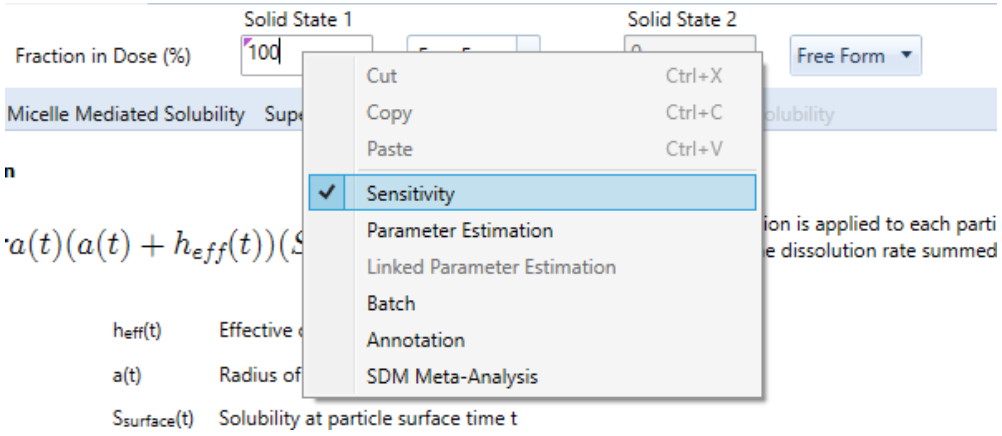
Mechanistic dissolution model with two solid states applied

Degree of crystallinity has significant impact on PK

PBPK Simulation Results 50 subjects HVs, NEC Mean Profiles



Alternative Approach for an Average Subject: Sensitivity Analysis on "Fraction"



Rapid assessment of potential impact of increasing degree of crystallinity

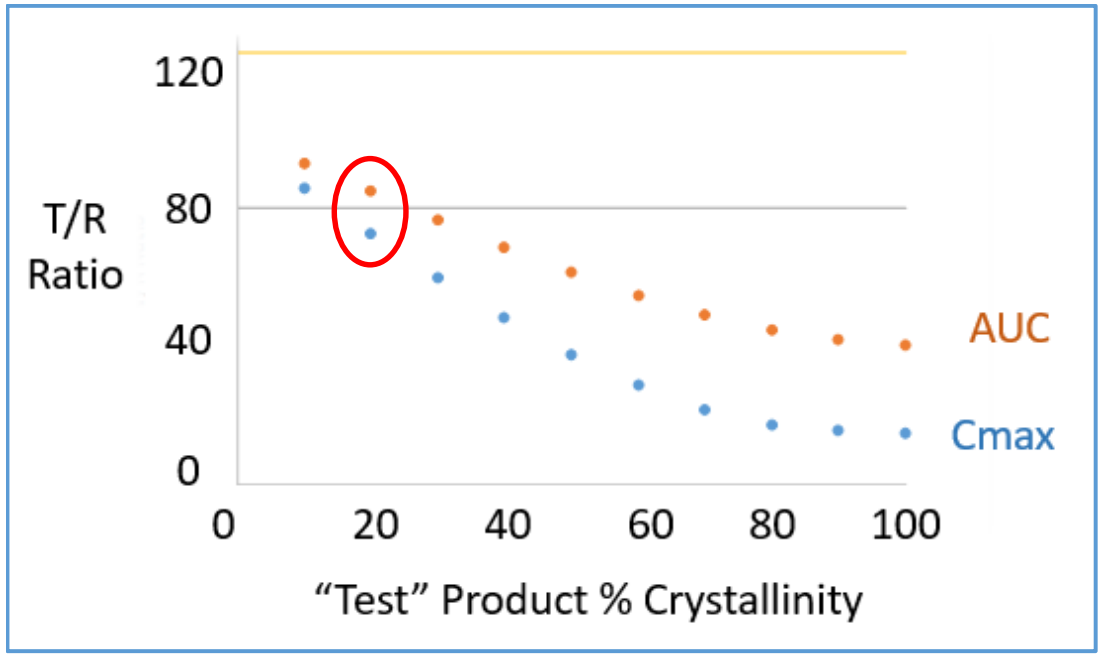
CERTARA

Tacrolimus VBE

Mechanistic
Dissolution Model
with two solid states

T/R Ratio
Ref -Fully amorphous form
Test – a partially crystallised form

2-way Crossover VBE evaluating the PK metrics C_{max} and AUC_{0-t} of 50 Healthy Volunteers

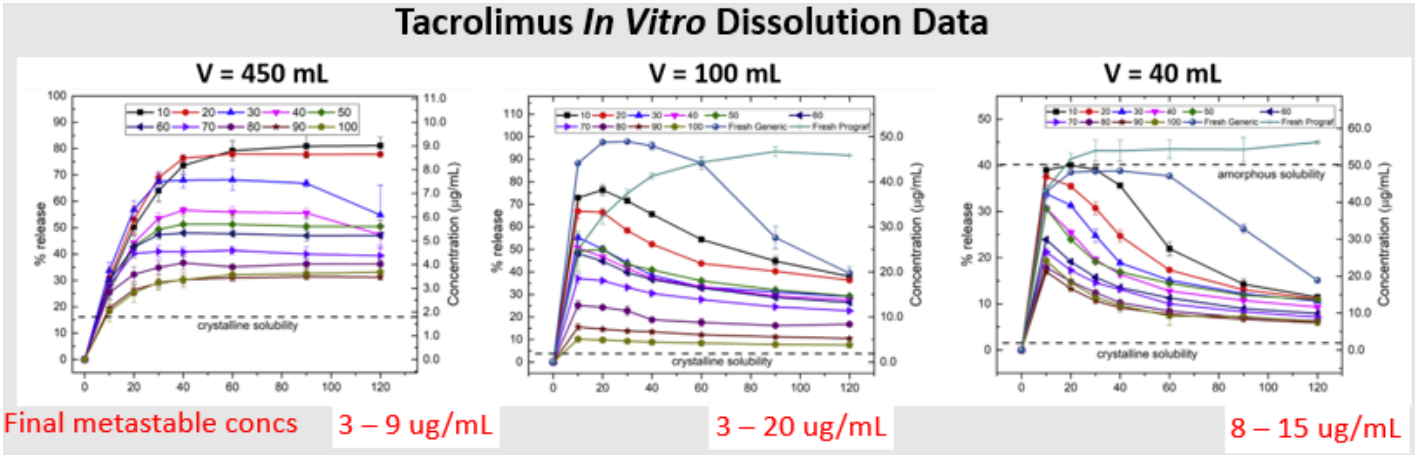


VBE performed in R in this example

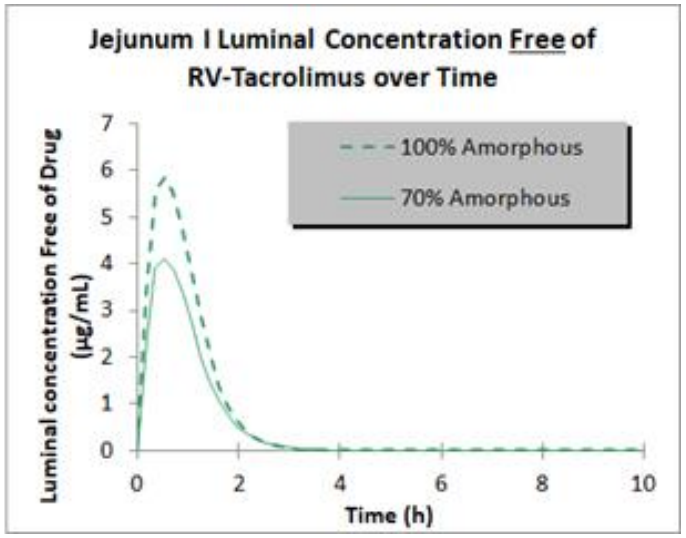
Mechanistic modelling, in this case, removed the need for potentially complex *in vitro* dissolution experiments with an absorptive phase/component.

CERTARA

In Vivo Relevance of *In Vitro* Conditions: Tacrolimus BCS 2



Jejunum I is the Site with Maximum Simulated Luminal Fluid Concentration of Tacrolimus



Even with precipitation blocked, simulated *in vivo* luminal concentrations are very low compared to *in vitro* concentrations

High permeability drug …

CERTARA

Excipient Binding Case Study

Drug X – Simcyp Consortium Member (Pharma) Compound

BCS 2

Low intrinsic solubility (<1 µg/mL), high P_{eff}, logP_{ow} 3 - 4
Low basic pKa

Precipitation risk

CERTARA

Cyclodextrin Binding Case Study

Drug X – Simcyp Consortium Member (Pharma) Compound

BCS 2

Low intrinsic solubility (<1 µg/mL), high P_{eff}, logP_{ow} 3 - 4
Low basic pKa

Precipitation risk

Drug X was formulated with 8 g Cyclodextrin with the aim to increase solubility, reduce precipitation risk

Clinical study: AUC, Cmax reduced significantly,
tmax increased significantly

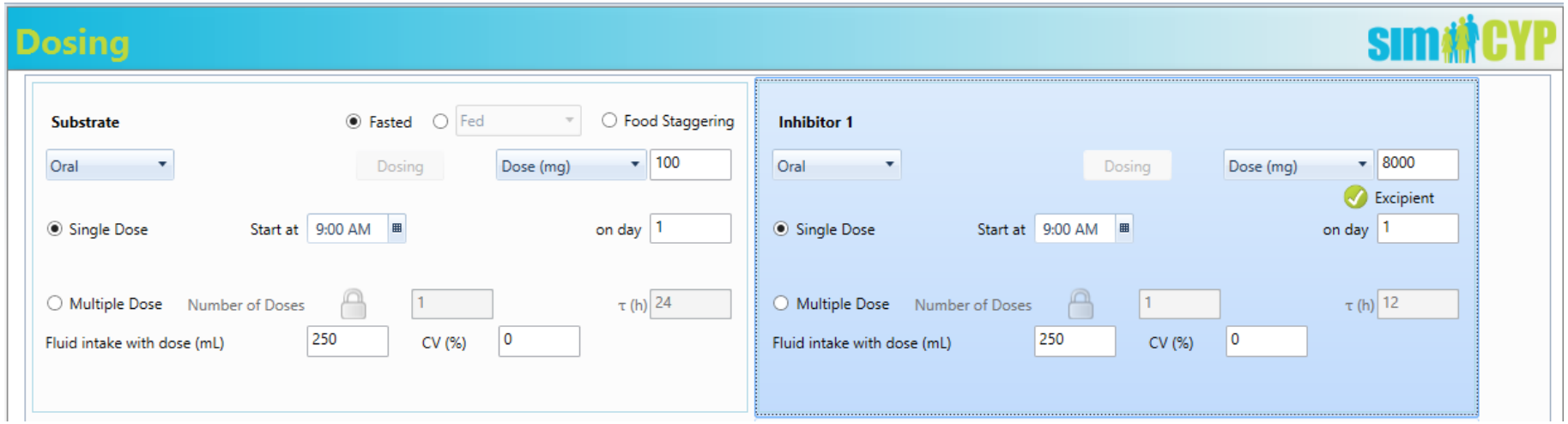
Explanation? PBPK Modelling …

CERTARA

Drug X – Setting up the CD Binding Model

Substrate – Drug X

Inhibitor 1 – HPβCD



Absorption Model: ADAM

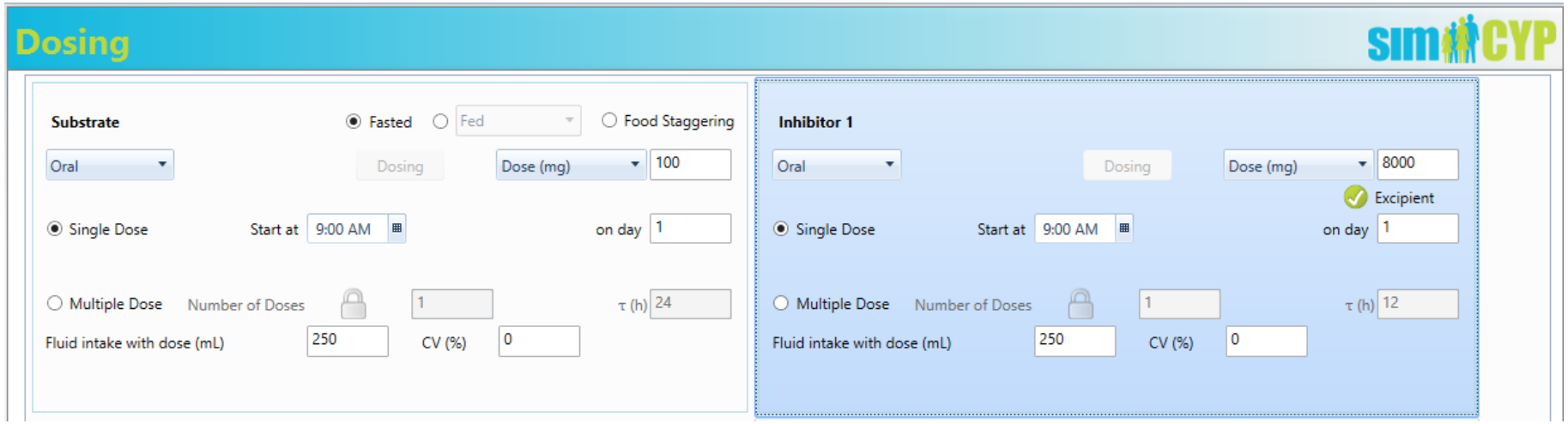
Absorption Model: ADAM

CERTARA

Drug X – Setting up the CD Binding Model

Substrate – Drug X

Inhibitor 1 – HPβCD



Absorption Model: ADAM

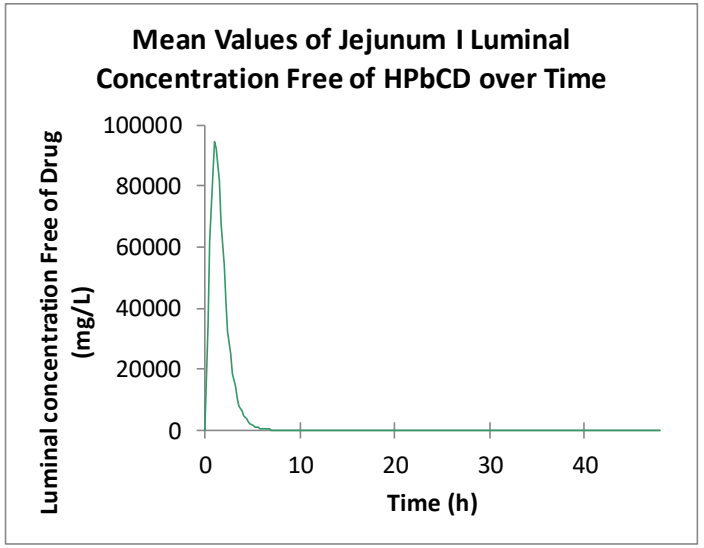
Absorption Model: ADAM

Decomposition of solubility to it's contributory factors is essential

$$S_{Tot}(t) = S_0 \cdot S_{0_{scalar}}(t) \cdot \left(1 + \frac{[BS](t)}{C_{H_2O}} \cdot K_{m:w,unionised}(t)\right)$$

$$+S_i(t) \cdot \left(1 + \frac{[BS](t)}{C_{H_2O}} \cdot K_{m:w,ionised}(t)\right) + S_{bound,excip}(t)$$

