Drug Delivery Foundation

Oral Drug Delivery (ODD) 2018
in vivo Predictive Dissolution (iPD),
formulation Predictive Dissolution (fPD)

FDA U.S. FOOD & DRUG ADMINISTRATION

Potential Impact of Gastric pH on Generic Drug Bioequivalence Evaluation

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Outline

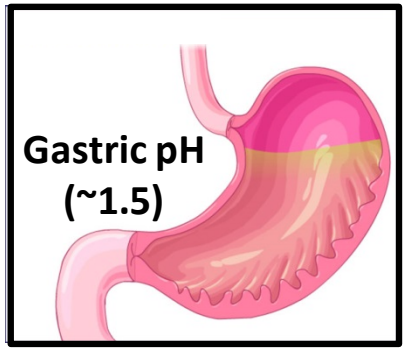
- Background
- Risk factors for pH-related PK issue
- Bioequivalence consideration for generic drug product
- Case examples to illustrate Agency's efforts
- Additional issues
- Regulatory activities

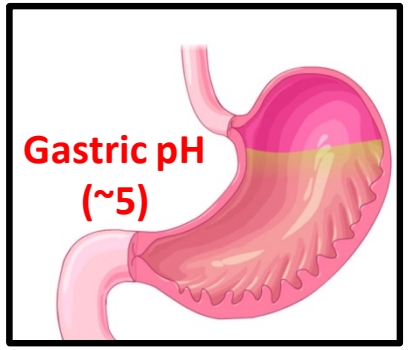
Gastric pH and Drug Absorption

PPI, Antiacid, H_2 blockers

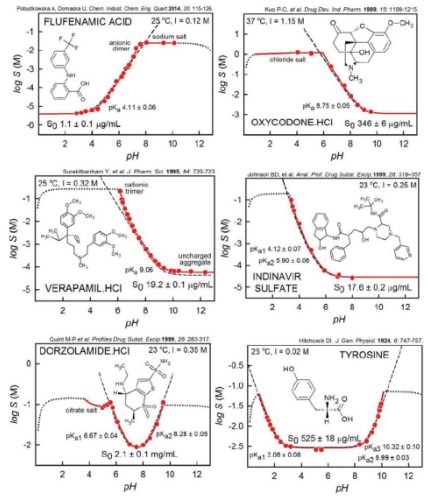
Disease, Age

Ethnicity





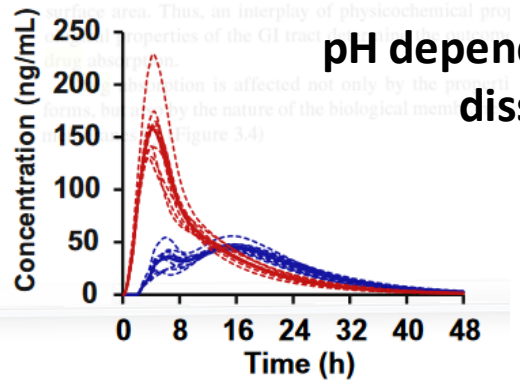
Drugs
(pH dependent)



IR or pH Sensitive MR

pH dependent release or dissolution

Systemic Absorption



Altered Absorption of the Drug May Occur When Gastric pH Changes

Observed in vivo DDI outcomes on 21 weak base new drugs (IR) approved between 2003 to 2013

For weak base drug:

↓ in exposure → efficacy concern

For weak acid drug:

↑ in exposure → safety concern

Indication	Drugs	DDI
HIV	Rilpivirine	+
HIV	Atazanavir	+
HIV	Darunavir	-
Lung Cancer	Gefitinib	+
Lung Cancer	Erlotinib	+
Lung Cancer	Crizotinib	-
Liver cancer	Sorafenib	-
Renal cancer	Axitinib	+
Chronic myelogenous leukemia	Bosutinib	+
Chronic myeloid leukemia	Dasatinib	+
Acute coronary syndrome	Prasugrel	+
Reduce risk of stroke and systemic embolism	Dabigatran	+
Atrial fibrillation	Dronedarone	-
Erectile dysfunction	Vardenafil	Uncategorized
Erectile dysfunction	Tadalafil	+
Invasive Aspergillus and Candida infection	Posaconazole	+
Antibiotic	Telithromycin	Uncategorized
Pneumonia	Gemifloxacin	+
Hepatic impairment	Nilotinib	+
Type 2 diabetes	Saxagliptin	-
Musculoskeletal pain	Tapentadol	-

"positive" was defined as >25% ↓ AUC & Cmax

Zhang L. et al. CPT, 96 (2014) 266-277.

Observed in vivo DDI Outcomes and Comment and Labeling Recommendation

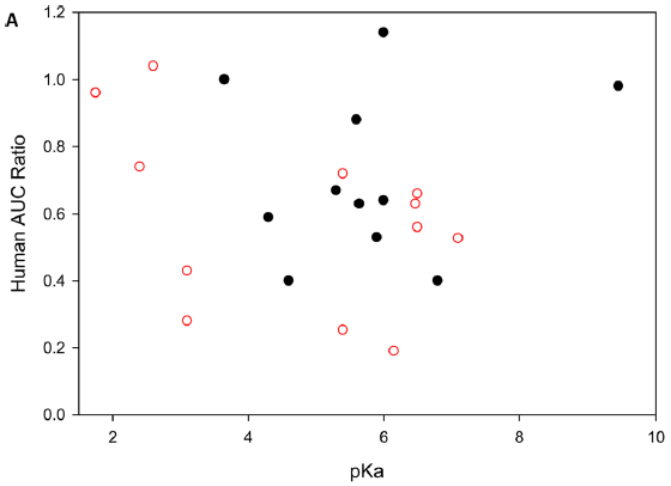
From efficacy and toxicity perspective,

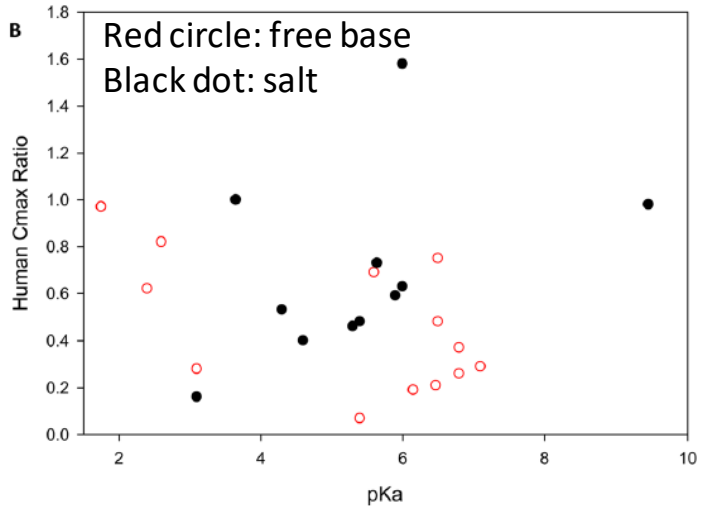
Drug	ARA	Dosing regimen during treatment period (drug/ARA)	Timing of administration	Effect on victim drug's PK	Comment and labeling recommendation
Prasugrel	H_2 blocker: ranitidine	Multiple-dose drug + multiple-dose ranitidine (150 mg b.i.d.)	Concomitant	C_{max} ↓14%; AUC ⇔	Prasugrel can be administered with drugs that elevate gastric pH, including PPIs and H_2 blockers No PPI effect
	PPI: lansoprazole	Single-dose drug + single-dose lansoprazole (30 mg)	Concomitant	C_{max} ↓29%; AUC ⇔	
Dabigatran	H_2 blocker: ranitidine	Single-dose drug + multiple-dose ranitidine (150 mg q.d.)	Staggered: drug administered 10 h after H_2 blocker	C_{max} ⇔; AUC ↑2%	No clinically meaningful change in drug exposure No PPI effect
	PPI: pantoprazole	Single-dose drug + multiple-dose pantoprazole (40 mg b.i.d.)	Concomitant	C_{max} ↓40%; AUC ↓28%	
Erlotinib	H_2 blocker: ranitidine	Single-dose drug + ranitidine (300 mg q.d. or 150 mg b.i.d.)	Concomitant or staggered: drug administered 10 h after the previous ranitidine evening dose and 2 h before the morning dose	Concomitant administration: C_{max} ↓54%; AUC ↓33%. Staggered administration: C_{max} ↓17%; AUC ↓15%	Erlotinib must be taken 10 h after the H_2-receptor antagonist dosing and at least 2 h before the next dose of H_2-receptor antagonist Partial PPI effect
	PPI: omeprazole	Single-dose drug + omeprazole (40 mg q.d.)	Concomitant	C_{max} ↓61%; AUC ↓46%	Avoid concomitant use with PPIs

Zhang L. et al. CPT, 96 (2014) 266-277.

Is There a Predictive Correlation Between Key Physiochemical Properties of the Compounds and Their Clinical pH-effect?

- pKa
- log D at pH 7
- Molecular weight (MW)
- Melting point
- Intrinsic solubility
- Clinical dose
- Polar surface area (PSA)
- Freely rotatable bonds (FRB)
- Hydrogen donors
- Hydrogen acceptors





$$\text{AUC ratio} = \text{AUC}_{\text{cotreated}}/\text{AUC}_{\text{untreate}} \qquad C_{\max}\ \text{ratio} = C_{\text{max-cotreated}}/C_{\text{max-untreated}}$$

Conclusion:

