Application of PBBM in risk assessment of effect of acid reducing agents (ARA) on PK and formulation development

Neil Parrott, Pharmaceutical Sciences,

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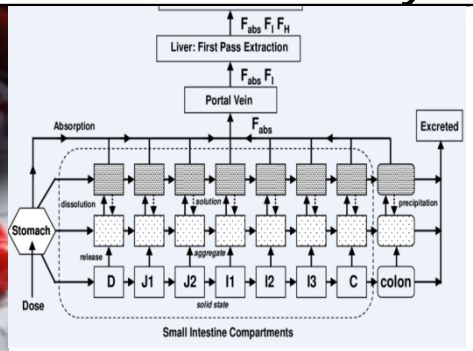
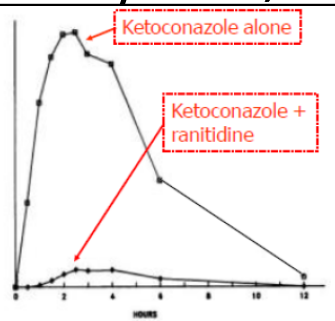




Overview

- Background to pH-dependent DDI
- Predicting the Effect of Acid Reducing Agents with PBBM
  - *in vitro* methods and PBBM examples
- Roche Case Studies
  - Alectinib
  - Erlotinib
- Future Directions

Background

- PK DDIs can cause toxicity or poor efficacy
- Adverse drug events contribute to patient harm and healthcare costs*
- PBPK used to predict and manage metabolic DDIs and inform labels
- Absorption-related DDIs may equal the magnitude of metabolic DDI effects but PBPK is having less impact in this area

* up to $177.4 billion annually. Ernst and Grizzle. J Am Pharm Assoc (Wash), 2001. **41**(2): p. 192-9

pH-dependent DDI for Poorly Soluble Weak Bases

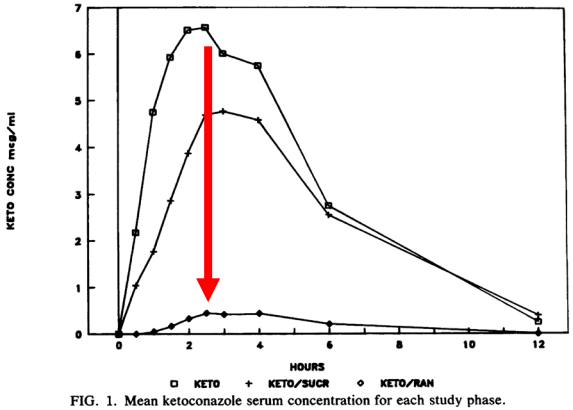
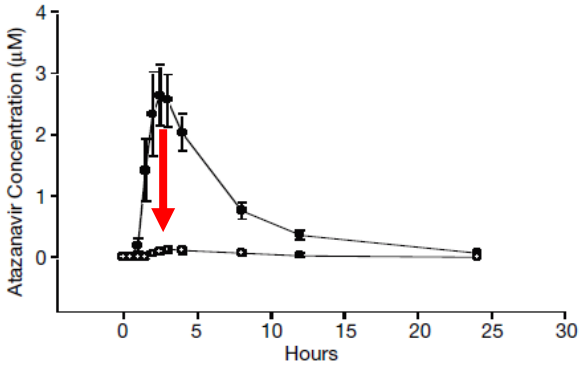


FIG. 1. Mean ketoconazole serum concentration for each study phase.

ketoconazole exposures↓ 95%
2 hours after ranitidine

Piscitelli, S.C., et al. (1991). *Effects of ranitidine and sucralfate on ketoconazole bioavailability.* Antimicrobial agents and chemotherapy. **35**(9): p. 1765-1771.