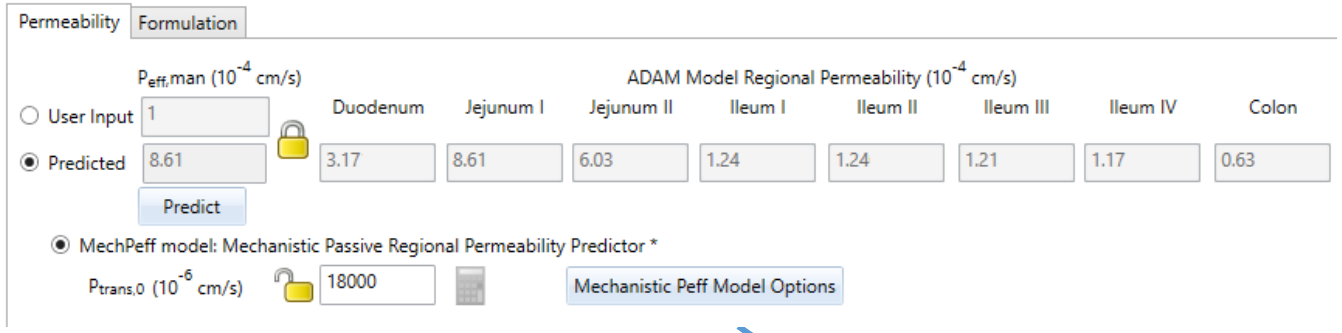
Substrate Solubility at time t

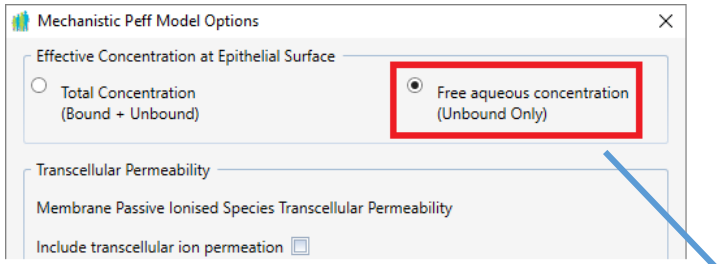


Drug X – Setting up the CD Binding Model

Substrate (Drug X)

Permeability Model: MechPeff





MechPeff with free conc. selected (default) required to capture free fraction effect on permeation rate

$$P_{eff} = \left(\left(\left(P_{Trans,0} \cdot f_{neutral,pH} + P_{para} \right) \cdot ACC \cdot MVE \cdot fu_{UBL} \right)^{-1} + \left(P_{UBL} \right)^{-1} \right)^{-1} \cdot FEp$$

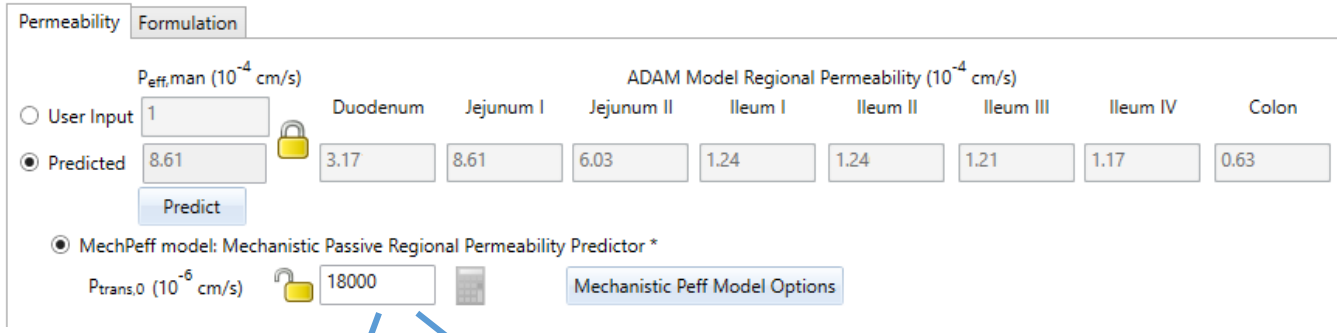
UBL = unstirred boundary (mucus/water) layer, local pH buffered to narrow range

Pade *et al.*, 2018 *BDD*

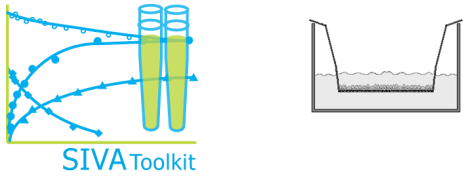
CERTARA

Drug X – Setting up the CD Binding Model

Permeability Model: MechPeff



MechPeff *Ptrans,0* is **<u>best obtained</u>** via modelling of *in vitro* cell line experiments

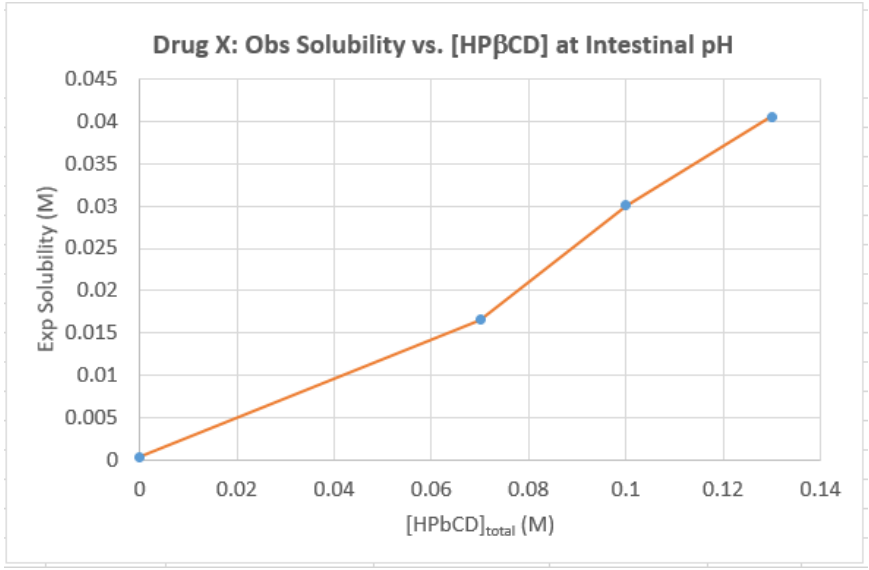


SIVA 4

$$P_{eff} = \left(\left(P_{Trans,0} \cdot f_{neutral,pH} + P_{para} \right) \cdot ACC \cdot MVE \cdot fu_{UBL} \right)^{-1} + (P_{UBL})^{-1} \Bigg)^{-1} \cdot FEp$$

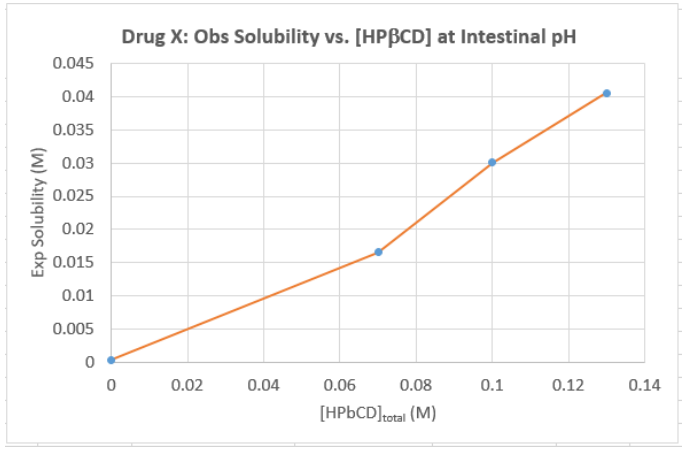
CERTARA

Cyclodextrin Binding Constants

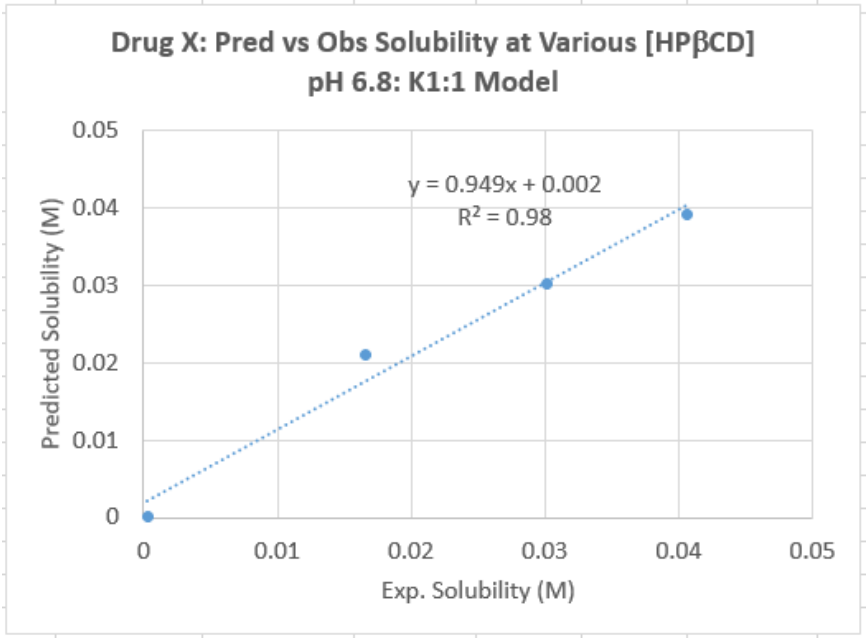


In vitro solubility available (in house) over a range of HPβCD concentrations

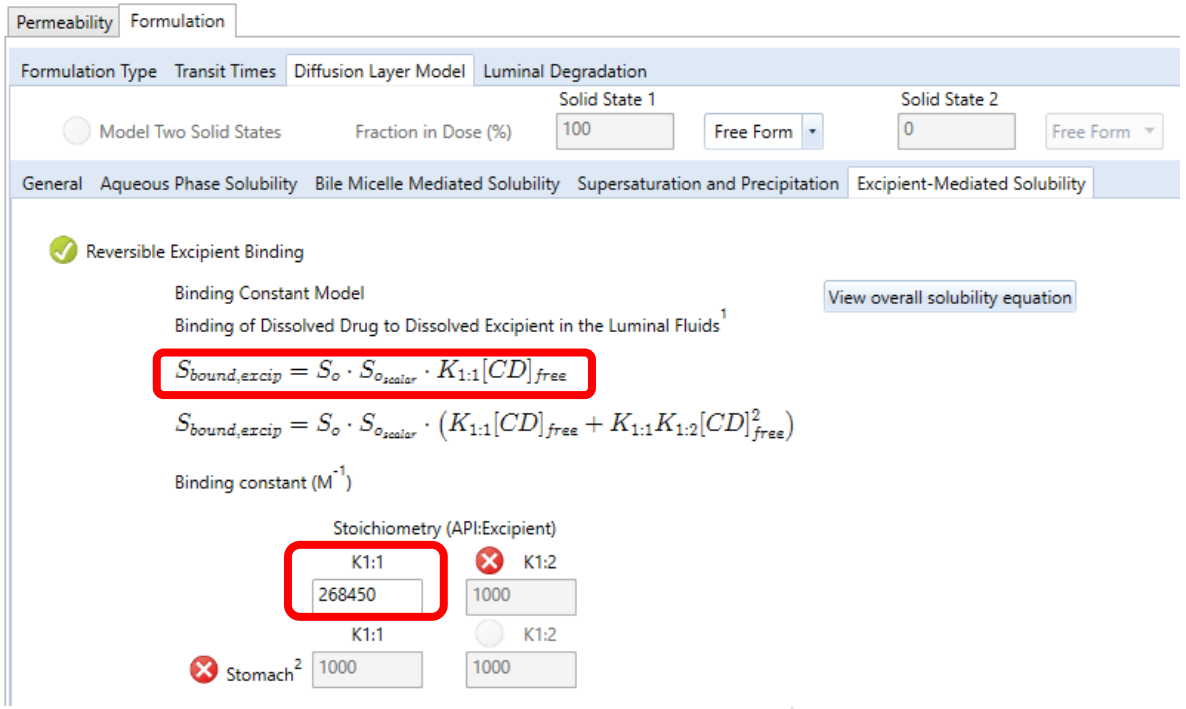
Cyclodextrin Binding Constants



In vitro solubility available (in house) at a range of HPβCD concentrations



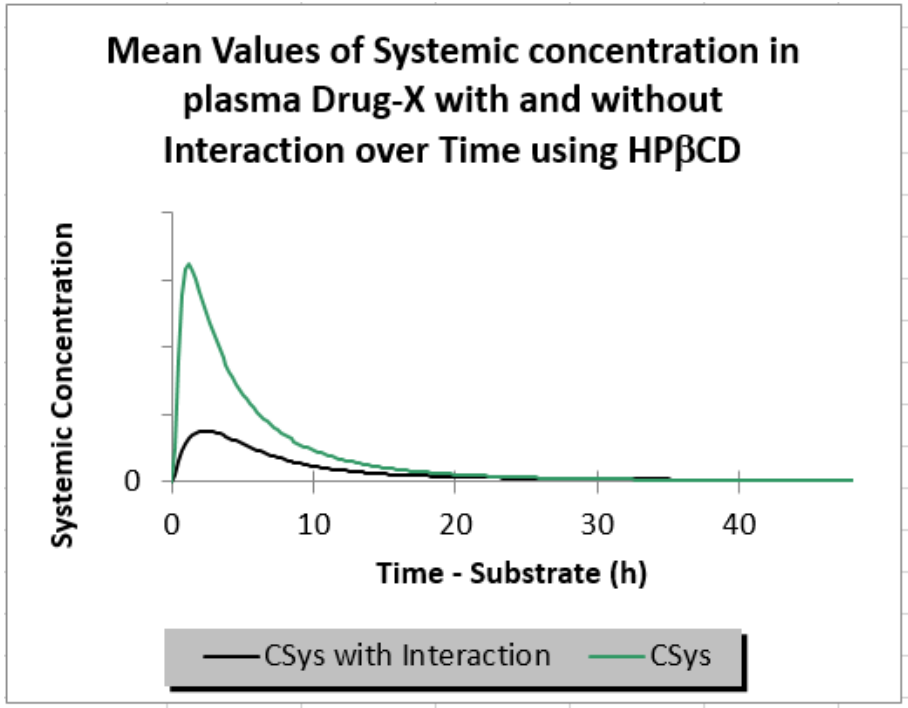
1:1 binding constant model fitted the data well

