Development of PBPK Model For Predicting Food Impact on Bioequivalence Assessment

PBPK 2021: Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches

Day 2 Session 2: Oral PBPK for Evaluating the Impact of Food on Bioequivalence

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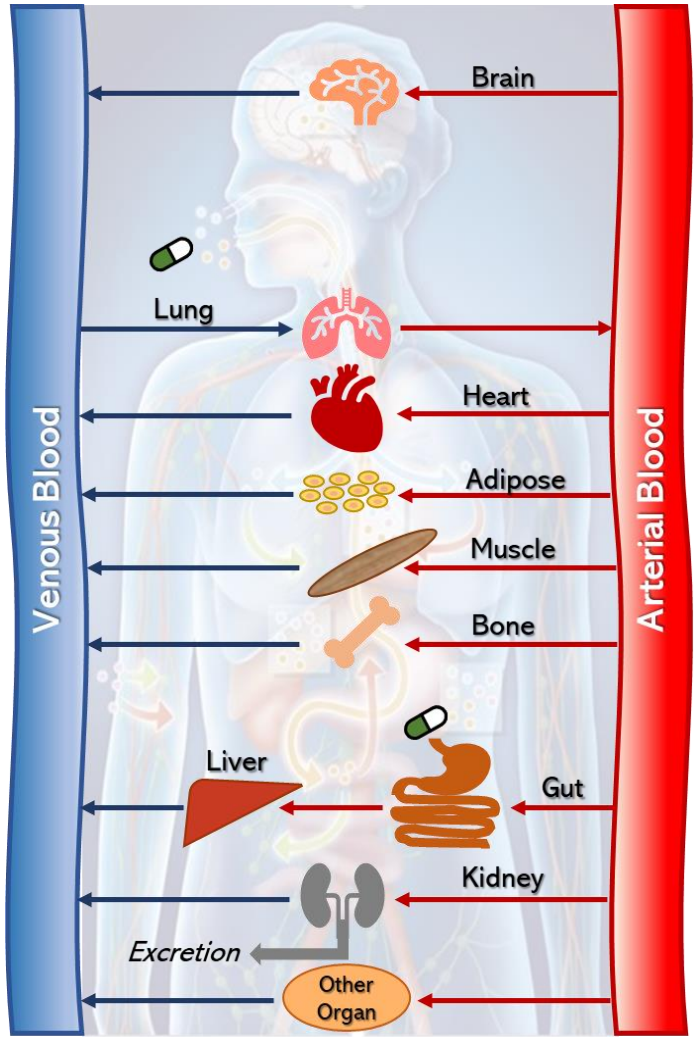
Physiologically Based Pharmacokinetic Model (PBPK)



- PBPK combines drug properties and physiological mechanisms using mathematical equations.