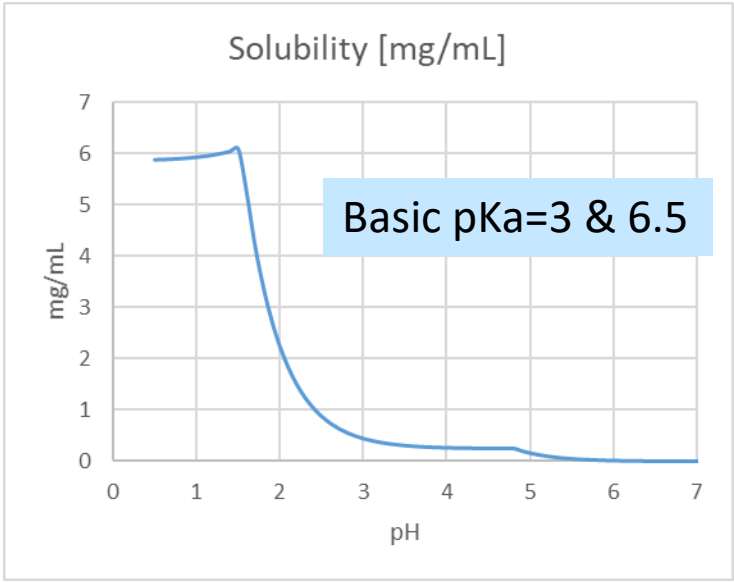


atazanavir exposures↓ 95%
after lansoprazole

Tomilo, D. L., et al. (2006). *Inhibition of Atazanavir Oral Absorption by Lansoprazole Gastric Acid Suppression in Healthy Volunteers.* Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 26(3): 341-346.

The Effect of Acid Reducing Agents

- pH-dependent DDI may occur in the stomach when a poorly soluble weakly basic drug with pH dependent solubility is co-administered with an acid reducing agent (ARA) e.g. proton pump inhibitor (PPI), histamine 2 receptor antagonist (H2RA) or antacid



Regulatory View

Support for the Value of PBBM

- Multiple published PBBM examples
- Mechanistic studies on the effect of different ARAs
- Proposed biorelevant media

Effect of Gastric pH on the Pharmacokinetics of a BCS Class II Compound in Dogs: Utilization of an Artificial Stomach and Duodenum Dissolution Model and GastroPlus,™ Simulations to Predict Absorption

SHOBHA N. BHATTACHAR,[1] EVERETT J. PERKINS,[2] JEFFREY S. TAN,[1] LEE J. BURNS[1]

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[2]Eli Lilly and Company, Drug Disposition, Lilly Research Laboratories, Indianapolis, Indiana 46285

Utilizing Physiologically Based Pharmacokinetic Modeling to Inform Formulation and Clinical Development for a Compound with pH-Dependent Solubility

JOHN CHUNG,[1] FERNANDO ALVAREZ-NUNEZ,[1] VINCENT CHOW,[2] DOMINICK DAURIO,[1] JOHN DAVIS,[2] MICHAEL DODDS,[2] MAURICE EMERY,[3] KEVIN LITWILER,[4] ANNE PACCALY,[2] JOANNA PENG,[2] BROOKE ROCK,[2] LARRY WIENKERS,[2] CHARLES YANG,[1] ZHIGANG YU,[3] JAN WAHLSTROM[2]

[1]Pharmaceutics Research and Development, Amgen, Inc., Thousand Oaks, California
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[3]Clinical Pharmacology, Amgen, Inc., Thousand Oaks, California
[4]Clinical Pharmacology, Array BioPharma, Inc., Boulder, Colorado

Virtual bioequivalence for achlorhydric subjects: The use of PBPK modelling to assess the formulation-dependent effect of achlorhydria

Kosuke Doki[a,b,*], Adam S. Darwich[a], Nikunjkumar Patel[c], Amin Rostami-Hodjegan[a,c]

[a] *Centre for Applied Pharmacokinetic Research, Division of Pharmacy & Optometry, University of Manchester, Manchester, UK*
[b] *Department of Pharmaceutical Sciences, Faculty of Medicine, University of Tsukuba, Ibaraki, Japan*
[c] *Simcyp Limited (A Certara Company), Sheffield, UK*

PBBM to Flag Compounds with High Risk

Drug Discovery—Development Interface

Prediction of ARA/PPI Drug-Drug Interactions at the Drug Discovery and Development Interface

Stephanie Dodd [1,*], Sivacharan Kollipara [2], Manuel Sanchez-Felix [1], Hyungchul Kim [1], Qingshuo Meng [4], Stefania Beato [5], Tycho Heimbach [3]

- Integration into GastroPlus of in silico properties or early discovery stage measured properties
- Risk correctly identified for 50% (in silico) & 78% (measured) of studies