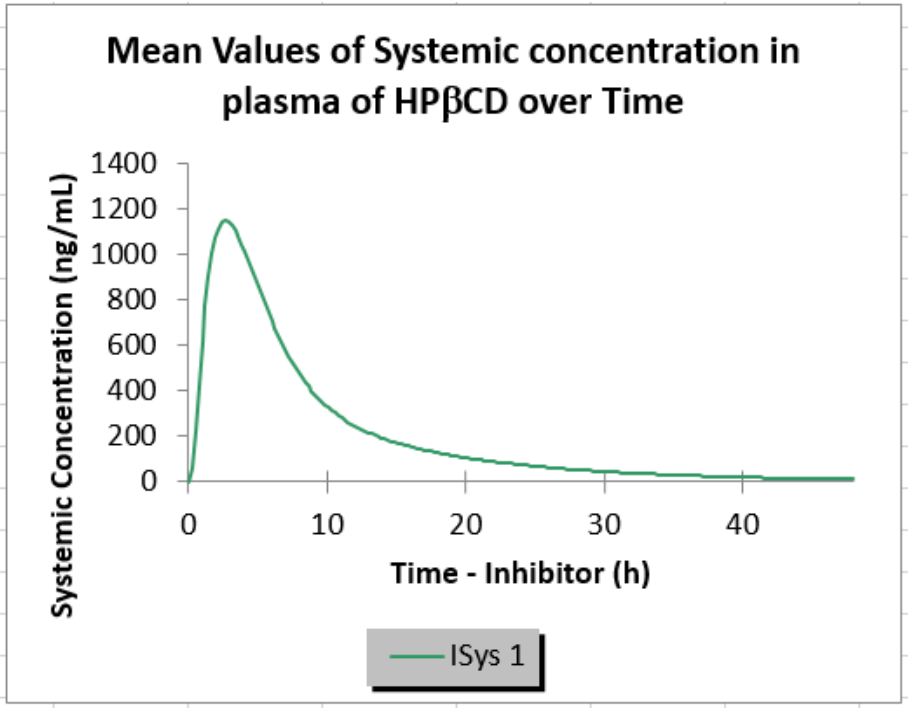


CERTARA

Simulation Results

Simulations Predict that Binding to HPβCD significantly reduces Cmax and AUC This could have been anticipated prior to the clinical study





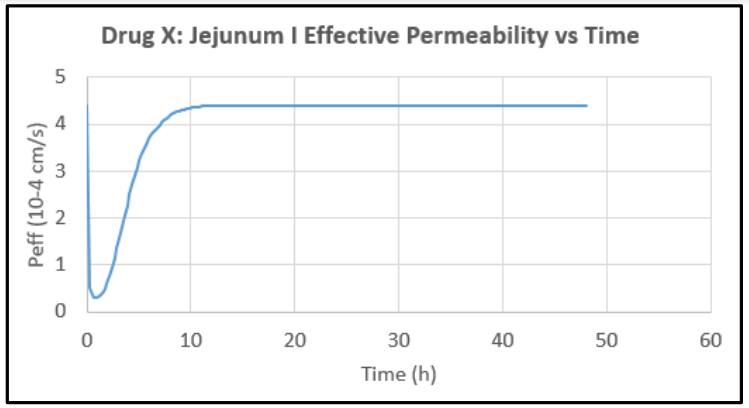
8 g HPβCD

Mean Profiles (100 simulated HVs)

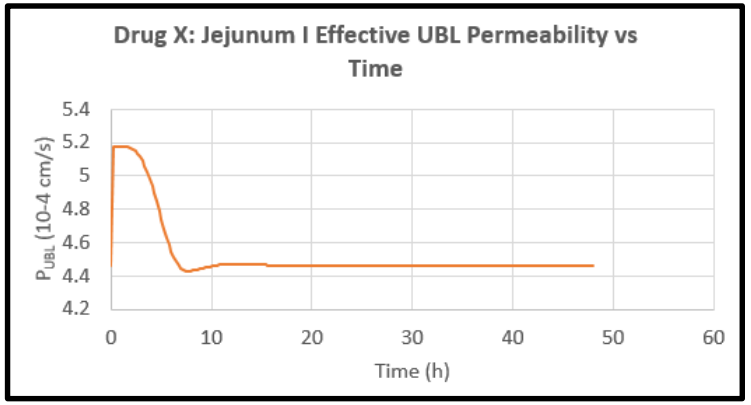
ms. to be submitted by Simcyp Industrial Consortium Member

CERTARA

Time-Variant Effective Gut Wall Permeability



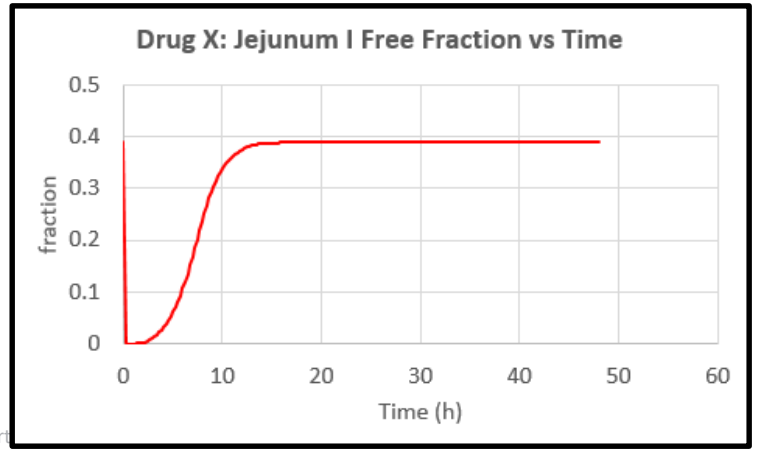
Peff is dramatically decreased at peak HPβCD concentration



$$P_{UBL}(t) = D_{eff,UBL}(t) / \text{UBL thickness}$$

Flux across the UBL (mucus/water layer is increased

$$\begin{aligned} & D_{eff,UBL}(t) \\ & = f_{ionised,UBL}(t) \cdot D_{ionised} \\ & + f_{neutral,UBL}(t) \cdot D_{neutral} \\ & + f_{micelle,UBL}(t) \cdot D_{micelle} \\ & + f_{excip,UBL}(t) \cdot D_{excip\_eff} \end{aligned}$$



Free fraction decreases significantly

– this is the dominant effect of CD binding in this example …
– model could be applied to other excipients

CERTARA

Evidence for Cyclodextrin Binding Impact Upon Peff

molecular pharmaceutics

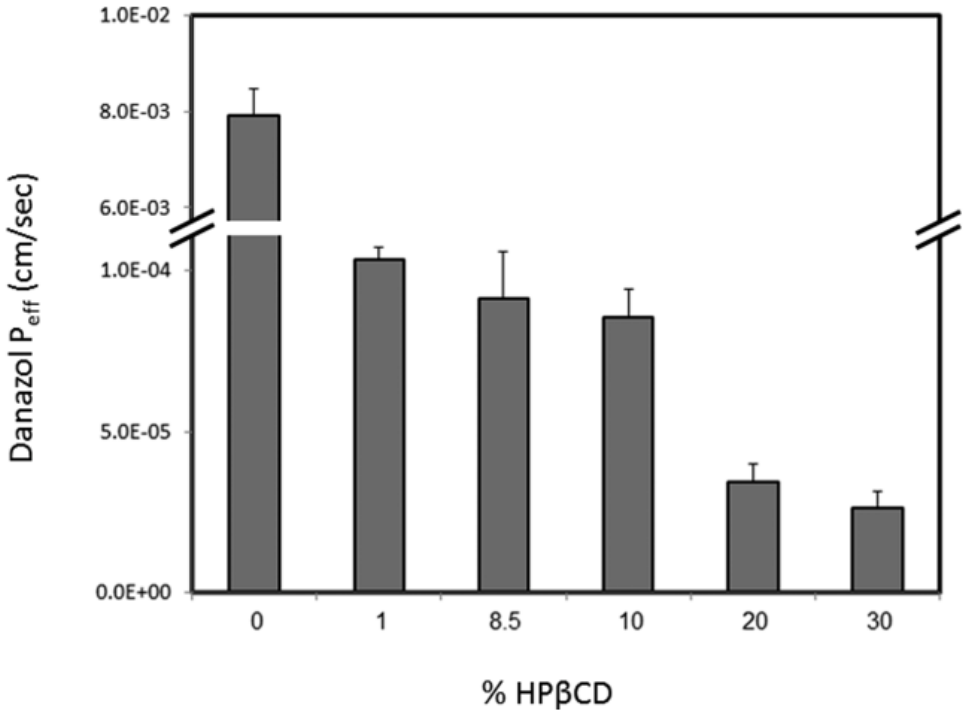
Article

pubs.acs.org/molecularpharmaceutics

Toward Successful Cyclodextrin Based Solubility-Enabling Formulations for Oral Delivery of Lipophilic Drugs: Solubility–Permeability Trade-Off, Biorelevant Dissolution, and the Unstirred Water Layer

Noa Fine-Shamir,[‡] Avital Beig,[‡] Moran Zur,[‡] David Lindley,[†] Jonathan M. Miller,[†,§] and Arik Dahan*[,‡]

In Vivo Rat Perfusion Studies: Danazol Peff vs HPβCD Concentration



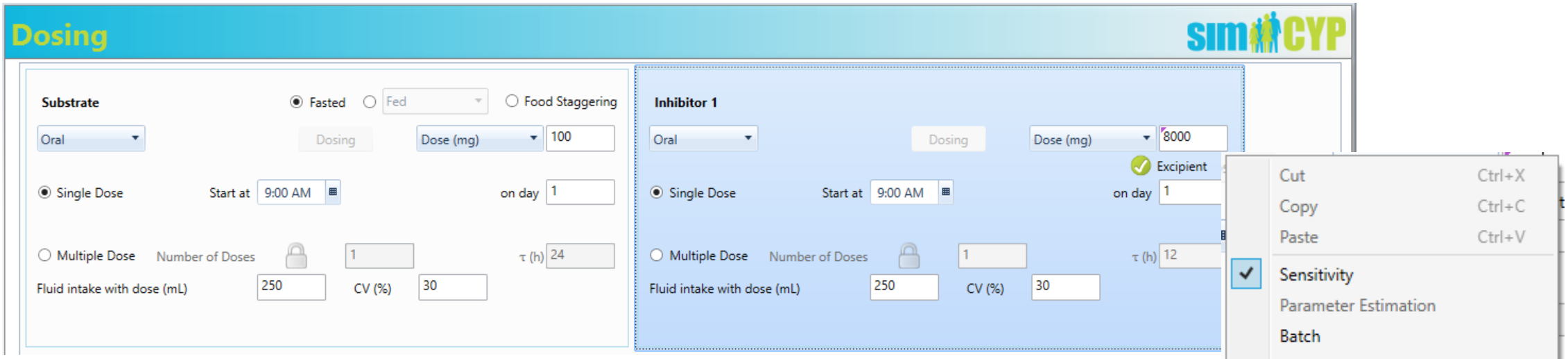
Fine-Shamir et al 2017 *Mol Pharm 14*:2138

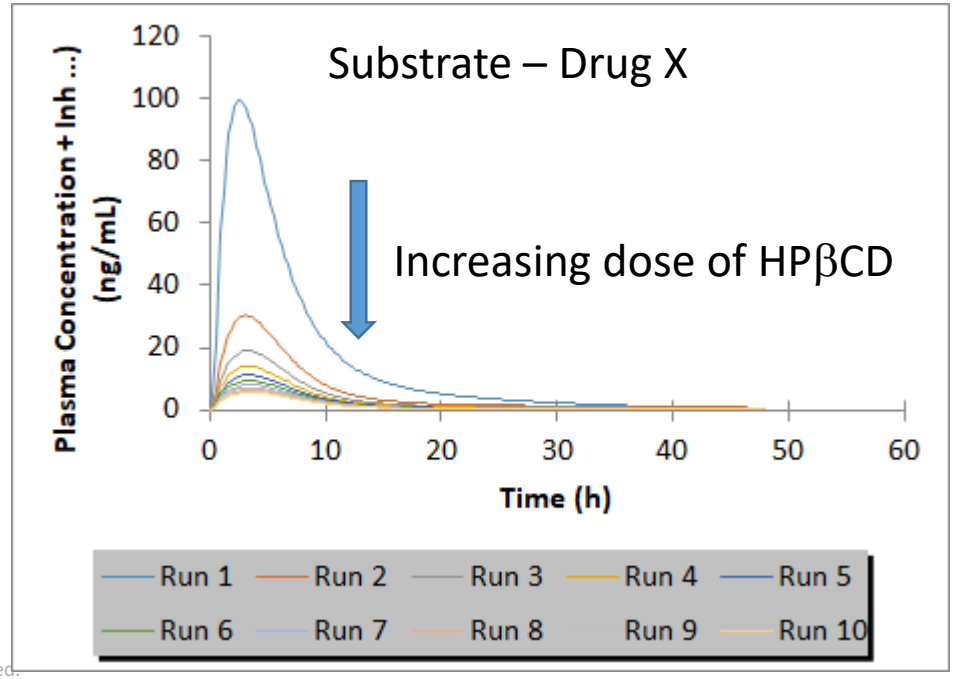
CERTARA

Automated Sensitivity Analysis on CD Dose

Substrate – Drug X

Inhibitor 1 – HPβCD





CERTARA

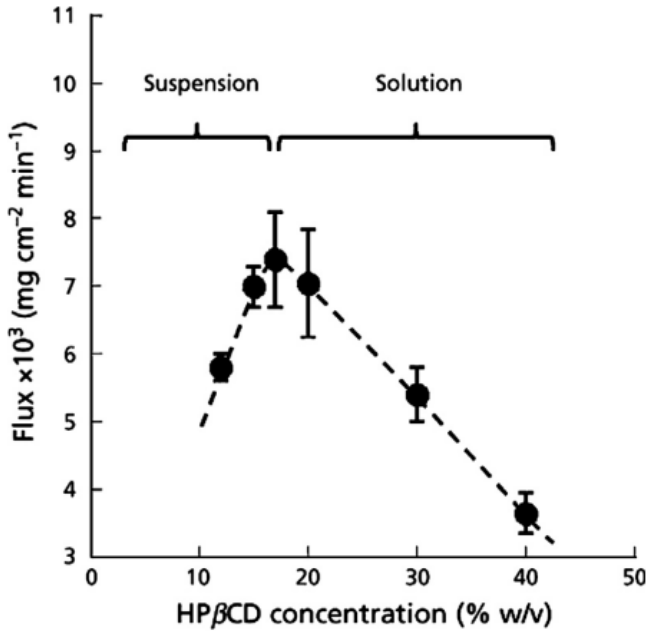
Estimation of Optimal Excipient Amount in a Formulation

