SimulationsPlus

Puppies Appreciate GastroPlus®

How Model-Informed Drug Development Can Reduce & Focus Clinical Trials Through Simulation

CRS 2024 Bologna

Simulations Plus Speakers

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Business Development
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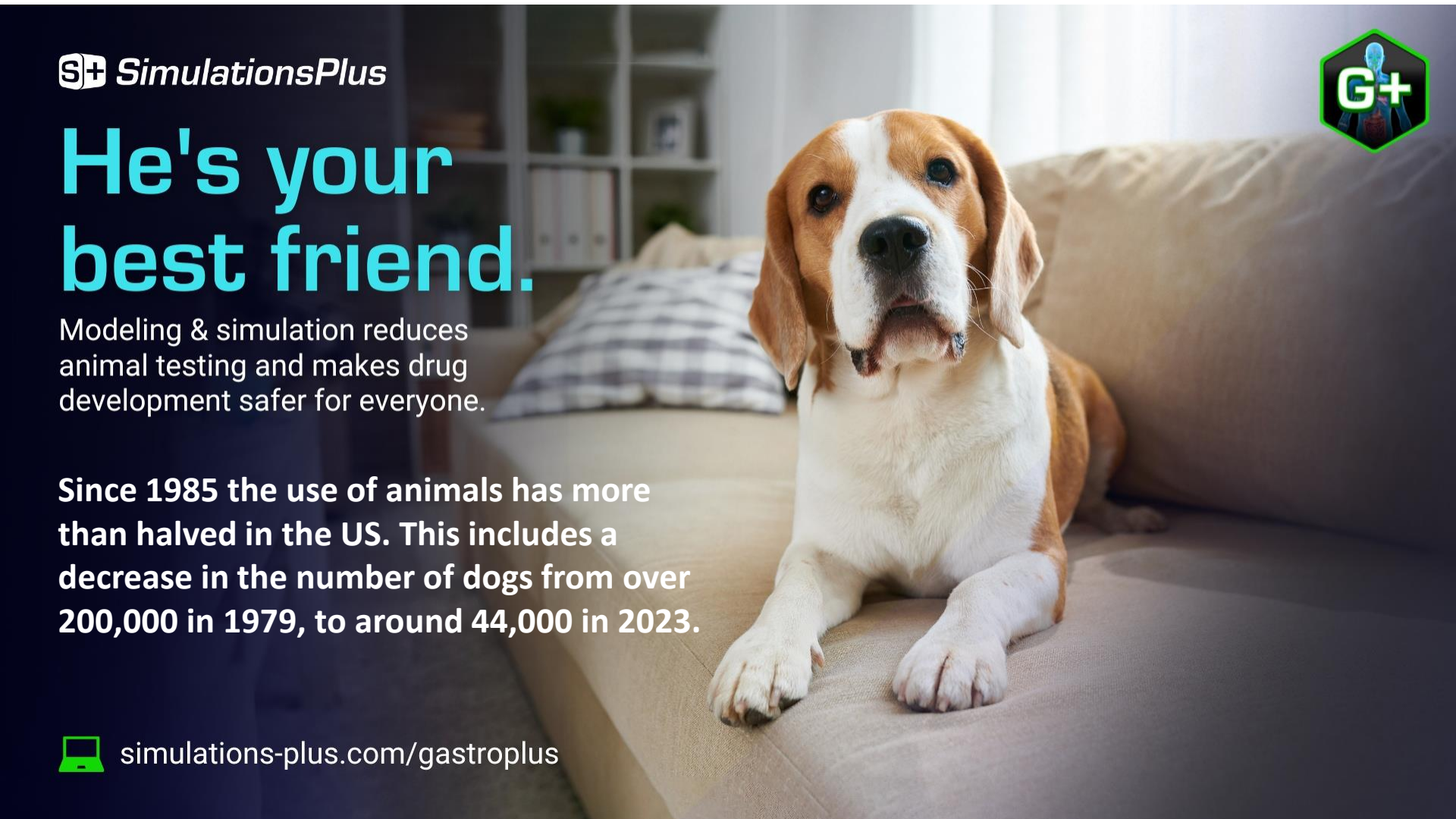
PBPK Research and
Development

SimulationsPlus

He's your best friend.

Modeling & simulation reduces animal testing and makes drug development safer for everyone.

Since 1985 the use of animals has more than halved in the US. This includes a decrease in the number of dogs from over 200,000 in 1979, to around 44,000 in 2023.



simulations-plus.com/gastroplus

Who We Are

NASDAQ: SLP

- **Cheminformatics**
  Software & Services
- **PBPK**
  Software & Services
- **Quantitative Systems Pharmacology (QSP)**
  Software & Services
- **Clinical Pharmacology & Pharmacometrics**
  Software & Services
- **Regulatory Strategies**
  Services

260
Employees Worldwide

>28 yrs.
Established In 1996

>300 Pharmaceutical, biotechnology, chemicals, cosmetics, and consumer goods companies in the U.S., Europe, Asia, and South America

SimulationsPlus

Modified release formulations in PBBM : The smart choice!

Outlook

- Some definitions & why develop PBBMs for MR formulations
- Case study 1: MR oral diltiazem formulation: Impact of physiology and determination of a biopredictive dissolution method
- Case study 2: Long acting injectable: Is a USP4 method biopredictive ?

Definitions

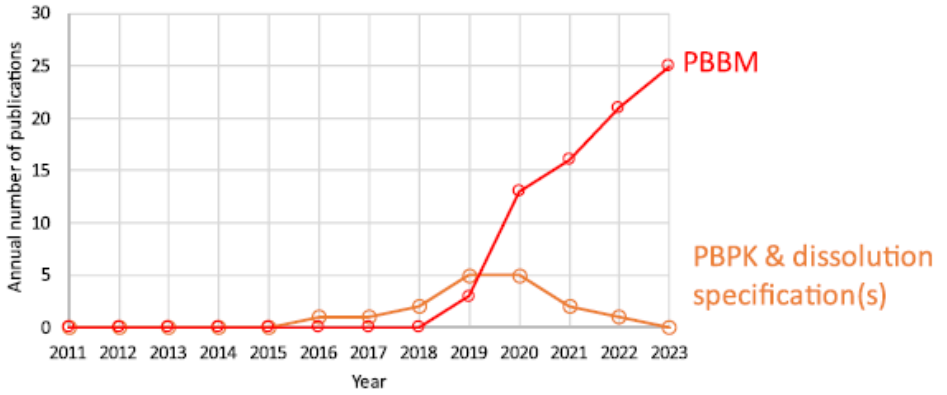
PBPK Model: Physiologically-Based Pharmacokinetic model