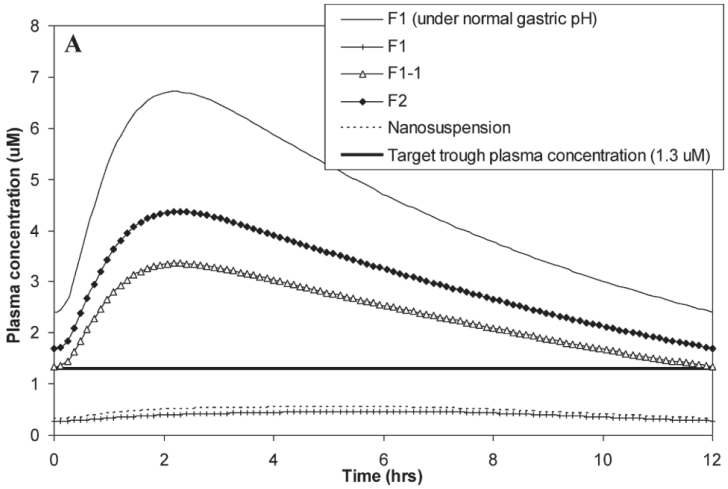
Journal of Pharmaceutical Sciences 2019 108 87-101

PBBM Aids Development of Improved Formulations

Using Absorption Simulation and Gastric pH Modulated Dog Model for Formulation Development To Overcome Achlorhydria Effect

Amitava Mitra,[*,†] Filippos Kesisoglou,[†] Martyn Beauchamp,[‡] Wei Zhu,[†] Fabio Chiti,[§] and Yunhui Wu[†]

- Free base F1 form. showed reduced AUC with ARA
- F1 compared to F1-1(citric acid & povidone) &
- F2 (HCl salt & citric acid)
- PBBM used to compare Cp(t) for each formulation



USP II, pH 3 NaCL medium at 37 °C
Intestinal absorption based on gastric pH 6 with PPI

Mol Pharm 2011 8(6): 2216-2223.

Mechanistic Clinical and *In vitro* Studies

Characteristics of the Human Upper Gastrointestinal Contents in the Fasted State Under Hypo- and A-chlorhydric Gastric Conditions Under Conditions of Typical Drug – Drug Interaction Studies

Chara Litou [1] • Maria Vertzoni [1] • Constantinos Goumas [2] • Vassilis Vasdekis [3] • Wei Xu [4] • Filippos Kesisoglou [4] • Christos Reppas [1]

Pharm Res. 2016 33(6): 1399-1412.

The impact of reduced gastric acid secretion on dissolution of salts of weak bases in the fasted upper gastrointestinal lumen: Data in biorelevant media and in human aspirates

Chara Litou [a], Maria Vertzoni [a], Wei Xu [b], Filippos Kesisoglou [b], Christos Reppas [a,*]

[a] Department of Pharmacy, School of Health Sciences, National and Kapodistrian University of Athens, Zografou, Greece
[b] Pharmaceutical Sciences and Clinical Supply, Merck & Co., Inc., Kenilworth, NJ, USA

EJPB 2017 115: 94-101.

- Famotidine and pantoprazole

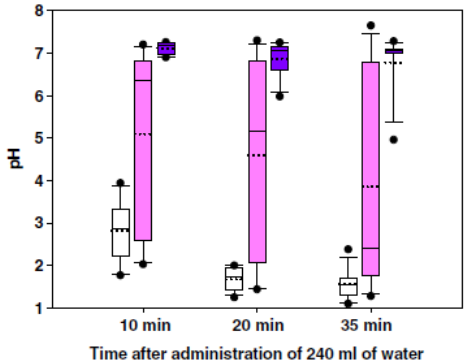


Fig. 2 pH in the stomach of fasted healthy adults as a function of time, after administration of 240 ml table water into the antrum of the stomach. Key: White boxes, Phase 1; Light pink boxes, Phase 2; Dark blue boxes, Phase 3. Each box was constructed by using 7–8 individual values.

