PBBM: IMPACT & FUTURE PERSPECTIVE

Jennifer Dressman

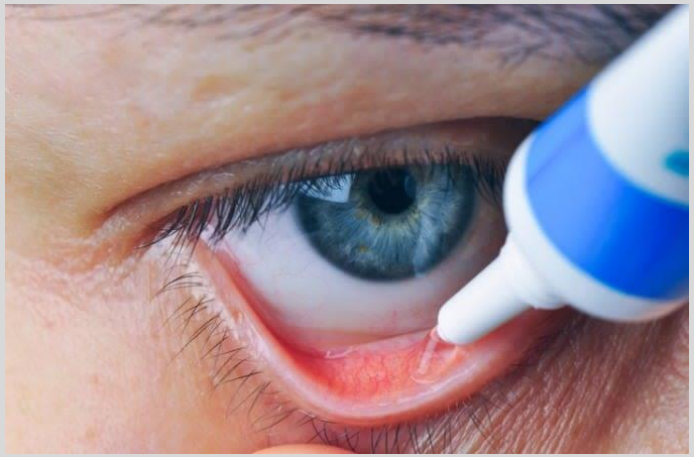
M-CERSI 29th August, 2023

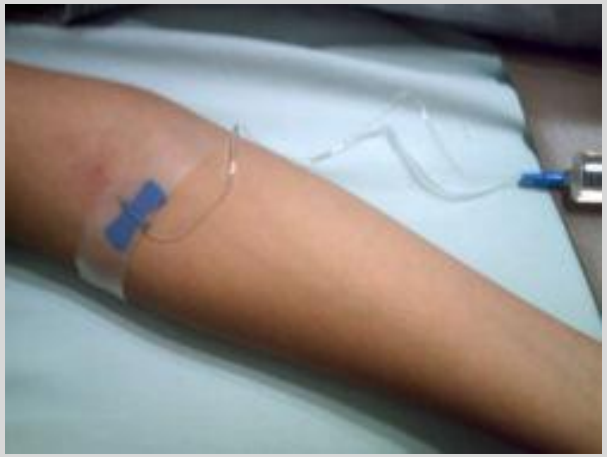
Brief disclosure: I am a member of the SAB at Certara-Simcyp. I also helped to develop PK-SIM in the initial stages. I have published papers in which STELLA, Simcyp, GastroPlus or PK-Sim was used in the simulations.

- Physiologically-based
- Biopharmaceutics
- Modeling

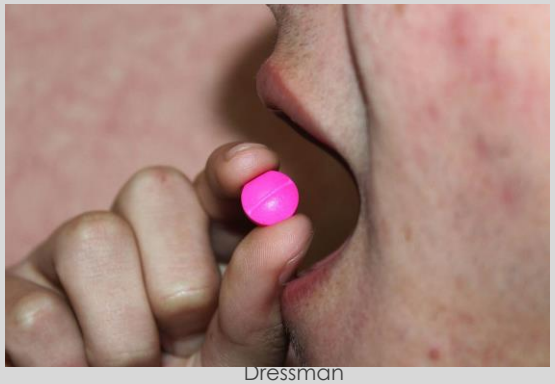
.....What does this mean?

Physiologically based ……



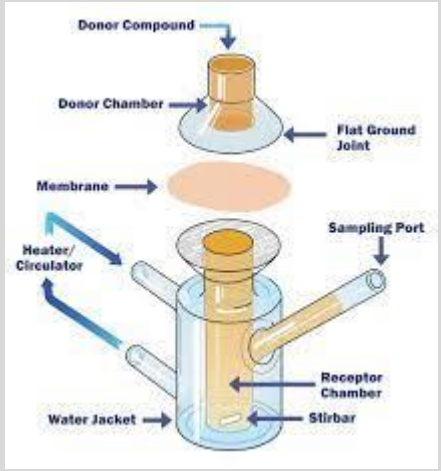


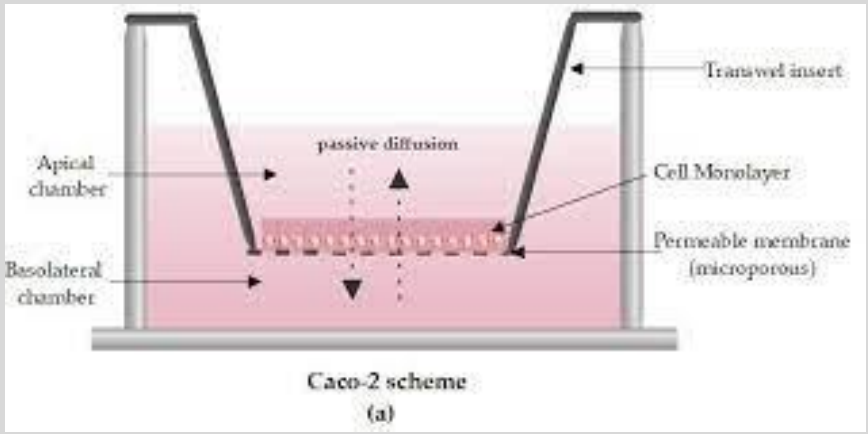
Means that the physiology of the route of delivery must be well characterized



Dressman

Biopharmaceutics……

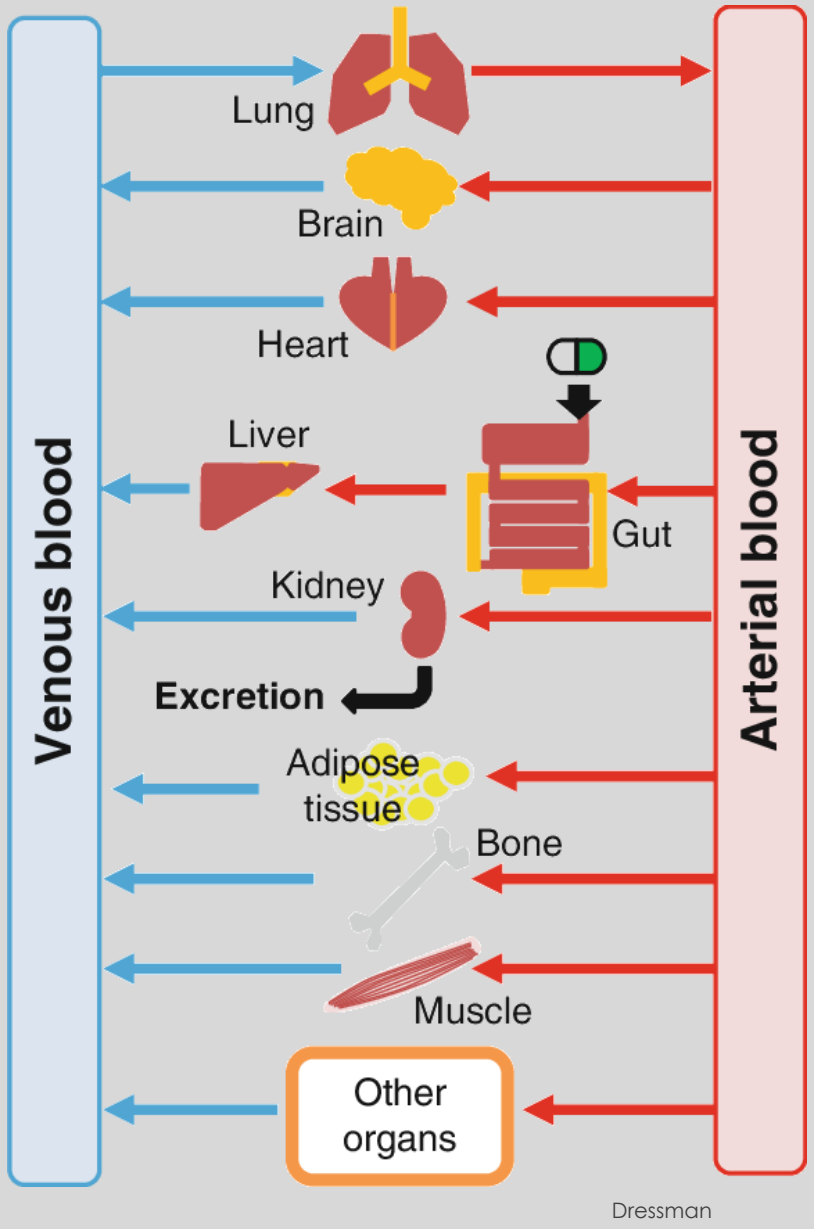




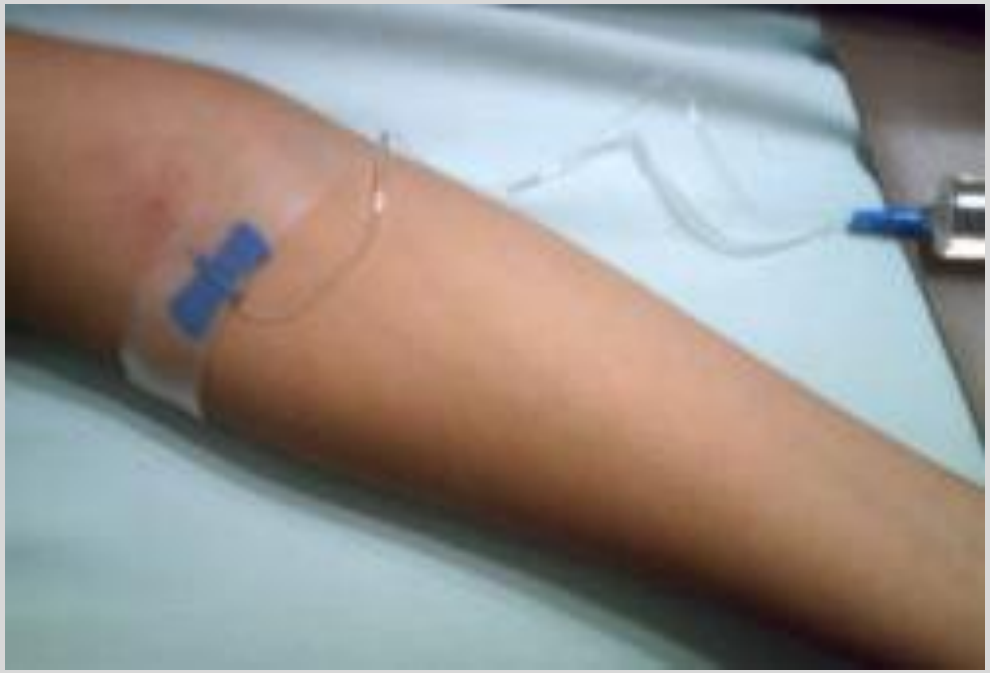
Means characterizing release of the API from the formulation, as well as its solubility, permeability and stability at the site of application