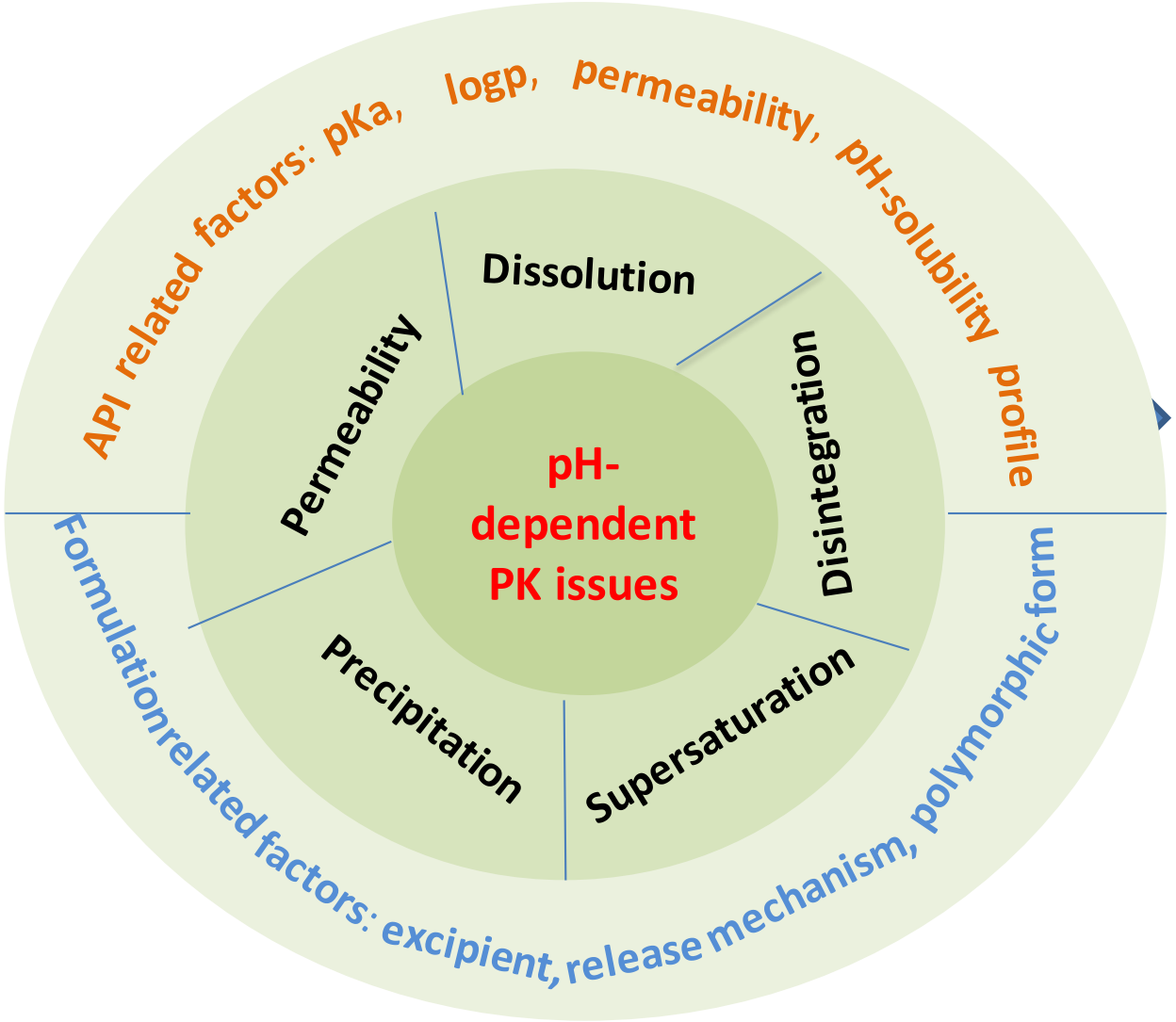
No significant linear correlation with any parameter or combination of parameters. While there may be a trend with respect to pKa, other related parameters can confound the analysis making simple correlations difficult.

High risk factors: free base, high dose, pKa range 3.5–6, low solubility at high pH

Mathias. et al. Mol. Pharma., 10 (2013) 4063-4073.

Potential Impact on Generic Drug Development

pH-related PK issue is a function of several factors that control disintegration, dissolution, supersaturation, and precipitation



Potential Impact on Generic Drug Development

Possible formulation-related factors which may cause pH-related PK issue:

- IR: different excipients, e.g. salt-base conversion
- IR: different polymorphic forms
- DR: different enteric polymers
- ER: different release mechanisms, e.g. osmotic pump vs hydrophilic matrix
- ER: different pH modifiers
- ER: different hydrophilic matrices
- ???

How to Make Sure Generic Drugs' in vivo PK Performance is Similar to the Brand Drugs in Subjects with Elevated Stomach pH?

Regulatory guidance:

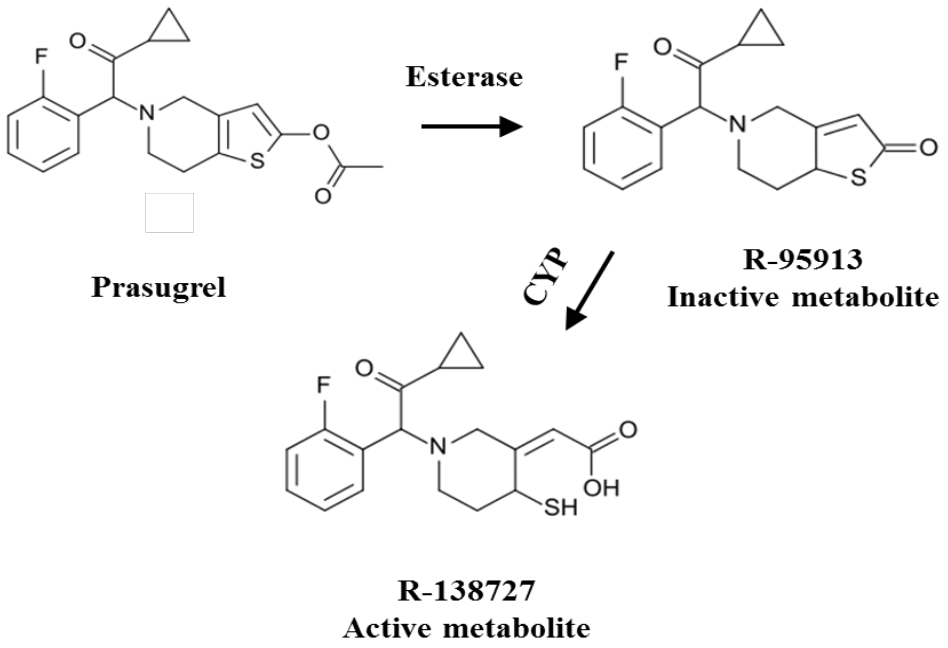
- ✓ Pharmaceutical equivalence
- ✓ In vitro dissolution study at different pHs (modified release)
- ✓ In vivo fast and fed BE PK studies in healthy subjects

Research activities:

- ✓ In vitro two-stage dissolution study
- ✓ In vivo PPI PK study
- ✓ Biopredictive dissolution development
- ✓ Modeling and simulation

Case Example A : Prasugrel (R vs T: different excipients)

Prasugrel -HCl
BCS: Class II, Weak base
Log p: 3.55
pKa=5.1
pH- solubility: base/salt
pH 1: 28 / 78 mg/mL
pH 4.5: 0.035 / 0.32 mg/mL
pH 6.8: 0.01/0.07 mg/mL
Formulation: HCl salt, IR tablet

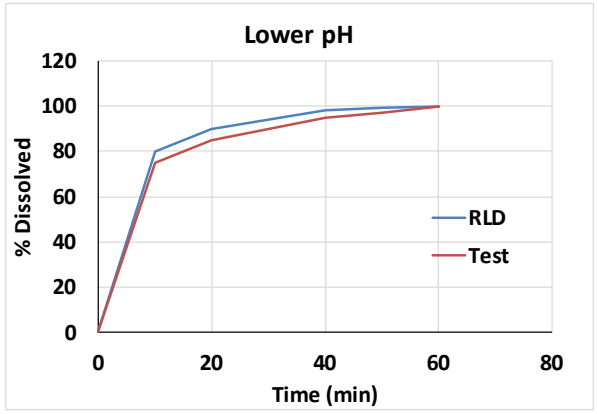


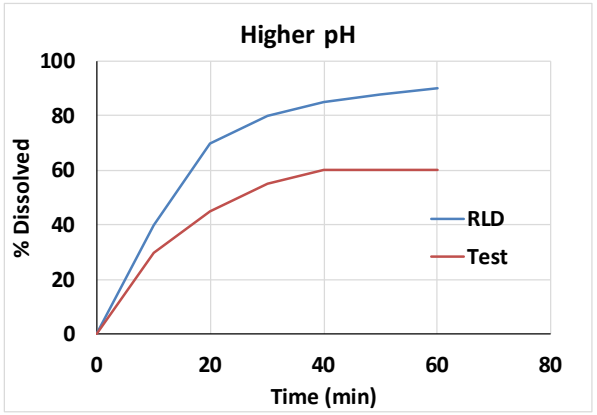
No PPI effect

Prasugrel	H_2 blocker: ranitidine	Multiple-dose drug + multiple-dose ranitidine (150 mg b.i.d.)	Concomitant	C_{max} ↓14%; AUC ⇔	Prasugrel can be administered with drugs that elevate gastric pH, including PPIs and H_2 blockers
	PPI: lansoprazole	Single-dose drug + single-dose lansoprazole (30 mg)	Concomitant	C_{max} ↓29%; AUC ⇔	

Zhang L. et al. CPT, 96 (2014) 266-277.

Information we have for the test product:





Please note that the data here are not real dissolution data, but has been generated simply to illustrate the in vitro dissolution situation for prasugrel salt test product.

Fast BE study: test is BE to the RLD.

Fed BE study: test is BE to the RLD.

RLD +PPI:

H_2 blocker: ranitidine	Multiple-dose drug + multiple-dose ranitidine (150 mg b.i.d.)	Concomitant	C_{max} ↓14%; AUC ⇔
PPI: lansoprazole	Single-dose drug + single-dose lansoprazole (30 mg)	Concomitant	C_{max} ↓29%; AUC ⇔

Question: Test +PPI?

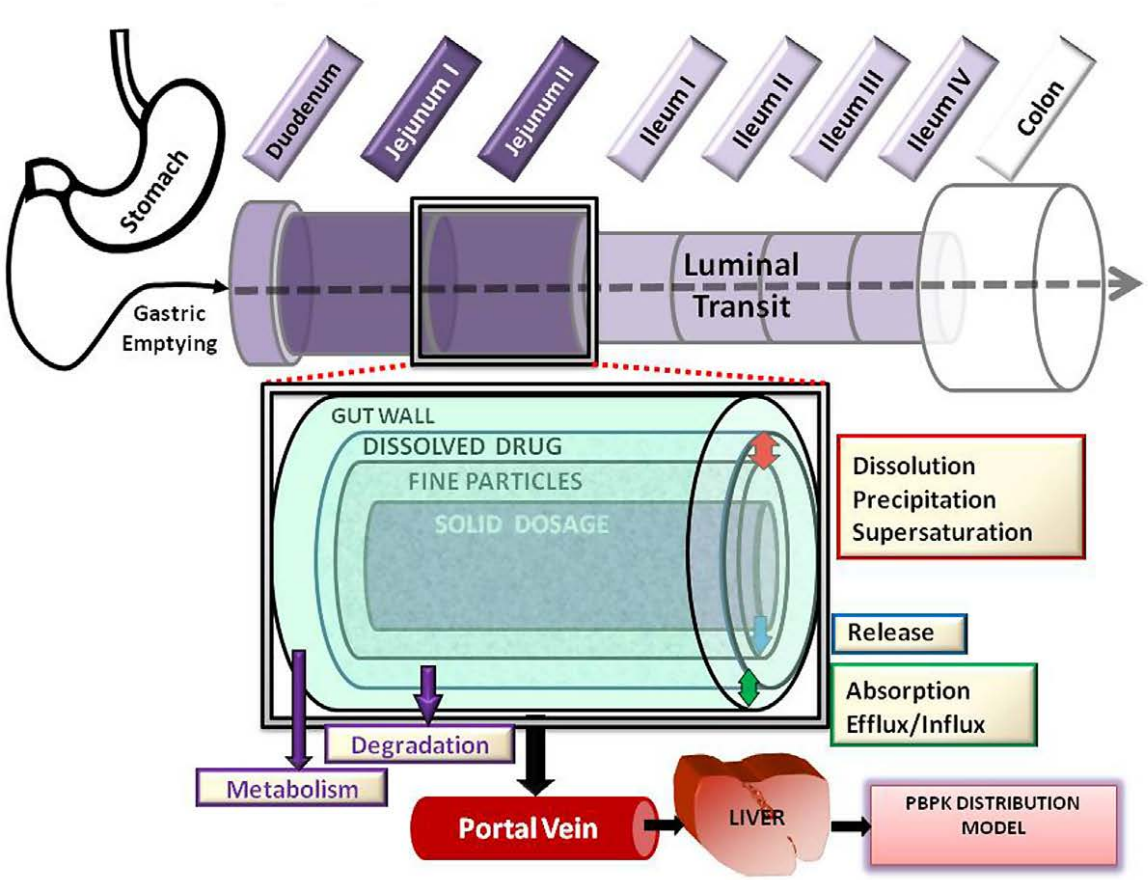
A Mechanistic Absorption Framework (ADAM model)