- Media for stomach proposed
- Dissolution data shown to be comparable to those obtained with gastric aspirates for 2 test compounds

Incorporation of Dissolution Data in PBBM

Physiologically Based Absorption Modeling of Salts of Weak Bases Based on Data in Hypochlorhydric and Achlorhydric Biorelevant Media

Filippos Kesisoglou,[1,3] Maria Vertzoni,[2] and Christos Reppas[2]

- Biorelevant GI transfer (BioGIT) measurements with new media used to inform PBBM
- Gastric supersaturation measured and accounted for (can be important for salt forms, acidulant formulations, etc…)
- Successful PBBM simulations for these 2 drugs where solubility vs pH profiles had under predicted the exposures with ARA

AAPS PharmSciTech. 2018

Biorelevant *In vitro* Tests

Impact of Acid-Reducing Agents on Gastrointestinal Physiology and Design of Biorelevant Dissolution Tests to Reflect These Changes

Domagoj Segregur [1], Talia Flanagan [2, 3], James Mann [2], Andrea Moir [2], Eva M. Karlsson [4], Matthias Hoch [5], David Carlile [5], Sakina Sayah-Jeanne [6], Jennifer Dressman [1, *]

In vitro stomach dissolution tests designed for H2-receptor antagonists and PPIs

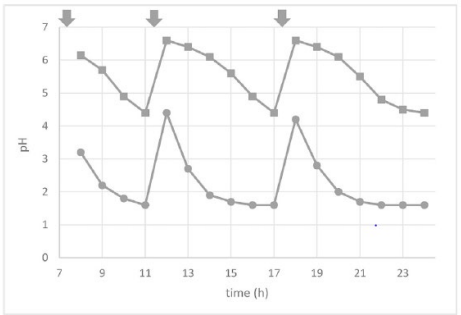


Figure 3. Typical gastric pH profile without (•) and during chronic PPI administration (■). Meal ingestion is indicated by an arrow.

Table 4
The Composition of Media Recommended for Simulating Fasted State Gastric Fluid Under PPI/H_2RA Co-administration

Component/Parameter	Acetate pH 4 Medium	Maleate pH 6 Medium
Pepsin (mg/mL)	0.1	–
Sodium taurocholate (mM)	0.08	0.08
Phosphatidylcholine (mM)	0.02	0.02
Sodium chloride (mM)	-	22.7
Maleic acid (mM)	-	2.31
Sodium acetate (mM)	33.3	-
+ NaOH (1 M) (mL)	-	qs. (~3.5)
+ HCl (1 M) (mL)	qs. (~25)	-
pH	4	6
Buffer capacity (mEq/pH/L)	7.5	1
Osmolality (mOsmol/kg)	91	50
Surface tension (mN/m)	64.49	67.21

Minus sign indicates the absence of component.

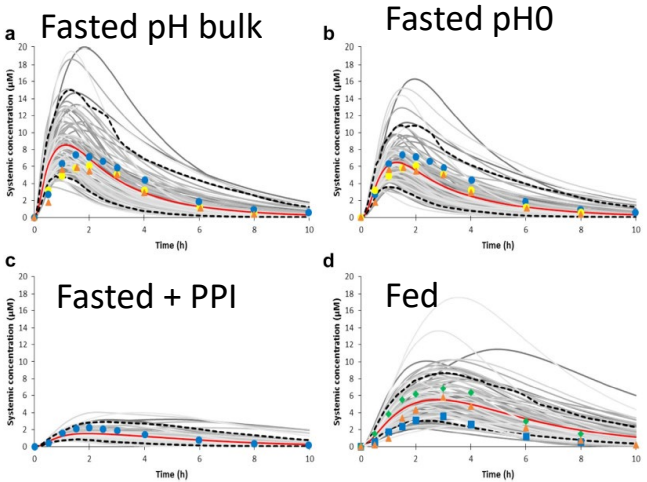
J Pharm. Sci. 2019

PBBM to Understand Variability

Assessment of Bioequivalence of Weak Base Formulations Under Various Dosing Conditions Using Physiologically Based Pharmacokinetic Simulations in Virtual Populations. Case Examples: Ketoconazole and Posaconazole

Rodrigo Cristofoletti [1,2], Nikunjkumar Patel [3], Jennifer B. Dressman [2,*]

- Model considers surface pH_0 & precipitation
- Self buffering and buffering effects by setting bulk pH to calculated pH0
- Verified with diverse clinical studies (food, coca-cola, PPI)
- Sensitivity analysis and virtual BE conducted



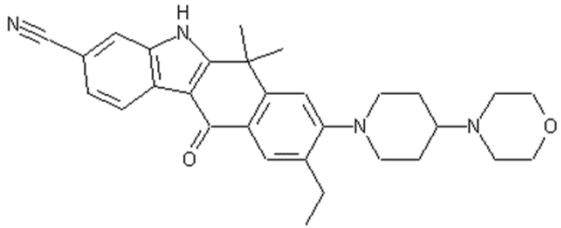
Journal of Pharmaceutical Sciences 2017 106(2): 560-569.