Modeling……

Means integrating physiological and biopharmaceutics data into an *in silico* model that can describe the time-course of the drug's interaction with the body



State of the Art in PBBM – 1. describing intravenous injection and infusion



- intravenous injections and infusions are usually aqueous solutions, so the biopharmaceutics is straight forward: the release pattern is set by the injection/infusion rate; permeability is not an issue).
- The Rogers and Rowland model for distribution may require some adjustments in order to fit the plasma profile, especially if the drug is lipophilic
- **Before proceeding to other routes of administration, it is ALWAYS a good idea to model i.v. data as a first step, as this forms the core disposition model for all PBBM.**

State of the Art in PBBM – 2. modeling DDIs

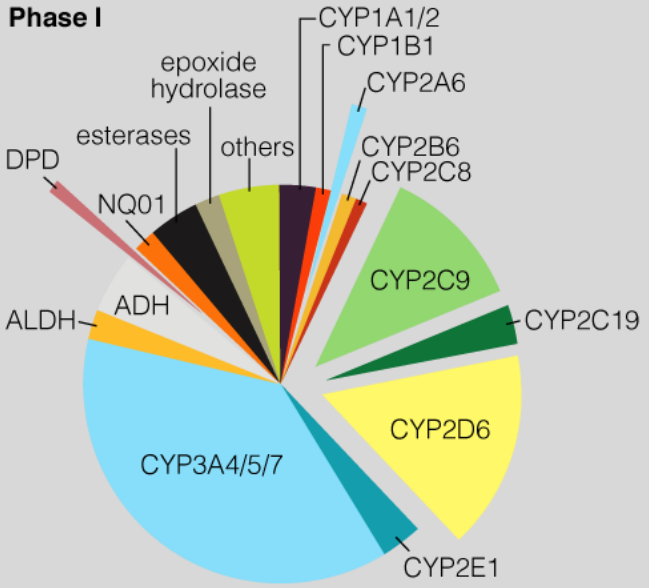
DDIs can be

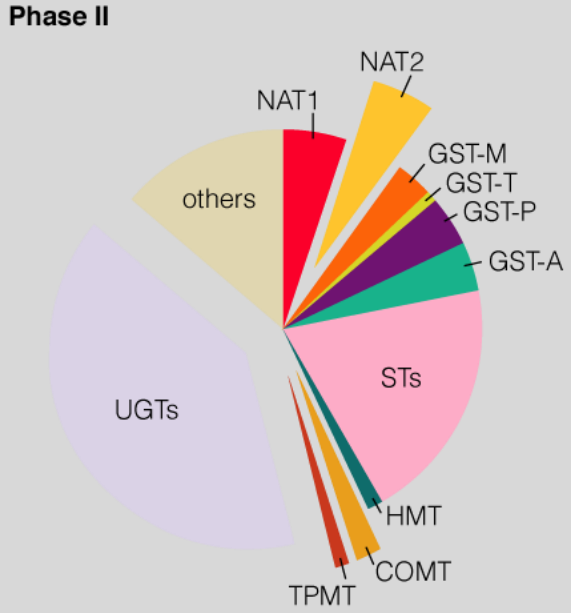
A) Metabolic through Phase 1 reactions

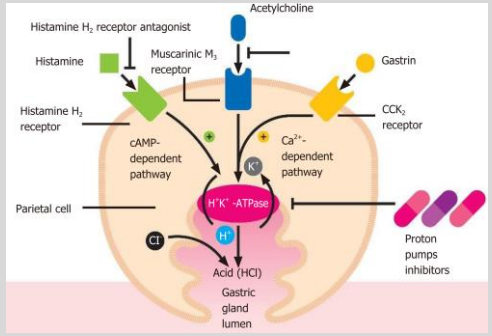
B) Metabolic through Phase 2 reactions

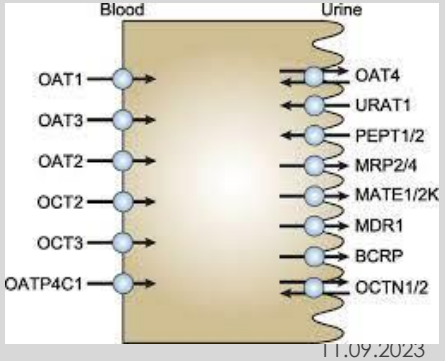
C) Transporter-related

D) Due to alteration of the physiology by the perpetrator (e.g. PPIs)

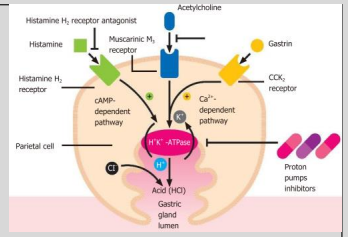








Spotlight on PBBM of PPI interactions



- for H2R-antagonists and PPIs the high pH in the stomach is due to a lack of acid output, **not** the addition of buffer => use of standard USP buffers at pH 4.5 or 6.8 is misleading!
- A better biopharmaceutics approach is to use **low buffer capacity** media at representative pH values e.g. pH 4 (moderate effect) / pH 6 (strong effect) => bracketing effect

Journal of Pharmaceutical Sciences 108 (2019) 3461-3477

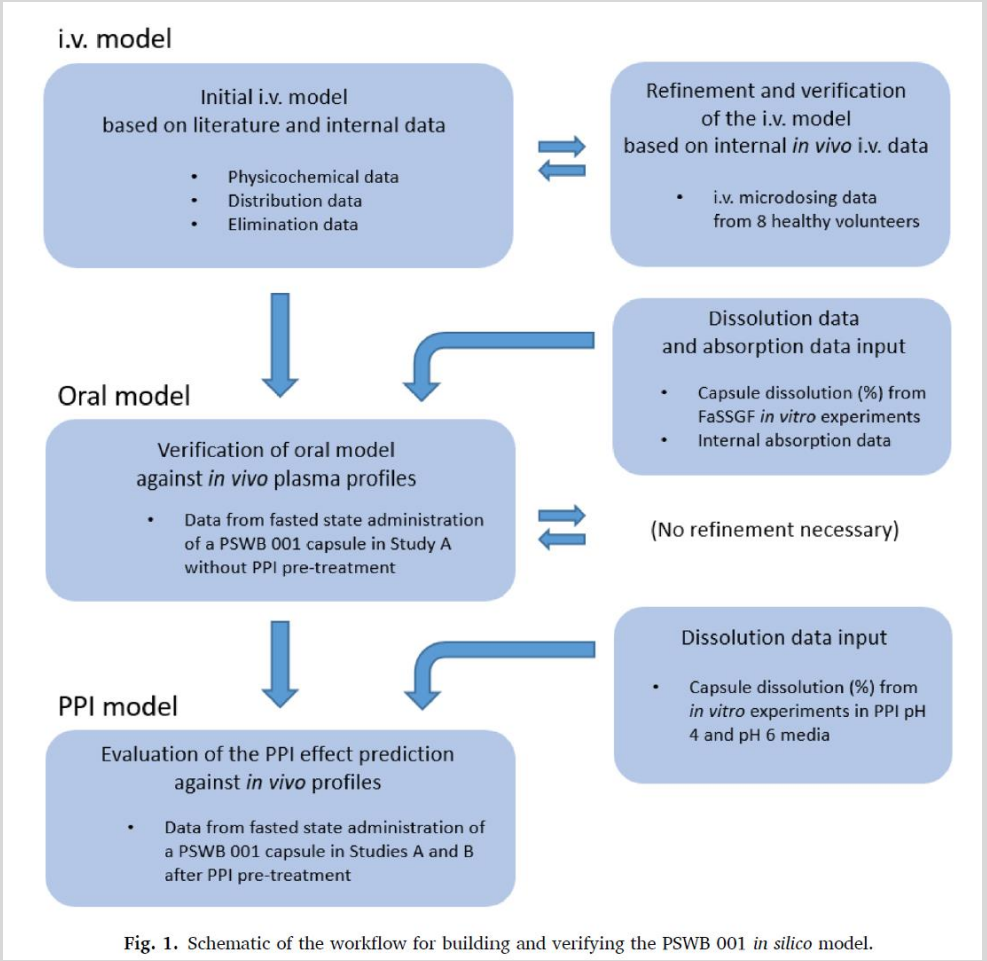
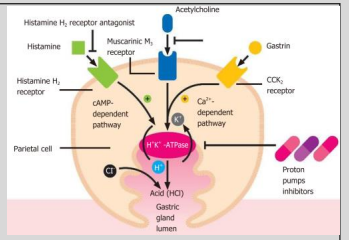


Fig. 1. Schematic of the workflow for building and verifying the PSWB 001 *in silico* model.

