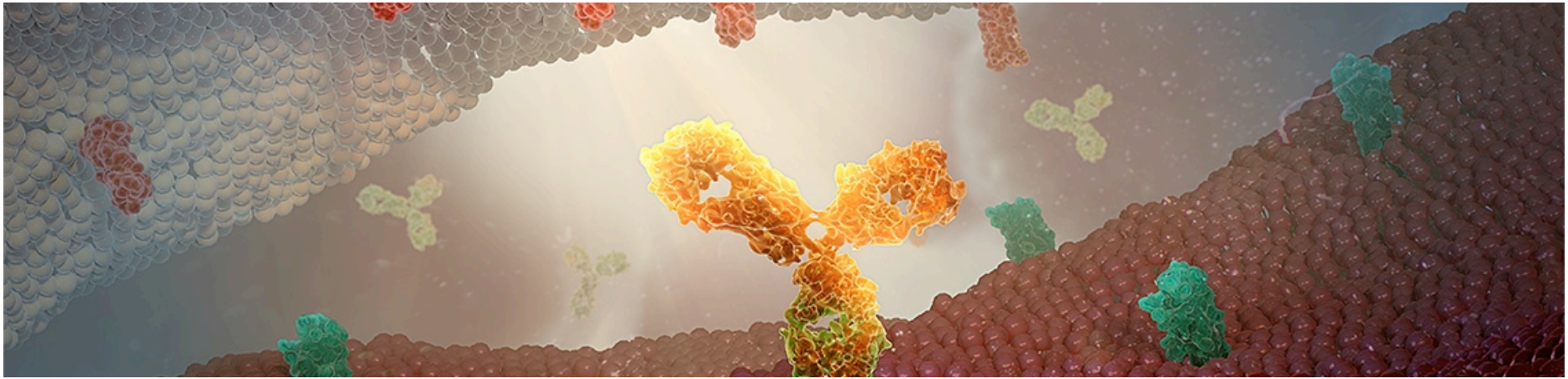
The use of PBBM and biomarkers to provide detailed mechanistic understanding of in vivo dissolution and absorption. An industrial example

Xavier Pepin

FDA workshop: Translational modelling strategies to support DP development

25 September 2019

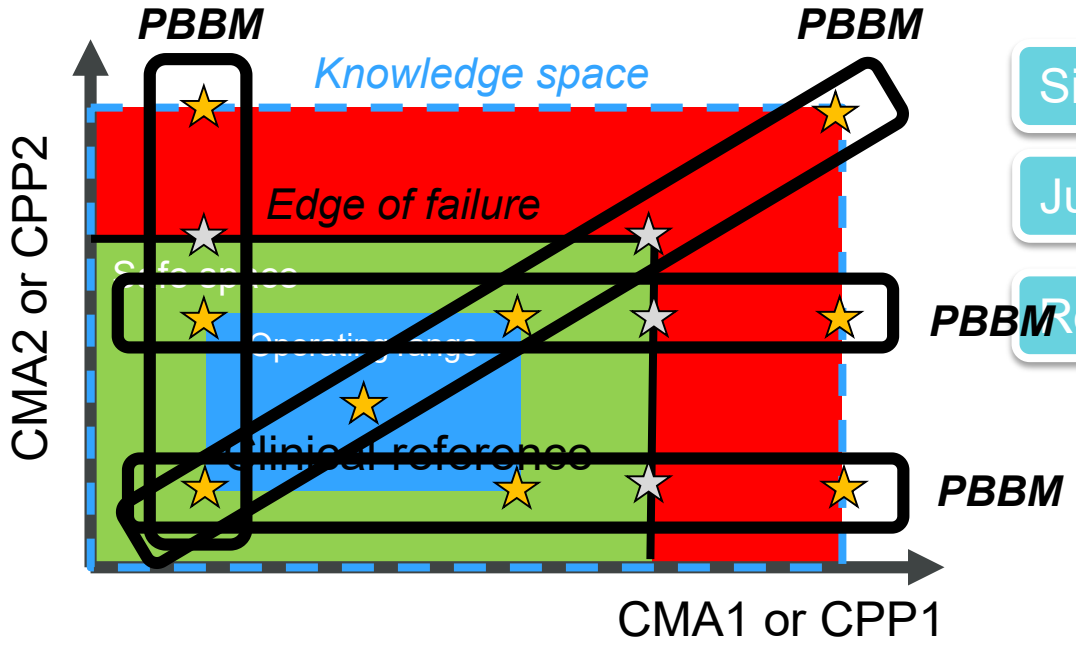


Outlook

- Uses of PBBM models to support quality of pharmaceutical products
- A case study from AZ illustrating the integration of dissolution in PBPK
- A vision for the future of PBBM modelling

What to evaluate with PBBM ?

- Batches bioequivalence : biowaivers
- Acceptable product specifications, acceptable content of excipients
- Edge of failure for Critical Material Attributes and Critical Process Parameters



Size of the safe space

Justified specifications

Regulatory flexibility

Calquence ® (Acalabrutinib)

Integration of dissolution in PBPK to support formulation evaluation and impact of physiological parameters – Setting the drug substance PSD “safe space”

Pepin, X. J. H., et al. (2019). "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 142: 421-434.

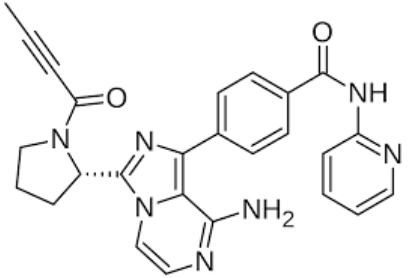
Pepin, X. J. H., et al. (2019). "Bridging in vitro dissolution and in vivo exposure for acalabrutinib. Part II. A mechanistic PBPK model for IR formulation comparison, proton pump inhibitor drug interactions, and administration with acidic juices." European Journal of Pharmaceutics and Biopharmaceutics 142: 435-448.

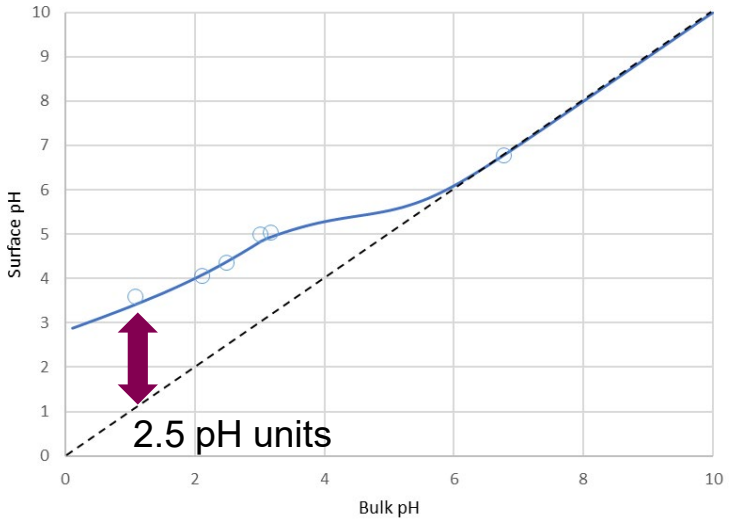
Calquence® (acalabrutinib): Selective, irreversible BTK inhibitor

- Approved in the US in Oct 2018 for the treatment of adults with mantle cell lymphoma (MCL) who have received at least one prior treatment for their cancer.