Estimation of Optimal Excipient "Dose"

Too much CD can inhibit absorption, very low free fraction

Too little CD, insufficient solubilisation

In Vitro: Acetazolamide Flux vs HPβCD Concentration



Loftsson et al 2011 *J Pharm Pharmacol* 63:1119

CERTARA

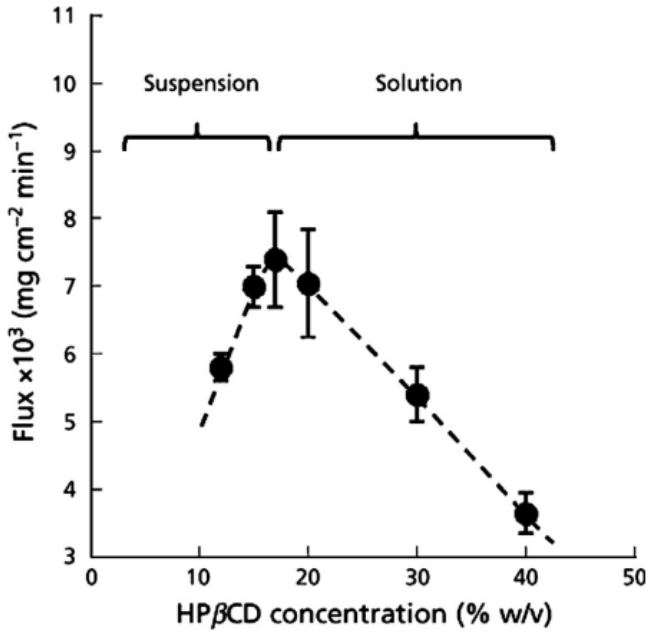
Estimation of Optimal Excipient Amount in a Formulation

Estimation of Optimal Excipient "Dose"

Too much CD can inhibit absorption, very low free fraction

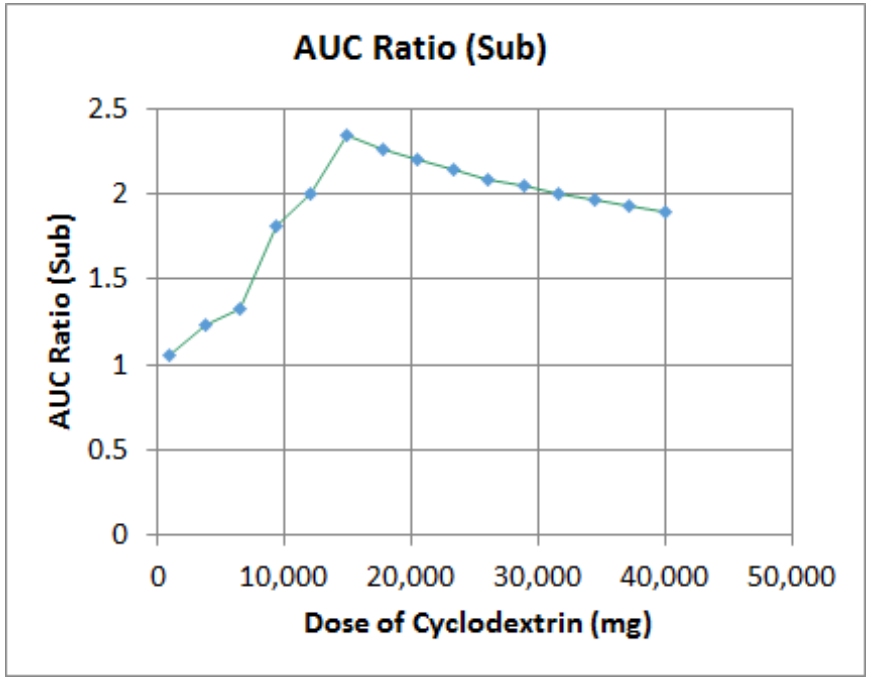
Too little CD, insufficient solubilisation

In Vitro: Acetazolamide Flux vs HPβCD Concentration



Loftsson et al 2011 *J Pharm Pharmacol* 63:1119

Sensitivity Analysis on CD Dose: Hypothetical Drug



CERTARA

V19 Additions: Salt Model and Surface Solubility

1. Tools for Handling Salts of API and Salt limited Solubility (Ksp Model)

2. Surface Solubility Models for acids, bases, ampholytes including Salts

Particle (surface) microenvironment pH and solubility

CERTARA

V19 Additions: Salt Model

1. Tools for Handling Salts of API and Salt limited Solubility (Ksp Model)

- Drug product
  - Formulated as a salt (~50% of top 200 US prescription drugs Prohotsky 2012)
  - Formulated as free acid/base/ampholyte with solubility limited by endogenous ions
- Common ion effect (e.g., HCl salt drug product + endogenous chloride ion)

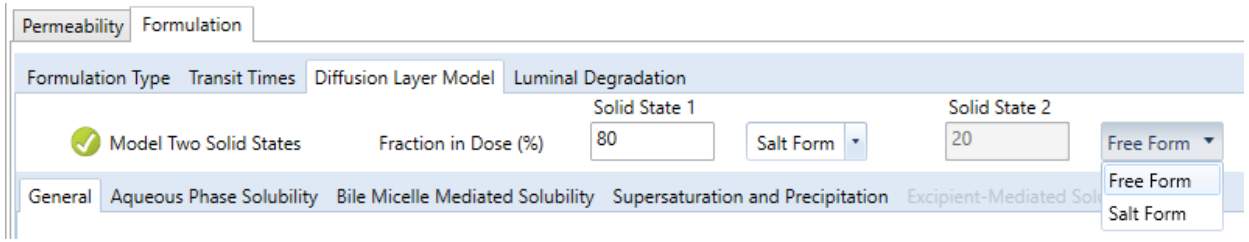
- Precipitation to salt or free acid/base

V19 Additions: Salt Model

1. Tools for Handling Salts of API and Salt limited Solubility (Ksp Model)

- Drug product formulated as a salt (~50% of top 200 US prescription drugs Prohotsky 2012)
- Free acid/base/ampholyte API with solubility limited by endogenous ions
- Common ion effect (e.g., HCl salt drug product + endogenous chloride ion)
- Precipitation to salt or free acid/base
- Disproportionation during storage (e.g., 80% salt, 20% free form)

Sensitivity analysis can be performed on fraction disproportionated

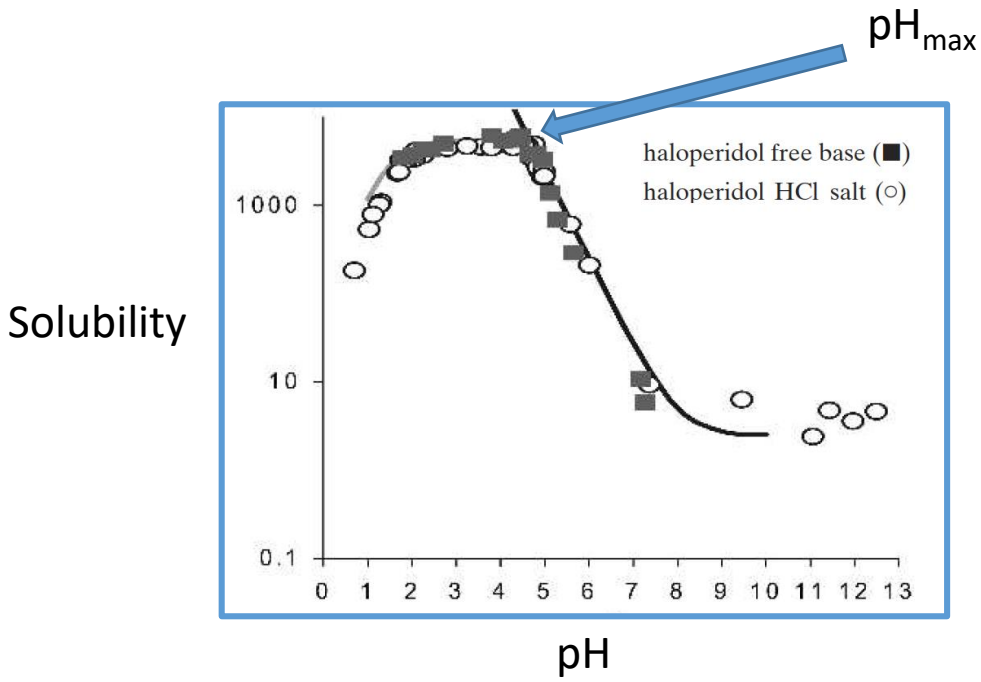


CERTARA

V19 Additions: Salt Model

1. Tools for Handling Salts of API and Salt limited Solubility (Ksp Model)

- Drug product formulated as a salt (~50% of top 200 US prescription drugs Prohotsky 2012)
- Free acid/base/ampholyte API with solubility limited by endogenous ions
- Common ion effect (e.g., HCl salt drug product + endogenous chloride ion)
- Precipitation to salt or free acid/base
- Disproportionation during storage (e.g., 80% salt, 20% free form)
- Ksp limited solubility

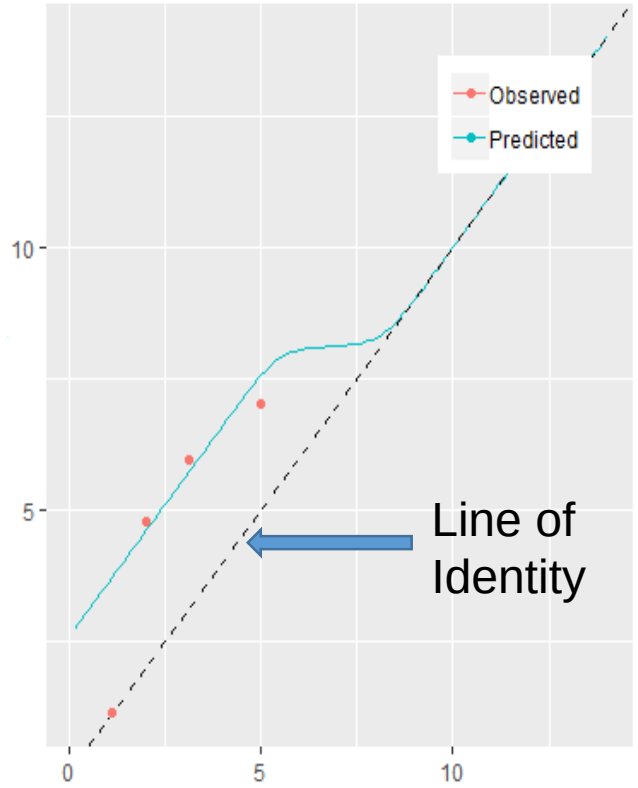


Haloperidol Experimental Solubility-pH Profile (basic pKa ~8.5)