Describes the software tool. Agnostic to the use

PBBM: Physiologically-Based Biopharmaceutics Model

Fit for purpose application: Focusses on the use of the model to support biopharmaceutics/drug product quality applications

Term invented in 2019



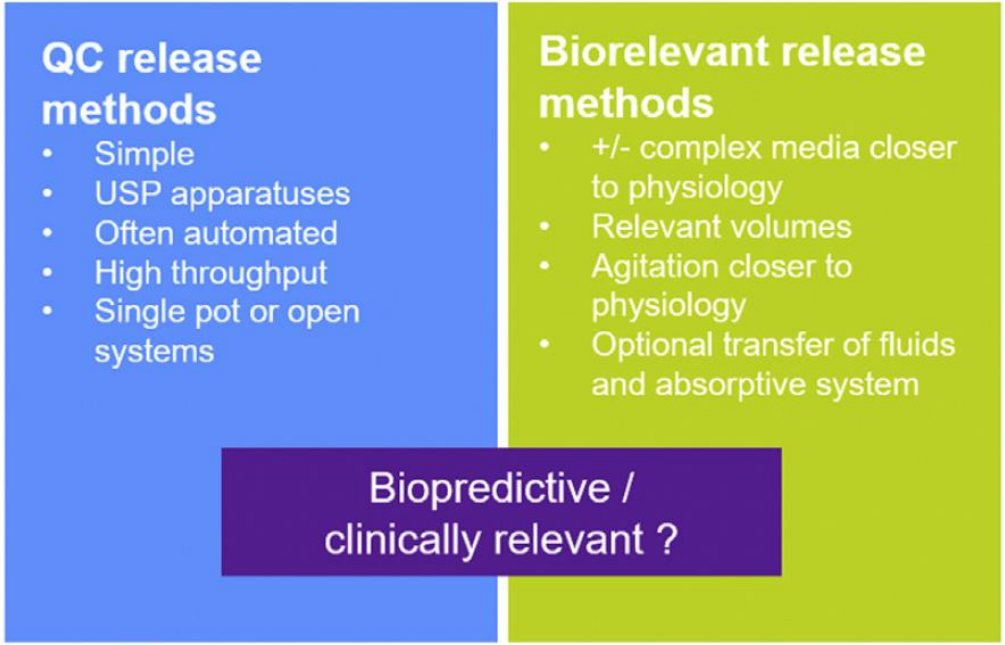
https://doi.org/10.1021/acs.molpharmaceut.4c00202

Benefits of PBBM

Mechanistic understanding → increase product value	Limitations to drug absorption (solubility, permeability, dissolution rate…) → guide formulators for 1st time right or LCM, Acceptable content of excipients,
Clinically relevant design spaces	Edge of failure for Critical Material Attributes and Critical Process Parameters
Justify drug product specifications	Enables the establishment of CRDPS
Support PACs	At submission, only a limited # of batches are manufactured. Product and process performance my deviate from initially filed specifications
Regulatory flexibility	Change in specifications: Flexibility granted within the safe space
Biowaivers	Reduction of unnecessary human testing. Best use of clinical resources combined with modelling and simulation

PBBM reduces the need for clinical trials and allows to optimize the clinical resources/timing, increase mechanistic understanding and allows informed decision making

Dissolution methods



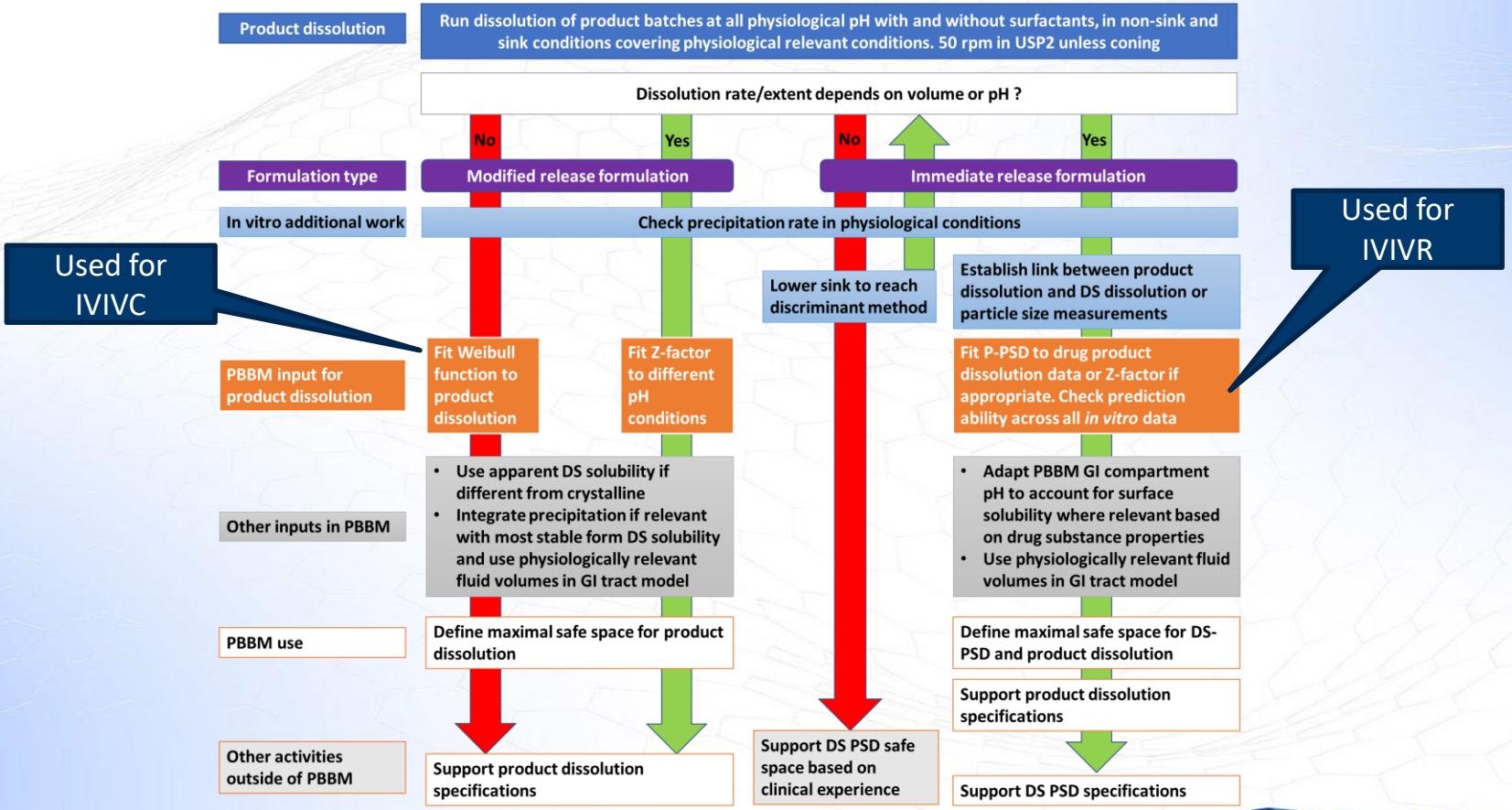
Biopredictive dissolution method A set of testing conditions for which in vitro dissolution profiles are capable of predicting pharmacokinetic profiles. These are typically based on classical or mechanistic IVIVC or PBBM.