Spotlight on PBBM of PPI interactions



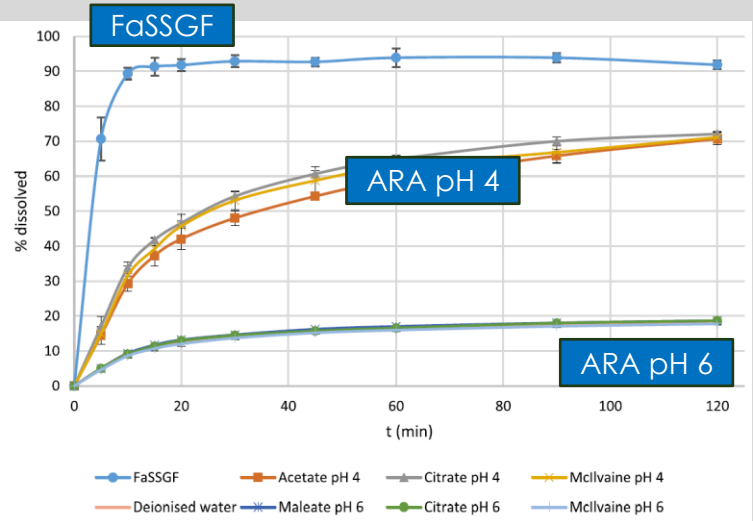
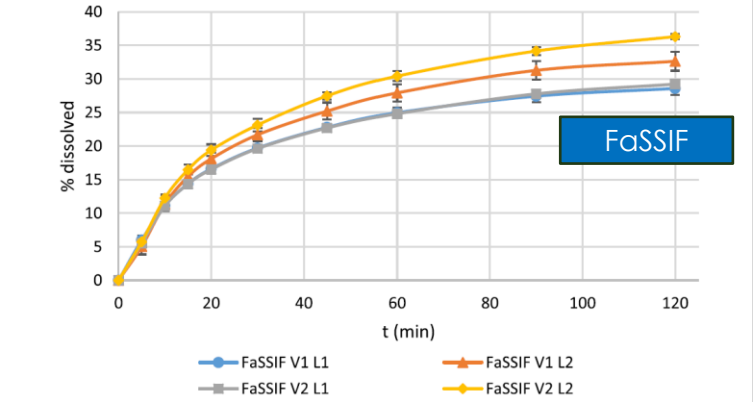
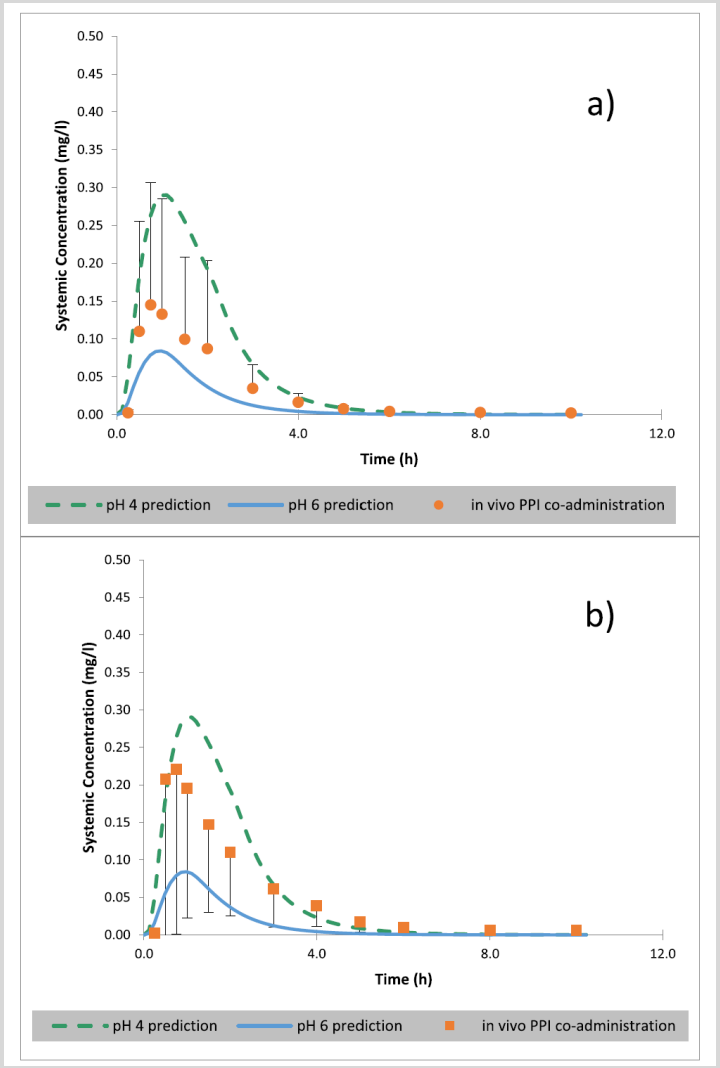


Fig. 2. Dissolution of PSWB 001 capsule in 250 ml of FaSSGF, PPI pH 4 and pH 6 media and in deionised water.

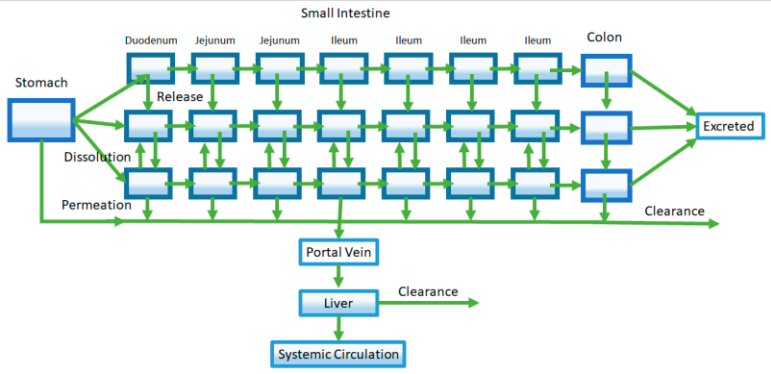


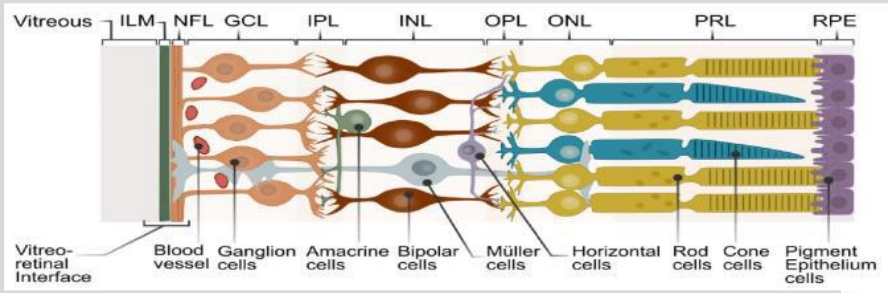
Dissolution testing of an AZ weak base product in ARA media (top) and FaSSIF (bottom)

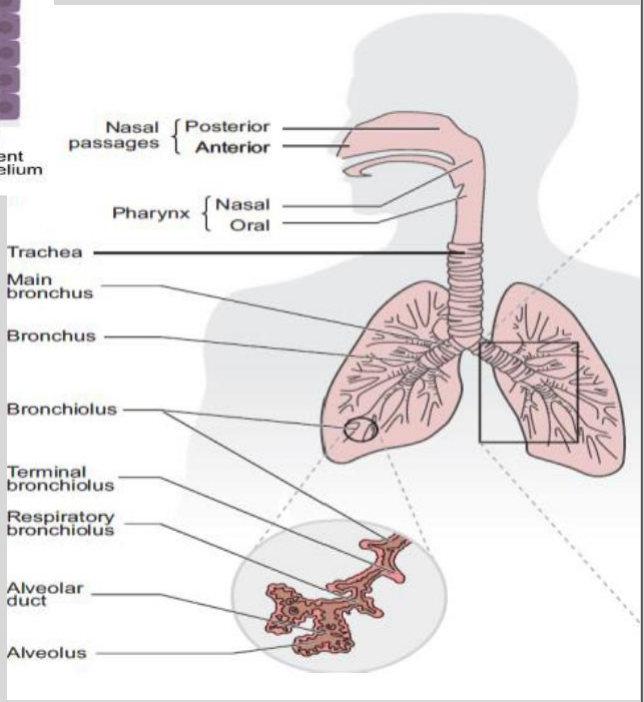


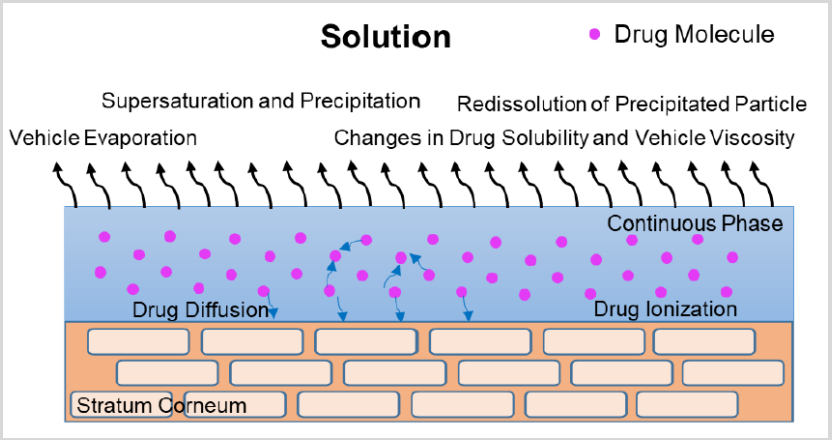
Comparison of dissolution/PBPK predictions with results in two AZ clinical studies

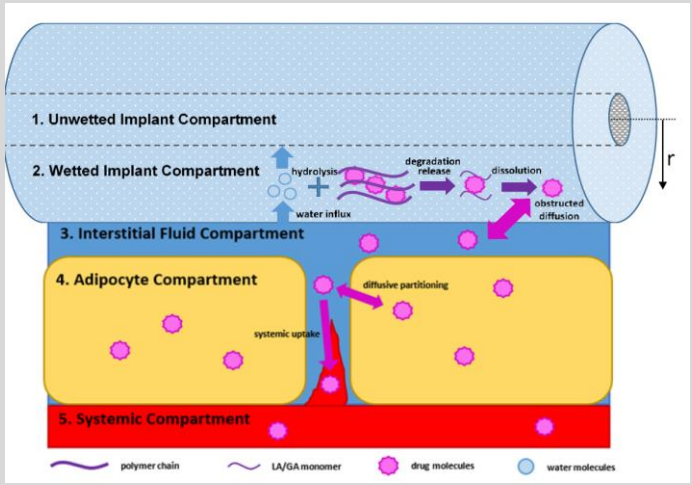
State of the Art in PBBM – 3. Routes of administration that have been modeled by PBBM