CERTARA

Verification of Models through Modelling of In Vitro Experiments

1. Advantages of Surface pH Model: Haloperidol Free Base (Non-Salt)

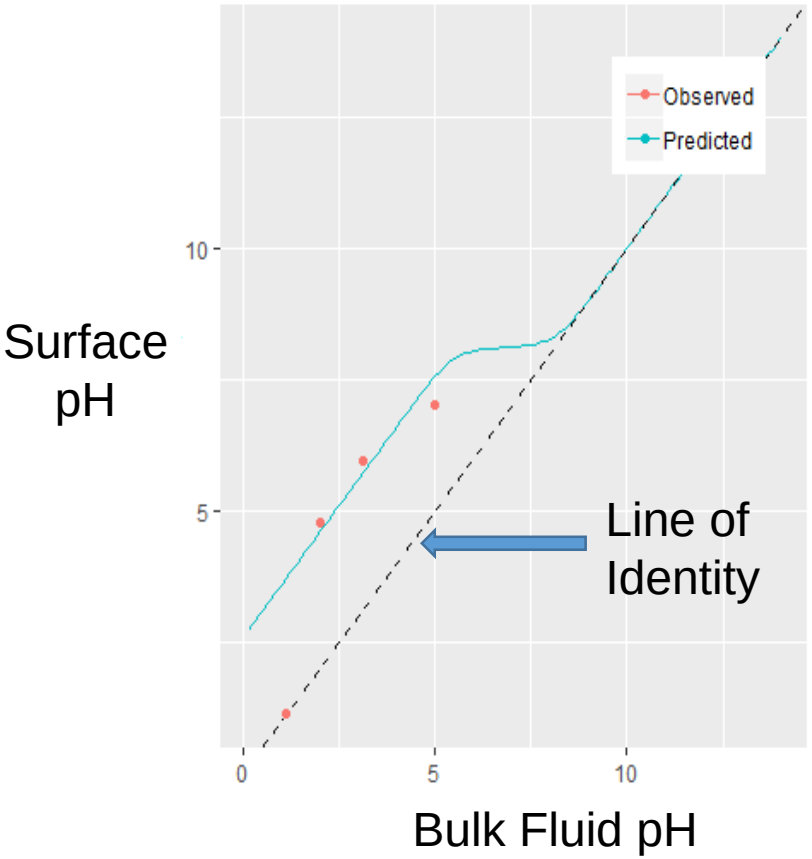


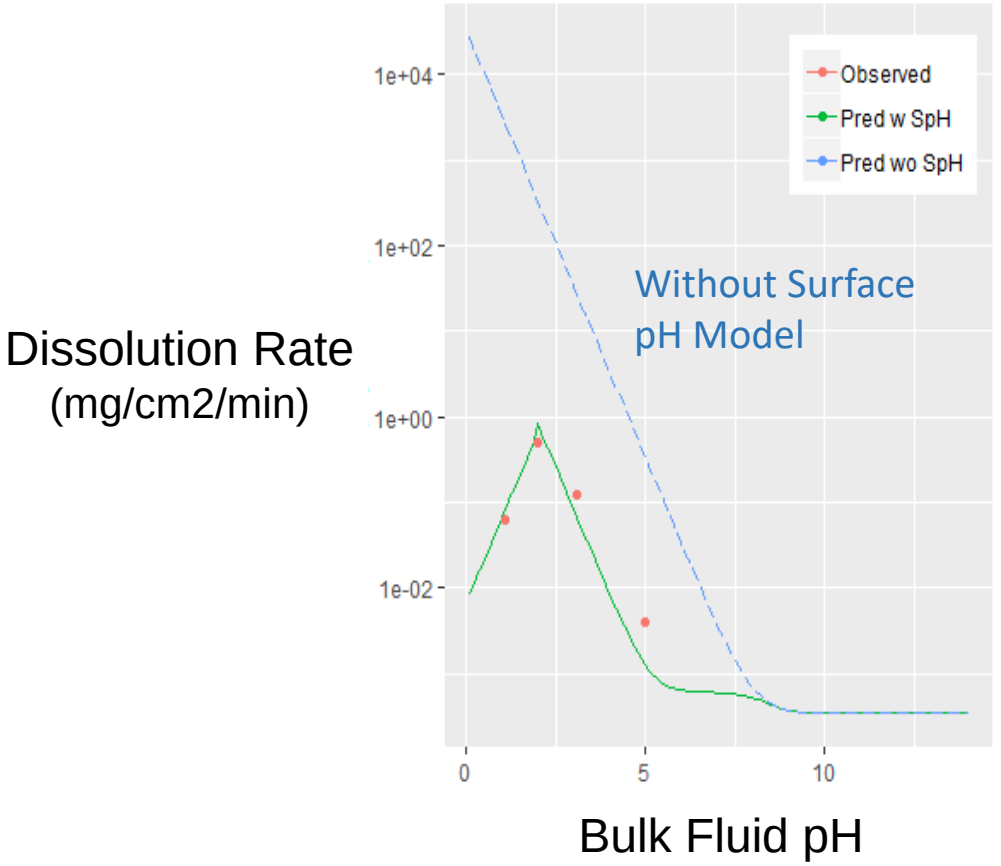
In vitro data: Li et al., 2005 *Pharm Res*

CERTARA

Verification of Models through Modelling of In Vitro Experiments

1. Advantages of Surface pH Model: Haloperidol Free Base (Non-Salt)





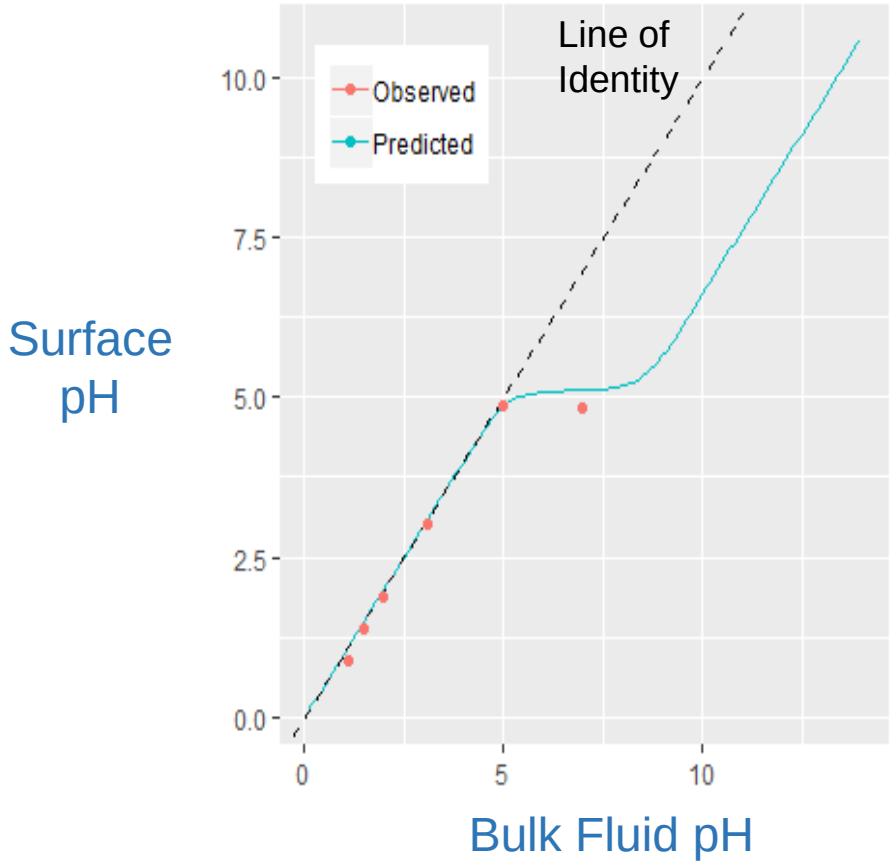
In vitro data: Li et al., 2005 *Pharm Res*

Rotating Disk Dissolution

CERTARA

Verification of Models through Modelling of In Vitro Experiments

2. Advantages of Salt + Salt Surface pH Model: Haloperidol Salt

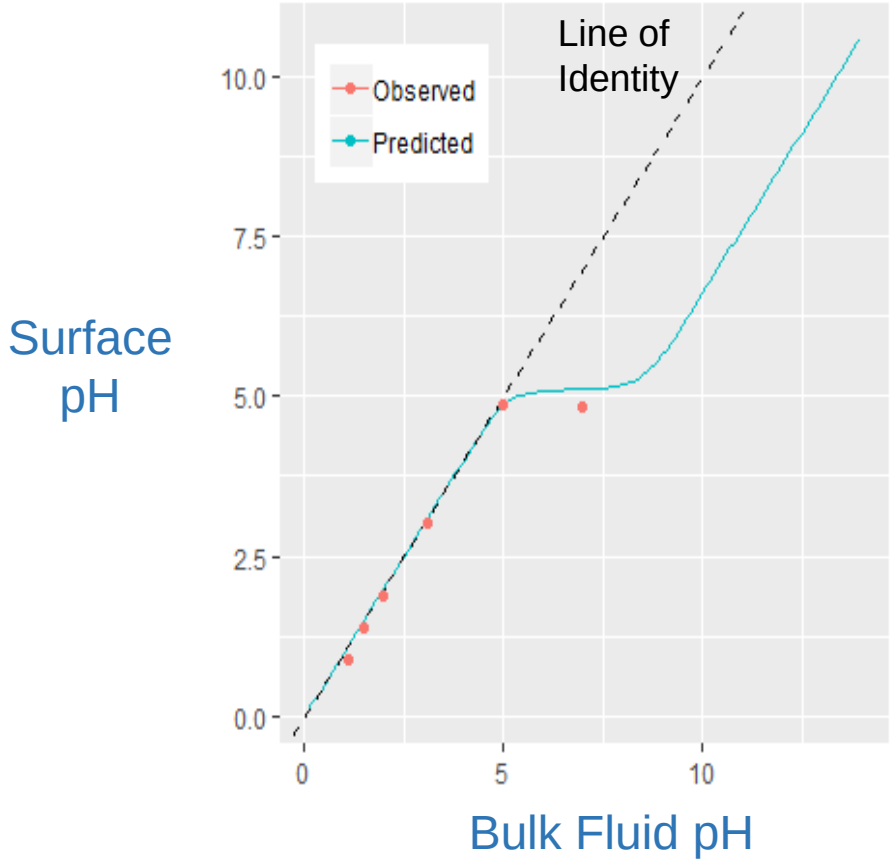


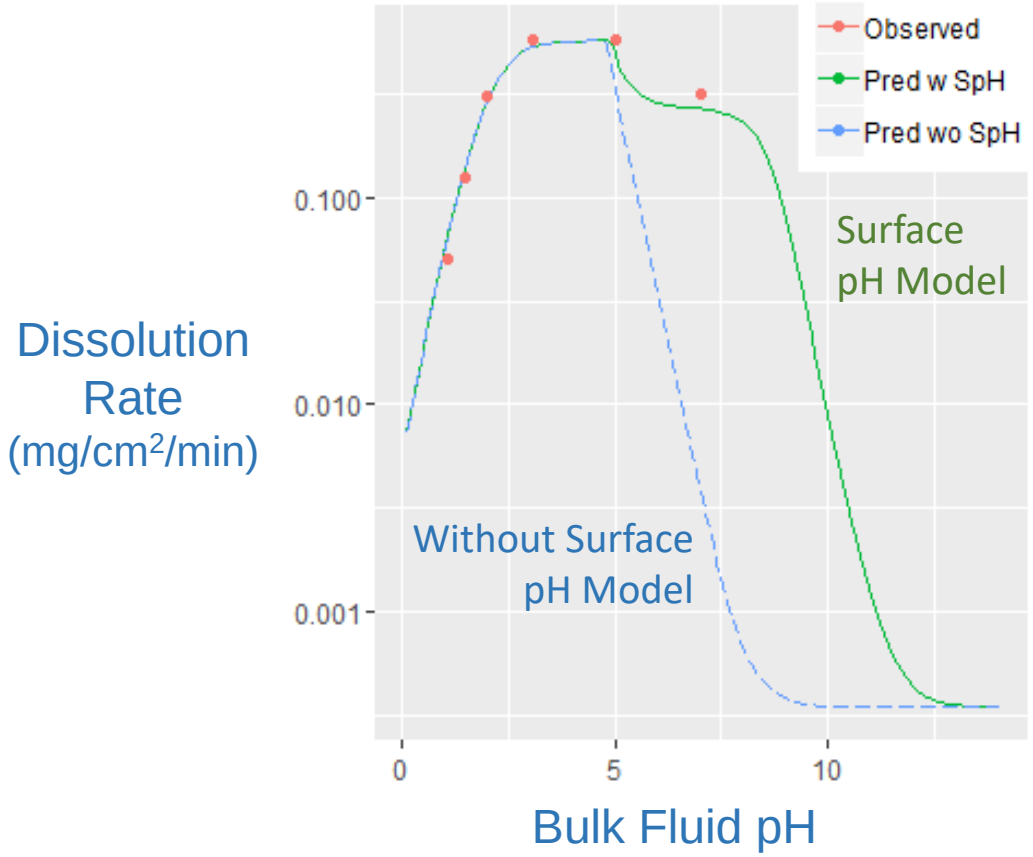
In vitro data: Li et al., 2005 *Pharm Res*

CERTARA

Verification of Models through Modelling of In Vitro Experiments

2. Salt + Salt Surface pH Model: Haloperidol Salt



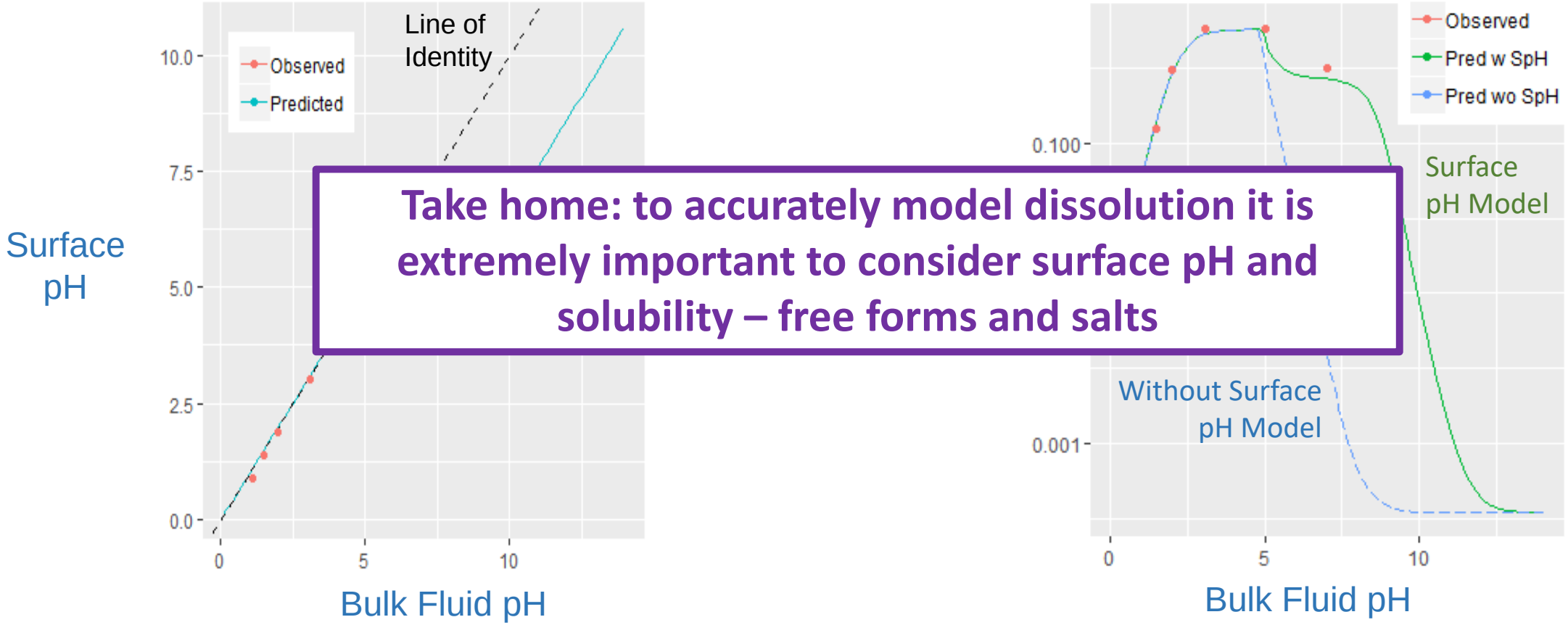


In vitro data: Li et al., 2005 *Pharm Res*

CERTARA

Verification of Models through Modelling of In Vitro Experiments

2. Salt + Salt Surface pH Model: Haloperidol Salt



In vitro data: Li et al., 2005 *Pharm Res*

CERTARA

Summary

Recent Additions

- New Models
- Tools – “Wrappers” – IVIVC, VBE
  GSA - Global Sensitivity Analysis
- Coupling in vitro experiments with PBPK Modelling

Case Studies / Examples

- Cyclodextrin (Excipient Binding/Solubilisation/Permeability interplay)
- Tacrolimus (VBE, formulation BE)

Salt and Surface pH Models

Acknowledgments

Funding Simcyp Consortium

FDA U.S. FOOD & DRUG ADMINISTRATION

FDA Grant 1U01FD005865

Team

Disclaimer

"The views expressed in this presentation are those of the author and should not be construed to represent the U.S. Food and Drug Administration (FDA)'s views or policies. The mention of commercial products, their sources, or their use in connection with material reported herein is not to be construed as either an actual or implied endorsement of such products by the FDA."