Clinically relevant dissolution specifications A set of in vitro dissolution testing conditions and acceptance criterion(ia) that can identify and reject drug product batches that are not expected to be bioequivalent to clinical pivotal product batches.

Going further : Heimbach, T., et al., *Dissolution and Translational Modeling Strategies Toward Establishing an In Vitro-In Vivo Link—a Workshop Summary Report. The AAPS Journal, 2019.* ***21(2).***

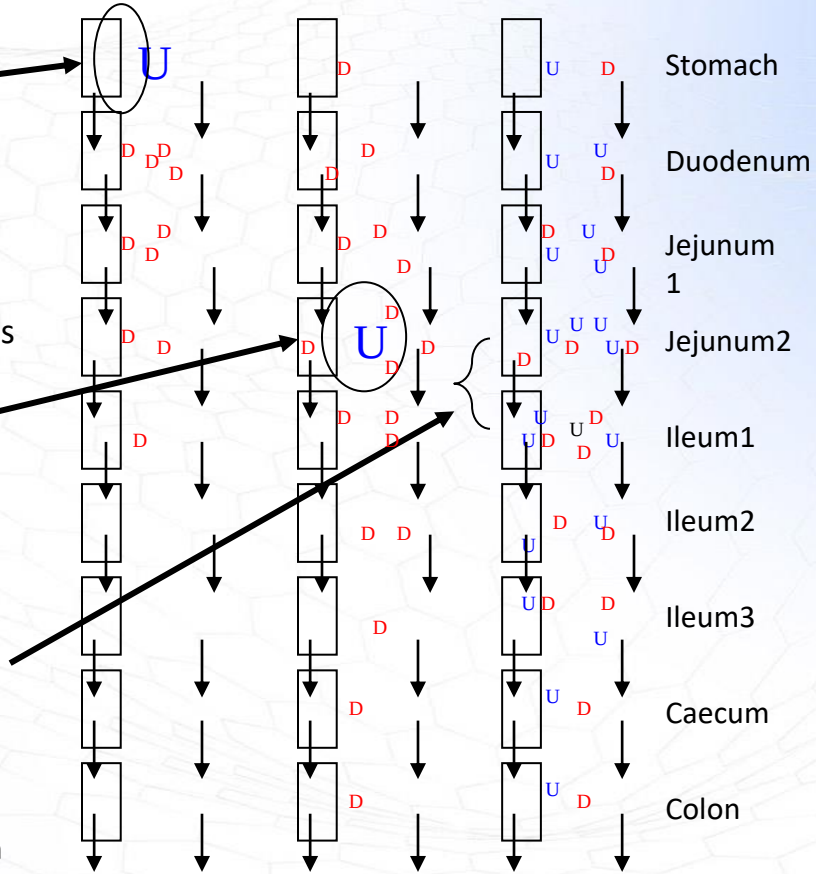
https://doi.org/10.1208/s12248-019-0298-x

Strategy for integration of dissolution in PBBM



3 Models Based on Where Drug is Released

- Gastric release:
  - Unreleased drug remains in stomach
- Integral tablet:
  - Unreleased drug remains in tablet – moves from one compartment to the next
    (e.g., erosion tablet, pulsed, multi-layer systems)
- Dispersed:
  - Unreleased drug disperses among compartments
    (e.g., beads)



U = unreleased **D = drug in solution**

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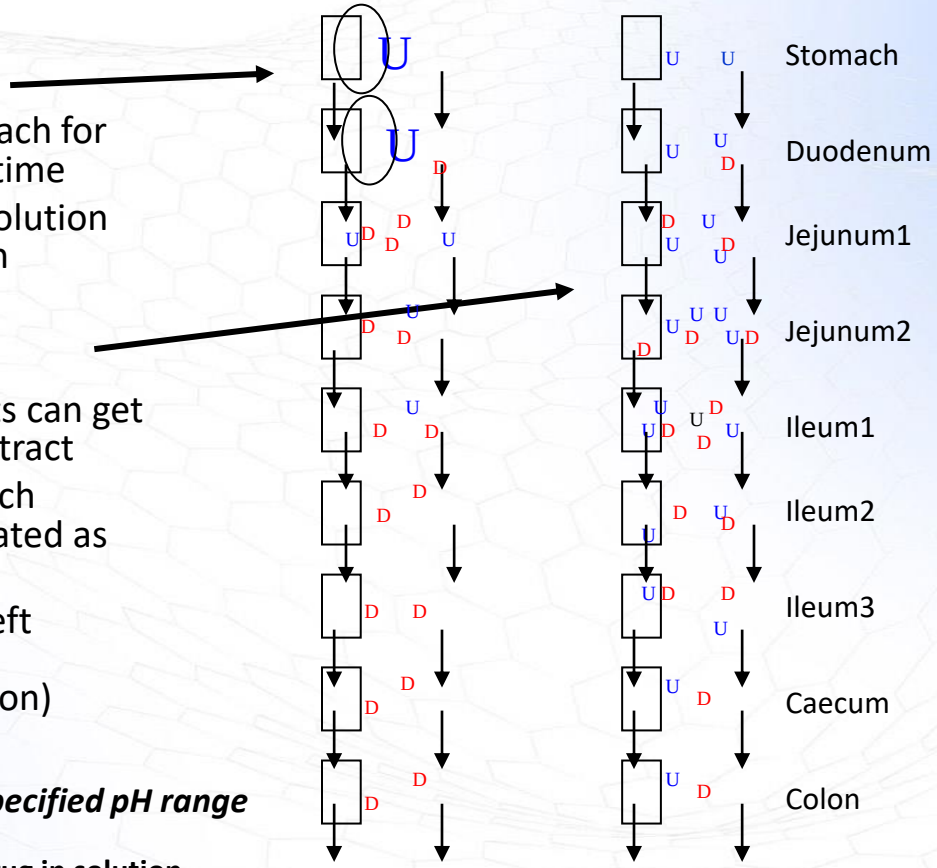
Delayed Release Technologies