State of the Art in PBBM – 3a. oral route

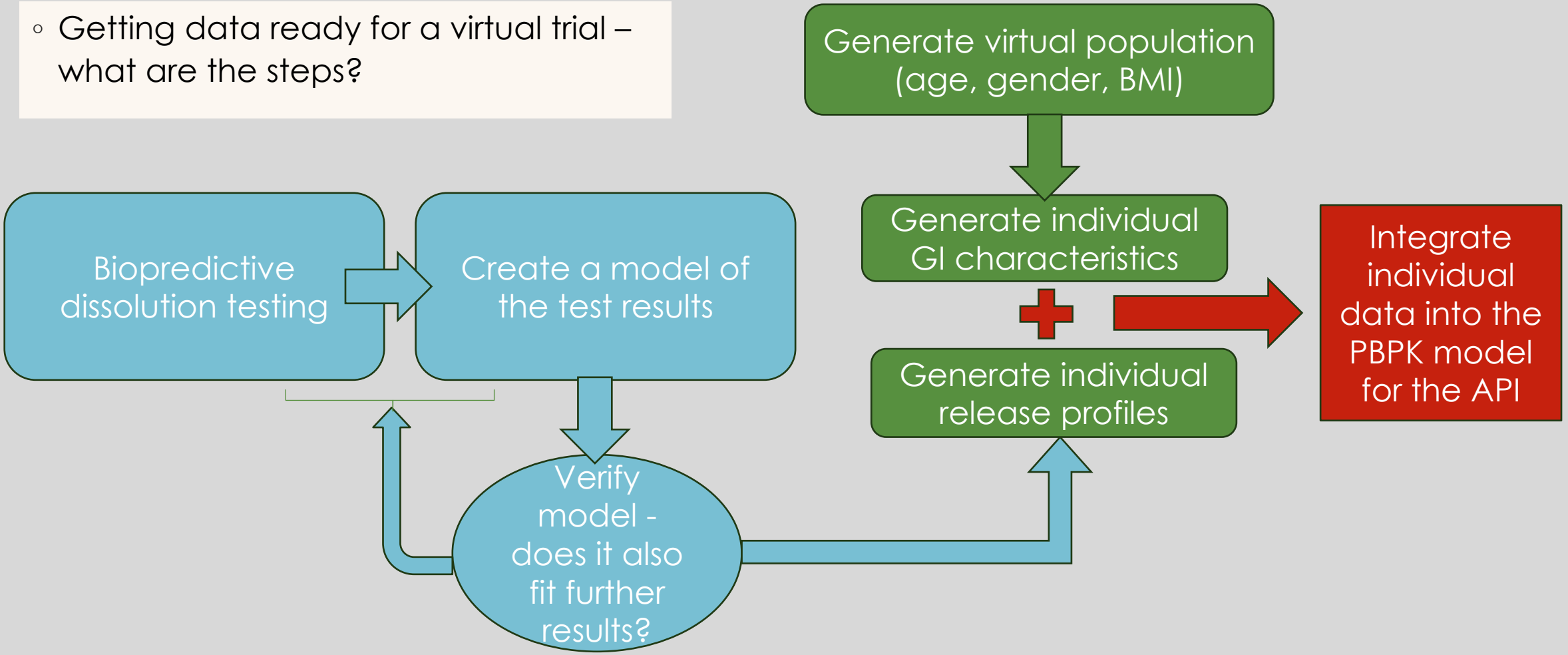
Physiology: the gastrointestinal tract is a complex organ with several unique regions, which vary in terms of luminal composition, passage times, mucosa and motility.

State of the Art in PBBM – 3a. oral route

Biopharmaceutics: Understanding the attributes of oral formulations which are critical to release and stability is usually achieved in USP 2 apparatus for human-scale formulations, but many other apparatus types can also be used, depending on the critical attributes of the formulation. Permeability is usually measured in Caco-2 cells and the results extrapolated to human Peff values

State of the Art in PBBM – 3a. oral route

- Getting data ready for a virtual trial – what are the steps?

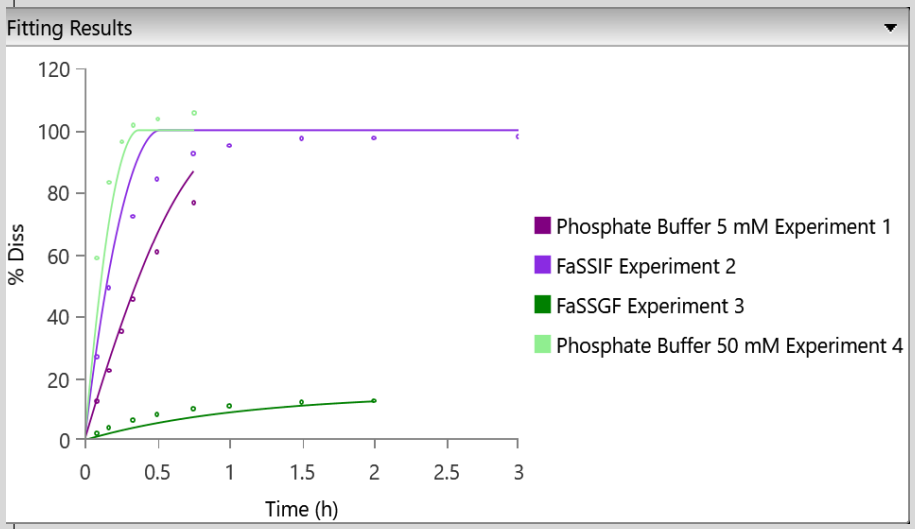


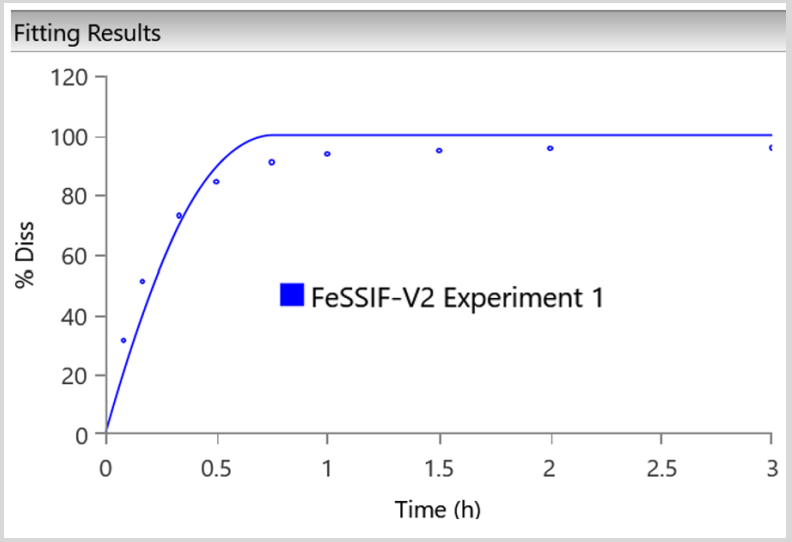
State of the Art in PBBM – 3a. oral route

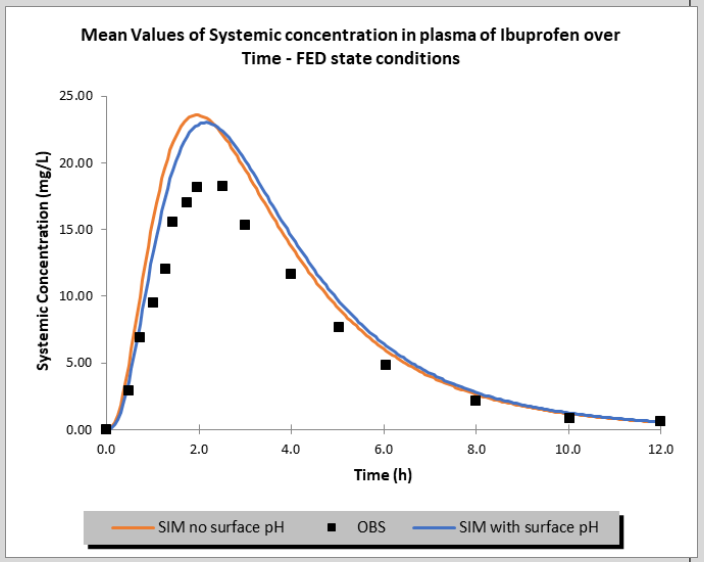
- **Case example – creating a model for ibuprofen dissolution**
- Ibuprofen 200 mg tablets were tested at 5mm and 50 mM phosphate buffer, in FaSSGF and in FaSSIF and the results were analyzed by the DLM model in the SIVA Toolkit.

$$DR(t) = -NS\frac{D_{eff}}{h_{eff}(t)}4\pi a(t)\left(a(t)+h_{eff}(t)\right)\left(S_{surface}(t)-C_{bulk}(t)\right)$$

- The DLM model was then used to predict the dissolution of the tablets in FeSSIF V2. The excellent fit indicated that the model is „fit for purpose“ and was subsequently used in the Simcyp Simulator to model plasma profiles of ibuprofen after food intake.