Note: The Simcyp Simulator is freely available, following completion of the relevant workshop, to approved members of academic institutions and other not-for-profit organizations for research and teaching purposes.

This webinar, upcoming and past webinars: https://www.certara.com/webinars/

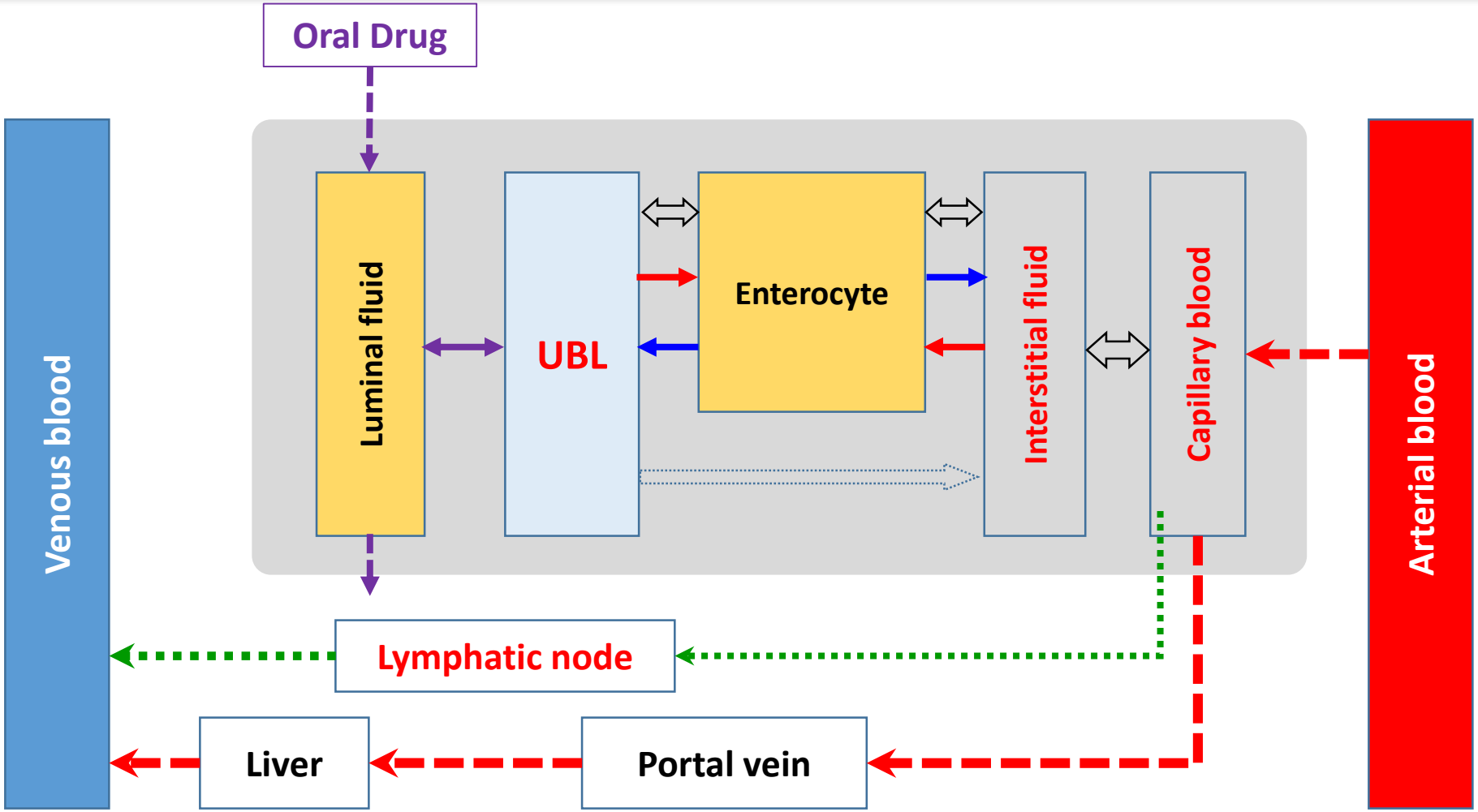
Upcoming Workshops: https://www.certara.com/resource-library/simcyp-workshops/?ap=PBPK

CERTARA

Questions?

Extra Slides

The Multi-compartment Gut Wall ADAM (M-ADAM) Model



CERTARA

Applying Knowledge Gained from In Vitro Experiments

Obtain Model settings for PBPK simulations?

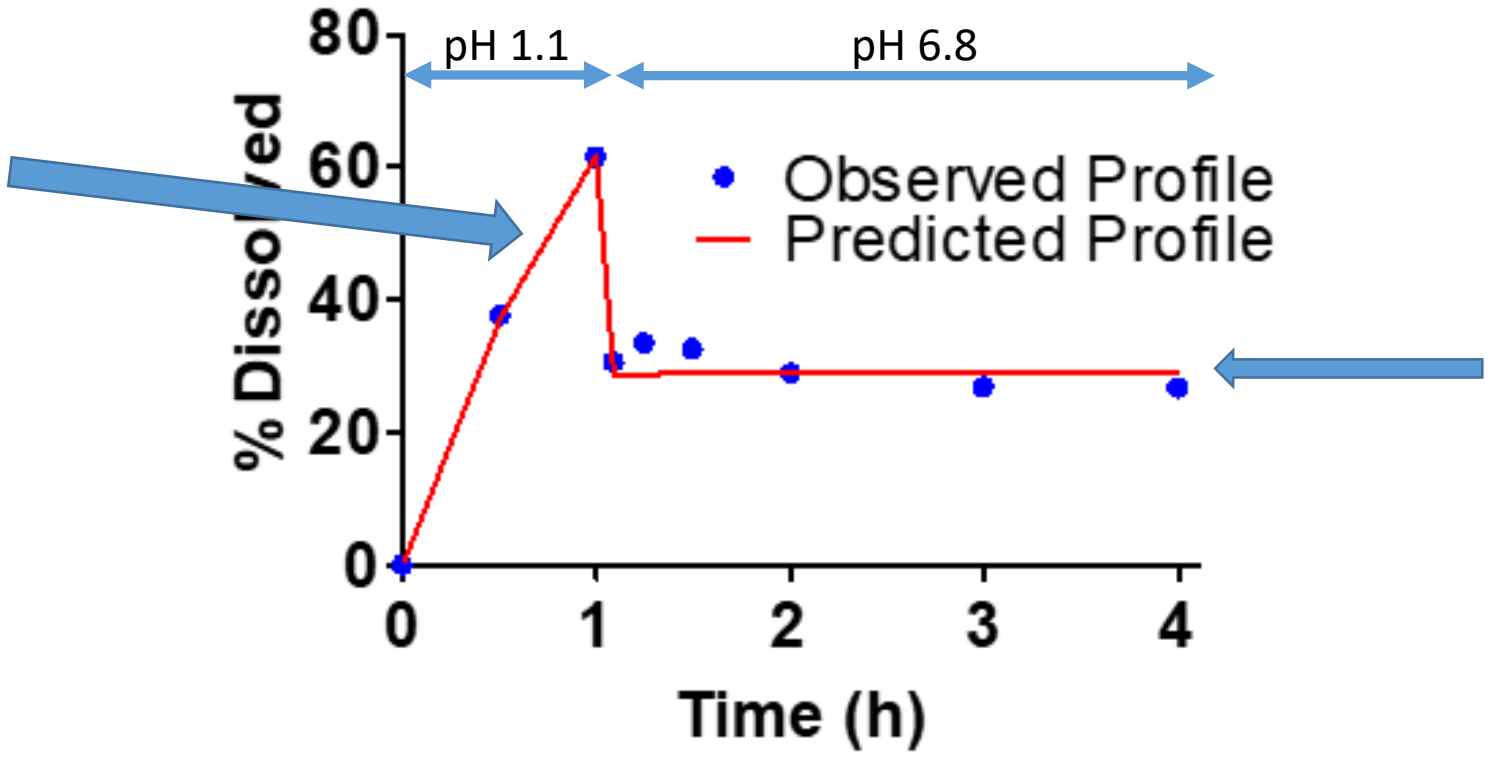
Do we need to model precipitation?

15% drug load
Hot Melt Extrusion

Polymer-controlled dissolution

(this is also the case at pH 6.8)
(Indulkar et al., 2019)

Simulated and Observed in vitro pH Shift Dissolution Profile of Ritonavir Norvir® ASD



Amorphous "solubility" $S_{amorphous}$

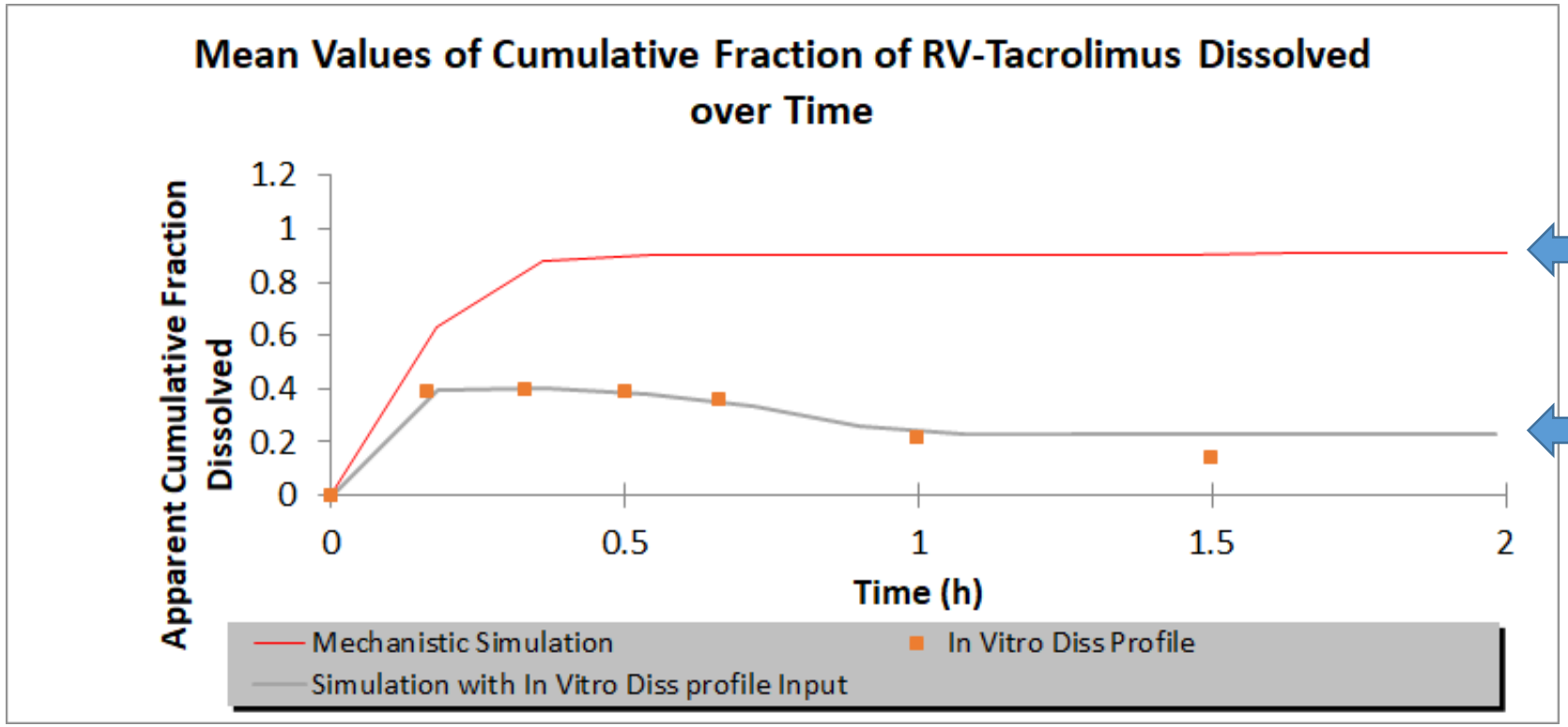
Ellenberger et al., 2018

Ritonavir modelling
Arora et al ms. submitted

See also Venetoclax - Emami Riedmaier (2018, J Pharm Sci)

CERTARA

Mechanistic Model vs. In Vitro Dissolution Input



Mechanistic 2 Solid State Model

In Vitro Dissolution Profile Input to PBPK Model

Mechanistic modelling, in this case, removed the need for potentially complex *in vitro* dissolution experiments with an absorptive phase/component.