CALQUENCE®
(acalabrutinib) 100 mg capsules

Biopharmaceutical properties of acalabrutinib

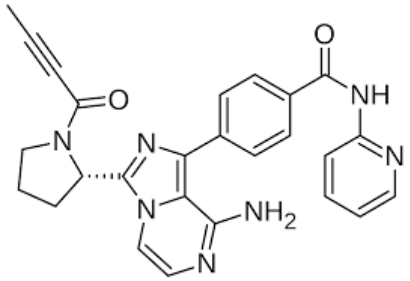


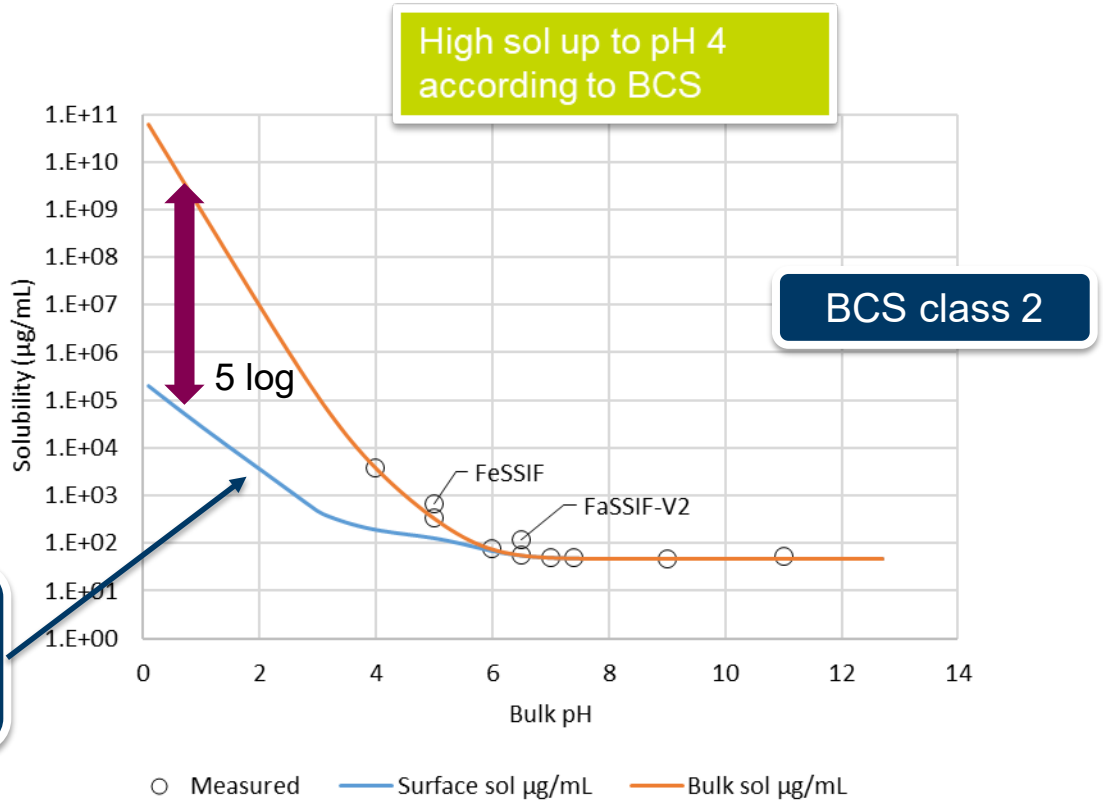


- Biopharm properties
  - pKas in the physiological range: 3.5(B), 5.8 (B)
  - Log P: 2
  - Intrinsic solubility = 50 ug/mL @ pH 9
  - Estimated human Peff = ~ 5-6 10^{-4} cm/sec
  - Limited impact of bile salts on solubility
  - No precipitation observed in vitro and in vivo at 100 mg dose upon transition from stomach to intestine
  - Main enzyme responsible for metabolism : CYP3A4
  - Negligible renal excretion
  - Acid base reaction at the surface : surface pH > bulk pH during dissolution below pKas

$$B + H^+ \leftrightarrow BH^+ + H^+ \leftrightarrow BH_2^{2+}$$

Biopharmaceutical properties of acalabrutinib

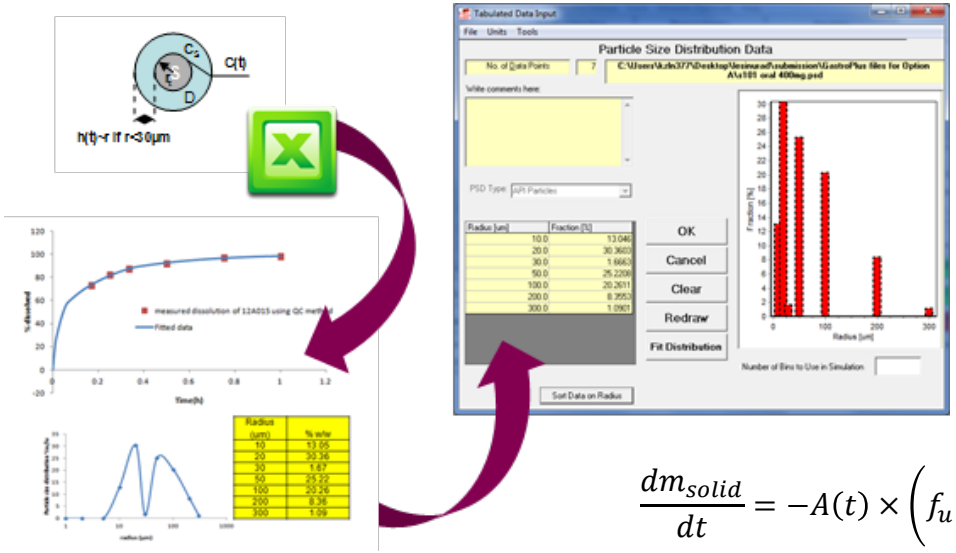




Surface solubility drives dissolution rate

Dissolution integration

- Fit of Product Particle Size Distribution (P-PSD)



1- Use of dissolution data
@ pH 6.8 (surface sol = bulk sol)
to extract the P-PSD

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

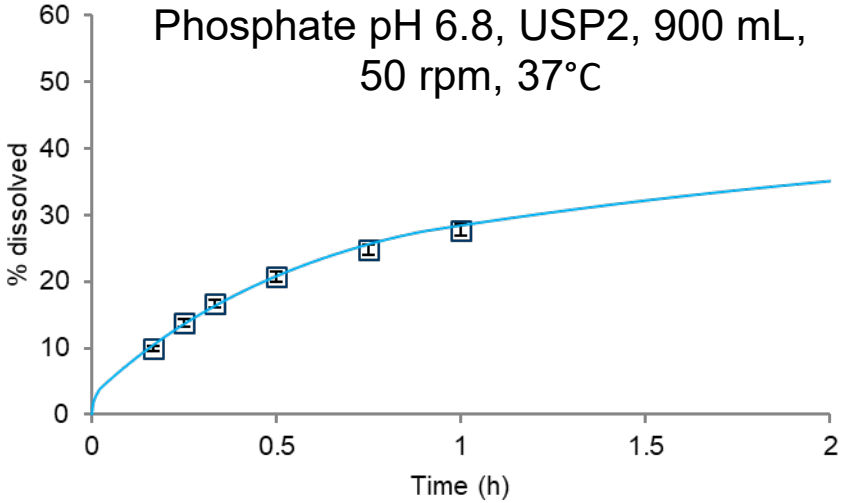
3- Use of P-PSD as input in PBPK model

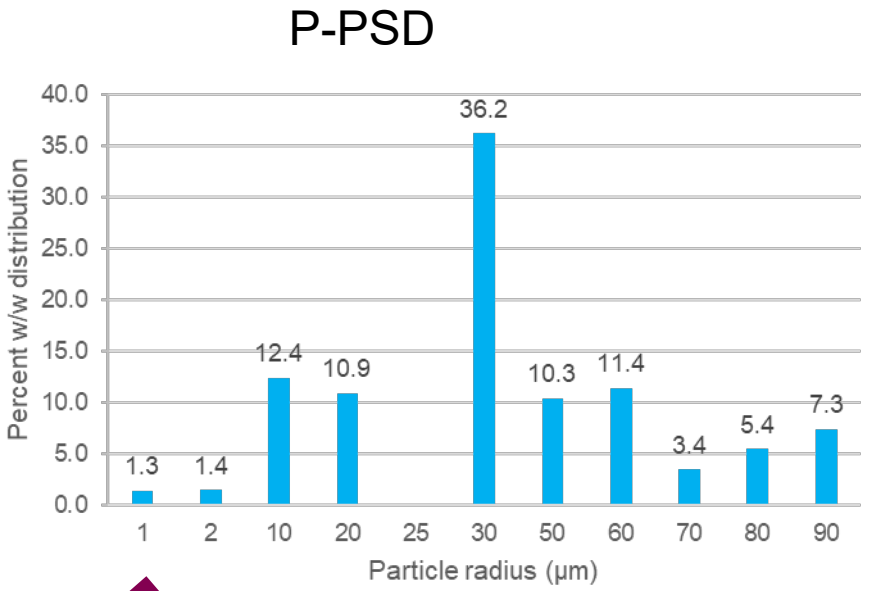
$$\frac{dm_{solid}}{dt} = -A(t) \times \left(f_u \times \frac{D_u}{h_u(t)} + \frac{1-f_u}{f_u} \times \frac{D_b}{h_b(t)} \right) \times \left(C_{S,u} - C_u(t) \right)$$