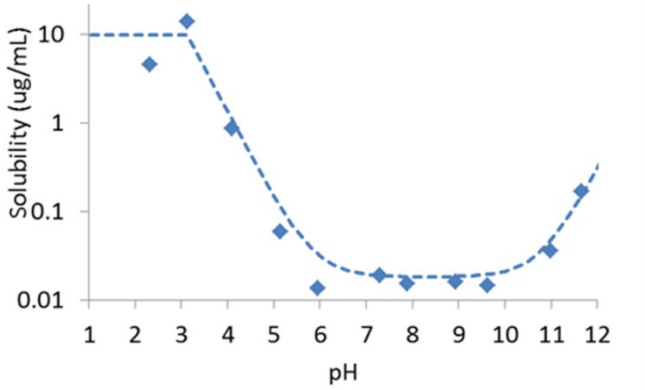
Alectinib

Physiologically Based Absorption Modeling to Explore the Impact of Food and Gastric pH Changes on the Pharmacokinetics of Alectinib

Neil J Parrott,[1,5] Li J Yu,[2] Ryusuke Takano,[3] Mikiko Nakamura,[4] and Peter N. Morcos[2]

Property	Value
logD	1.96 at pH 3.575
pKa	7.05 base
Permeability	2.5 *10-4 cm/s
Kinetic solubility of granules in clinical capsules measured at 37°C in 50 mL of biorelevant media after 4 hours stirring with a paddle speed of 50 rpm . Five milligram of RO5424802 was applied.	FaSSIF (23 µg/mL) FeSSIF (77 µg/mL)
Clinical Dose	600 mg

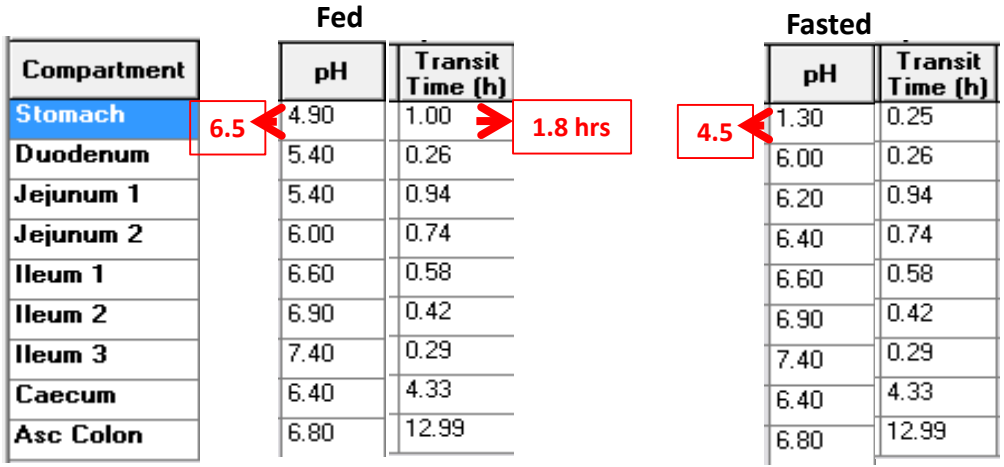




The AAPS Journal (2016)

Model Changes for PPIs

- Fasting gastric pH increased to 4.5
- Postprandial gastric pH increased to 6.5
- Decreased gastric emptying rate