- Enteric Coated Tablet
  - the whole tablet stays in stomach for the period of stomach transit time
  - after leaving stomach the dissolution continues as for IR formulation
- Enteric Coated Capsule
  - the small enteric coated pellets can get distributed throughout the GI tract
  - the pellets start leaving stomach immediately at the rate calculated as “1/transit time”
  - Only the pellets that already left stomach will start dissolving (dissolution as for IR formulation)



Enteric coating – <u>not</u> user specified pH range

U = unreleased **D = drug in solution**

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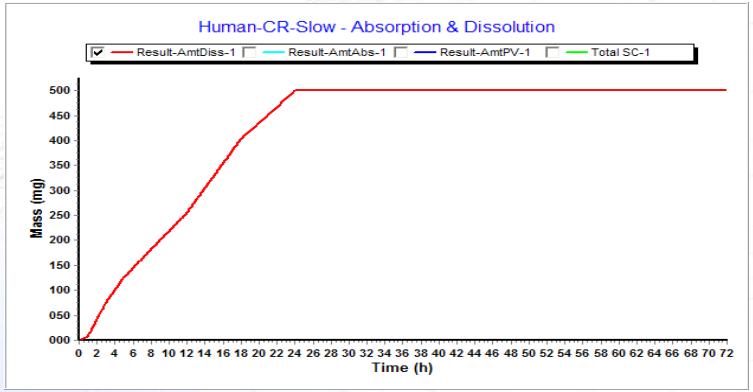
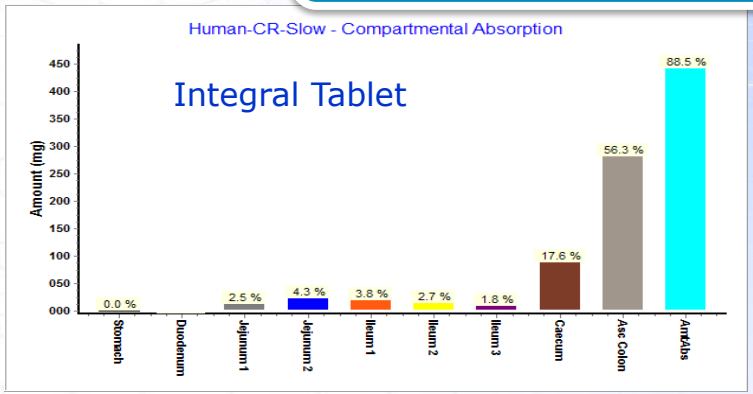
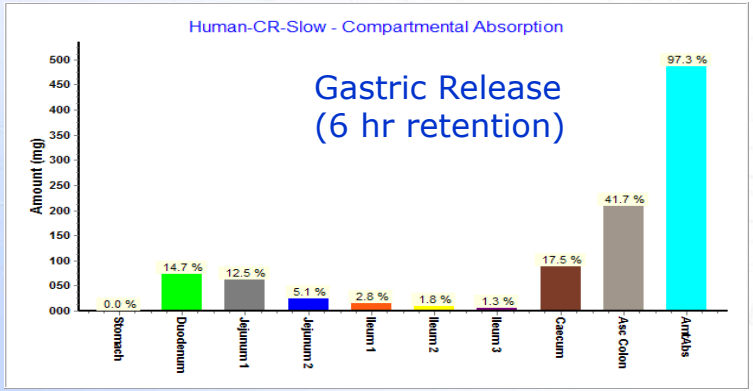
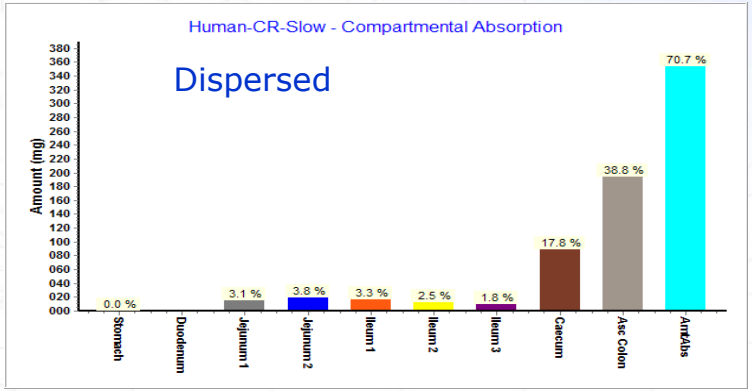
Differences in simulations with various CR models

If drug is subject to first pass degradation, the Cmax and AUC will depend on absorption site









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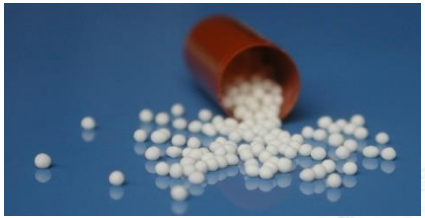
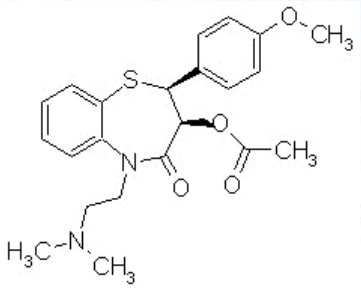


Case study #1

Diltiazem MR

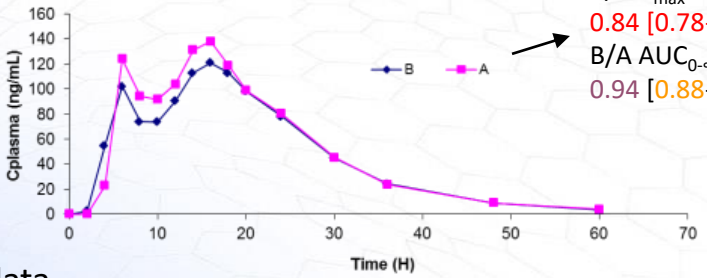
Transfer from plant A to plant B of a modified release product, BEQ failed despite comparable dissolution using QC method. Can PBBM be used to understand root causes and make recommendations for future BE study ?