Mechanistic absorption model

- Dissolution
- Disintegration
- Supersaturation
- Precipitation
- Degradation

In vitro information

In vivo PK performance

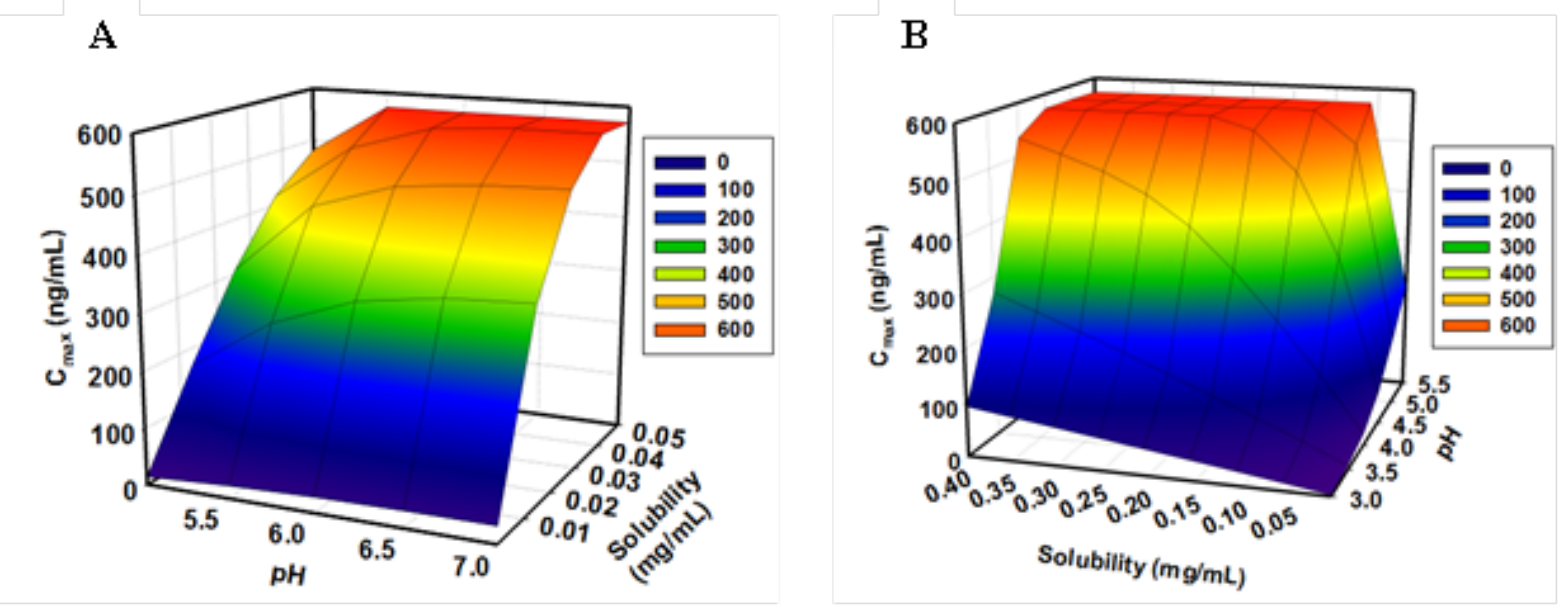


Question 1: Why test product has slower dissolution compared to the RLD?

Observation: Conversion from salt to free base during storage or manufacturing (~40%)

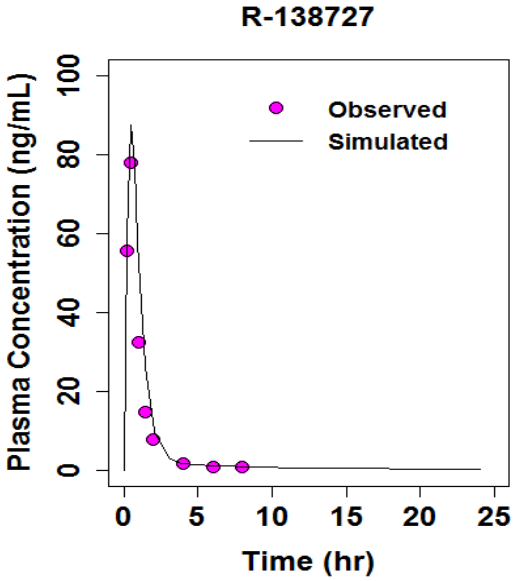
Question 2: How much control over disproportionation % is needed to ensure bioavailability in subjects with elevated gastric pH?

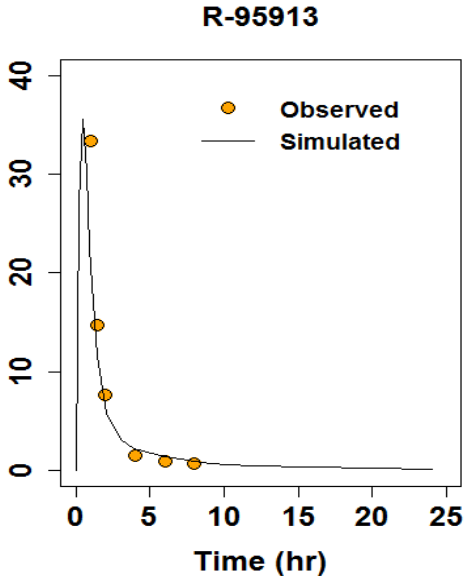
Cmax is Sensitive to the Solubility Values at pH 4.5 and Between pH 5 to 7

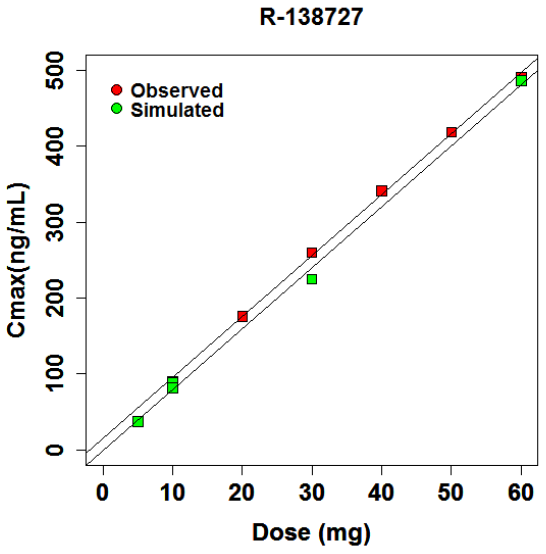


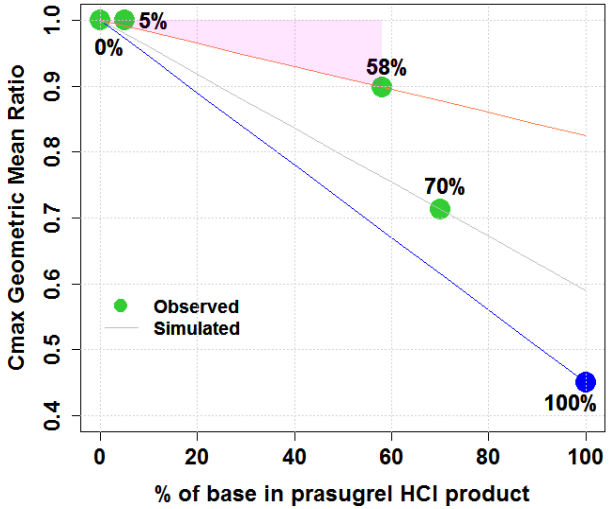
Fan et al. AAPS J 19 (2017) 1479-1486

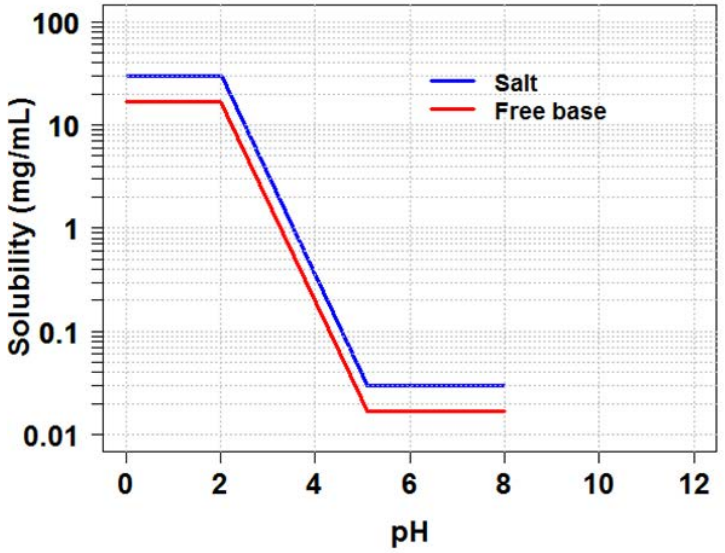
In Vivo Intrinsic Solubility





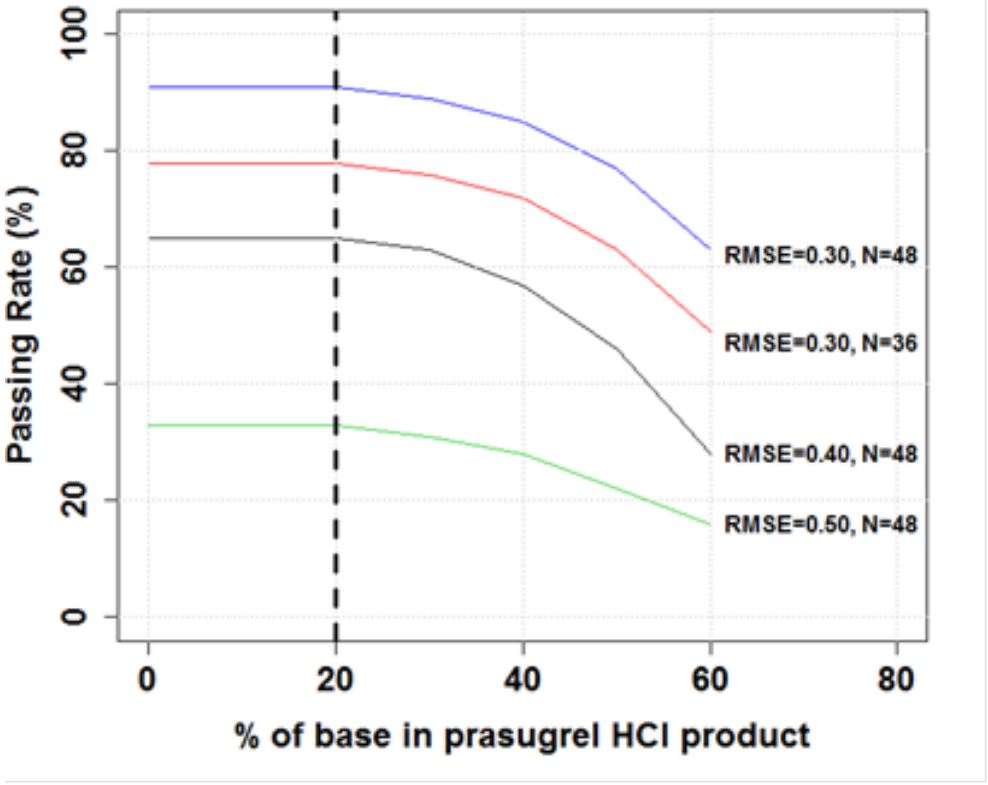






Fan et al. AAPS J 19 (2017) 1479-1486

Effect of Extent of Conversion of Salt to Free Base on BE Evaluation



Less than 20% free base in prasugrel HCl product ensures in vivo BE of the generic product including in subjects that may be taking PPI