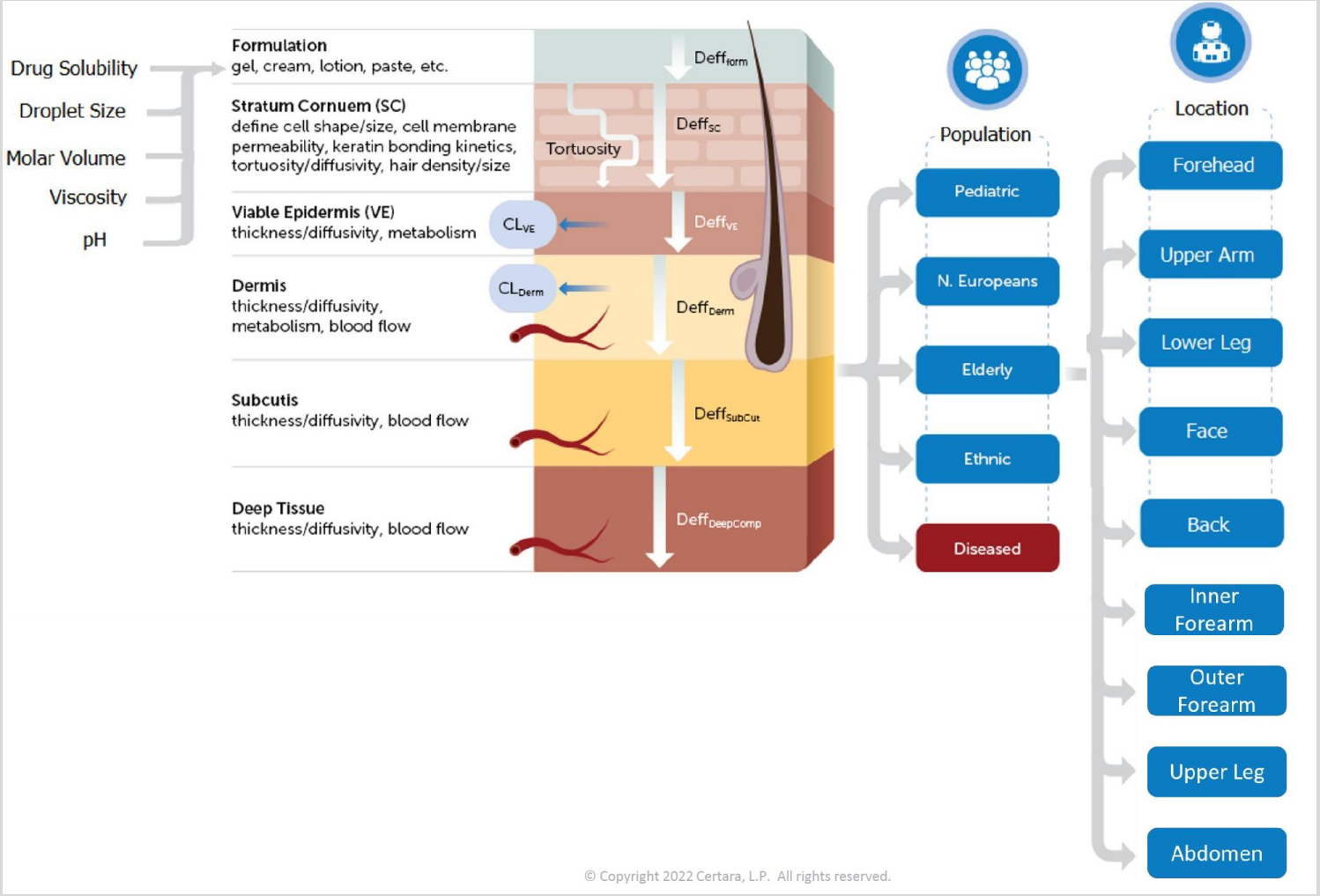






State of the Art in PBBM – 3b. dermal route

Physiology: passage through the skin to the site of action is often a multi-step process which is also affected by patient age and whether the skin is healthy or diseased, as well as the site of application.



State of the Art in PBBM – 3b. dermal route

Diverse formulations:

Solutions

Lotions

Suspensions

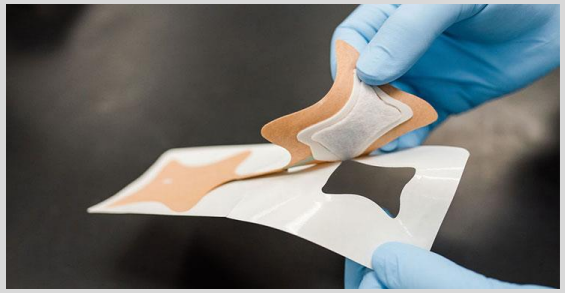
Gels

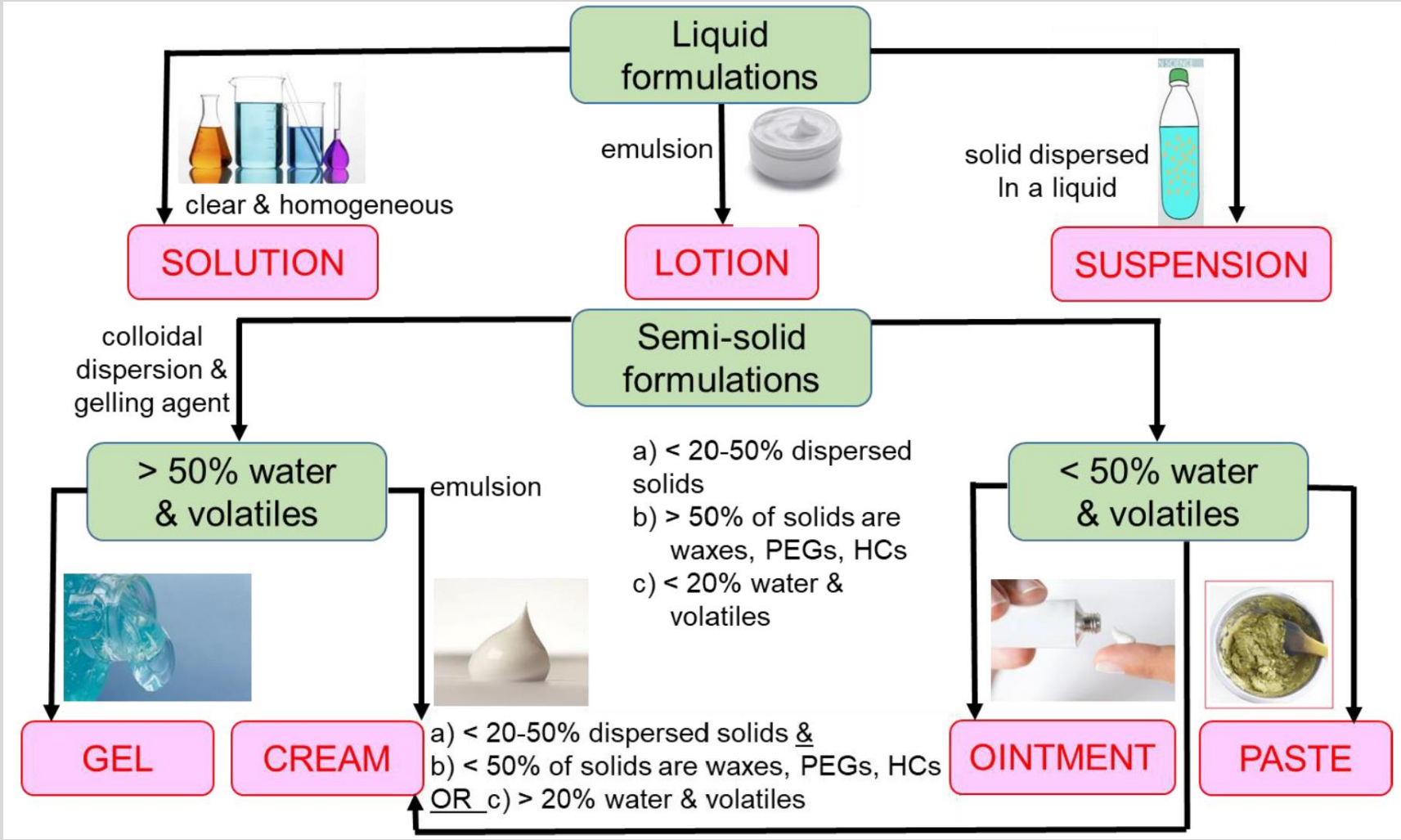
Creams

Ointments

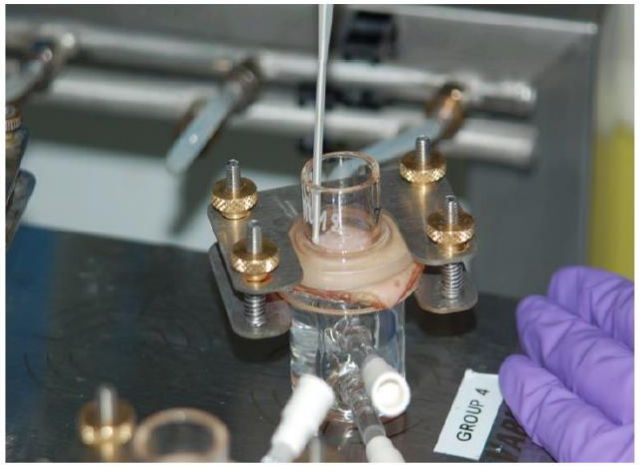
Pastes

Patches

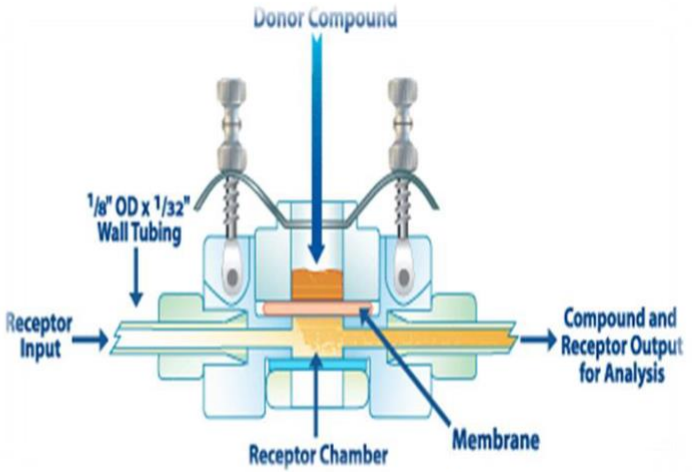




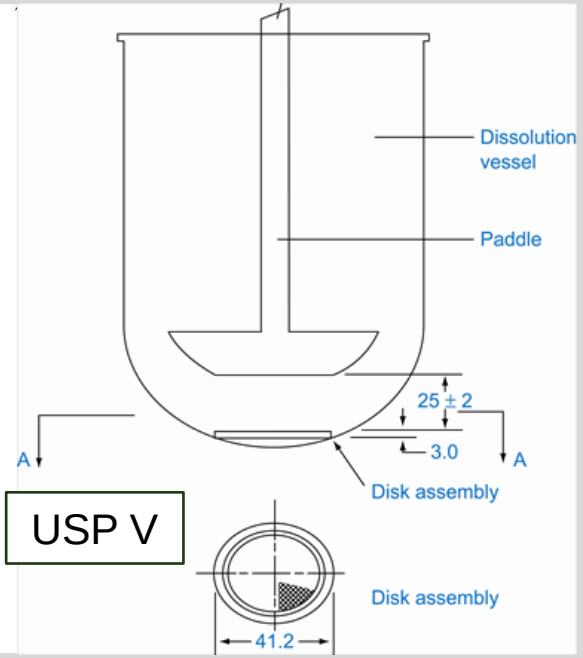
State of the Art in PBBM – 3b. dermal route



Franz Diffusion Cells



Flow Through Cells



USP V

Biopharmaceutics: Understanding the attributes of topical formulations which are critical to penetration into and/or through the skin is usually achieved in Franz diffusion cells, flow through cells or USP V apparatus . Tape stripping can also be used to evaluate depth of penetration.