Transfer from plant A to plant B

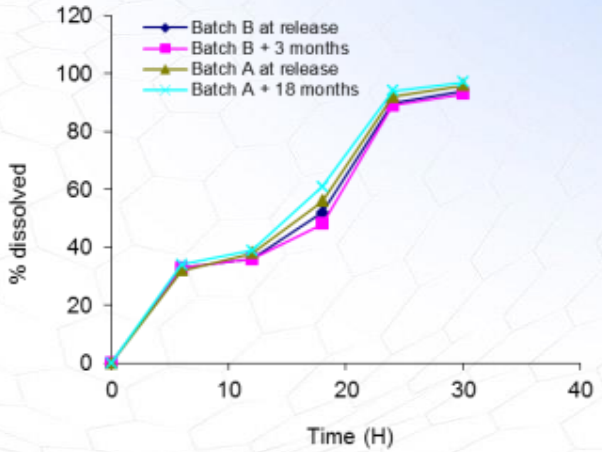
- Extended release formulation of diltiazem comprising a mixture of IR and ER pellets
- ER technology : coating with Eudragit RS/RL polymer

- BE study failed on Cmax



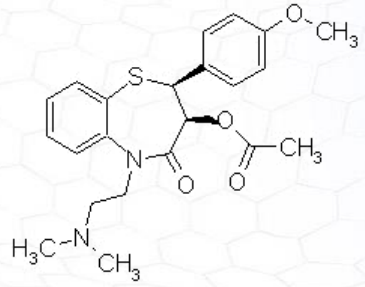
B/A C_{max}
0.84 [0.78-0.90]
B/A $AUC_{0-\infty}$
0.94 [0.88-0.99]

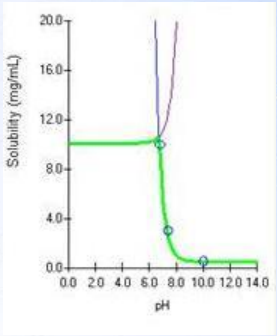
- In vitro pH 1 data
- Slight difference between batches but within specs
- Questions
- Why did the BE study fail ?
- How can we avoid similar failures in the future ?



Biopharmaceutical properties

- Phys-chem properties
  - Log P = 2.89
  - pKa 8.02 (Base)
  - Permeability
    - Scaled from Caco2 data





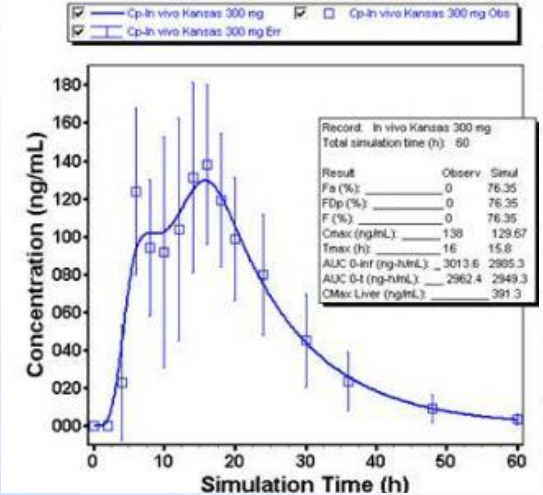
Compartment	pH fasted	Papp fasted	Peff fasted
Stomach	1.3		
Duodenum	6	119.2	3.35
Jejunum 1	6.2	149	3.86
Jejunum 2	6.4	178.8	4.35
Ileum 1	6.6	208.6	4.81
Ileum 2	6.9	253.3	5.46
Ileum 3	7.4	327.8	6.47
Caecum	6.4	178.8	4.35
Asc Colon	6.8	238.4	5.25

Good solubility and permeability down to the lower sections of the GI tract

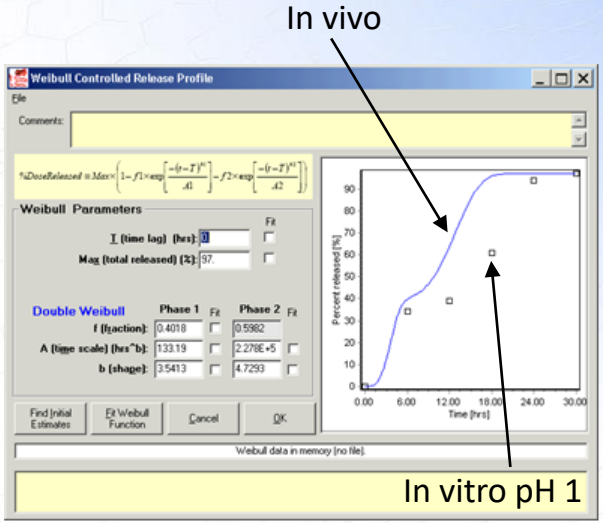
European Journal of Pharmaceutical Sciences 24 (2005) 333–349
European Journal of Pharmaceutical Sciences, 14, 281 –291 (2001)
Pharmaceutical Research, 14(9), 1210-1215, (1997)