Fan et al. AAPS J 19 (2017) 1479-1486

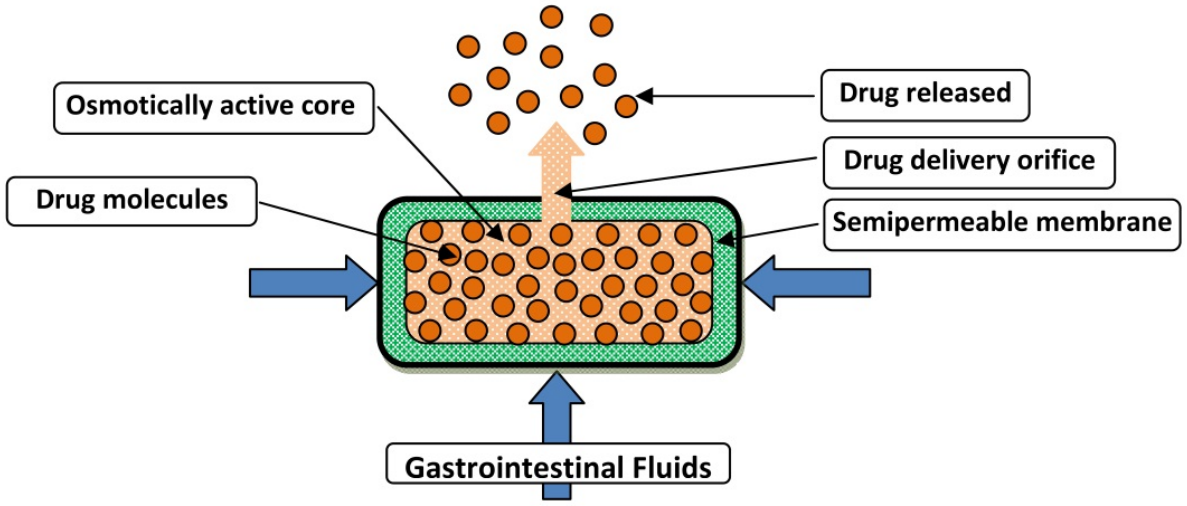
Conclusions (Prasugrel HCl)

- Less than 20% free base in prasugrel HCl product ensures in vivo BE of the generic product including in subjects that may be taking PPI
- For BCS 2 and 4 immediate-release formulations, mechanism-based modeling could be challenging as in vitro solubility and dissolution might not be predictive.
- Multiple datasets with or without PPI are desired for model calibration and parameter estimation.

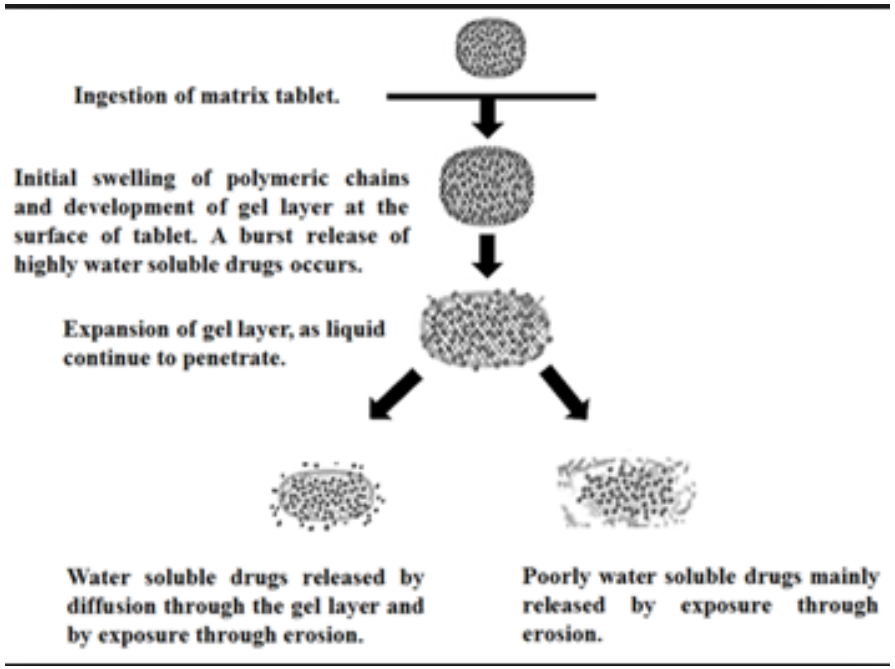
Case Example B : Nifedipine ER (R&T: different release mechanism)

BCS class II
pKa=3.93, weak acid
very low solubility across the physiological pH range

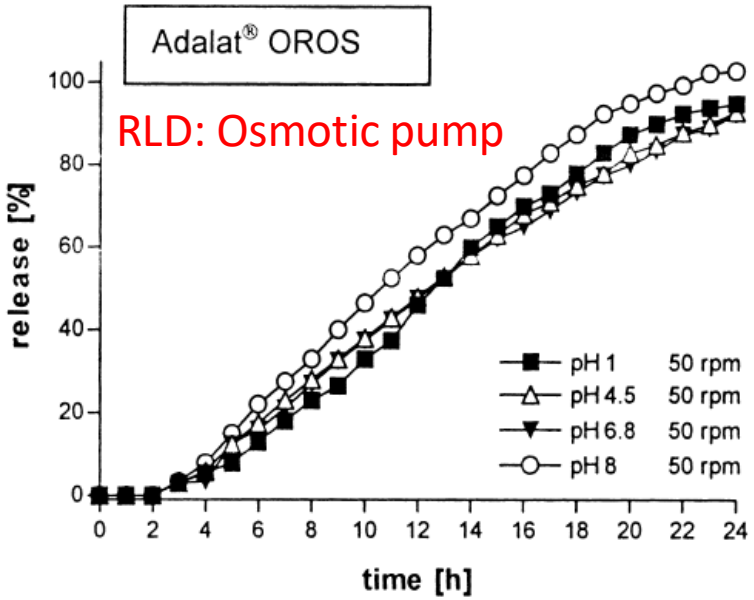
Reference: Adalat® OROS(Bayer AG, Leverkusen, Germany): osmotic pump
Test: CORAL ® (D.R. Drug Research S.R.L., Milano, Italy) : hydrophilic matrix