The set-up of the experiment can be modeled in a pre-step to PBPK input

Spotlight: virtual BE for the dermal route

Virtual Bioequivalece (VBE): M&S Application of IVIVE and PBPK

Physiologically-based pharmacokinetic modeling to support bioequivalence and approval of generic products: A case for diclofenac sodium topical gel, 1%

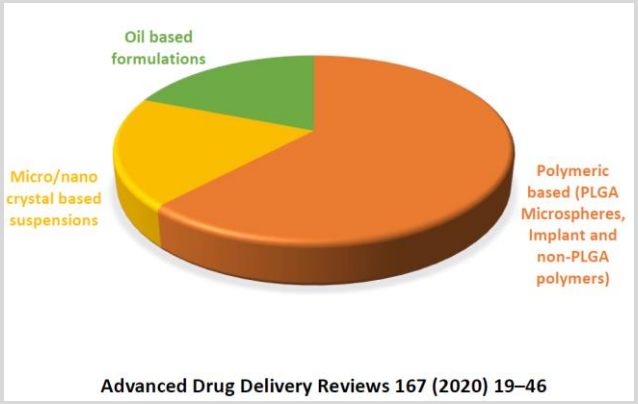
Eleftheria Tsakalozou | Andrew Babiskin | Liang Zhao

CPT Pharmacometrics Syst. Pharmacol. 2021;00:1–13.

This report summarizes the ***approval*** of an Abbreviated New Drug Application (***ANDA***) for a generic diclofenac sodium topical gel, 1% (referencing Voltaren topical gel, 1%), where ***for the first time a VBE assessment*** leveraging dermal PBPK modeling and simulation supported by a totality of evidence approach resulted in approval of the ANDA and discusses the lessons learned from this submission.

A recent report from the FDA shows the way to accepting the PBBM approach to **virtual bioequivalence** for approval of topical formulations

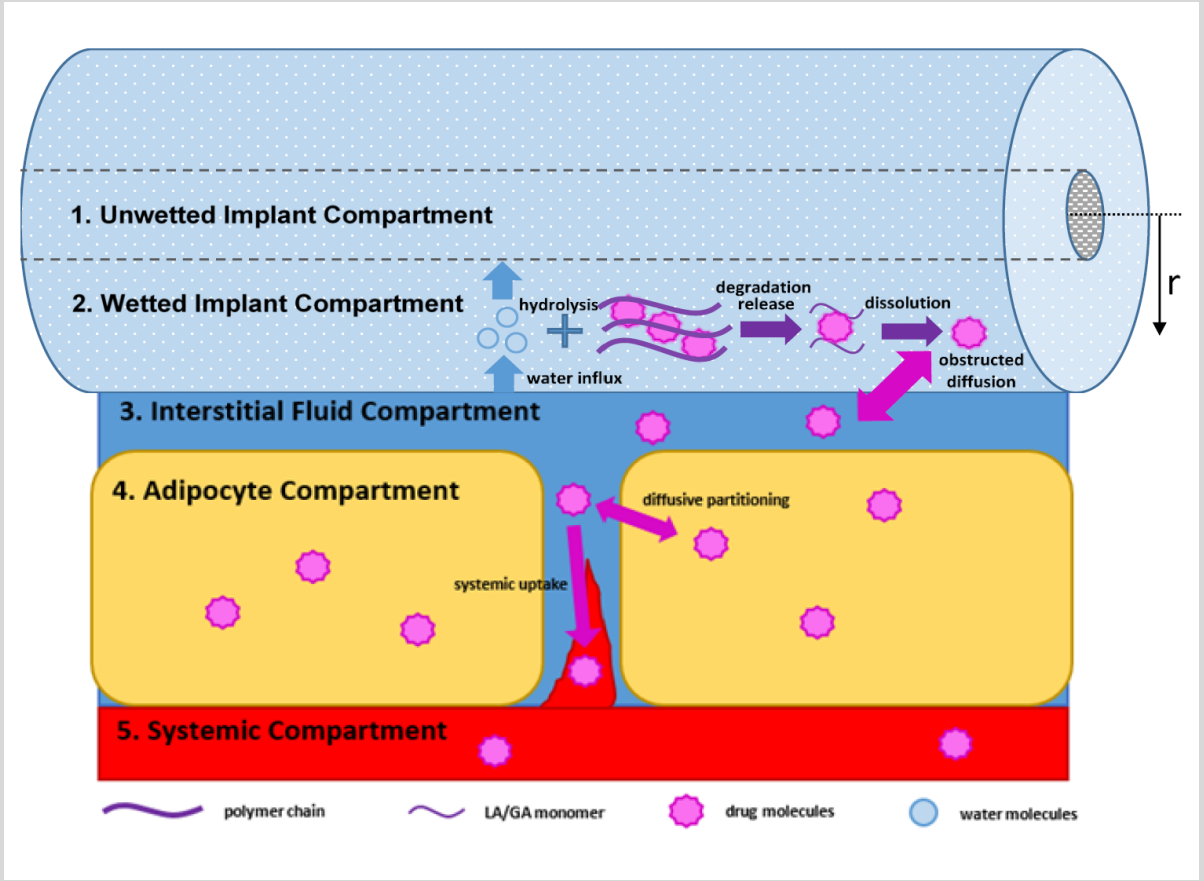
State of the Art in PBBM – 3c. long-acting injections



Advanced Drug Delivery Reviews 167 (2020) 19–46

Almost half of the long-acting injectables on the market are based on PLGA.

The model includes fluid influx into the porous structure of the implant, non-catalytic and catalytic hydrolysis of PLGA, dissolution of small oligomers, dissolution of the solid drug in the wetted pores and liberation from the implant, drug permeation through local tissues and absorption into the systemic circulation. It can also adjust for different lactic to glycolic acid ratios in the PLGA carrier.

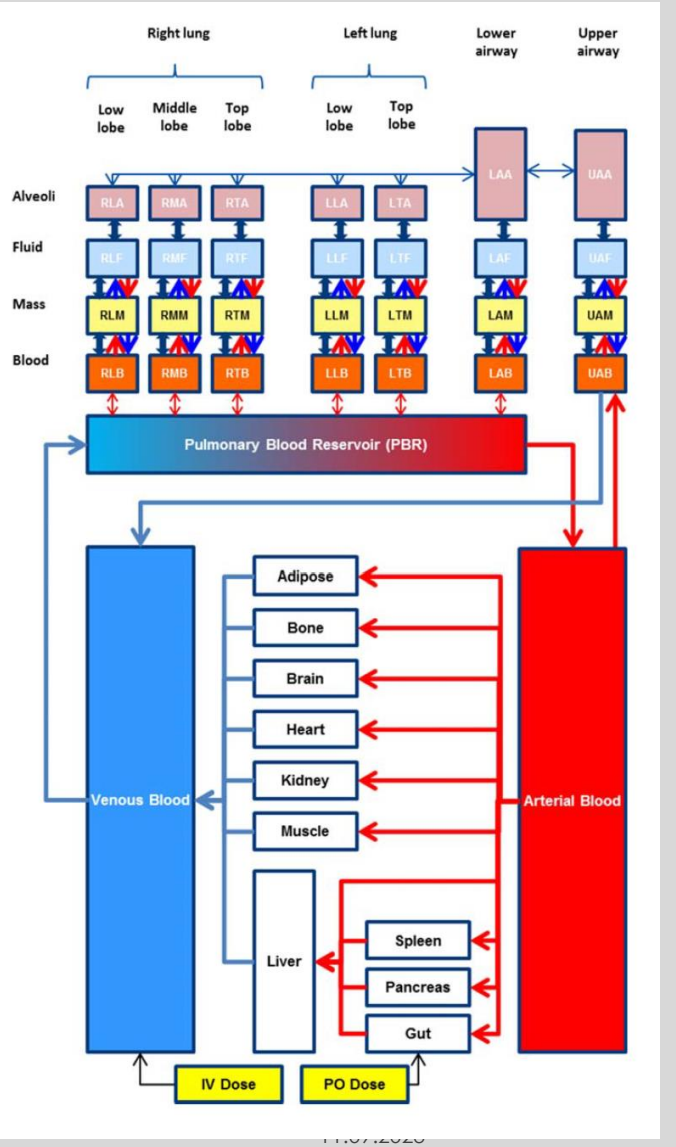


State of the Art in PBBM – 3d. inhalations

Inhalation is a key route of administration for treating airways infections and diseases.

Biopharmaceutics focuses on achieving the particle size and morphology necessary to target the site of action, while permeability is often measured in Calu-3 cell lines.

The **PBPK model** must reflect the distribution of the drug into the target tissue for assessing treatment of upper and lower airways diseases, as well as systemic levels to assess potential side effects.



CPT Pharmacometrics Syst. Pharmacol. (2015) 4, 605–613; doi:10.1002/psp4.12034

Spotlight: recent research in food effects

A question that has been hotly debated lately – also in regulatory circles - is whether we need clinical studies in both the fed and the fasted state to show BE?