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

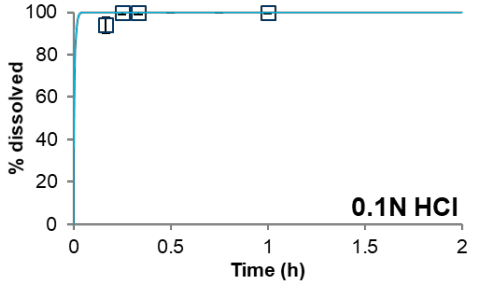
1- Fitting the P-PSD

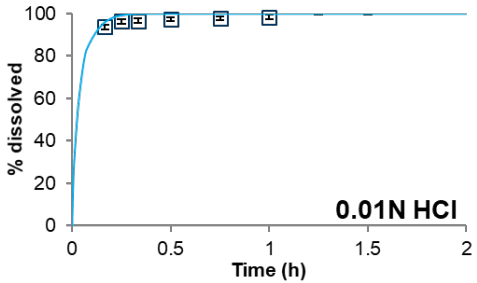
100 mg capsule
batch W027180

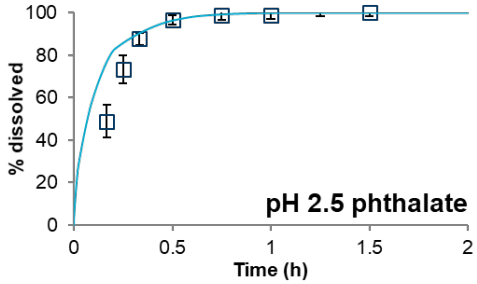


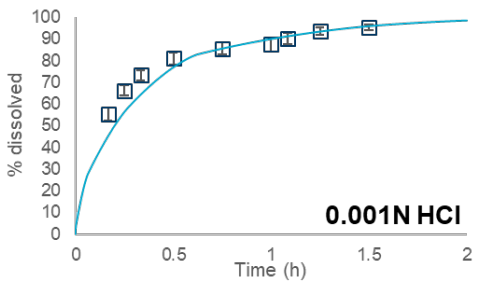


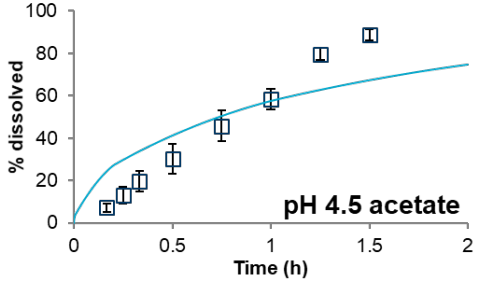
2-Verification : Predicting other conditions

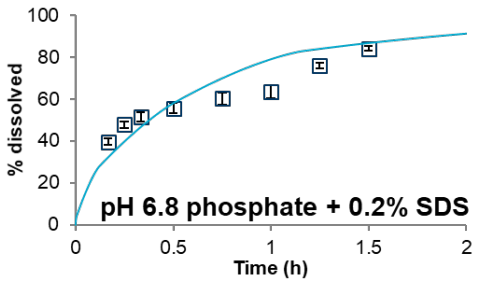












100 mg capsule
batch W027180

P-PSD able to reproduce the observed dissolution rates in other conditions of pH with and without surfactant

Use of surface pH
Different UWL thicknesses (if micelles)

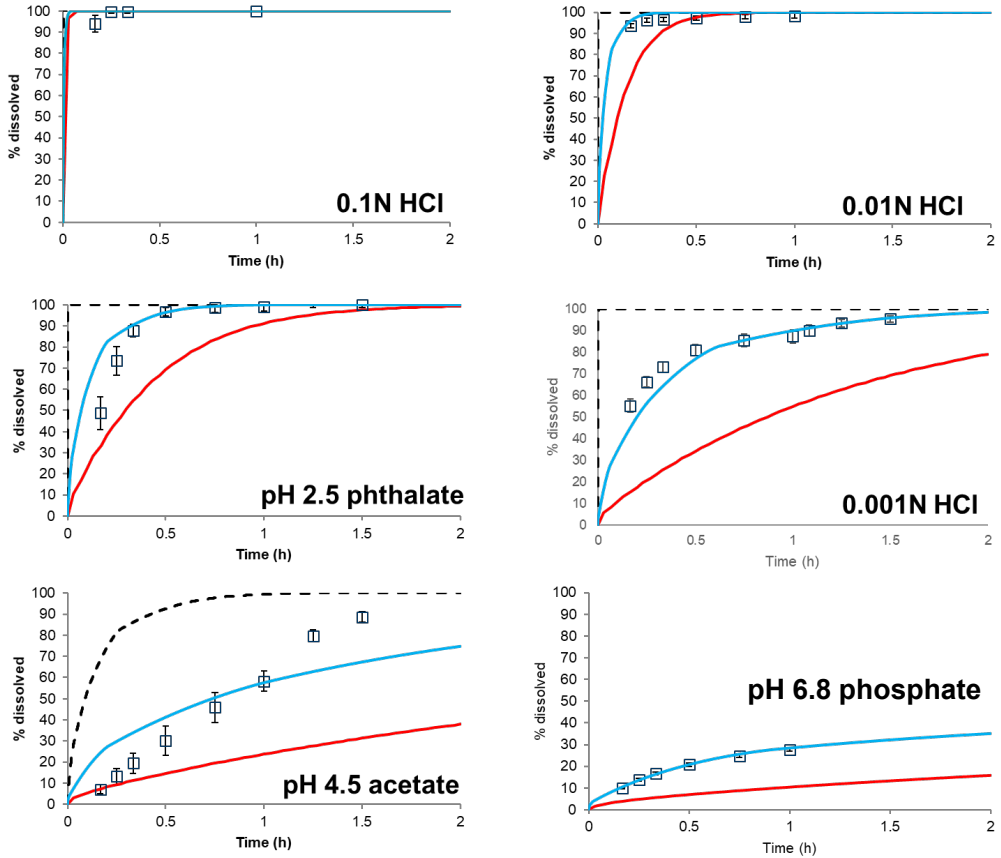
Other alternatives to predict dissolution (DS-PSD or bulk solubility)

100 mg capsule
batch W027180

DS-PSD underestimates dissolution

Bulk solubility and P-PSD overestimates dissolution

Surface solubility and P-PSD is the way forward !



Why do we need P-PSD : Could we use DS PSD instead ?