Methodology : top-down analysis of PK to extract in vivo dissolution

- Use of 2-phase Weibull equation in GastroPlus®

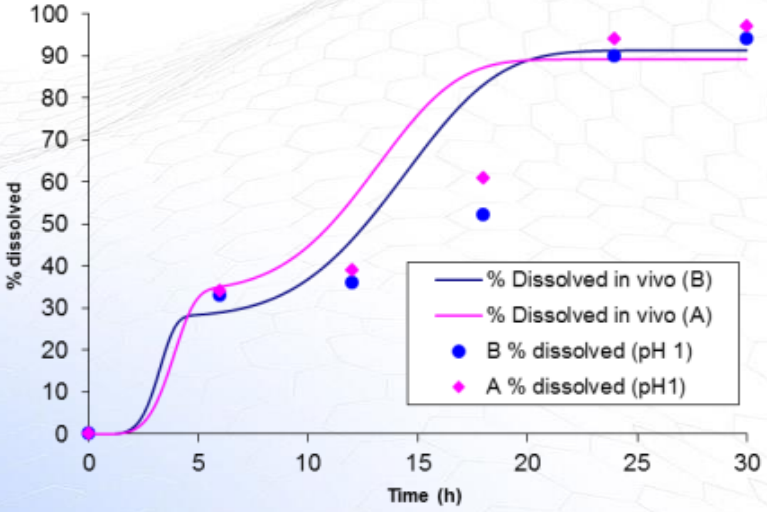


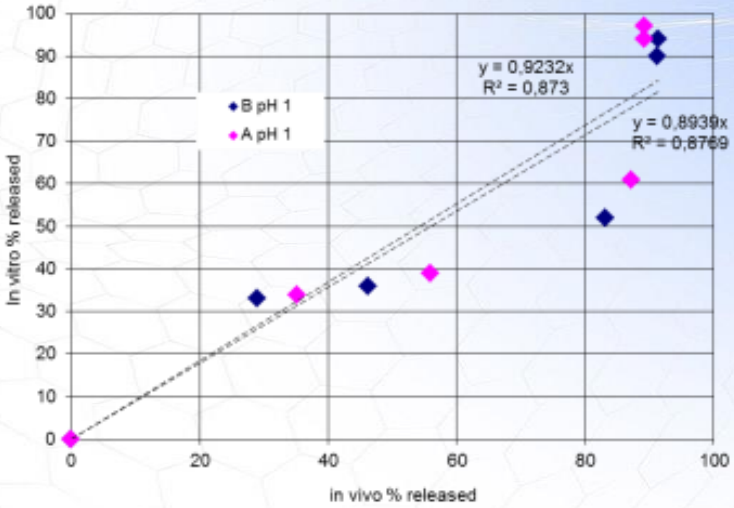
deconvolution



Significantly quicker in vivo dissolution compared to that measured at pH1

IVIVC with pH 1 dissolution data





No IVIVC: In vivo dissolution is ~6h quicker than in vitro dissolution

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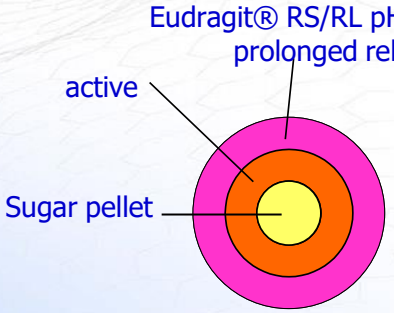
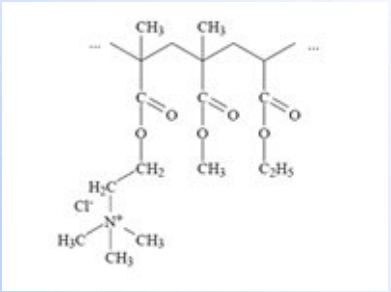
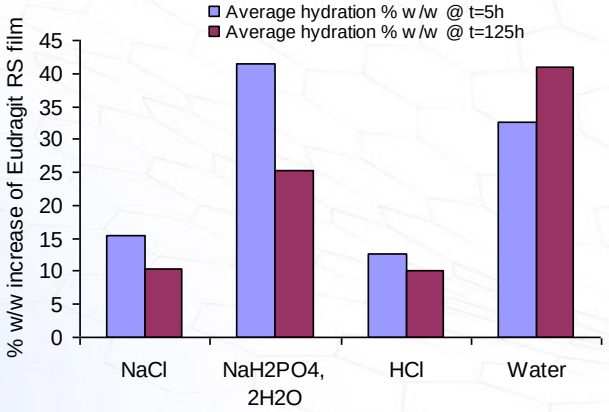
Root cause identification for lack of IVIVC with pH 1 data

Reasons for failure

Eudragit RS/RL contains chloride anions.







Reduced hydration of Eudragit RS/RL with Cl-

HCL 0.1N not adapted to the product !

Recommendation to use pH6.8 without NaCl

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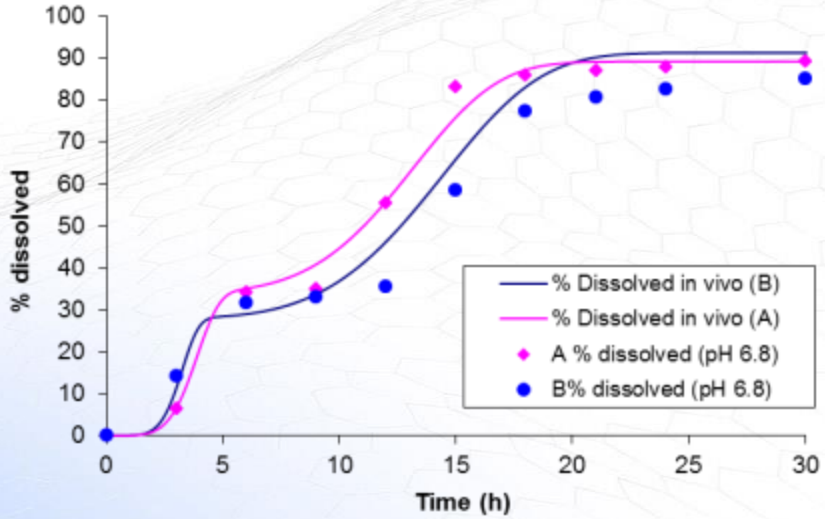
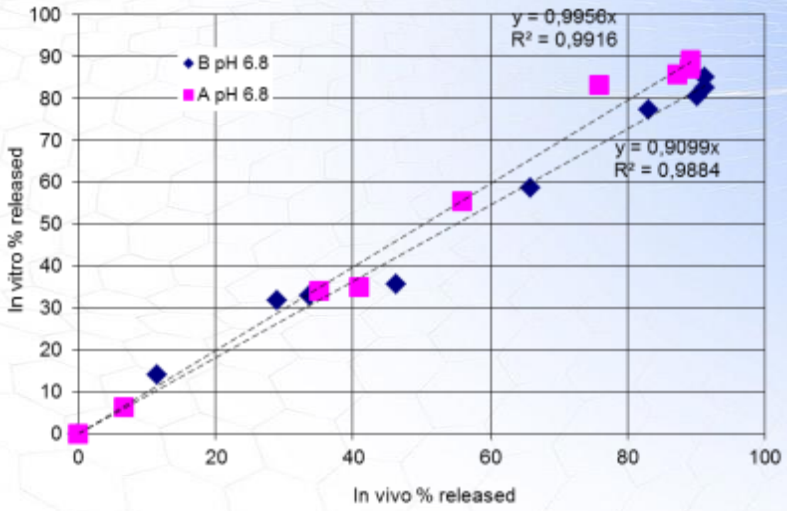
IVIVC with pH 6.8 dissolution data