- **Case example – ITRACONAZOLE solid dispersions (Sporanox and Tolsura)**
  - **Sporanox (100mg) consists of itraconazole fixed on pellets in an ASD with HPMC**
  - **Tolsura (65mg) consists of a powdered ASD of itraconazole with HMPCAS**

Spotlight on food effects for amorphous solid dispersions (ASD)

Biopharmaceutics Approach: compare the two ASDs in biorelevant media representing the fed state (FedGAS and FeSSIF-V2)

Results I. FedGAS

The Sempera (= Sporanox) pellets released best in late FedGAS, where the pH is lower (follows ITRA pH trends in solubility)

The Tolsura powder only released well in early FedGAS, where the pH is high (follows HPMCAS pH trends in solubility)

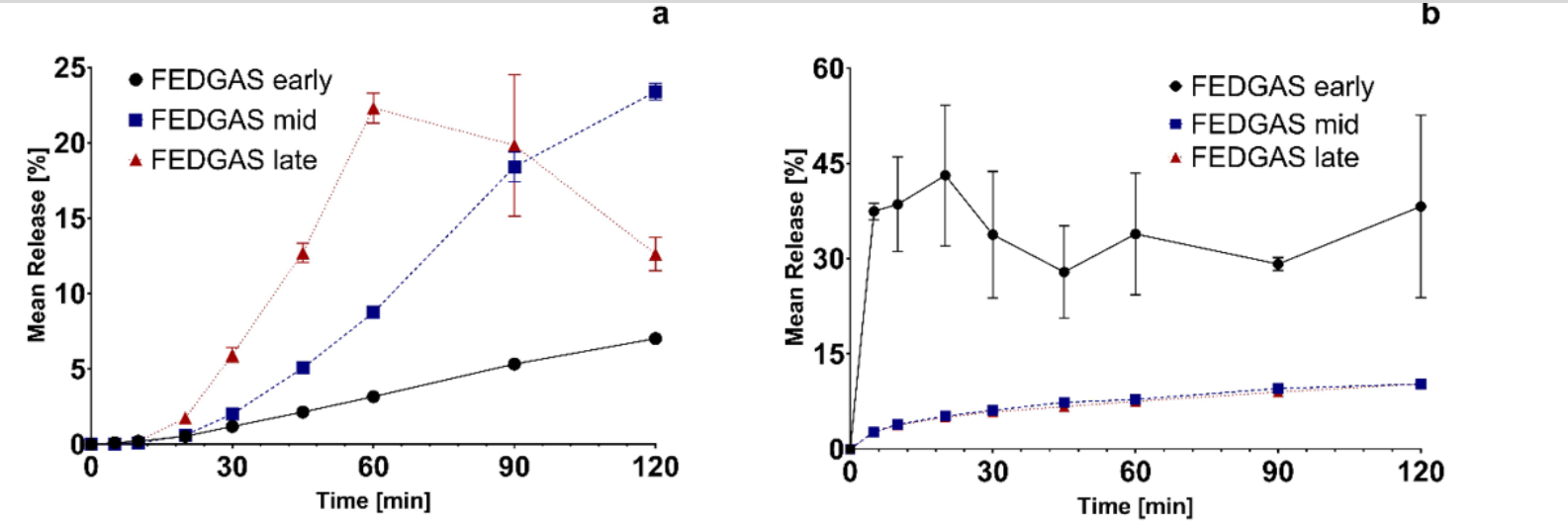
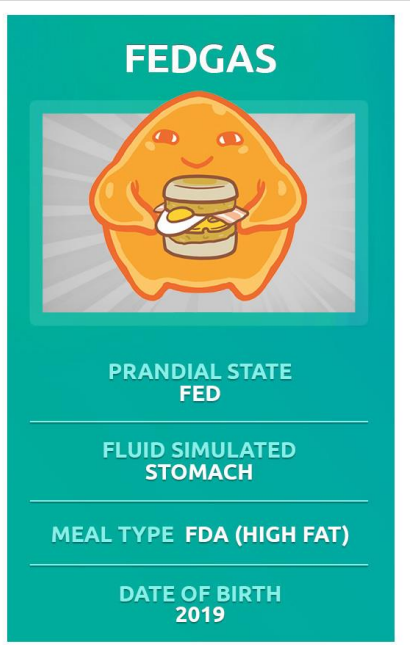


Figure 1: Mean release [%] of ITRA from (**a**) Sempera 100 mg pellets and (**b**) Tolsura 65 mg powder in FEDGAS with a paddle speed of 75 rpm.



Spotlight on food effects for amorphous solid dispersions (ASD)

Results II. FeSSIF-V2

The release from Tolsura powder was clearly higher than from Sempera (=Sporanox) pellets in FeSSIF-V2

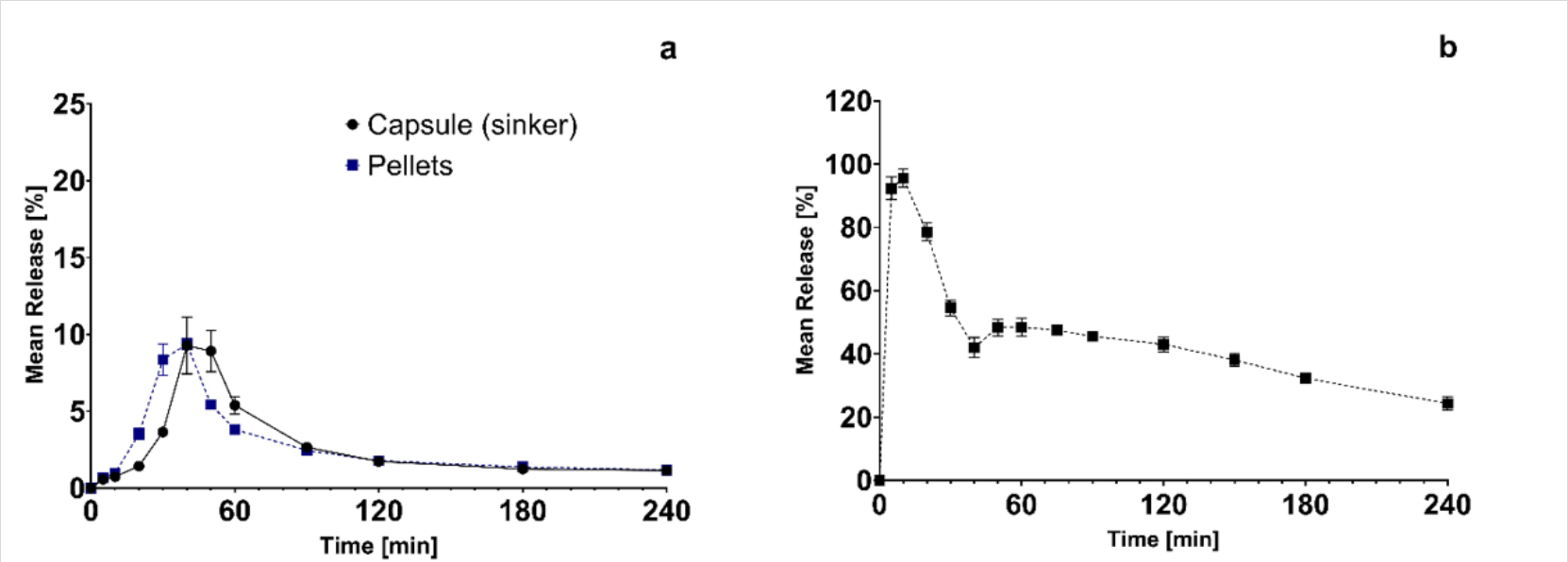
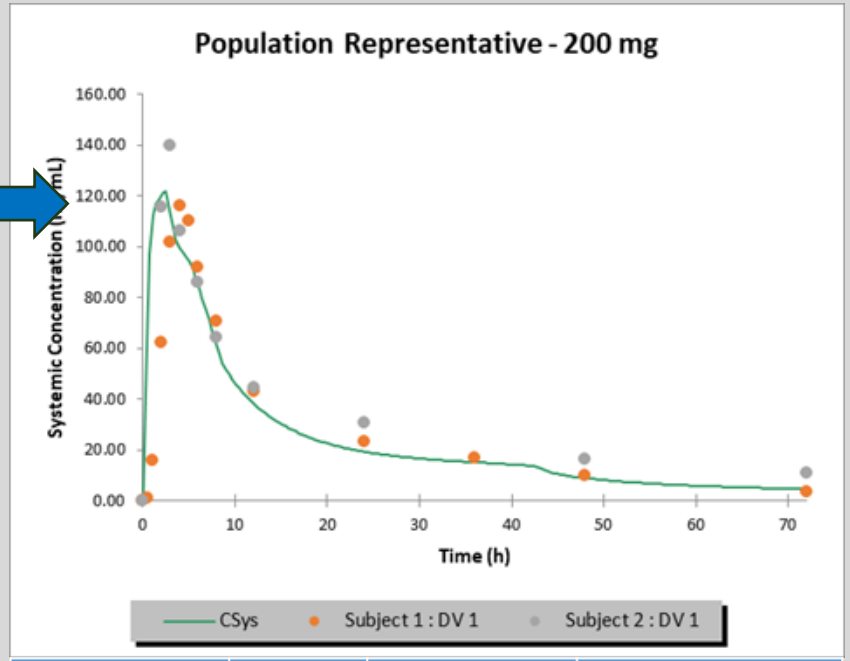


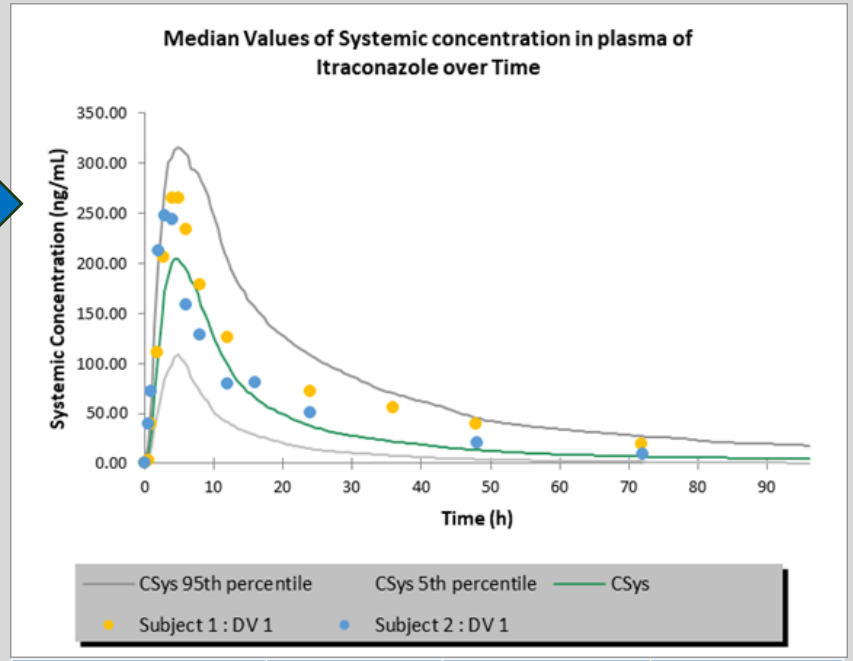
Figure 2: Mean release [%]of ITRA from (**a**) Sempera 100 mg capsules (sinker) (black dots) or pellets (blue squared) and from (**b**) Tolsura 65 mg powder in FeSSIF-V2 with a paddle speed of 75 rpm.