P-PSD

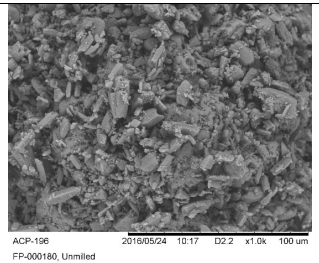
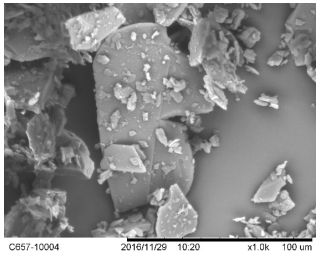
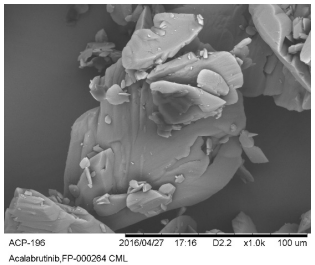
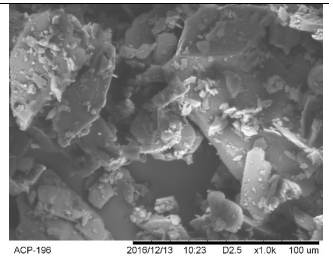
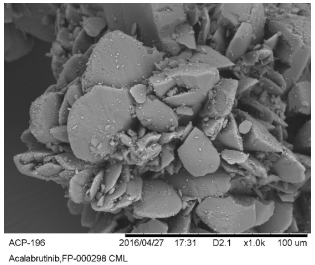
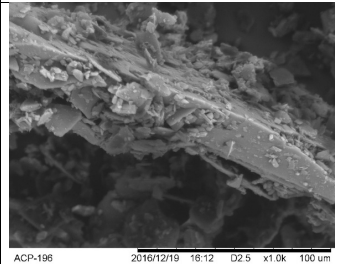
Integrates excipients, process parameters, wettability issues
Is based on the product that we give to patients.
Is extracted from dissolution : link to in vitro performance (integrates hydrodynamics using same hypotheses than in silico tools)
Provides a size distribution using spherical morphology : adapted to in silico models

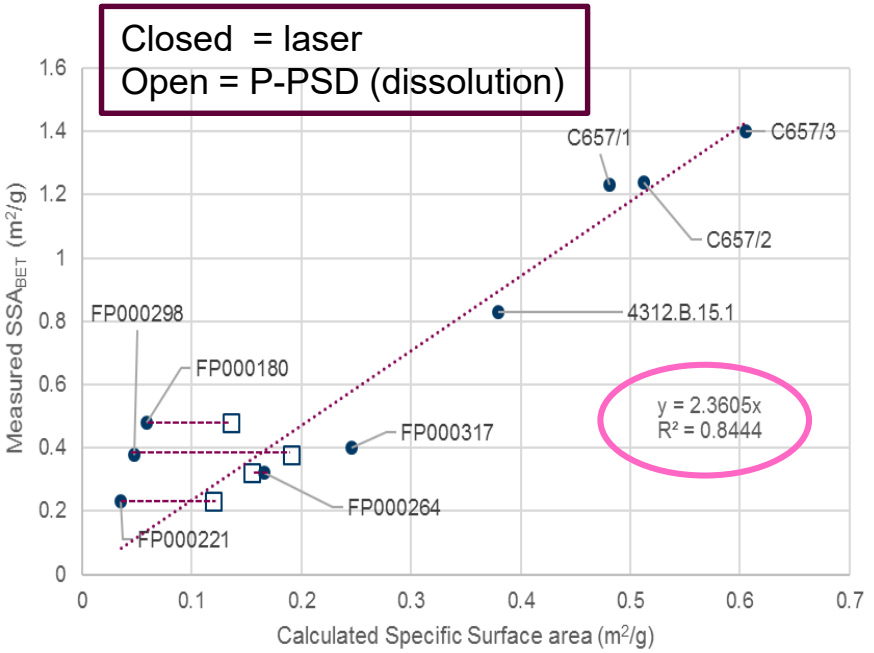
DS-PSD : laser diffraction (or other methods)

DS is an intermediate to the product (Process → attrition or consolidation)
Real particle shape is not spherical and can be aggregated
→ underestimation of dissolution of dissolution rate
Wettability issues → overestimation of dissolution rate and extent

Sorted with a single DLM scaling factor ?

Sphericity/aggregation of “real” DS batches

FP000180		C657/1	
FP000264		C657/2	
FP000298		C657/3	

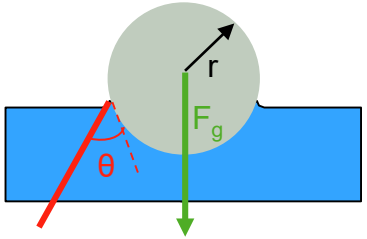


Laser under-estimates surface area esp. if particles show aggregation

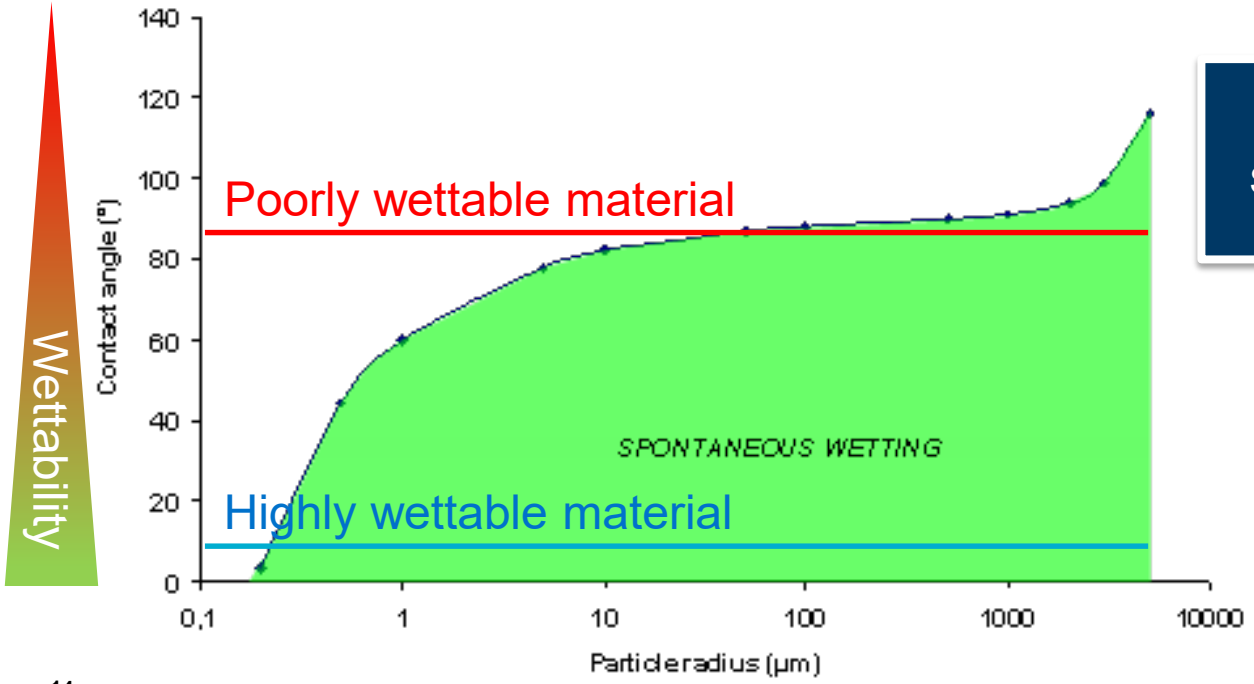
Wettability of drugs : not all particles are equal !

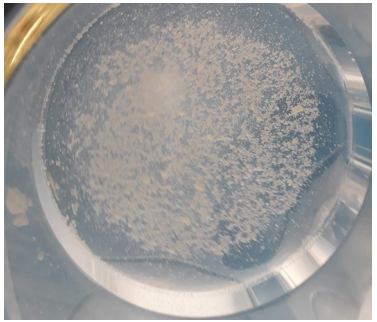
Limiting contact angle for spherical particle spontaneous wetting due to gravitation