Rate of Drug Change in a Tissue = Rate of Drug In – Rate of Drug Out

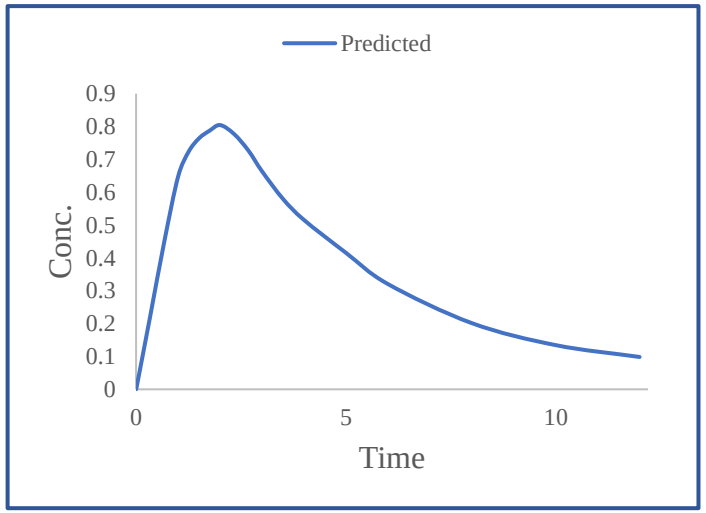


Fig-1: PBPK simulated drug profile in plasma

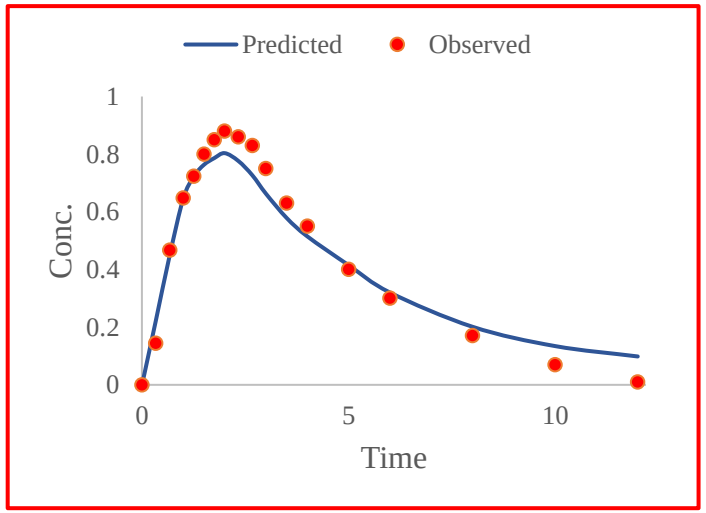


Fig-2: Observed & simulated profile in plasma

PBPK and Food Effect

- PBPK can be used during drug development for assessing[1]
  - Drug-drug interaction
  - Renal impairment
  - Setting Clinically Relevant Specifications
  - Pediatric dosing
  - Food effect
  - Risk Assessment
  - Hepatic impairment
  - Pharmacogenetics
  - Biowaiver
- Currently, 62.02% of all marketed drugs are intended for oral delivery[2]
- 40% of approved oral drugs show significant food effect on its pharmacokinetics[3]
- PBPK has been used to predict food effect along with probable mechanisms[4,5,6]
- PBPK has been used for conducting bioequivalence study in virtual population (VBE)[7]

[1]Wu F, The AAPS Journal-2021; [2]Zhong H, Pharmaceutics-2018; [3]O'Shea JP, J Pharm Pharmacol.-2019; [4]Li M, CPT Pharmacometrics Syst. Pharmacol.-2018; [5]Riedmaier AE, The AAPS Journal-2020; [6]Pepin XJH, The AAPS Journal-2020; [7]Zhang F, Clinical Pharmacokinetics-2021

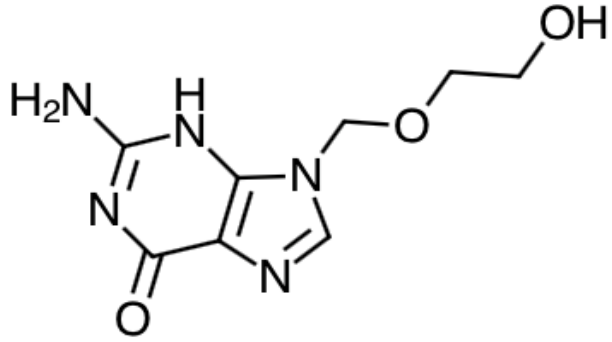
Aim of the Study

Acyclovir **PBPK Model Development** and Prediction of **Food Impact** on Bioequivalence Assessment of Acyclovir IR Tablet

Acyclovir (RLD-Zovirax®)

Acyclovir is an antiviral drug effective against herpes simplex virus.