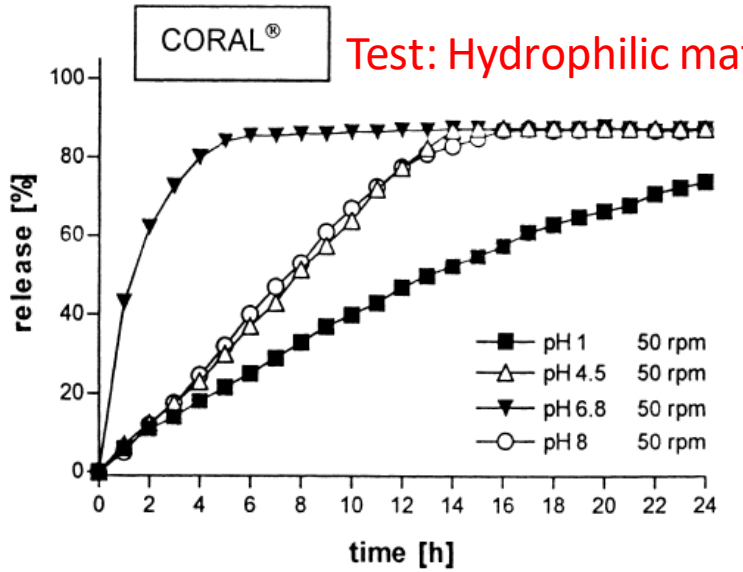
Osmotic pump



hydrophilic matrix



RLD: Osmotic pump



Test: Hydrophilic matrix

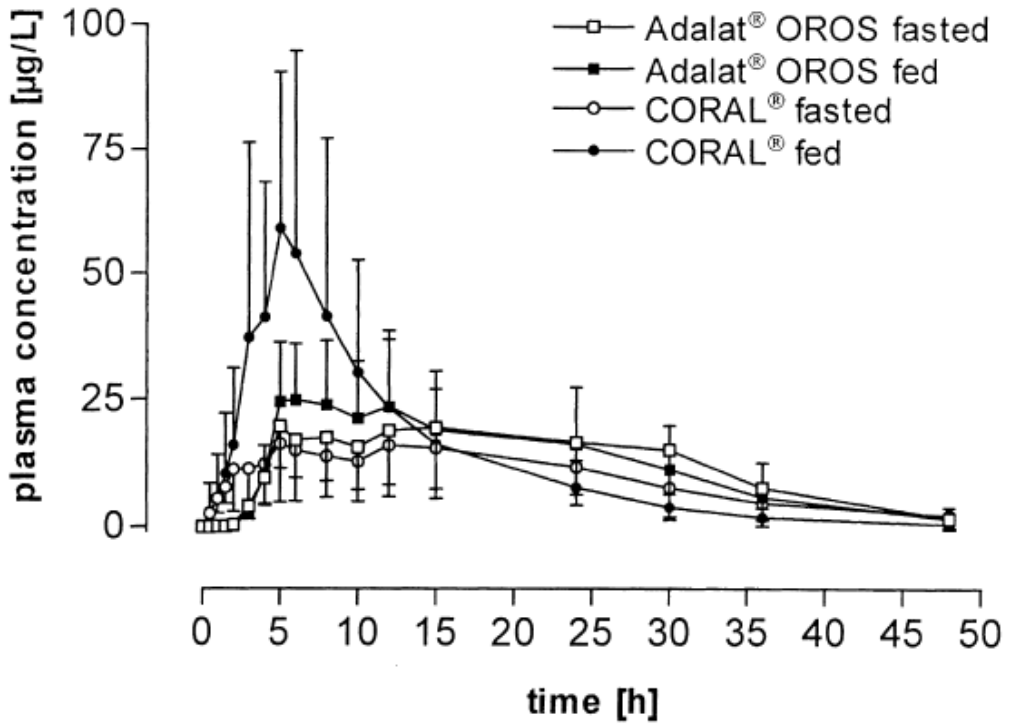
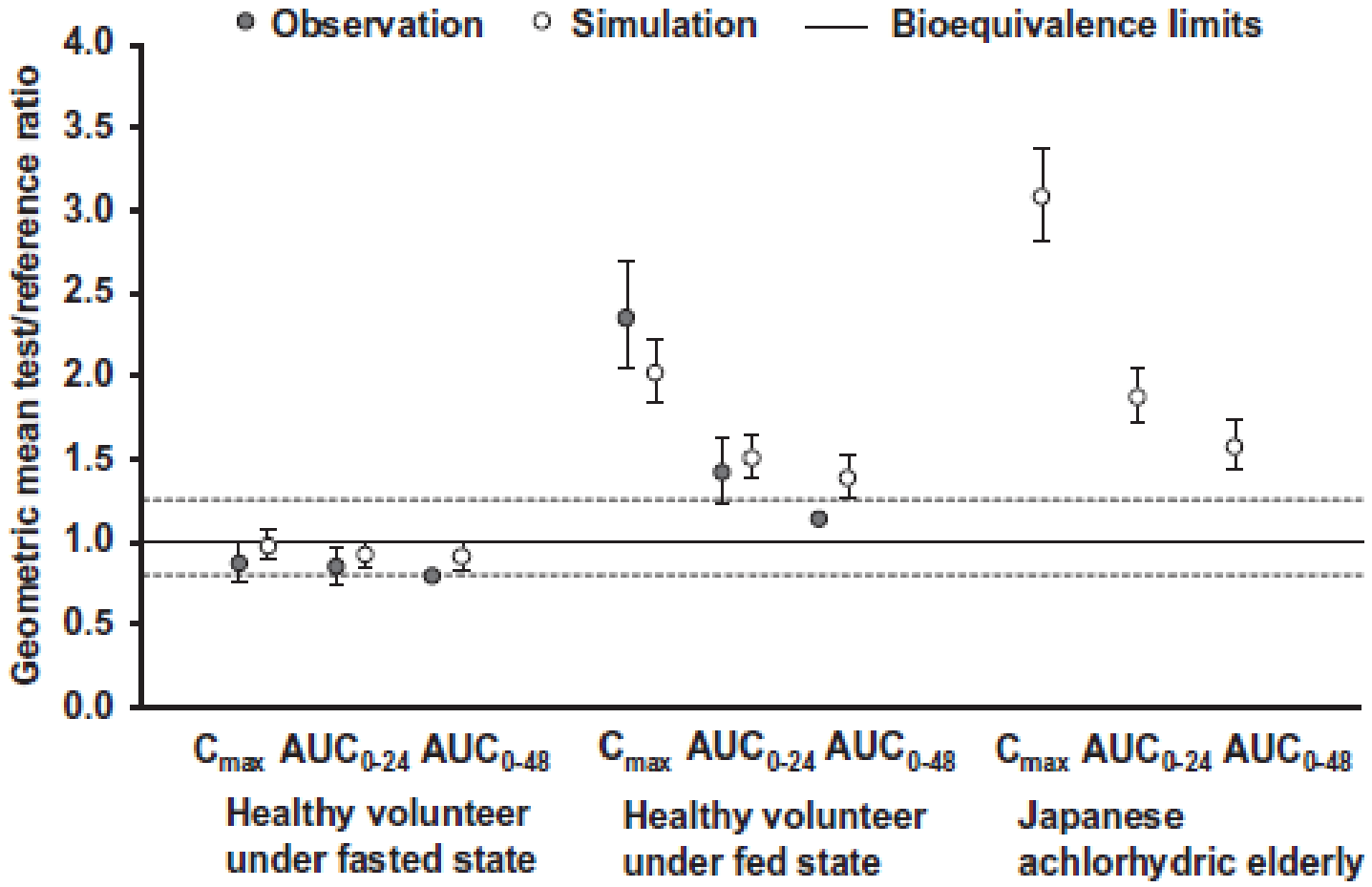


Fig. 1. Mean plasma concentration (±S.D.) vs. time curves of nifedipine determined after oral administration of Adalat® OROS and CORAL® under fasting conditions and after a high-fat breakfast in 24 healthy young volunteers in a four-period changeover design.

Schug et al. EJPS. 15 (2002) 279-285

pH dependent PK issue?



K. Doki et al. EJPS. 109 (2017) 111-120

Dose the Test Nifedipine Product Have PPI Effect?

Regulatory activity:

Test: Nifedipine ER, 60 mg, Hydrophilic matrix

Reference: PROCARDIA XL extended-release tablet, 60 mg (Pfizer, Inc.), Osmotic pump

1. **Clinical study (2017): Drug Interaction With Proton Pump Inhibitors for Nifedipine ER Tablets**

2. **In vitro dissolution study**

3. **PBPK modeling and simulation**

NIH U.S. National Library of Medicine

ClinicalTrials.gov

Sponsor:

Food and Drug Administration (FDA)

Collaborator:

BioPharma Services, Inc

NCT 00768560

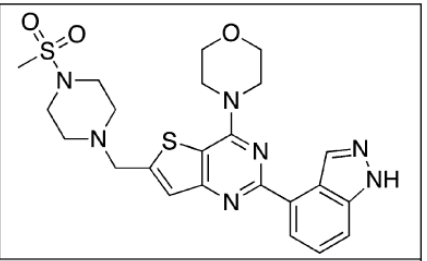
Some additional issues we may need to consider:

1. How much information obtained from the fed BE study in healthy subjects can be used to identify the potential pH-related PK issue?
2. Is the in vitro dissolution method in vivo predictive?
3. Is pH-related PK issue dissolution rate dependent or other kinetics dependent?

How much information obtained from Fed BE study in healthy subjects can be used to identify the potential pH related PK issue?

PPI interaction effect > Food effect

Table 1. Physicochemical Properties of GDC-0941

BCS: Class II	
MDCK permeability (A to B): 10 x 10^{-6} cm/s	
Formula weight: 513.6 (freebase)	
Log P: 3.22 ± 0.22	
pKa: 1.54 (basic), 4.24 (basic)	
Solid form: Crystalline salt	
pH-solubility:	
pH 1: 0.75 mg/mL	
pH 4.4: < 0.001 mg/mL	
Simulated gastric fluid (SGF, pH 1.2): 0.25 mg/mL	
Fasted state simulated intestinal fluid (FaSSIF, pH 6.8): < 0.001 mg/mL	
D:S ratio > 100L	

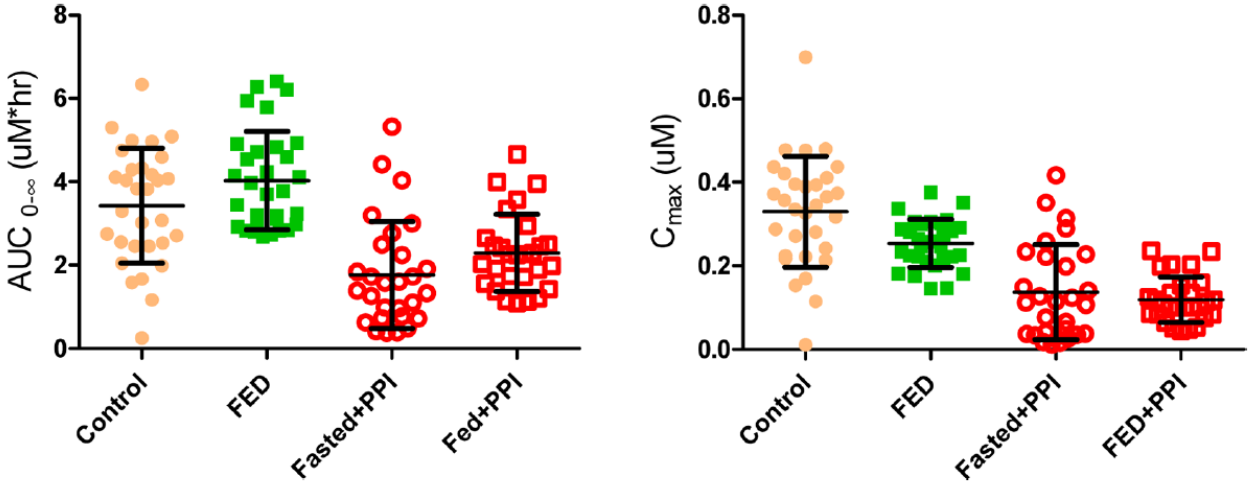
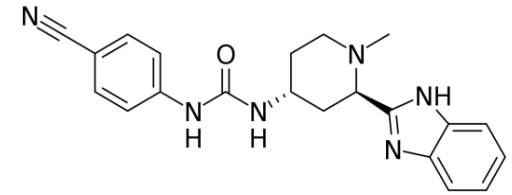


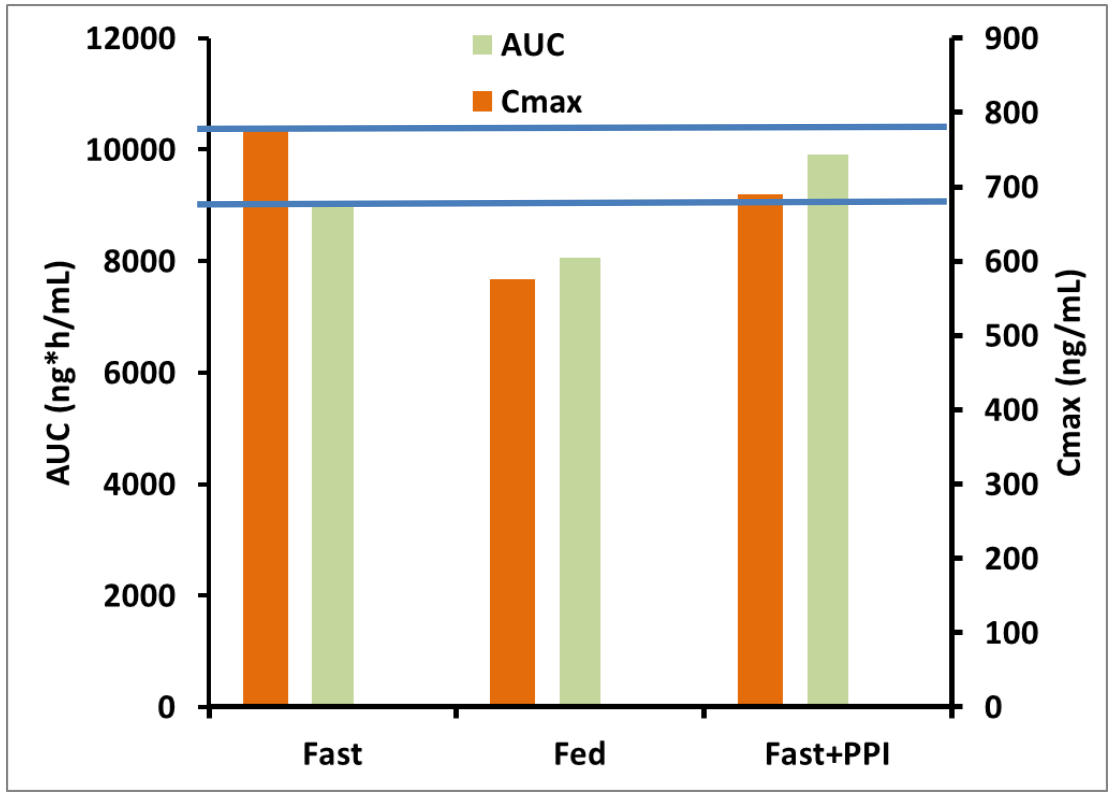
Figure 4. Individual GDC-0941 exposure after oral administration of 40 mg GDC-0941 under fasting, fed (high-fat meal), and hyopchlorhydric (PPI-altered pH) conditions.