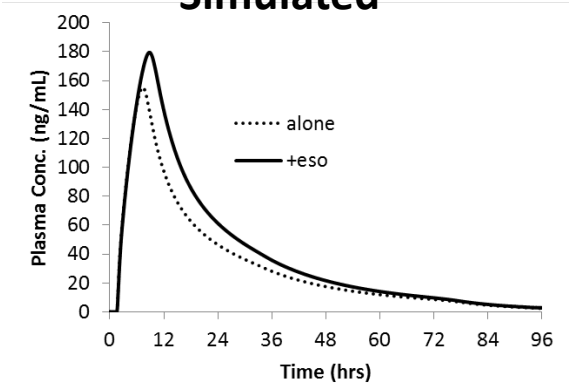


Prediction

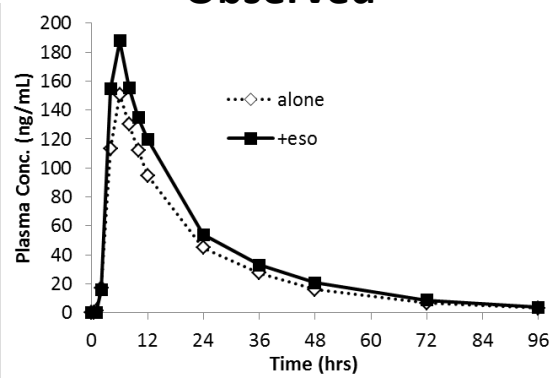
- Negligible effect of elevated gastric pH predicted
  - Very limited dissolution in the stomach irrespective of pH
  - Solubility of alectinib at normal healthy gastric pH << 2.4 mg/mL (the value needed for complete dissolution of the dose in a glass of water (600 mg dose / 250 mL))
- Solubility decreases with increased gastric pH have little effect
- This prediction was useful to design pivotal study w.r.t. patient exclusion criteria

Confirmation - No Clinically Relevant Effect

Simulated



Clinically Observed



Proposal: In such cases PBBM could be sufficient to waive a clinical DDI

E.g.Pabinostat FDA Review *Model simulations suggested the lack of effect of elevating gastric pH on panobinostat oral absorption and PK"*

Ribociclib Bioavailability Is Not Affected by Gastric pH Changes or Food Intake: *In Silico* and Clinical Evaluations

Tanay S. Samant[1], Shyeilla Dhuria[2], Yasong Lu[1], Marc Laisney[3], Shu Yang[1], Arnaud Grandeury[3], Martin Mueller-Zsigmondy[3], Kenichi Umehara[3], Felix Huth[3], Michelle Miller[1], Caroline Germa[1] and Mohamed Elmeliegy[1]

Erlotinib

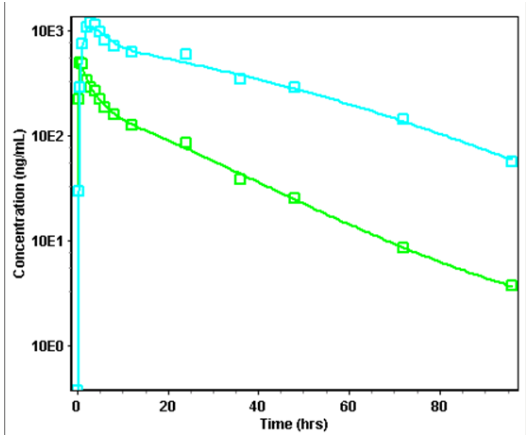
- Lipophilic with high permeability and low solubility
- CYP3A4 & CYP1A2 substrate
- The effect of omeprazole and ranitidine on erlotinib has been studied clinically. Modelling was done retrospectively

Parameter				
$logP_{(O/W)}$	2.7			
pk_a	5.65			
fu	0.046			
B/P	0.55			
Permeability (cm/s)	caco-2 $33.6x10^{-6}$ -> human Peff $4.3x10^{-4}$			
Buffer solubility at different pH (mg/ml)	pH	mg/mL		
	2.5	0.6		
	3.4	0.32		
	5	0.0145		
	6.5	0.0058		
Biorelevant solubility at 37°C (mg/ml)	Media	start pH	end pH	mg/mL
	FaSSIF	6.5	6.4	0.0085
	FeSSIF	5	5	0.0533

Step 1: Disposition Model

- Mean Cp(t) for IV and PO crossover study 150-mg tablet vs 25-mg 30 minute intravenous infusion in 20 healthy mainly female subjects
- 2 compartmental model with **nonlinear clearance** fit gives best fit
- Bioavailability estimated with saturable clearance is **59%** vs 106% based on a simple non-compartmental analysis