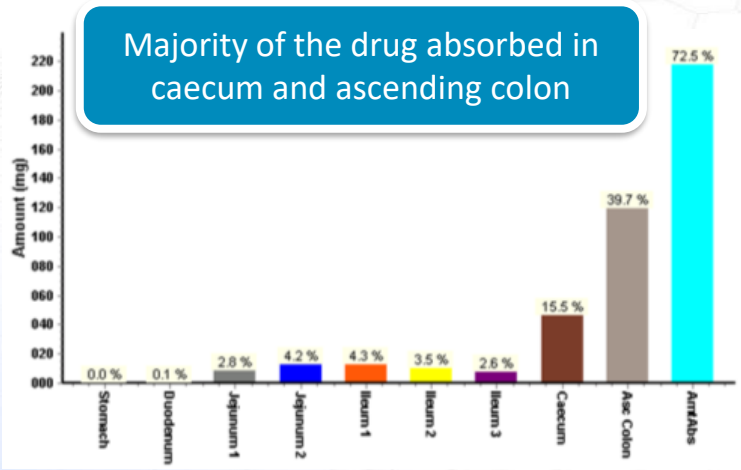


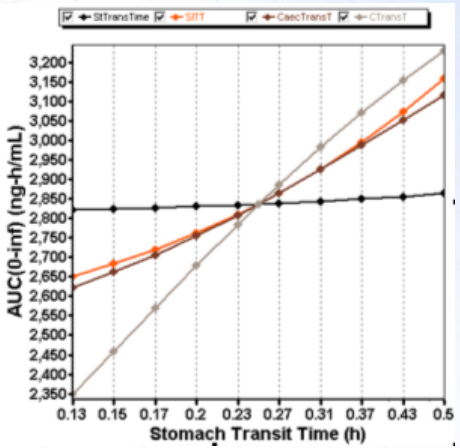


Good IVIVC: New dissolution method at pH 6.8 is biopredictive

Diltiazem extended release
Impact of gender on BE study

Majority of the drug absorbed in caecum and ascending colon





4H more transit time per large intestinal segments for females vs males [a]

- Males CTT estimated at 12h
- Females CTT from 16h to 20h

	Female/male Cmax ratio	Female/male AUC ratio
Anticipated with female CTT = 16h	1,08	1,06
Anticipated with female CTT = 20h	1,13	1,10
Measured	1,12	1,14

Longer transit times in lower intestine could explain female larger exposure

a: http://www.icrp.org/publication.asp?id=ICRP%20Publication%20110

CTT = Colon Transit Time

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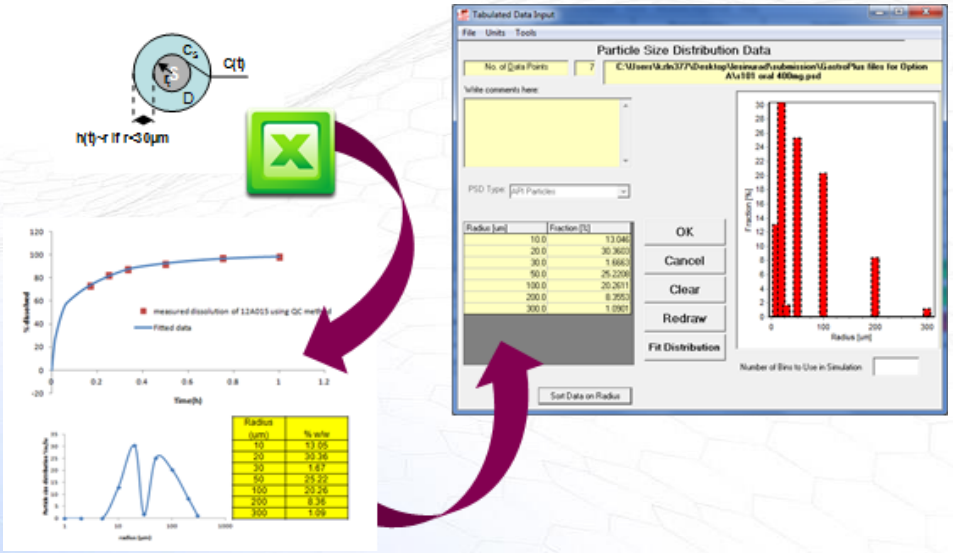
Case study #2

Drug X

Long acting injectable : Dissolution in burst followed by prolonged release. Can the in vivo prolonged release be informed from USP4 dissolution?

P-PSD (Classic) [A]



$$\frac{dm_{solid}}{dt} = -A(t) \times \left(f_u \times \frac{D_u}{h_u(t)} + \frac{1 - f_u}{f_u} \times \frac{D_b}{h_b(t)} \right) \times \left(C_{S,u} - C_u(t) \right)$$

$$f_u = \frac{C_u(t)}{C(t)} \qquad \frac{h_b}{h_u} = \sqrt[3]{\frac{D_b}{D_u}}$$

1- Use of one dissolution data to extract the P-PSD

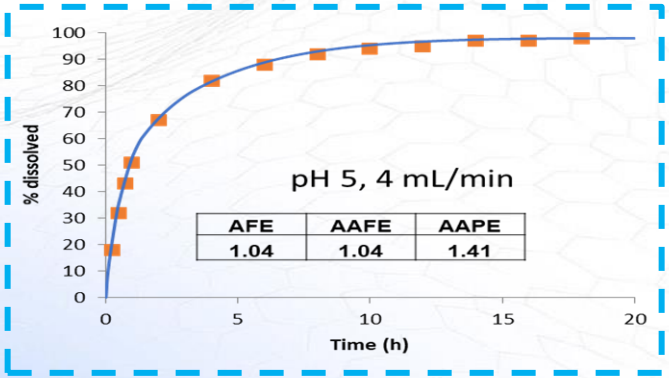
2- Verification that P-PSD is predictive of other dissolution conditions for same batch

3- Use of P-PSD as input in PBPK model

A: Pepin, X.J.H., et al., Bridging in vitro dissolution and in vivo exposure for acalabrutinib. Part I. Mechanistic modelling of drug product dissolution to derive a P-PSD for PBPK model input. European Journal of Pharmaceutics and Biopharmaceutics, 2019. 142: p. 421-434.