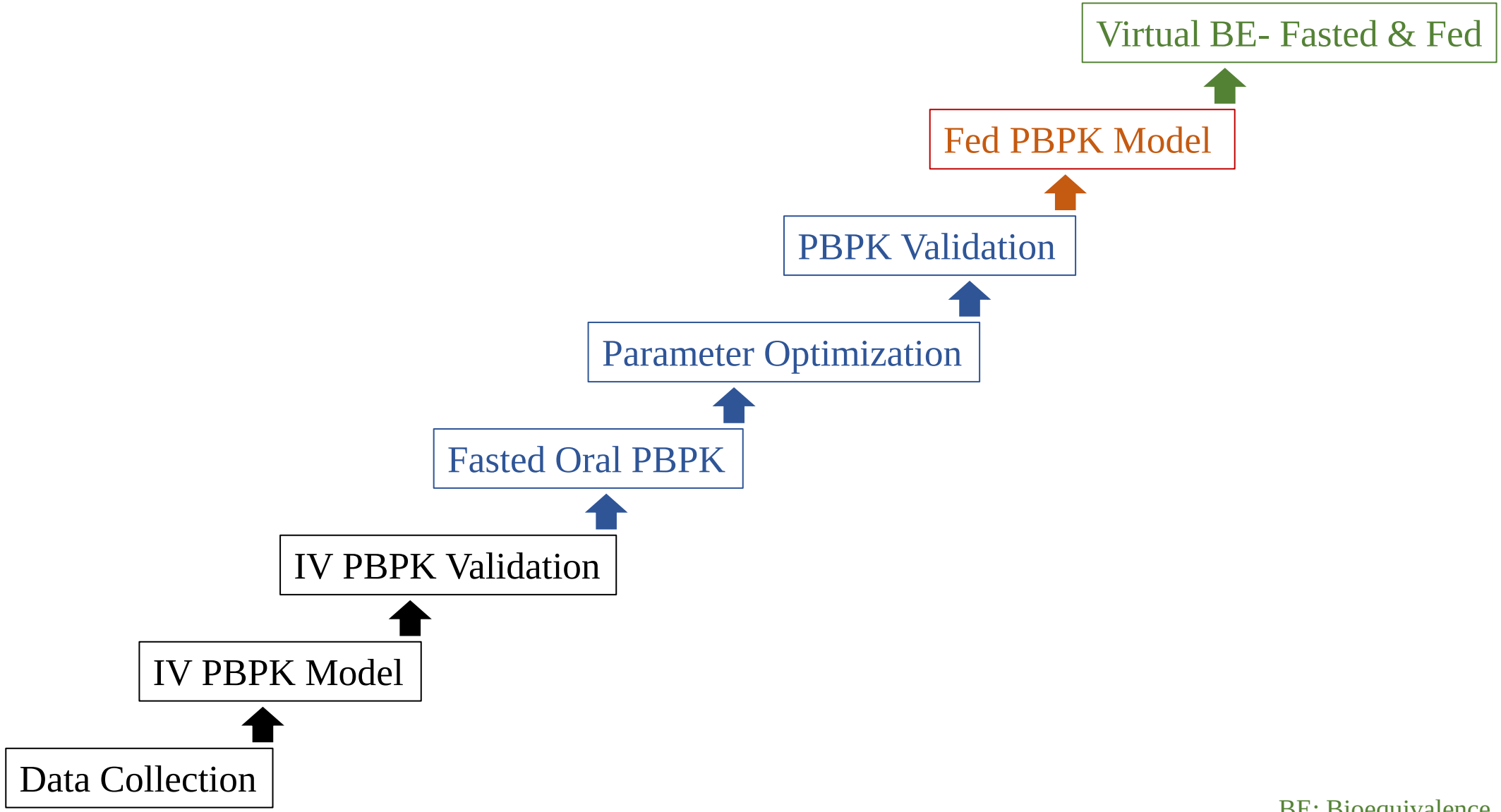
- ❑ Slightly soluble in water
- ❑ Ampholyte with both acidic and basic groups
- ❑ BCS III (at low dose) or BCS IV (at high dose)
- ❑ Available immediate release (IR) tablets are 200, 400, and 800 mg
- ❑ Absolute bioavailability (10 – 30%) in humans



Acyclovir

This poor systemic bioavailability (BA) is considered to be a result of the characteristics of the drug itself and not its delivery vehicle.