ρ_S = 1.2 g/mL, ρ_L = 1 g/mL, η_L = 1 mPa.s

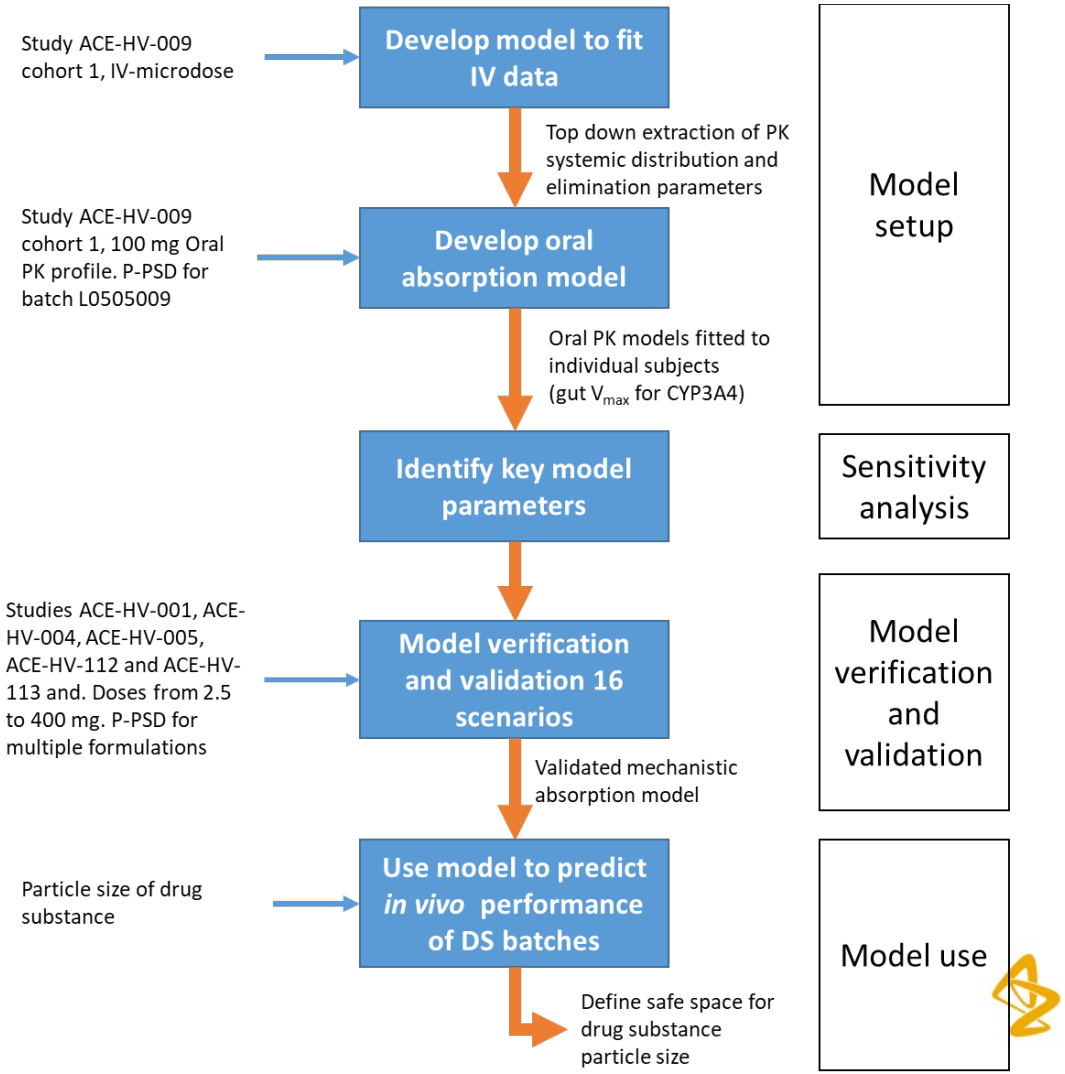


Size of particles determines spontaneous wetting
Small particles wet less easily than large particles





PBBM modelling strategy



Variability in exposure to 100 mg acalabrutinib capsules

Average Bioavailability = 0.25

$F = Fa \times (1-Eg) \times (1-Eh)$

Liver extraction (Eh = average = 0.5)
Within subject variability
(2-fold difference in systemic clearance not BW related)

Fraction absorbed (Fa)
Stomach pH decreases Fa
Stomach emptying time if incomplete dissolution
Acidic conditions → Fa=1

Gut extraction (Eg = average 0.5)
Between subject variability enzyme expression
(11-fold difference in gut CYP3A4 expression)
Permeability (reduces gut extraction). P_{eff} between subject variability : 60% RSD

Model set-up

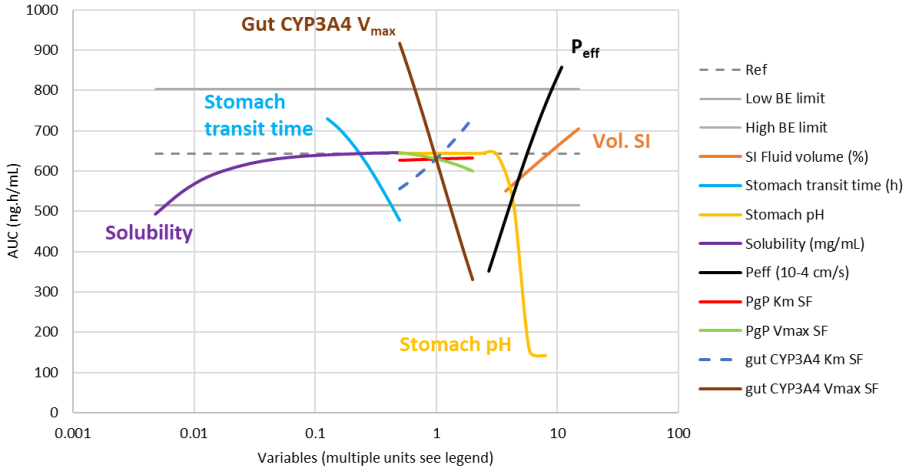
Individual 8 subject models using IV micro-dose for systemic disposition

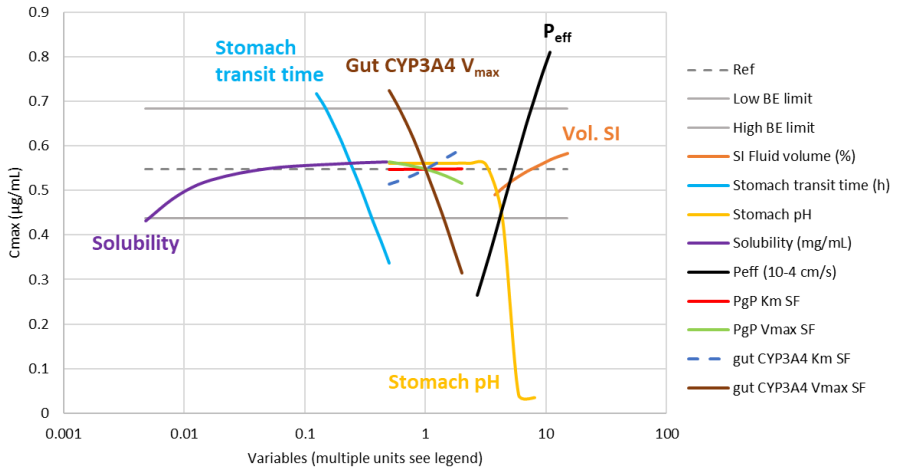
Subject	S007	S008	S009	S010	S011	S012	S013	S014
BMI ($kg.m^{-2}$)	28.6	24.5	27.9	24.6	21.4	23.0	24.0	26.8
BW (kg)	88.8	71.9	74.5	87.8	79.5	65	65.8	75.9
CL_H ($L.h^{-1}.kg^{-1}$)	0.296	0.580	0.365	0.486	0.692	0.694	0.494	0.380
V_c ($L.kg^{-1}$)	0.0861	0.1825	0.0701	0.3002	0.2389	0.2447	0.1940	0.1321
k_{12} (h^{-1})	4.080	1.891	6.143	0.962	2.417	1.363	1.522	3.900
k_{21} (h^{-1})	1.955	1.911	2.651	2.249	1.633	1.645	1.882	3.700
k_{13} (h^{-1})	0.144	0.397	0.305	0.178	0.312	0.049	0.226	0.182
k_{31} (h^{-1})	0.164	0.042	0.044	0.078	0.033	0.146	0.044	0.026
V_{max} CYP3A4 ($mg.s^{-1}$)	6.2	1.8	5.5	1.0	0.5	2.6	4.7	5.8
K_m CYP3A4 (µM)	20	20	20	20	20	20	20	20
P_{eff} ($cm.s^{-1} \times 10^{-4}$)	5.4	5.4	5.4	5.4	5.4	5.4	5.4	5.4
V_{max} PgP ($mg.s^{-1} \times 10^{-3}$)	4.22	4.22	4.22	4.22	4.22	4.22	4.22	4.22
K_m Pgp ($\mu g.mL^{-1}$)	2.78	2.78	2.78	2.78	2.78	2.78	2.78	2.78