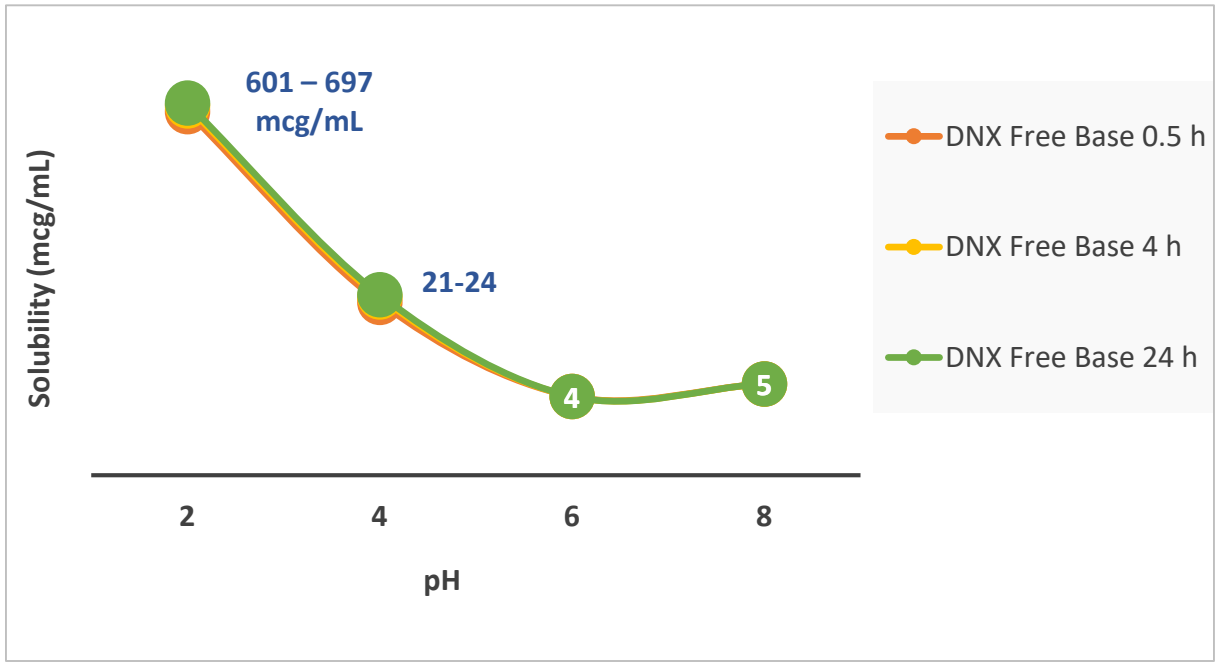
CERTARA

Danirixin Hydrobromide (DNX HBr) Case Study

Compared to “Free” API forms salts can provide

- Dissolution rate advantage
- “Solubility” advantage provided there is not precipitation to the free form (DNX is an ampholyte >99% ionised in physiological pH range)

pH Solubility Profiles of Free Ampholyte DNX Measured at 3 Time Points up to 24 h



XXX Solubility at given time and pH

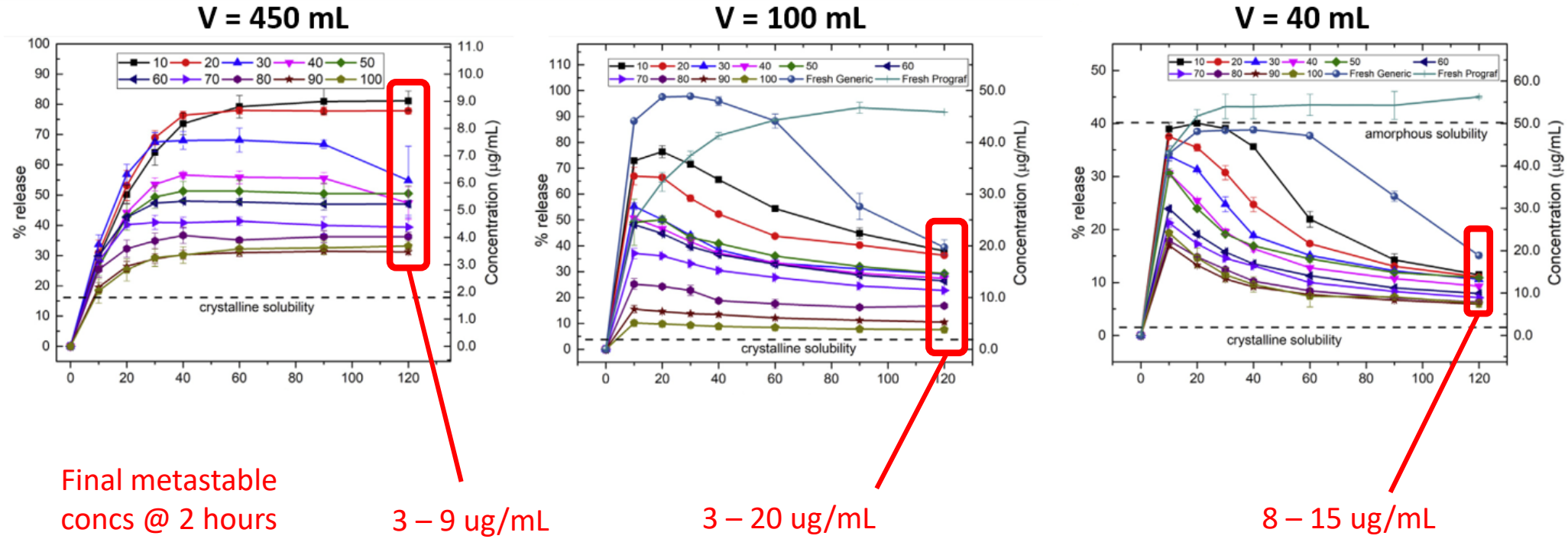
NB It is assumed that the reported pH values are the final pH values

Refs: 1) GSK patent WO 2015/071235 Al
2) Bloomer et al., 2017

CERTARA

In Vivo Relevance of *In Vitro* Conditions: Tacrolimus BCS 2

Tacrolimus *In Vitro* Dissolution Data



Non-micellar buffer *in vitro*

Final metastable concs @ 2 hours

3 – 9 ug/mL

3 – 20 ug/mL

8 – 15 ug/mL

What (maximum) luminal concentrations of tacrolimus do we expect in vivo?

Run simulations with precipitation prevented – this can give estimates of maximum conc.

In Vitro data Purohit et al, 2018

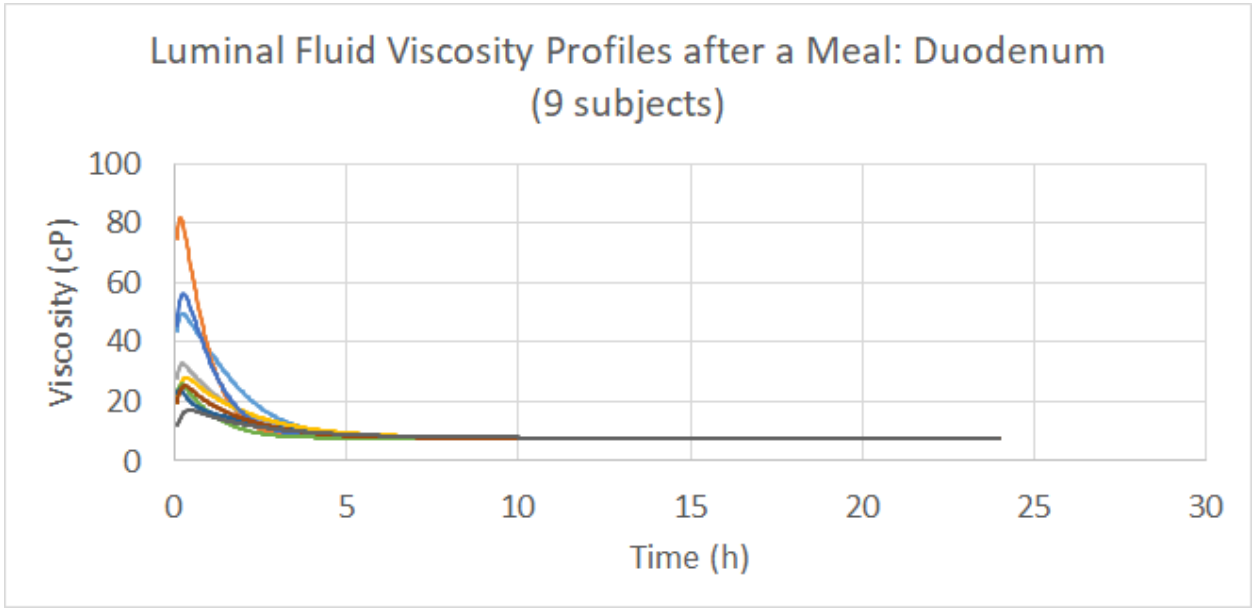
CERTARA

LUA Scripting Tools – Custom Models – Research Tool

Substrate: PD Basic 1

File Edit Options Tools Functions

```
25
26  function popSimSetup(...)
27      --set the number of differential equations used in the model
28      sc:setNUserOdes(27);
29      -- assign names to user state variables (for output on "PD Custome ODE" WS
30      local SEG_names = { "Stomach", "Duodenum", "Jejunum 1", "Jejunum 2", "Ileum 1
31      local su_nname = {};
32      for i=1,9 do
33          su_nname[i] = tostring("Vfood " ..SEG_names[i] .." (mL)");
34          sc:setUserStateName(i,su_nname[i]);
35      end
36      for i=10,18 do
37          su_nname[i] = tostring("Fdil " ..SEG_names[i-9]);
38          sc:setUserStateName(i,su_nname[i]);
39          --sc:setUserStateName(index, name)
40      end
41      for i=19,27 do
42          su_nname[i] = tostring("Viscosity " ..SEG_names[i-18] .." (cP)");
43          sc:setUserStateName(i,su_nname[i]);
44          --sc:setUserStateName(index, name)
45      end
46  end
47  function individualSetup(...)
48      --get transit rate constants, ids from AB 9/4/2019 v18
49      -- idSITransitTime, -- idGastricET, -- idColonTransitTime
50      -- idFluidIntakeSub, idFluidIntakeInh1 - these two NOT available in v18
51      MRT_stomach = sc:GetIndividualValueByID("idGastricET");
52      kt_seg[1] = 1 / MRT_stomach;
53      MRT_SI = sc:GetIndividualValueByID("idSITransitTime");
54      --assign kt_SI
55      for i=2,8 do
56          kt_seg[i] = 1 /  (MRT_SI * SI_fractions[i-1]);
57      end
58      MRT_Colon = sc:GetIndividualValueByID("idColonTransitTime")
59      kt_seg[9] = 1 / MRT_Colon;
60  end
61  function compoundSetup(...) -- this assigns values to array P
62      -- assign some parameters to P[]
63      sc:setParameter(1, 531) --Vfood initial stomach
64      sc:setParameter(2, 0)   --Vfood initial duo
65      sc:setParameter(3, 0.1) --Vfood base line or minimum global
66      sc:setParameterName(1,"Vfood_init");
67      sc:setParameterName(2,"Vfood initial duo");
68      sc:setParameterName(3,"Vfood base line or minimum global");
69  end
70  --function individualCompoundSetup(...)
71      --assign individualised parameter values from distribution
```



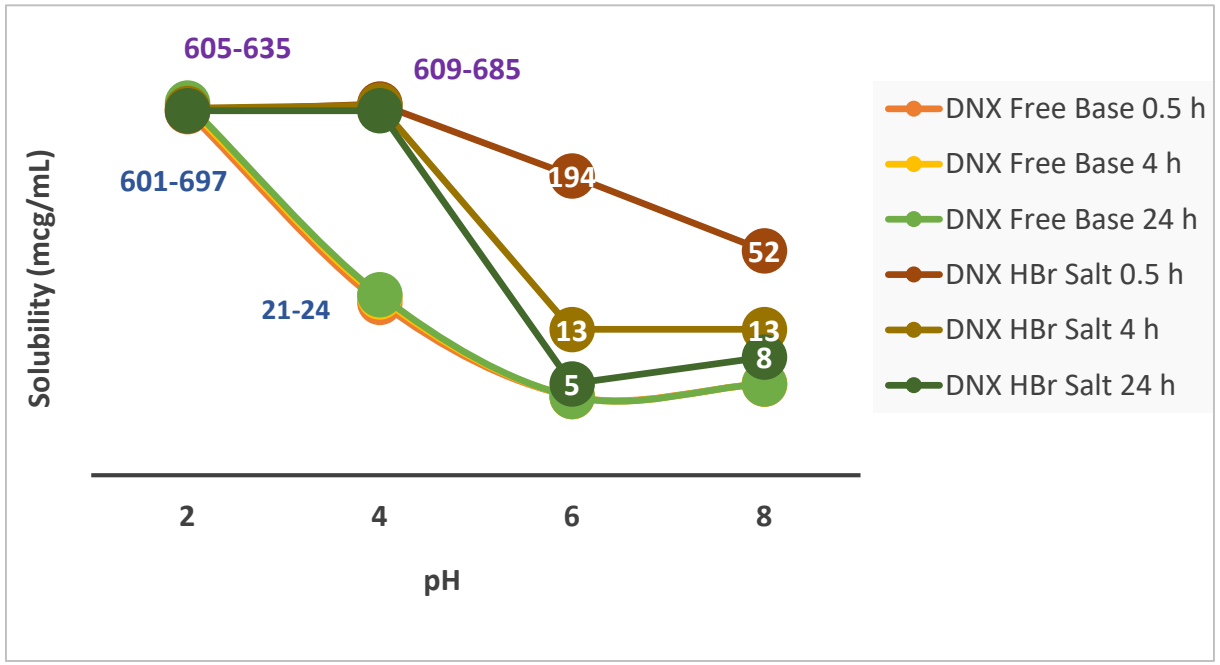
CERTARA

Danirixin Hydrobromide (DNX HBr) Case Study

Compared to “Free” API forms salts can provide

- Dissolution rate advantage
- “Solubility” advantage provided there is not precipitation to the free form (DNX is an ampholyte >99% ionised in physiological pH range)

pH Solubility Profiles of Free Ampholyte DNX and DNX HBr Salt Measured at 3 Time Points up to 24 h



XXX Solubility at given time and pH

The HBr salt

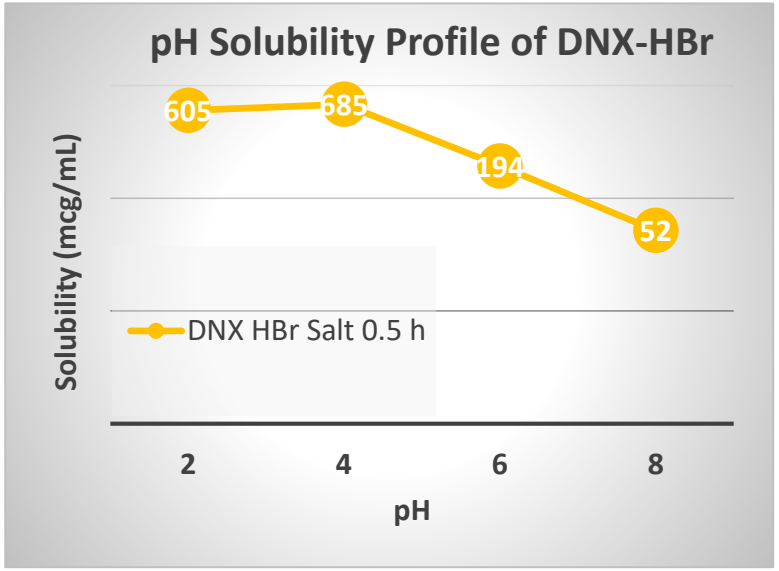
- Creates solutions that are supersaturated with respect free ampholyte
- That is quite stable up to 24 h (very stable at pH 4)