Ware et al. Mol. Pharm. 10 (2013) 4047-4081

PPI interaction effect < Food Effect

Glasdegib
BCS: Class II, Weak base
Log p: 2.28
pKa=6.7 (basic)
Waster solubility: 0.0469 mg/mL
Formulation: maleate salt IR tablet

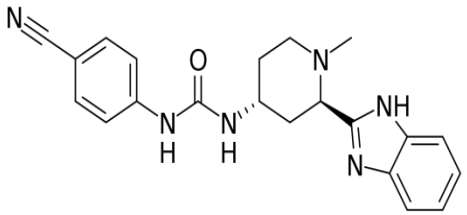




Giri et al. Cancer Chemother Pharmacol. 80 (2017) 1249-1260.

In vivo Predictive Dissolution Method?

Pioglitazone-HCl
BCS: Class II, Weak base
Log p: 2.3
pKa=5.8 and 6.8 (basic)
pH- solubility:
pH 1.2: 4.4 mg/mL
pH 3.0: 0.042 mg/mL
pH 4.0: 0.005 mg/mL
pH 5.0: 0.0005 mg/mL
pH 6.8: 0.0003 mg/mL
Formulation: maleate salt IR tablet



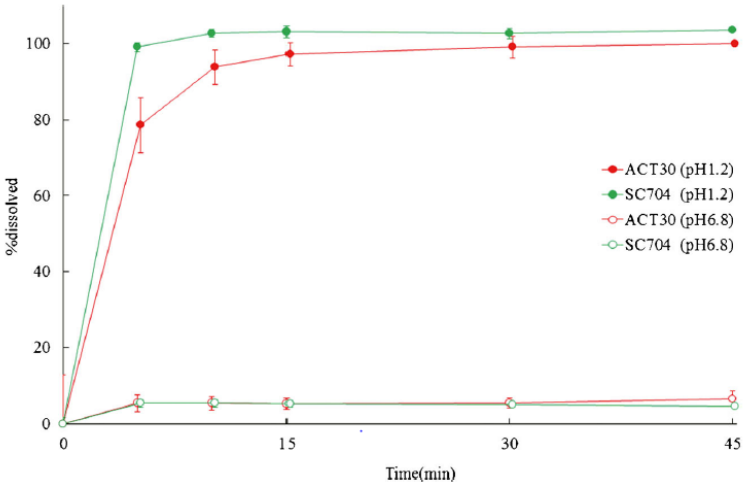


Fig. 1. Dissolved drug-time profiles with USP apparatus II dissolution test in JP1 medium (pH 1.2) and in JP2 medium (pH 6.8). Each data point represents mean±S.D. (n=12)

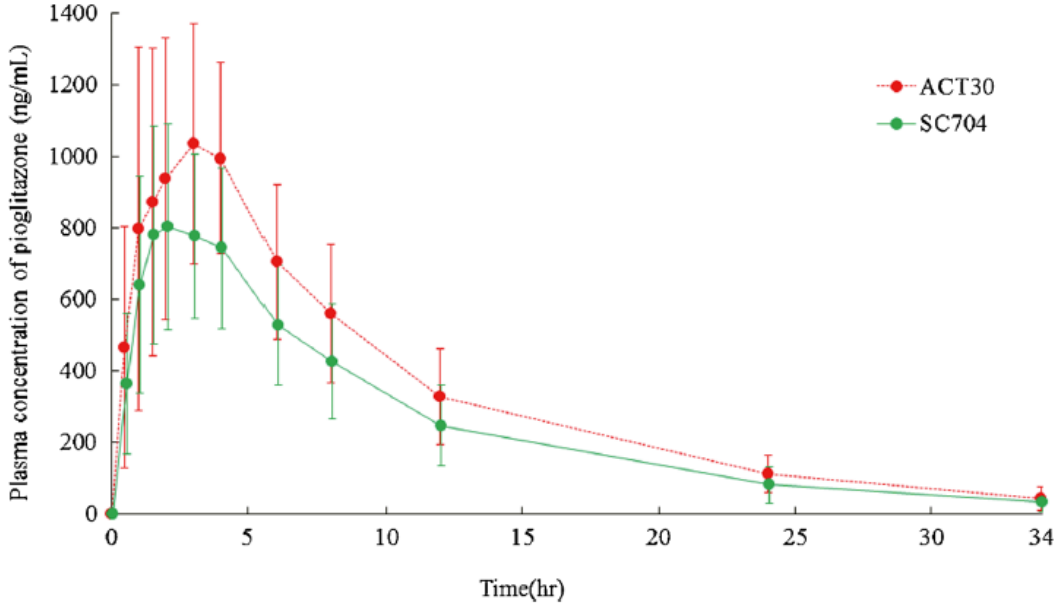


Fig. 2. Plasma concentration–time profiles of pioglitazone after an oral administration of a product in healthy male volunteers. Each data point represents mean±S.D. (n=20)

90% CI AUCt: 68.3-83.6%
Cmax: 70.5-88.8%

Sugita et al. The AAPS Journal. 16 (2014) 1119-1127.

The amount of HPC in the oral formulation of pioglitazone-HCl affected the particle size distribution of precipitated pioglitazone and further affect the in vivo PK performance

HPC : hydroxypropyl Cellulose

SC704: HPC/pioglitazone (w/w)=1/100
ACT30: HPC/pioglitazone (w/w)=10/100

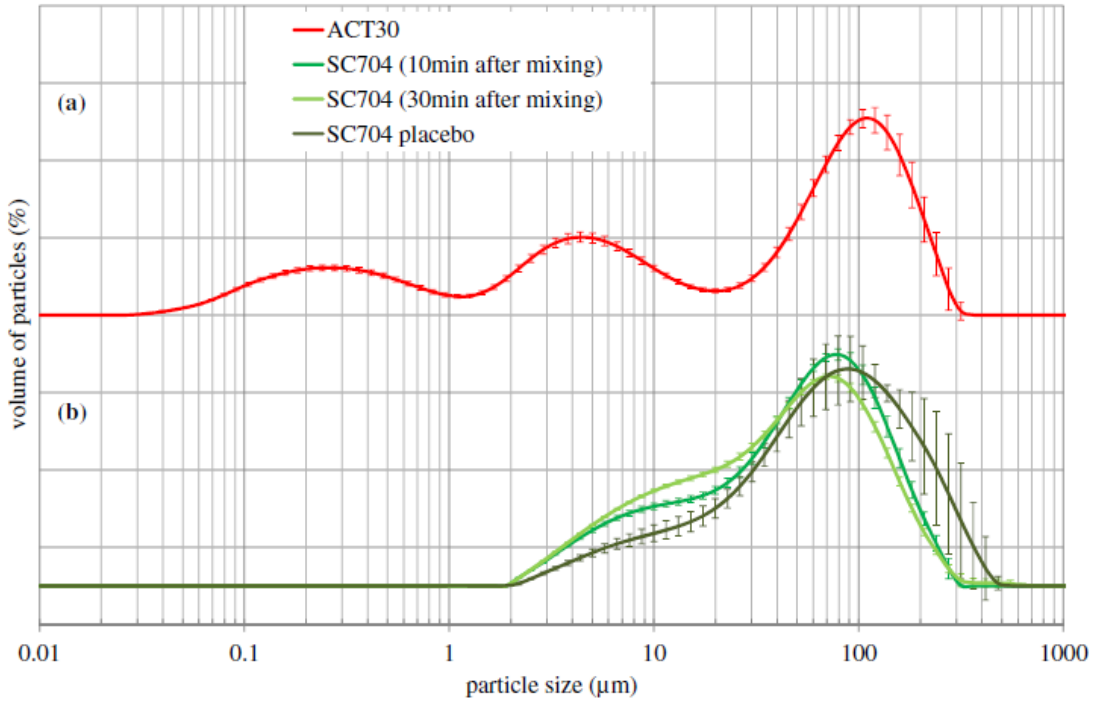


Fig. 3. The particle size distributions of the precipitated drug from ACT30 (**a**), SC704 and SC704 $_{(placebo)}$ (**b**). Each data line represents mean±S.D. (n=5)

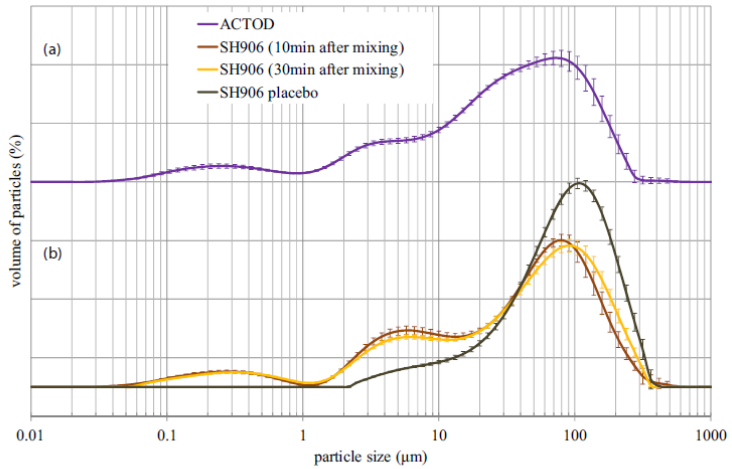


Fig. 7. The particle size distributions of the precipitated drug solutions of ACTOD30 (**a**), SH906 and SH906$_{(placebo)}$ (**b**). Each data line represents mean±S.D. (n=5)