Use of oral data to fit Vmax gut CYP3A4 and gastric retention times

Use of the “8-subject” population to predict average clinical outcome of separate studies without system parameter adjustments

Sensitivity analysis





Stomach pH is the most influential parameter controlling exposure

Interplay between Peff and gut extraction

Model Verification

Dose

Formulation

16 clinical scenarios

Parameters / Clinical scenario tested	Dose administered	Vc, distribution micro-constants, CL_T, body weight, effective permeability, stomach residence time, stomach gastric emptying post residence time, gut V_{max} and K_m for PgP, gut K_m for CYP3A4	Gut V_{max} for CYP3A4	*In vitro* dissolution (P-PSD)	Stomach pH
ACE-HV-001 Normal stomach pH + batches NCZP or NCZS with water	2.5, 5, 25, 50, 75 and 100 mg	No change compared to ACE-HV-009	No change compared to ACE-HV-009	Batch NCZP or NCZS from observed *in vitro* dissolution data in HCl 0.1 N	3.55[B]
ACE-HV-113 Normal stomach pH + batch W026394 with water	100 mg			Batch W026394 from observed *in vitro* dissolution data in simple buffers)	
ACE-HV-004 Normal stomach pH + batch NVTF with water	100 mg			Batch NVTF from observed *in vitro* dissolution data in HCl0.1N	
ACE-HV-004 Omeprazole pre-treatment + Batch NVTF with water	100 mg			Batch L0505009 from observed *in vitro* dissolution data in simple buffers	5.54[C]
ACE-HV-005 Normal stomach pH + batch L0505009 with water	100 mg and 400 mg				3.55[B]
ACE-HV-112 Normal stomach pH + batch L0505009 with water	100 mg				
ACE-HV-112 Omeprazole pre-treatment + batch L0505009 with water	100 mg				5.54[C]
ACE-HV-112 Normal stomach pH + batch L0505009 with orange drink	100 mg			Batch L0505009 from observed *in vitro* dissolution data in juices	3.8[D]
ACE-HV-112 Normal stomach pH + batch L0505009 with grapefruit juice after grapefruit juice pre-treatment	100 mg		Individual V_{max} from ACE-HV-009 with scaling factor of 0.3[A]		
ACE-HV-112 Normal stomach pH + batch L0505009 with water after grapefruit juice pre-treatment	100 mg			Batch L0505009 from observed *in vitro* dissolution data in simple buffers	3.55[B]

Acid reducing agents

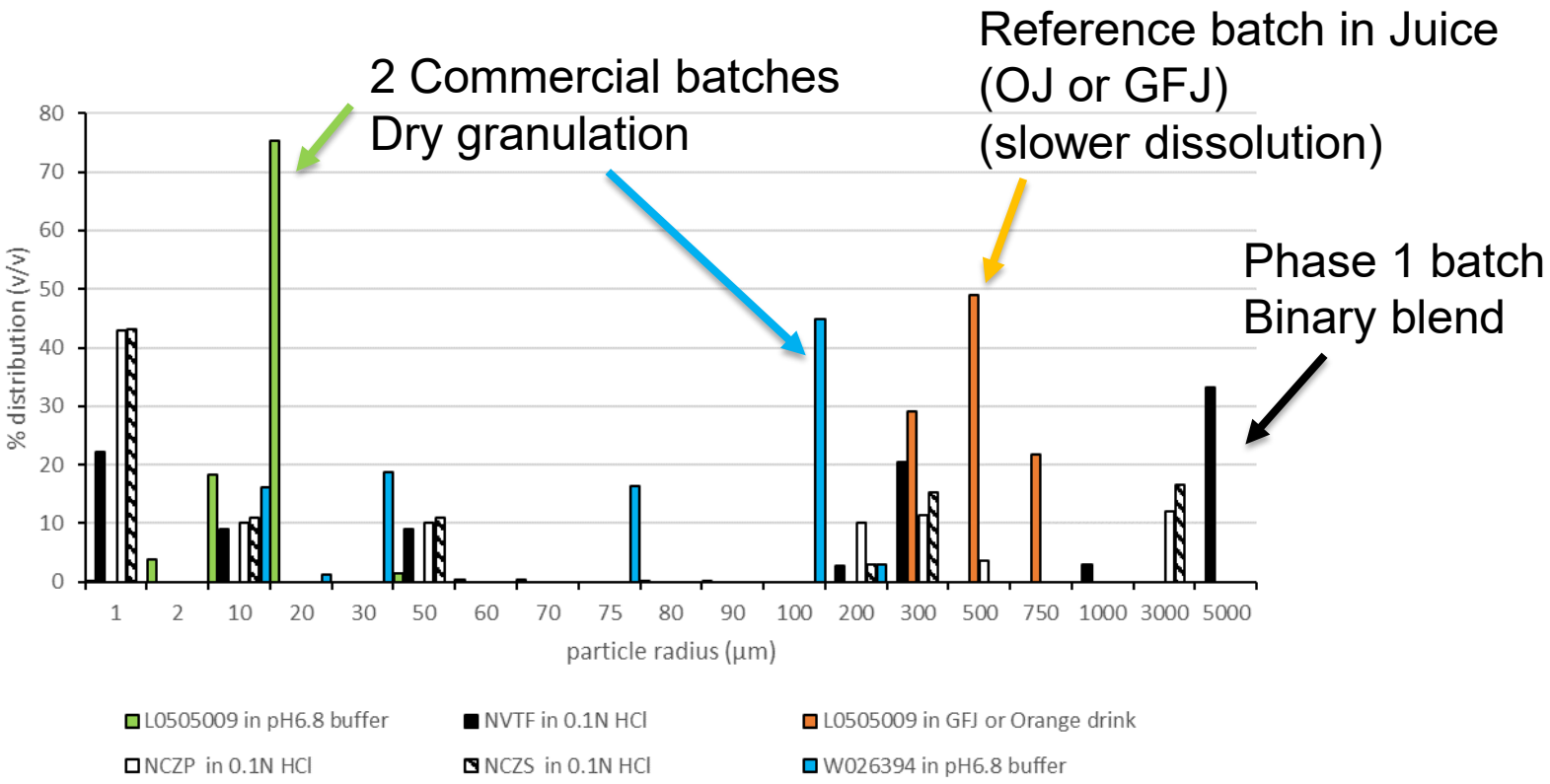
Juices on dissolution

GFJ as gut CYP3A inhibitor

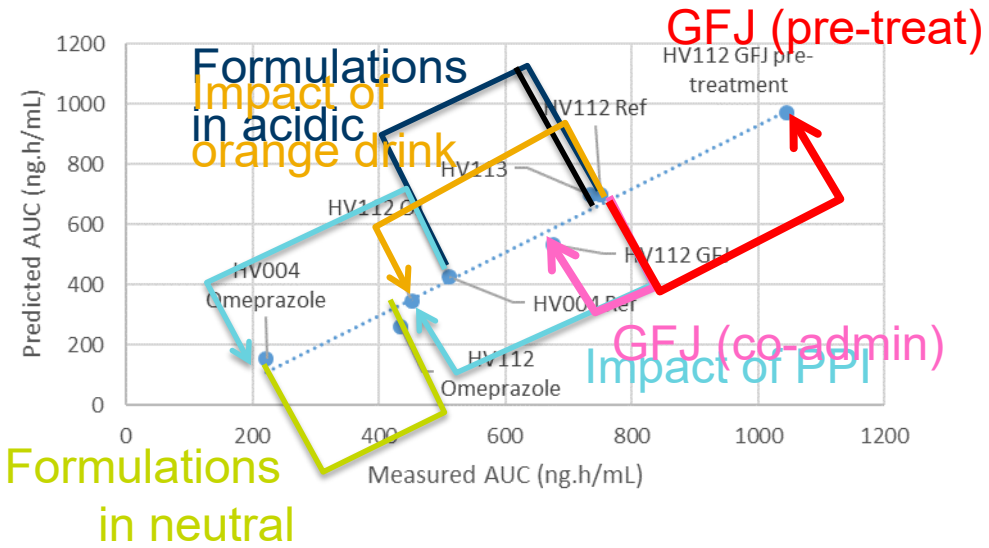
A: Ho et al. have shown than 70% of CYP3A gut activity can be inhibited by treatment with grapefruit juice[37]. Scaling factor for gut CYP3A4 V_{max} in model is set at 0.3 to account for the reduction in CYP activity. B: The normal default model value for fasted pH in the stomach is raised from 1.3 to 3.55, which is the calculated surface pH for acalabrutinib at bulk pH of 1.3 C: The stomach pH in the model is raised to pH 5.54 which corresponds to the surface pH of acalabrutinib crystals when the bulk pH is at 5. This pH is that of the dosing water, assuming it controls the pH of stomach where hydrochloric acid secretion is inhibited. D: Measured surface pH of acalabrutinib in juices