NB It is assumed that the stated pH values are the final pH values

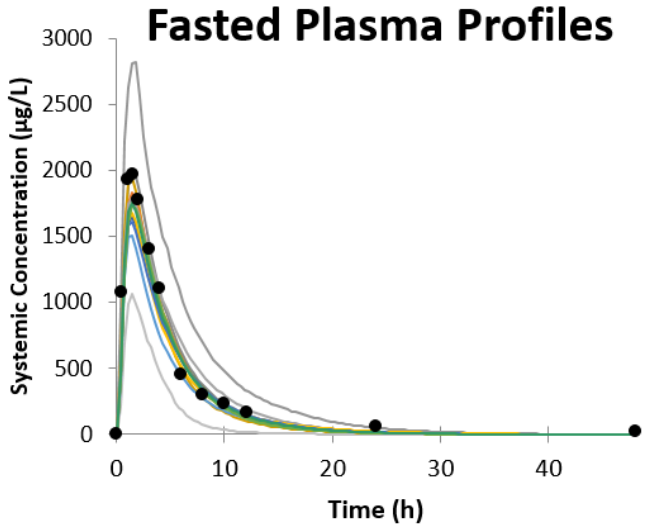
Refs: 1) GSK patent WO 2015/071235 Al
2) Bloomer et al., 2017

CERTARA

Salt Model Danirixin Case Study



Additional bile micelle-mediated solubilisation is added where relevant

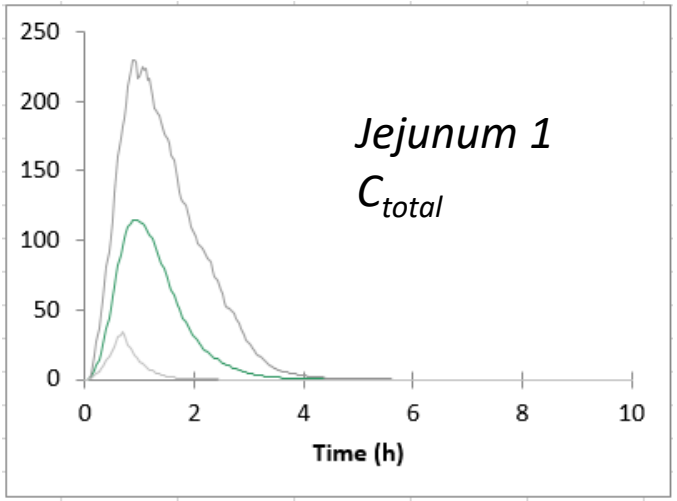


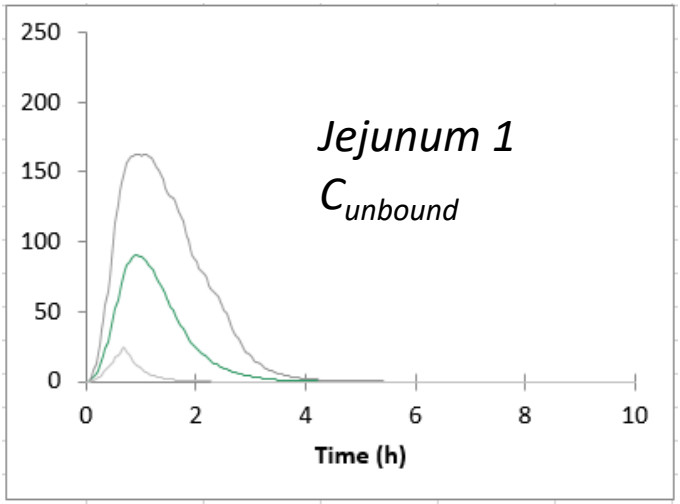
50 mg API DNX HBr

10 trials of 18 subjects
Geriatric-NEC Population (COPD)

Lines – simulation
Points – clinical data

[DNX] (mcg/mL)





Mean and 5th and 95th percentiles

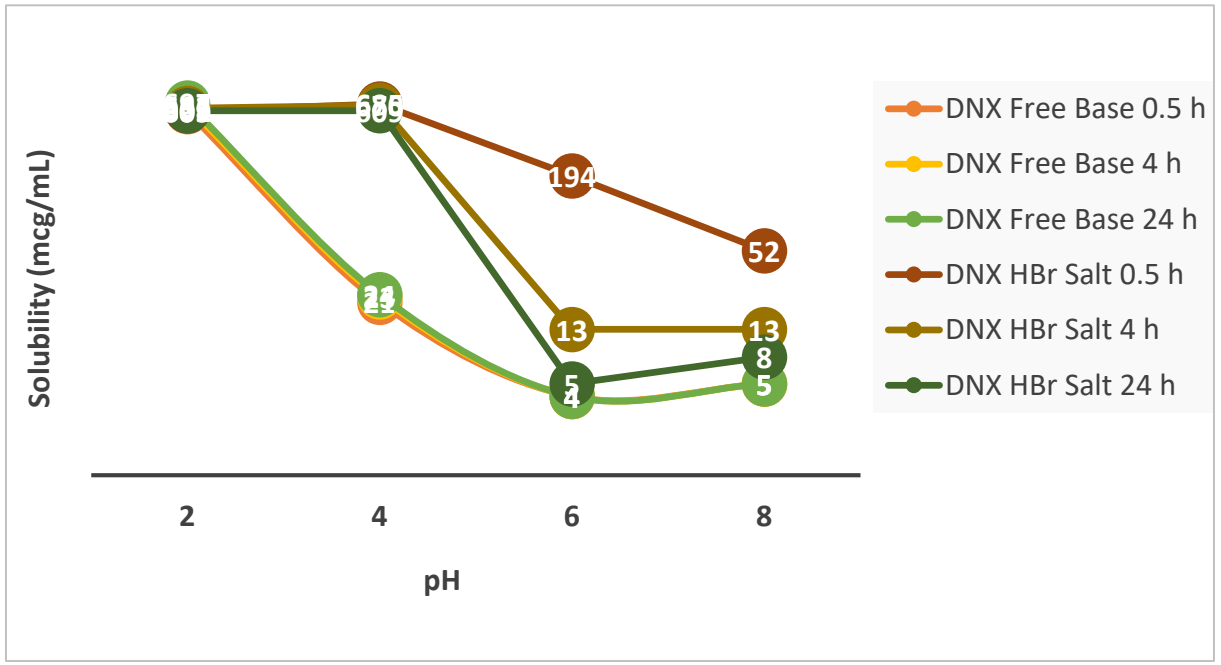
CERTARA

Danirixin Hydrobromide (DNX HBr) Case Study

Compared to “Free” API forms salts can provide

- Dissolution rate advantage
- “Solubility” advantage provided there is not precipitation to the free form (DNX is an ampholyte >99% ionised in physiological pH range)

pH Solubility Profiles of Free Ampholyte DNX and DNX HBr Salt Measured at 3 Time Points up to 24 h



XXX Solubility at given time and pH

The HBr salt

- Creates solutions that are supersaturated with respect free ampholyte
- That is quite stable up to 24 h (very stable at pH 4)

NB It is assumed that the stated pH values are the final pH values

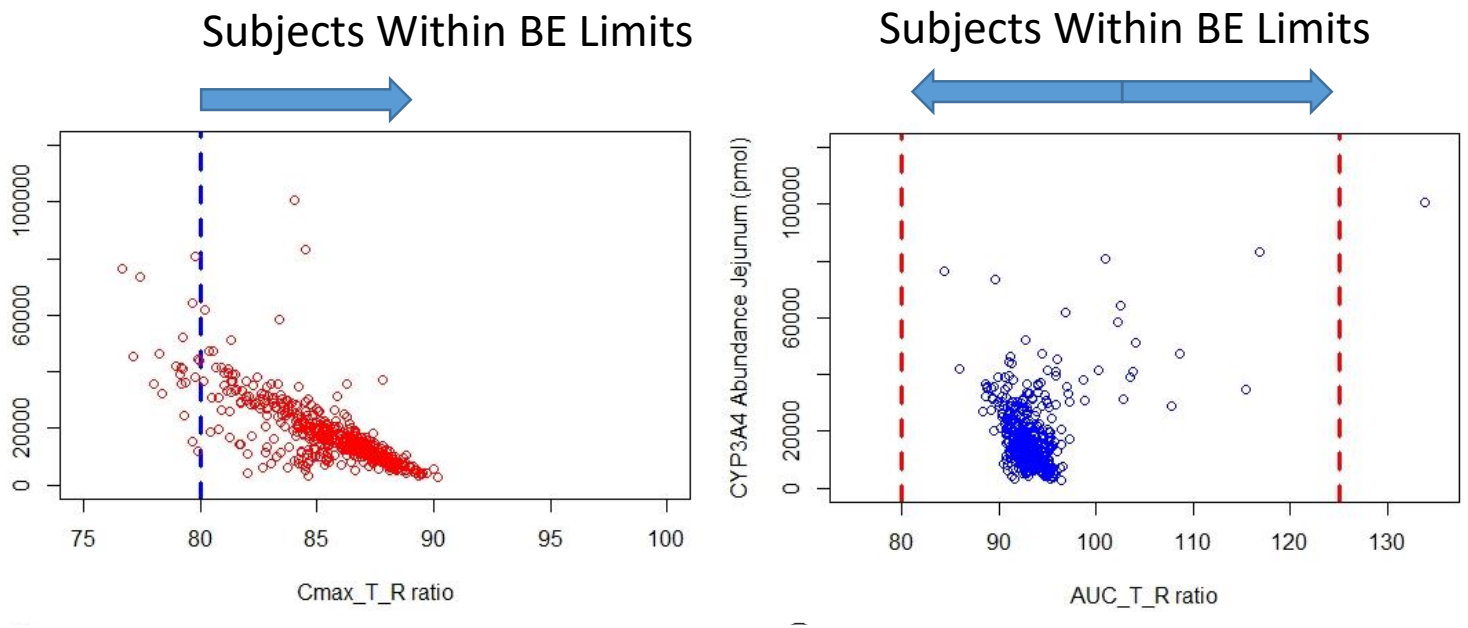
Refs: 1) GSK patent WO 2015/071235 Al
2) Bloomer et al., 2017

CERTARA

VBE Covariate Analysis – example

Simulation – Reference – Amorphous (100%)
– Test – Amorphous (90%) + Crystalline (10%)

Jejunum CYP3A4 Abundance (pmol)



Each marker point relates to a single subject

Residence time in the gut lumen is also a key covariate

CERTARA

In Vivo Relevance of *In Vitro* Conditions: 2. Excipient Effects on Solubility and Dissolution

Clinical Example: Tween 80 (T80) was used to solubilise an extremely lipophilic BCS 2 compound, low basic pKa – Drug "Y"

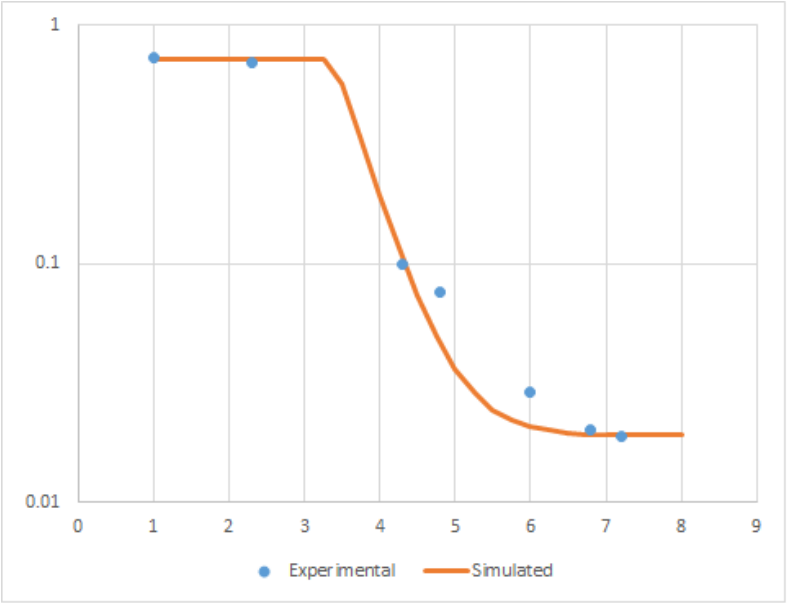
S_o, API alone <10 ng/mL (predicted)

T80 self-associates to form micelles (CMC 0.012 mM)

Available In Vitro Data in the Presence of Tween 80

Scenario	Final Vol (mL)	Final Conc T80 (mM)	$S_{o,app}$ (mg/mL)
In Vitro Solubility	129	1.71	0.019
In Vitro Dissolution	500	0.44	0.005
In Vivo Dispersion (suspension)	160	1.29	0.0143

Figure 1: Aqueous phase equilibrium solubility of Drug Y in the presence of 1.7 mM Tween 80 (no bile salts).



Analogous data following the same pattern were available for a TPGS formulation and a "Quotient" Formulation containing another solubiliser

SIVA Toolkit

CERTARA

Importance of Dissecting the Components of Solubility – free fraction

$$S_{Tot}(t) = S_0 \cdot S_{0_{scalar}}(t) \cdot \left(1 + \frac{[BS](t)}{C_{H_2O}} \cdot K_{m:w,unionised}(t)\right)$$

$$+S_i(t) \cdot \left(1 + \frac{[BS](t)}{C_{H_2O}} \cdot K_{m:w,ionised}(t)\right) + S_{bound,excip}(t) \qquad Equation\ 1$$

Diffusion coefficients
Luminal fluids – dissolution
UBL/Mucus/water – permeability
(ADAM/MechPeff model or M-ADAM only)

Free concentration at UBL-membrane interface

Identifiability of *Km:w* values?
Please do measurements in more than 2 biorelevant media!

$$P_{eff} = \left(\left(\left(P_{trans,0} \cdot f_{neutral,pH} + P_{para}\right) \cdot ACC \cdot MVE \cdot f_{u,UBL}\right)^{-1} + (P_{UBL})^{-1}\right)^{-1} \cdot FE_p$$

$$P_{UBL} = \frac{D_{eff,UBL}}{h_{eff,UBL}}$$

CERTARA