Spotlight on food effects for amorphous solid dispersions (ASD)

PBPK and clinical results – Sporanox fasted vs. fed => positive food effect



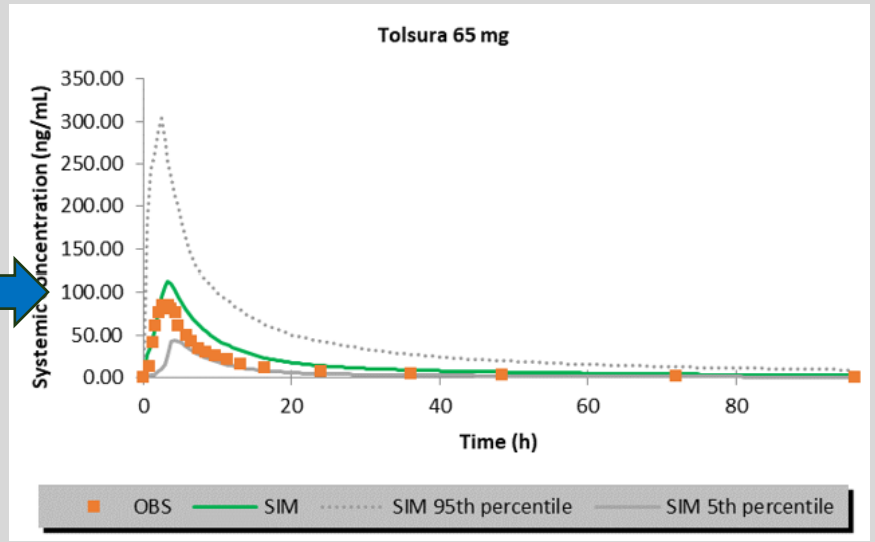
Parameter	SIM	OBS	Ratio
AUC	1966	1968 - 2094	0.94 – 1.00
C_{max}	122	120 - 125	0.98 – 1.02

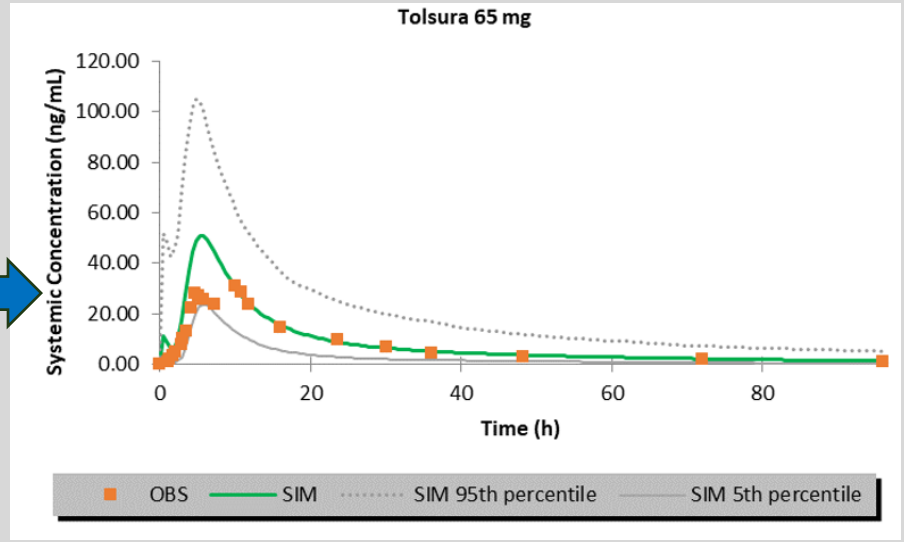


Parameter	SIM	OBS	Ratio
AUC	3962	3417 - 4160	0.95 – 1.16
C_{max}	223	239 - 272	0.82 – 0.93

Spotlight on food effects for amorphous solid dispersions (ASD)

PBPK and clinical results – Tolsura fasted vs. fed => negative food effect





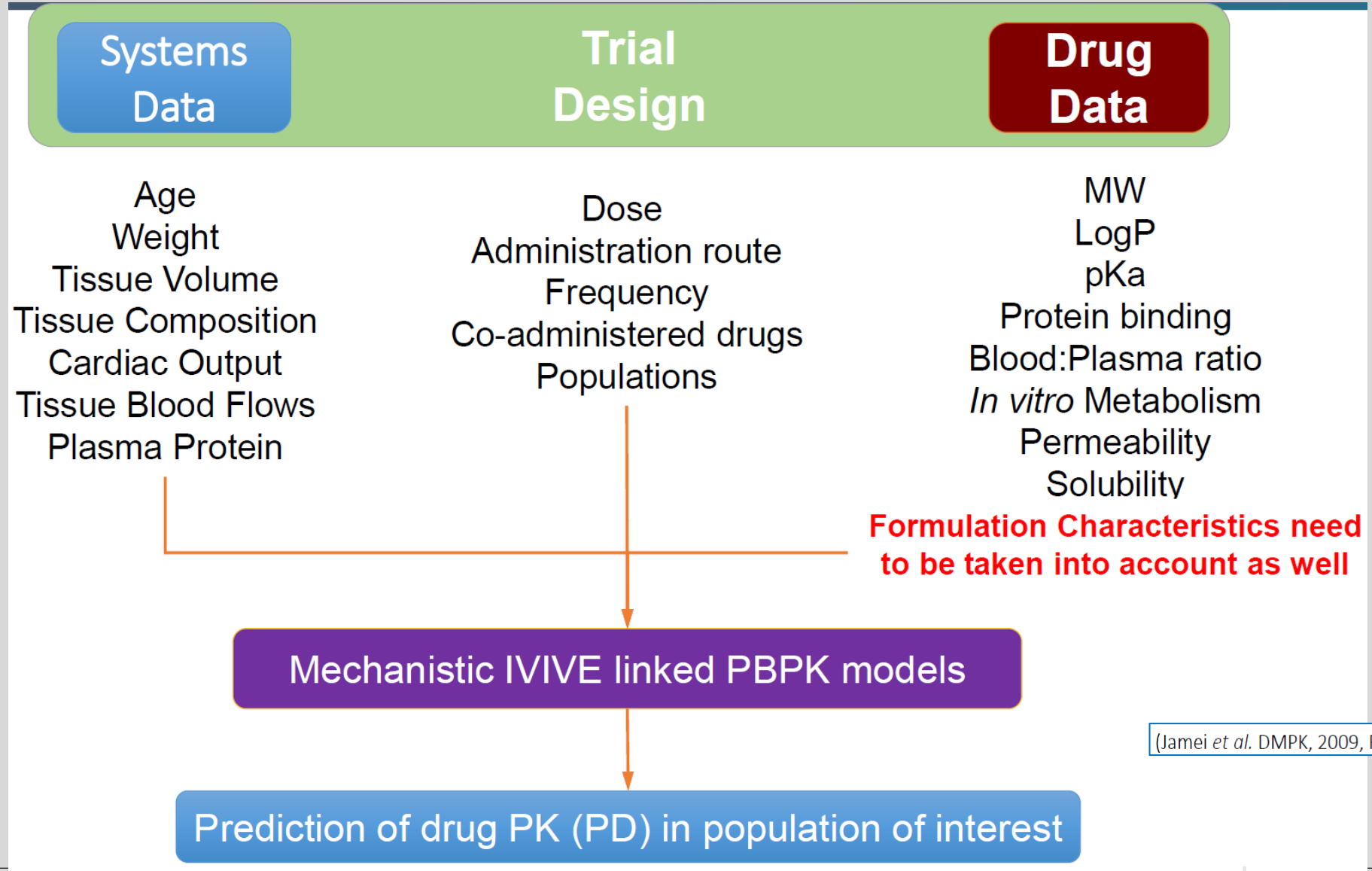
Whereas Sporanox has a *positive* food effect, Tolsura has a negative *food effect.*

***This could be explained by input to PBPK from dissolution in* biorelevant media, including FedGAS for the fed state gastric conditions – a classical application of PBBM!**

Current challenges in PBBM: what do we need to know to waive clinical studies?

- Physiologically Based
- Still some questions about physiology – e.g. GI motility; ontology; disease states; ethnic background
- CYP metabolism is quite well characterized; work on Phase 2 reactions making progress
- More work on transporters needed
- Biopharmaceutics
- identification of a biopredictive test for the particular API/formulation/route of administration/dosing condition – beware using the QC test results, as these are intended to show close to 100% release and this may or may not be the case *in vivo*.
- Creating better models to translate Papp into Peff values for modeling absorption. As there are some questions about Papp <=> Peff correlations, there is a drive to model Peff mechanistically.
- Modeling
- Efforts to mechanistically model formulation effects (particle size, cyclodextrins, PLGA etc.) continue
- Platform Qualification – requirements need to be harmonized across regulatory jurisdictions
- PBPK model validation for the API – case by case, requirements need to be harmonized

Advantages of PBBM



(Jamei *et al.* DMPK, 2009, Rostami-Hodjegan, CPT, 2012)

the future impact of PBBM

- **More biowaivers** – ability to base approvals on in vitro data plus a reliable PBPK model for the API (beyond BCS and SUPAC)
- Recognition of clinically relevant **„safe spaces“** for dissolution
- **VBE** – various routes – will be possible with more systems data and bespoke biopredictive test methods
- Extension to **Beyond Rules of Five** drugs – PROTACs and peptides
- PBBM has the potential to **eliminate / reduce animal experiments** run for PK reasons
- PBBM has the potential to **reduce the number of clinical studies and/or the number of subjects** enrolled in some kinds of studies – this will require better systems data for ontogeny, ethnic background and disease states.

Acknowledgments

Dom Segregur (now at UCB)

Rodrigo Cristofoletti

Amin Rostami-Hodjegan

….as well as AstraZeneca (ARA) and FDA (food effects) for sponsoring the work

Greetings from…..

…….and many thanks for your attention!