Model verification - results

P-PSDs used as model inputs



Model verification – results (100 mg only)



Model is verified: predictions well within clinical variability, AFE 0.92 for C_{max} and 0.72 for AUC

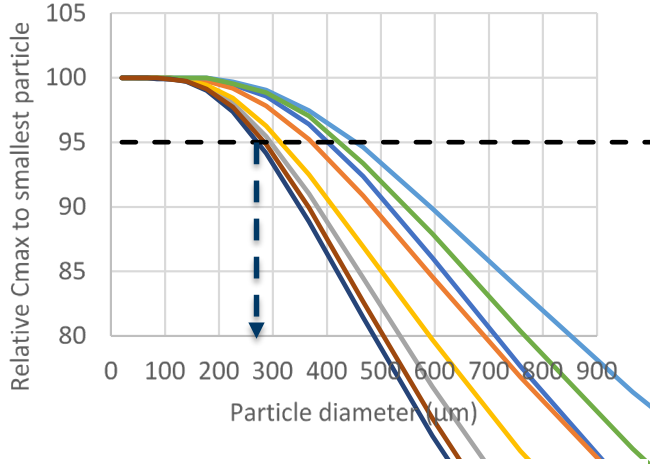
Formulation effect captured by P-PSD

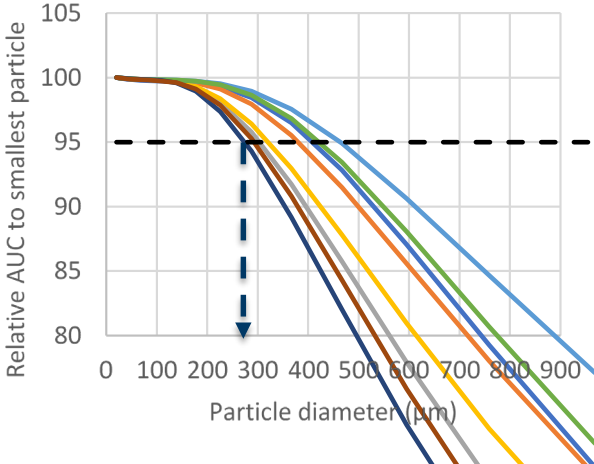
P-PSD is mechanistic : ARA effect well predicted by just changing stomach pH

Orange drink and GFJ slow down dissolution

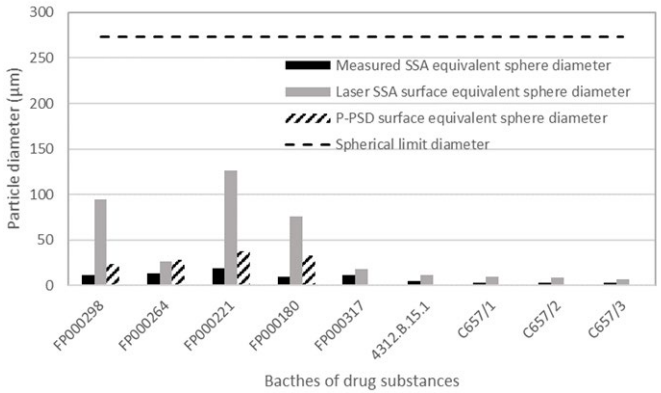
GFJ inhibits gut CYP3A4 and exposure is higher than for Orange drink

Model Use – PBPK model: sensitivity analysis to determine DS PSD safe space





Particle limit of 270 µm from PBPK model



DS-PSD Safe space

$$d_{eq} = \frac{1}{\rho_S} \times \frac{6}{SSA}$$

Bridging simulations with spherical morphology and measurements

Acalabrutinib: The importance of biomarkers to assess within and between subject variability

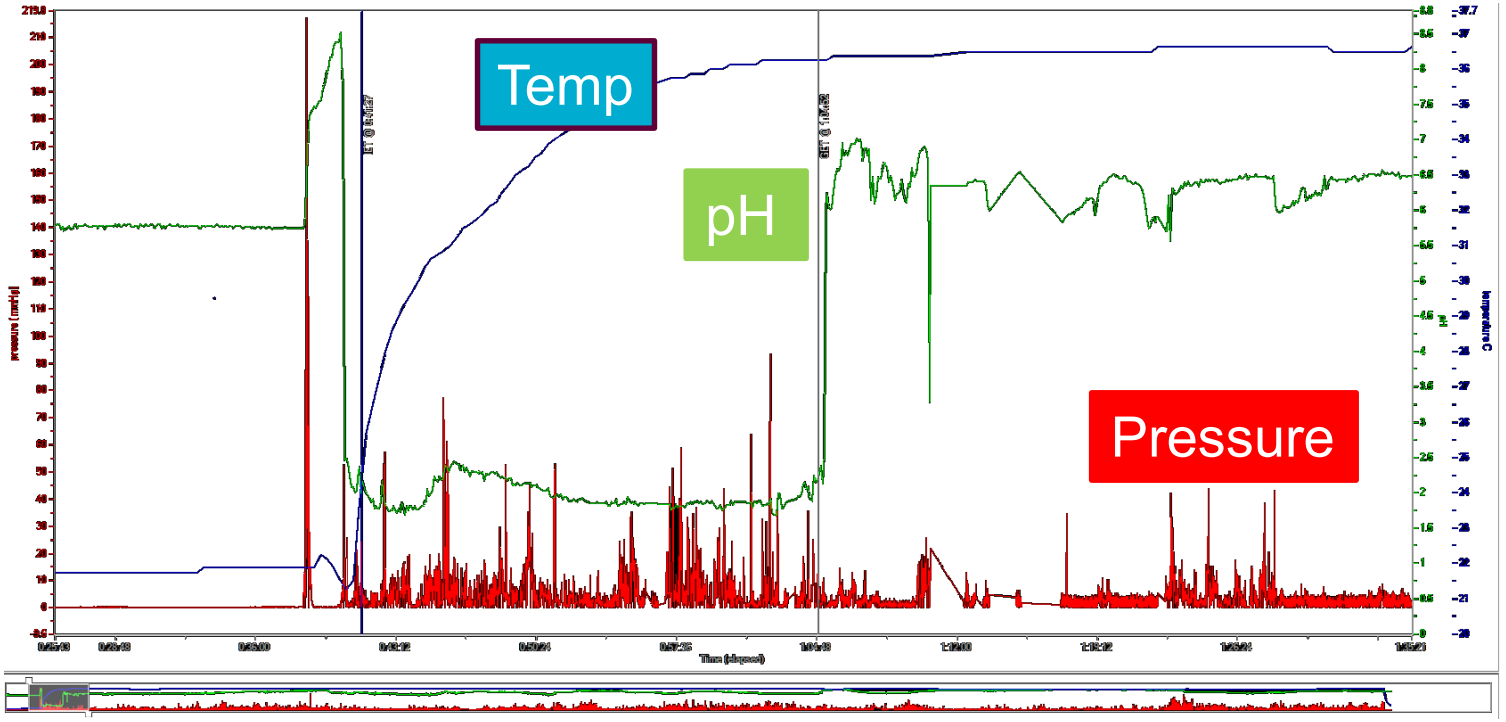
Biomarkers of physiological functions

- Disposition-total clearance: IV microdosing
- Liver CYP3A4: ^{14}C-erythromycin breath test

- Gastro-intestinal parameters
  - Localization : MMM, gamma imaging
  - Gastric emptying liquid (MRI, paracetamol, caffeine)
  - Gastric emptying solid (^{13}C-Octanoic acid breath test)
  - pH (smartpill®, pH probe @ given length. Only colocalized @administration)
  - Volume drank during study (smartpill® T°C if still in stomach)
  - Pressure (smartpill) but not co-localized
  - Bile salt concentration (blood reabsorption)

Research needed to quantify proteome functionality with biomarkers !