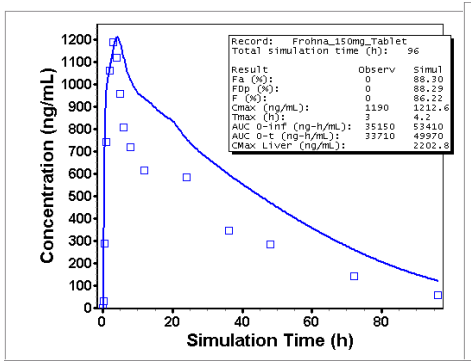
nonlinear model fit in PKPlus

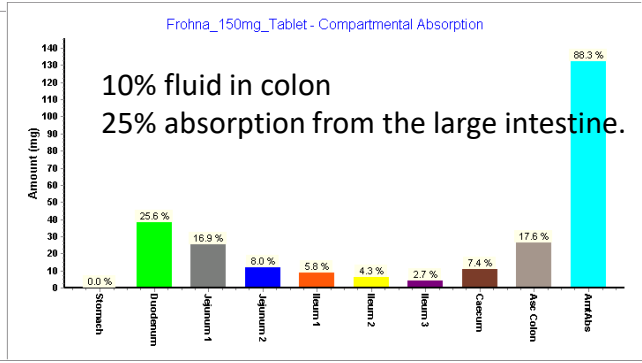


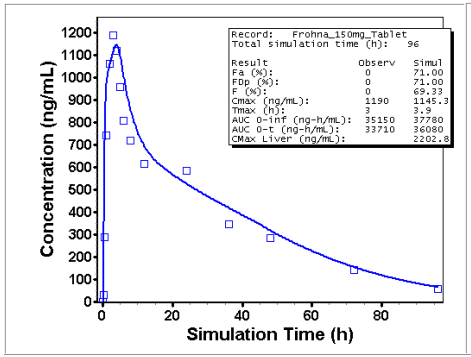
Vc/kg=	0.826	L/kg	CV= 26%
CL2/kg=	0.150	L/h/kg	CV= 54%
V2/kg=	1.138	L/kg	CV= 33%
Vmax =	**4.47E-4**	**mg/s**	**CV= 53%**
Km =	**0.232**	**µg/mL**	**CV= 77%**
K12 =	0.182	1/h	CV= 60%
K21 =	0.132	1/h	CV= 63%
Tlag =	0.228	h	CV= 19%
Ka =	0.731	1/h	CV= 53%
F =	**59.27**	%	CV= 19%

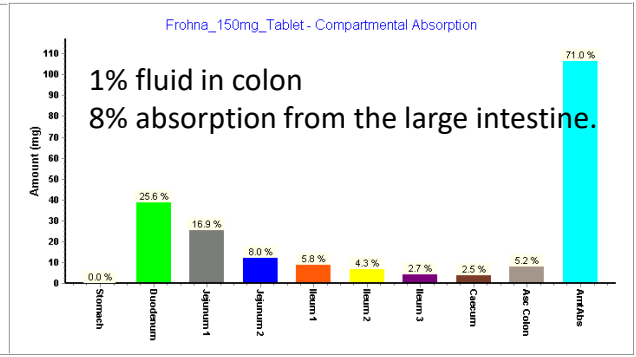
Step 2: Oral Tablet Simulation (Fasted State)

- Vmax and Km transferred to the enzyme table accounting for changed units and free fraction in plasma
- Default model simulation over estimates observed Cp(t)
- Reduction in %fluid colon improves match