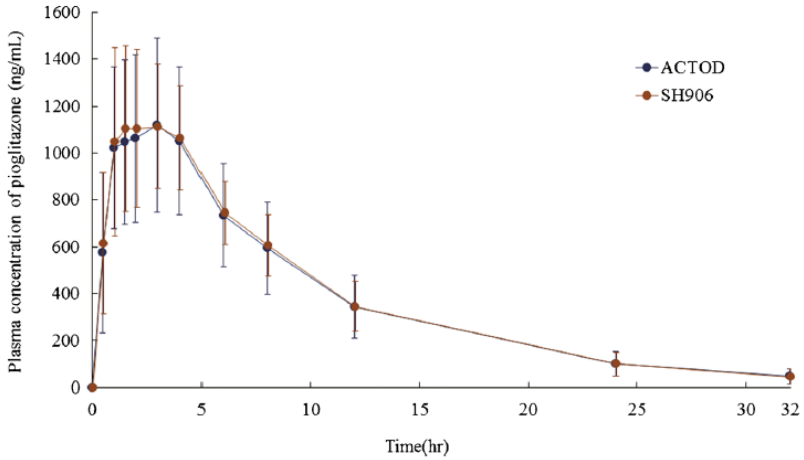
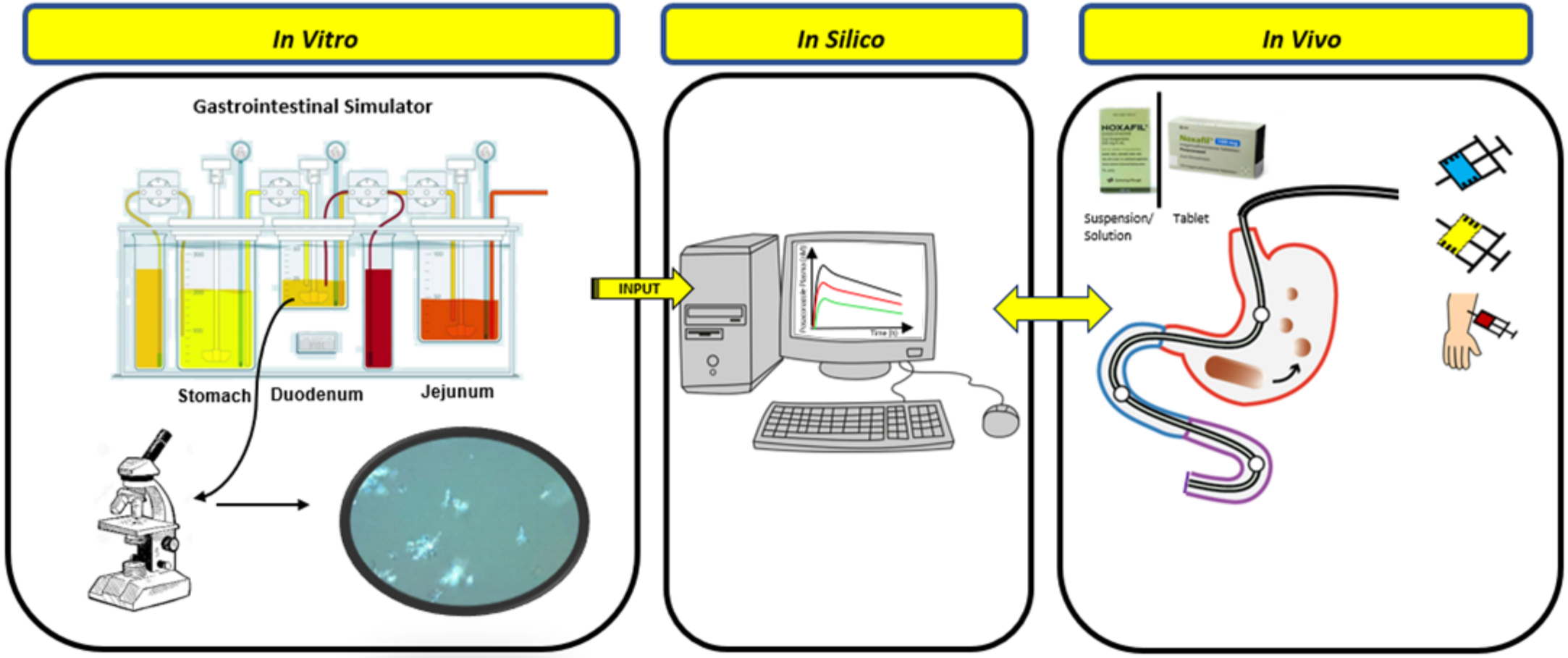


Fig. 8. Plasma concentration–time profiles of pioglitazone after an oral administration of a product in healthy male volunteers. Each data point represents mean±S.D. (n=24)

Sugita et al. The AAPS Journal. 16 (2014) 1119-1127.

Evaluation and Optimized Selection of Supersaturating Drug Delivery Systems of Posaconazole (BCS class 2b) in the Gastrointestinal Simulator (GIS): an in vitro-in silico-in vivo Approach



Hens et al. EJPS, 115 (2018), 258-269.

Kinetic Dissolution from In Vitro Microdissolution Test for Model Compounds

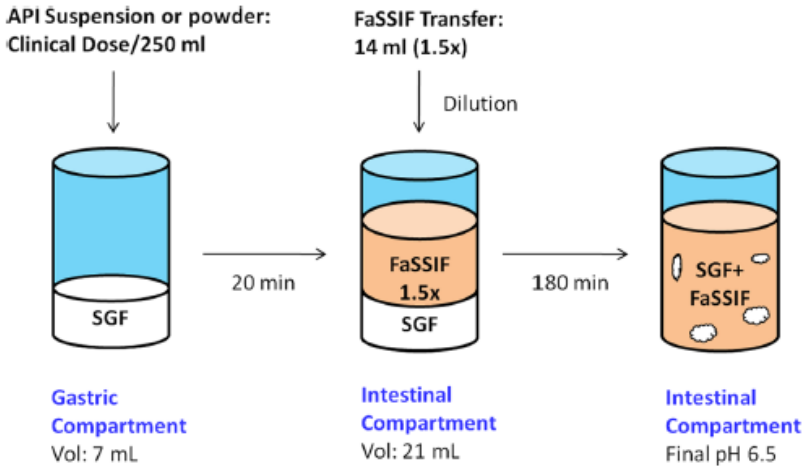


Figure 1. Schematic diagram of *in vitro* microdissolution pH-shift test.

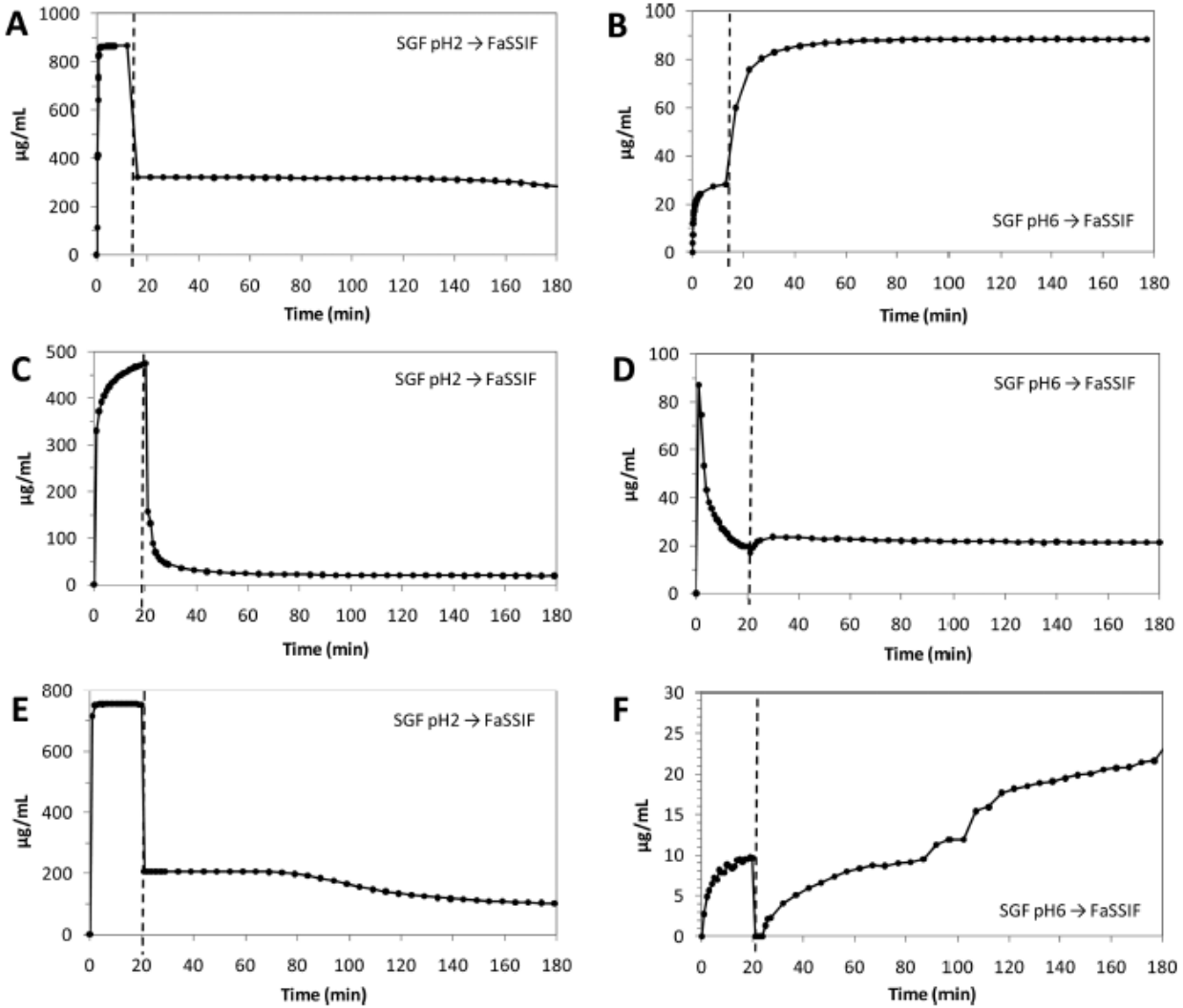
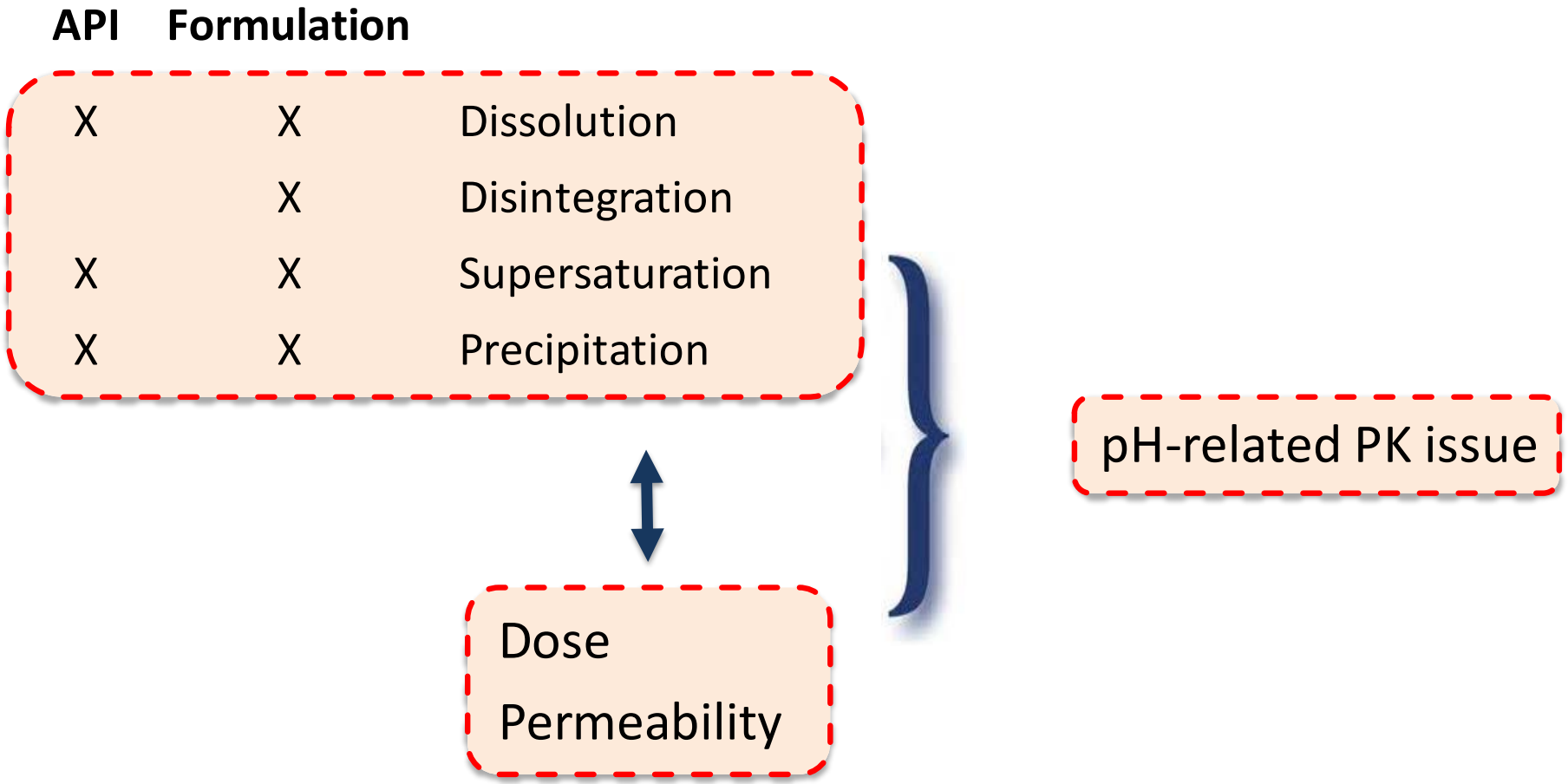