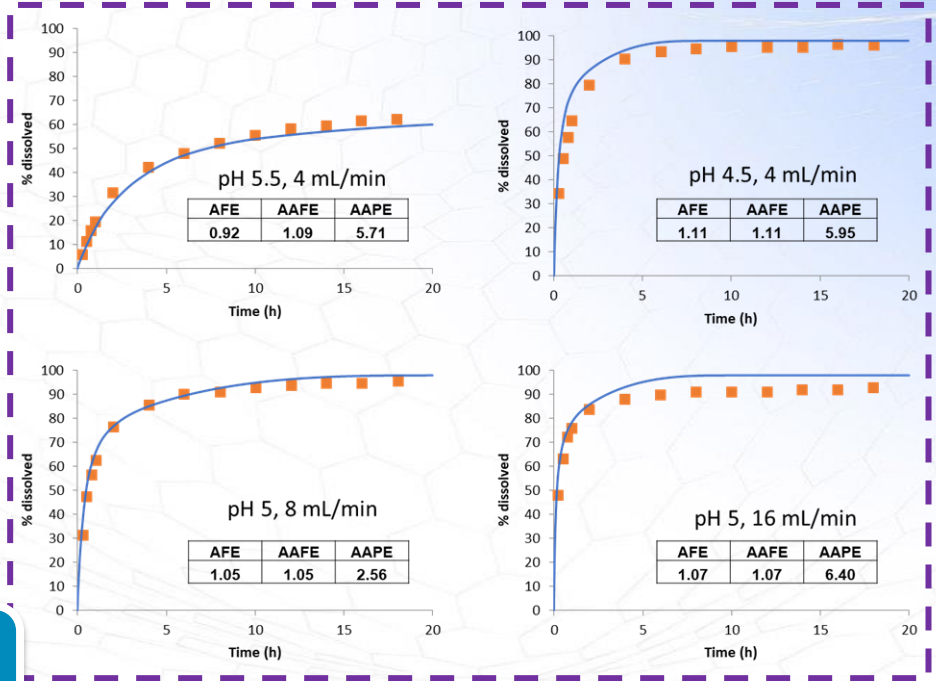
USP4 dissolution modeled with Product-Particle Size Distribution

Profile fitted to extract P-PSD



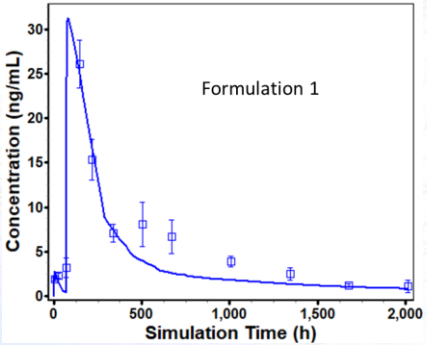
20h release profile fitted with P-PSD

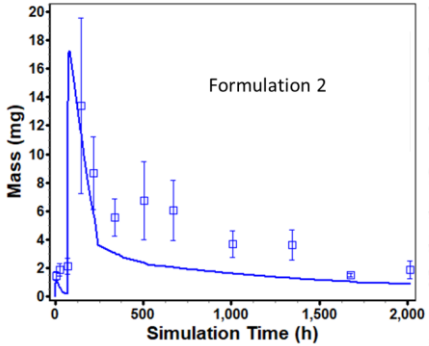
P-PSD used to verify other in vitro dissolution conditions

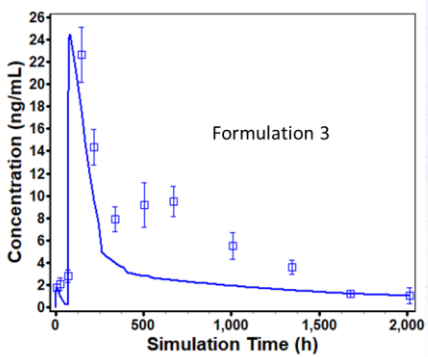


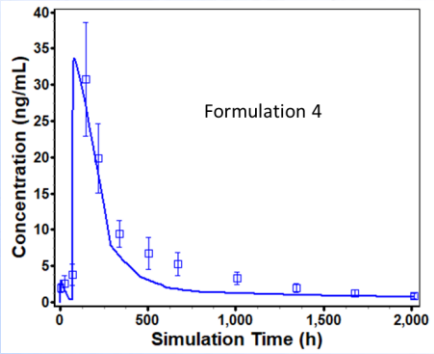
Good prediction performance of same batch in other dissolution conditions

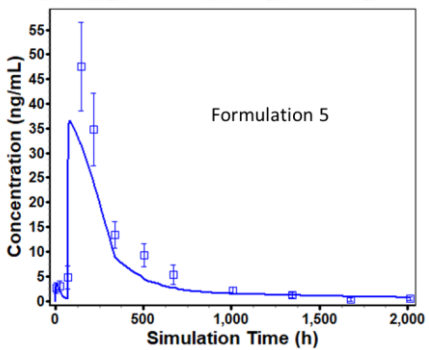
Application to preclinical data











P-PSD obtained on 5 different formulations enabled PK profile prediction for the main release phase

Conclusions

- PBBM offers a physiologically relevant modeling framework
- PBBM is adapted to modified formulations
- PBBM is applicable to all routes of administration
- The link between in vitro release and in vivo exposure can be mechanistically interogated

Grazie!

SimulationsPlus

Glossary

ADMET Predictor®: Flagship machine learning platform for absorption, distribution, metabolism, excretion and toxicity (ADMET) modeling

AI-Driven Drug Design (AIDD): ADMET Predictor module

DDDPlus™: For *in vitro* dissolution experiment of pharmaceutical dosage forms

DILIsym®: Quantitative systems toxicology (QST) software capable of predicting and explaining drug-induced liver injury (DILI)

GastroPlus® X: Physiologically based pharmacokinetic (PBPK) software that simulates absorption, biopharmaceutics, pharmacokinetics, and pharmacodynamics in humans and animals

High-Throughput Pharmacokinetic Simulations (HTPK): ADMET Predictor module

ILDsym®: Quantitative systems pharmacology (QSP) modeling software for interstitial lung disease (ILD)

IPFsym®: QSP modeling software for ideopathic pulmonary fibrosis (IPF)

Glossary

MedChem Designer™: Chemical structure drawing and property prediction

MembranePlus™: Mechanistic *in vitro* permeability and hepatocyte modeling

Monolix™: Non-linear mixed effect model parameter estimation

NAFLDsym®: QSP software for modeling nonalcoholic fatty liver disease

PKanalix™: Compartmental analysis (CA), non-compartmental analysis (NCA) and bioequivalence studies (BE)

RENAsym: QST software for predicting and understanding drug-induced kidney injury

Simulx™: Clinical trial simulations

Thales™: A model building platform that automates and streamlines the QSP modeling process