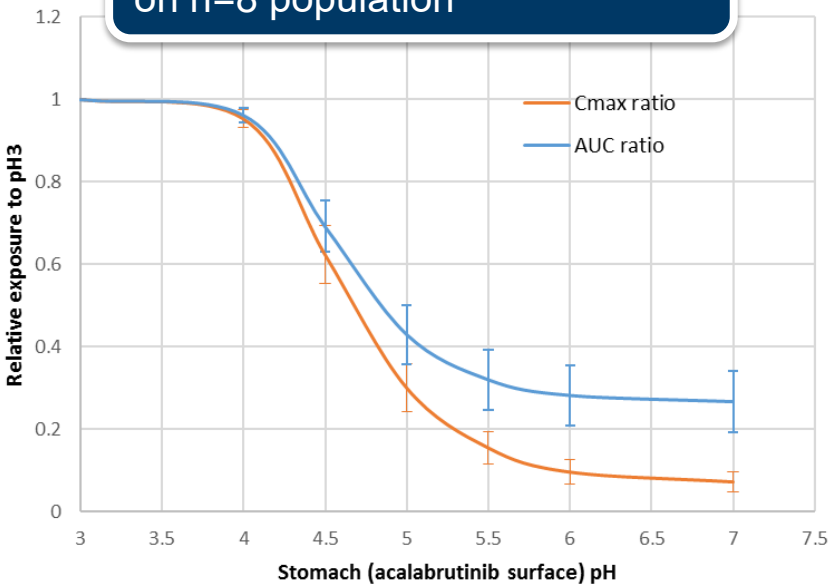
SmartPills®

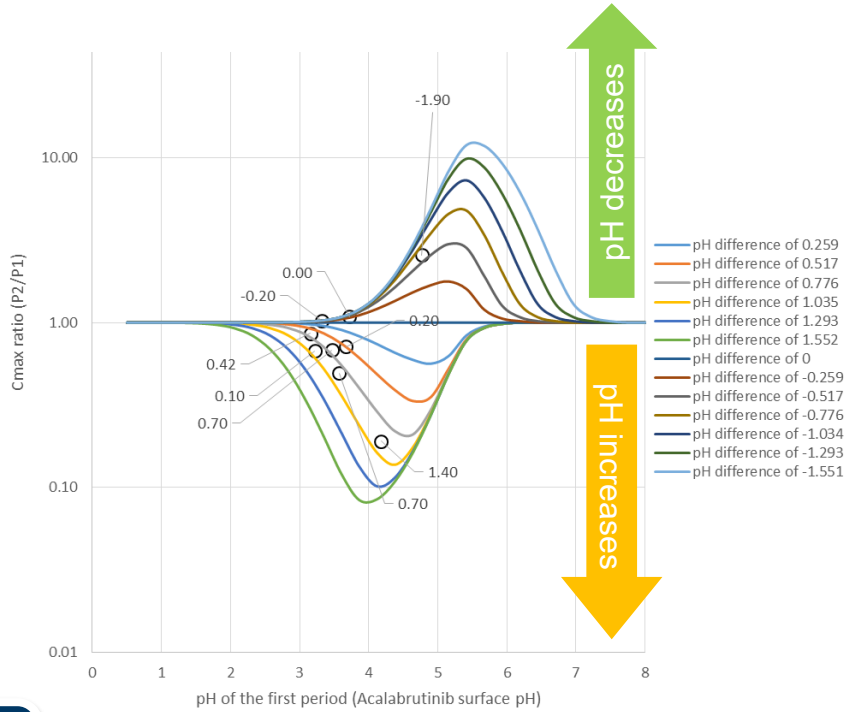


Human SmartPill study - Acalabrutinib

Human volunteers received the same batch of 100 mg capsule + SmartPill® in two periods

GastroPlus sensitivity analysis on n=8 population



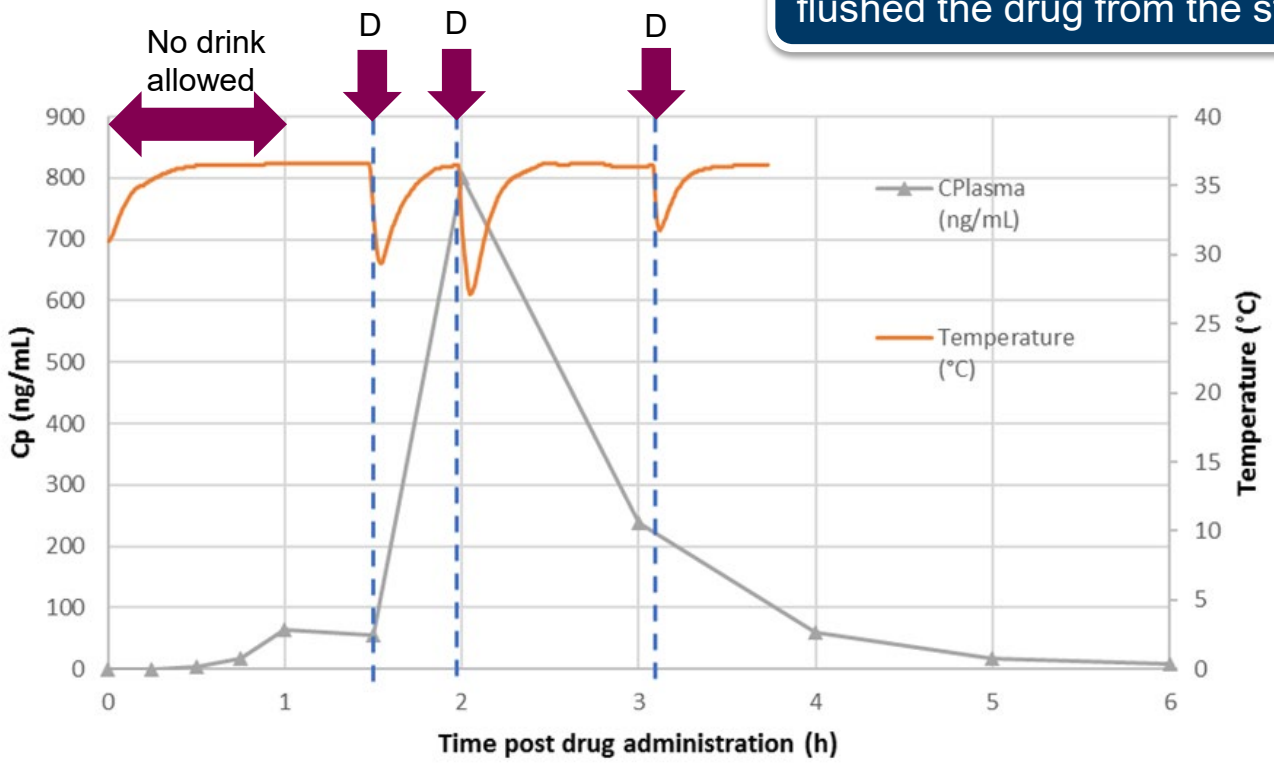


Within subject variability partly explained by stomach pH

Human SmartPill study - Acalabrutinib

Delayed gastric emptying for some subjects

Drinking event during study has probably flushed the drug from the stomach



A vision for the future of absorption modelling

Move from mechanistic understanding of populations to personalized/precision medicine

Introduction of biomarkers : Understand subject variability. Reduce statistical variation to a minimum: Differentiate system parameters from drug related parameters in the PK data analysis → Introduce a mechanistic understanding of populations

Mechanistic integration of dissolution (P-PSD, Z-factor...)
The right biomarker for the right drug : pH, transit, bile salt, enzyme expression etc
Use Individual disposition parameters

Run a pilot clinical study with formulation variants with biomarkers. Build a mechanistic absorption model to explain observed exposure

Run virtual cross-over BE trials to define edge of failure of CMA and CPP on larger populations with right variability of key parameters (spec settings)

Thanks

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Questions ?