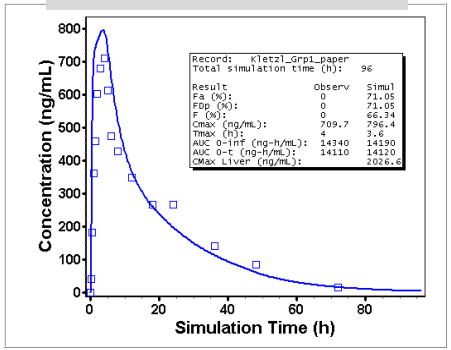




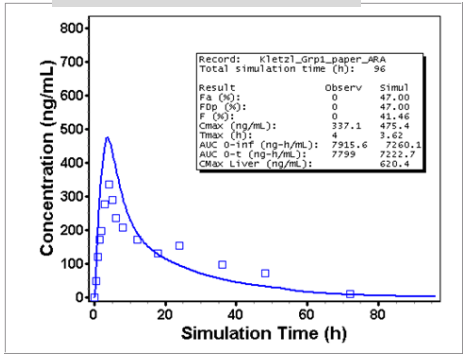


Step 3: Simulation with/without ARA

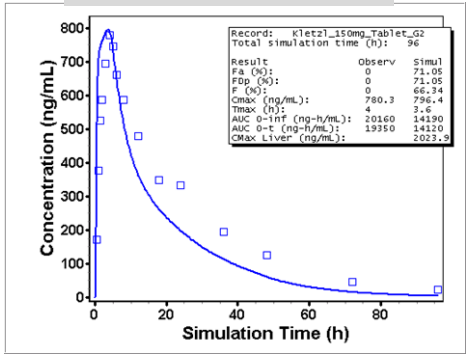
Without omeprazole



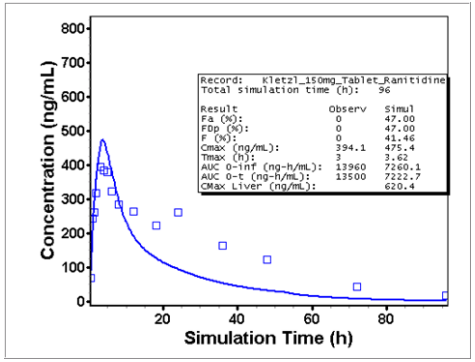
With omeprazole



Without ranitidine



With ranitidine

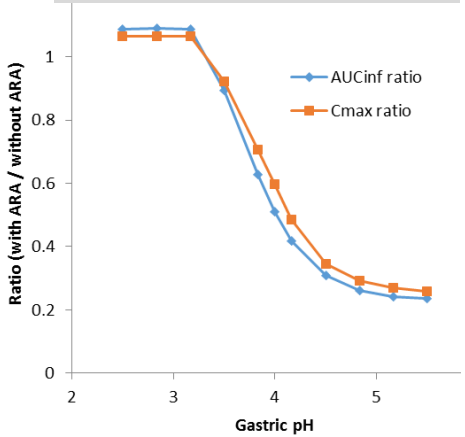


- Stomach pH changed from 1.3 to 4.0
- Gastric transit increased from 0.25h to 0.5h

AUCinf	omeprazole	ranitidine
Observed	54%	67%
Simulated	51%	51%

Cmax	omeprazole	ranitidine
Observed	39%	46%
Simulated	60%	60%

Sensitivity to gastric pH



Erlotinib Conclusions

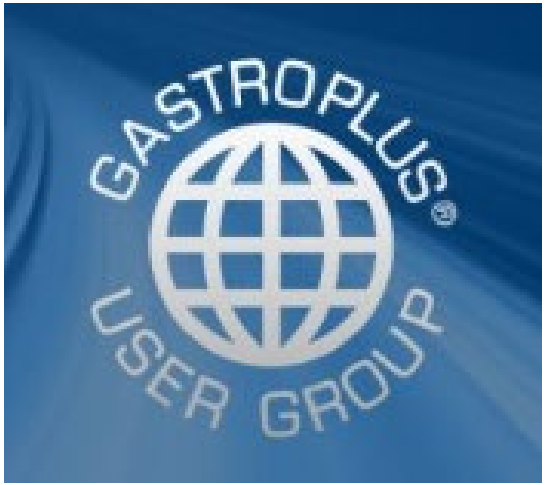
- PBBM indicates high risk of pH-dependent DDI
- Precise prediction of extent of effect is challenging
  - Complex non-linear PK
  - HCl salt dosed
  - Uncertainty in colonic absorption
  - High sensitivity to gastric pH in range 3 – 5
- Model verification with clinical data recommended
- Subsequent application of a verified PBBM for waiver can be envisaged
  - Formulation changes
  - Different patient populations

PBBM for ARA DDI Risk & Formulation Development

- PBBM should play a role in integrating physicochemical, in vitro, in vivo and physiological data into a mechanistic framework to yield fuller understanding of pH dependent DDIs
- A bottom-up approach and PSA is useful for early internal decisions
- Multiple PBBM examples support the value during clinical development
- Wider application to streamline drug development and waive unnecessary studies is warranted

Acknowledgements

- Colleagues from Roche pRED Pharmaceutical Sciences
- Colleagues from the GastroPlus User Group



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