Figure 2. Kinetic dissolution from *in vitro* microdissolution test for model compounds: Gefitinib at gastric pH 2 (panel A) and pH 6 (panel B) at a dose equivalent to a 250 mg human dose; Erlotinib at gastric pH 2 (panel C) and pH 6 (panel D) at a dose equivalent to a 150 mg human dose; Ketoconazole at gastric pH 2 (panel E) and pH 6 (panel F) at a dose equivalent to a 200 mg human dose. The dotted line denotes the time of the media transfer to FaSSIF.

Mathias et al. Mol. Pharmaceutics 10 (2013) 4063-4073.

Is pH-related PK Issue Dissolution Rate Dependent or Other Kinetics Dependent?



Dissolution Rate Dependent

Changes in Cmax >> AUC

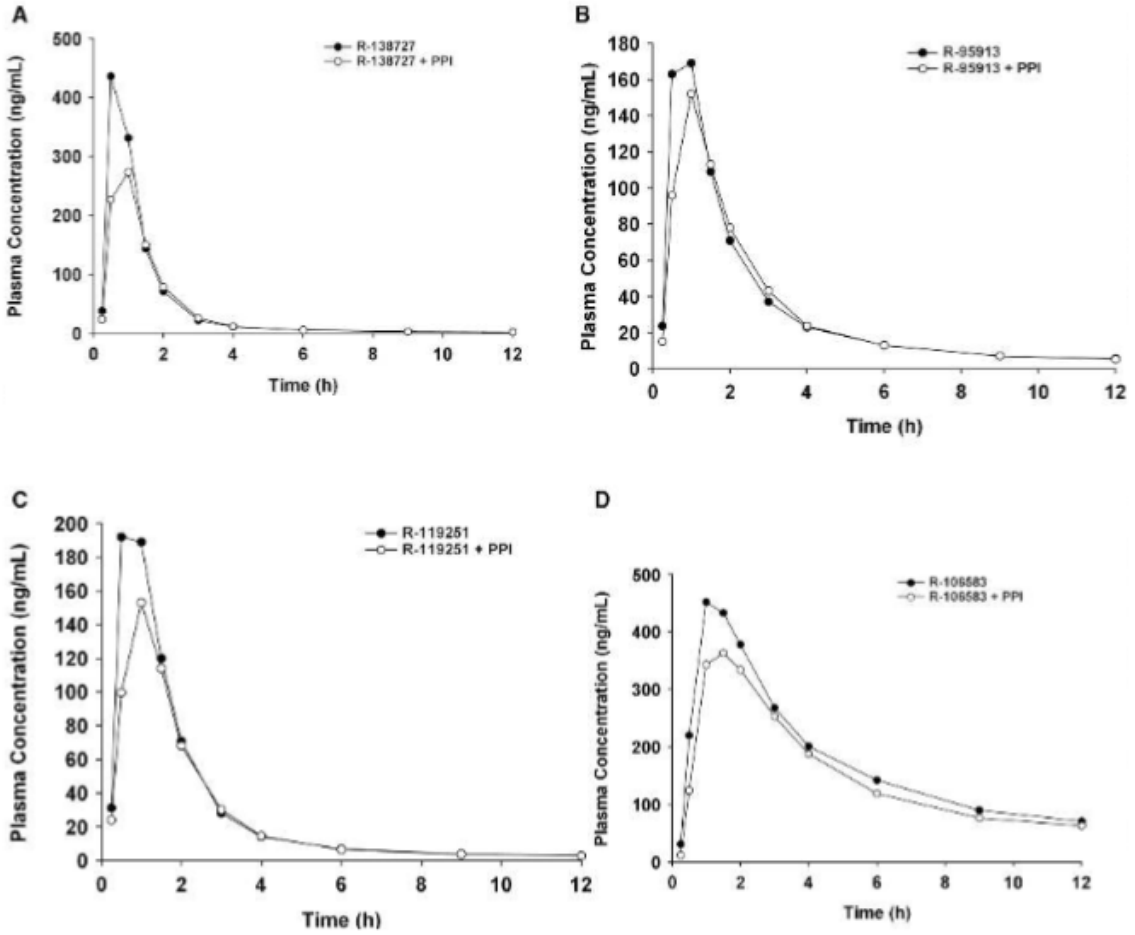


Figure 2. Geometric mean plasma concentrations for the prasugrel and clopidogrel metabolites with and without lansoprazole. (A) R-138727, (B) R-95913, (C) R-119251, (D) R-106583, and (E) SR26334. PPI, proton pump inhibitor.

Small et al. J Clin Pharmacol 48 (2008) 475-484.

Both Dissolution and Other Kinetics Dependent

Changes in AUC >> Cmax

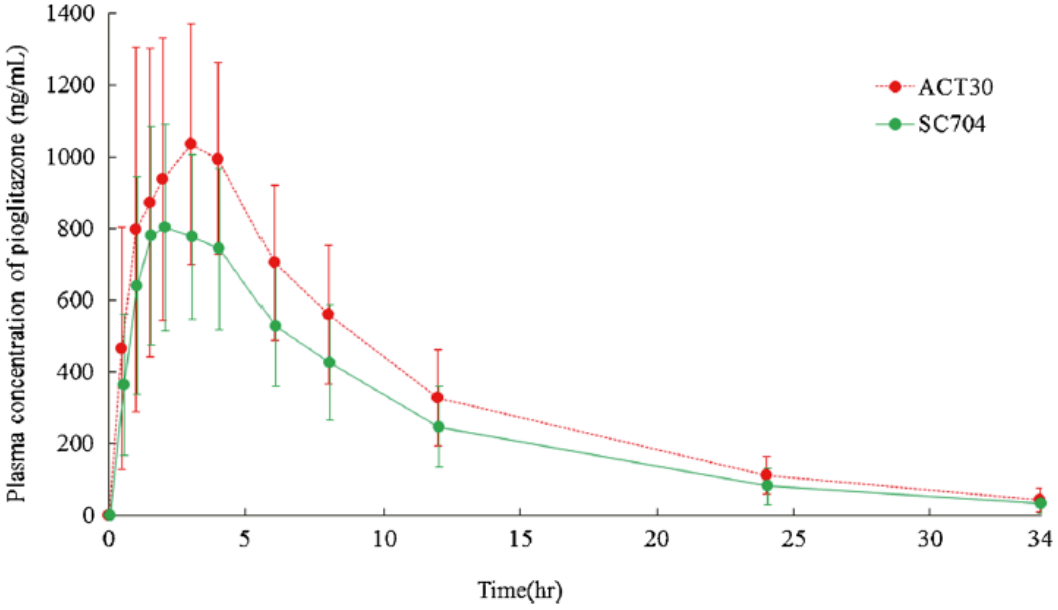


Fig. 2. Plasma concentration–time profiles of pioglitazone after an oral administration of a product in healthy male volunteers. Each data point represents mean±S.D. (n=20)

Sugita et al. The AAPS Journal. 16 (2014) 1119-1127.

Regulatory Research Activities

- In Vivo Predictive Dissolution (IPD) to Advance Oral Product Bioequivalence Regulation
  Awarded to the University of Michigan (#HHSF223201510157C)
- Wireless Analysis Device to Measure In Vivo Drug Dissolution in the Gastrointestinal Tract
  Awarded to the University of Michigan (#HHSF223201510146)
- Modernization of in vivo-in vitro oral bioperformance prediction and assessment
  Awarded to the University of Michigan (#HHSF223201310144C)
- Integrating supersaturation-precipitation mechanisms in mechanistic oral absorption models for predicting in vivo performance
  Awarded to Simcyp Limited (1U01FD005862)
- Phase behavior and transformation kinetics of a poorly water soluble weakly basic drug upon transit from low to high pH conditions
  Awarded to Purdue Univeristy (#HHSF223201710137C)
- Evaluation of formulation dependence of drug-drug interaction with proton pump inhibitors (PPIs) for oral extended-release drug products
  Awarded to BioPharma Services USA INC. (#HHSF223201610004I)

https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/genericdrugs/ucm567695.htm

Summary

- pH-related PK issue is a function of several factors that control disintegration, dissolution, supersaturation, and precipitation
- In vivo predictive dissolution method is needed to evaluate pH-related PK issue
- Fully validated PBPK model may be used to predict pH-related PK issue

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Dr. Gregory E. Amidon (University of Michigan, USA)

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Dr. Lynne Tayler (Purdue University)

BioPharma Services USA INC

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