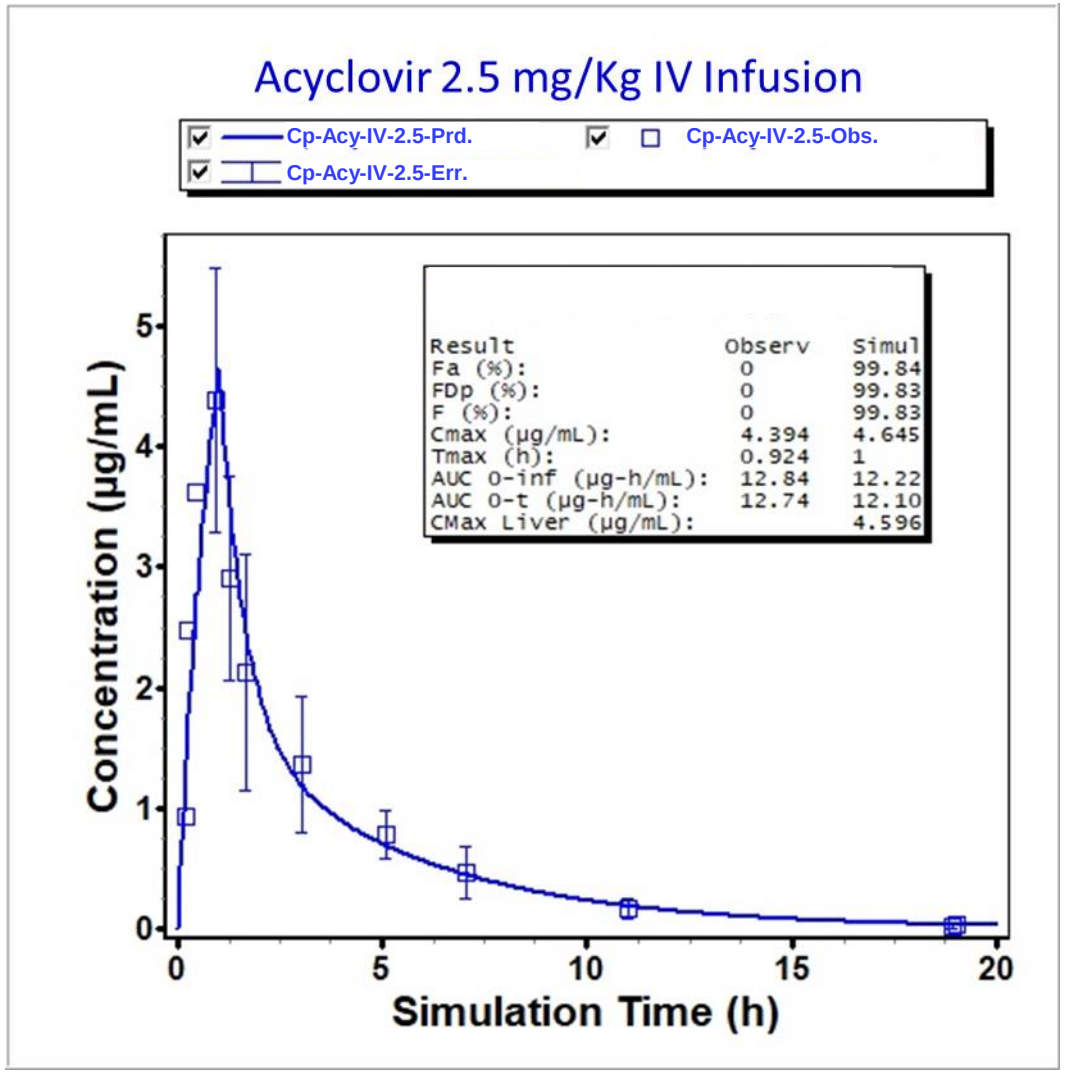
PBPK Model Development Steps



BE: Bioequivalence

Development of Acyclovir PBPK for **IV Administration**

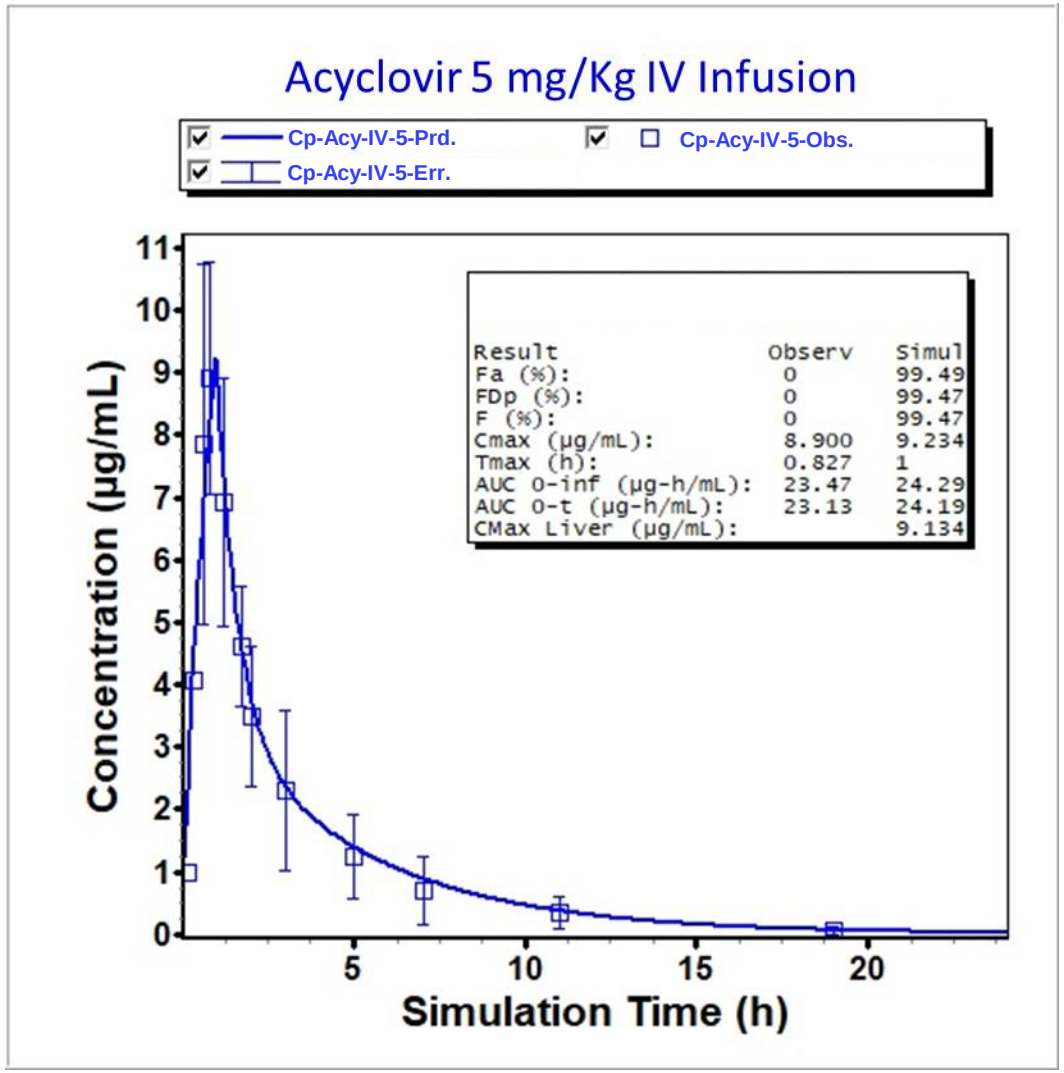
Acyclovir Disposition Model Development



Parameter	PE%
C max	5.7
AUC (0-inf)	-4.8
AUC (0-t)	-5.0

Laskin RL, Antimicrobial Agents and Chemotherapy-1982

Acyclovir Disposition Model Validation

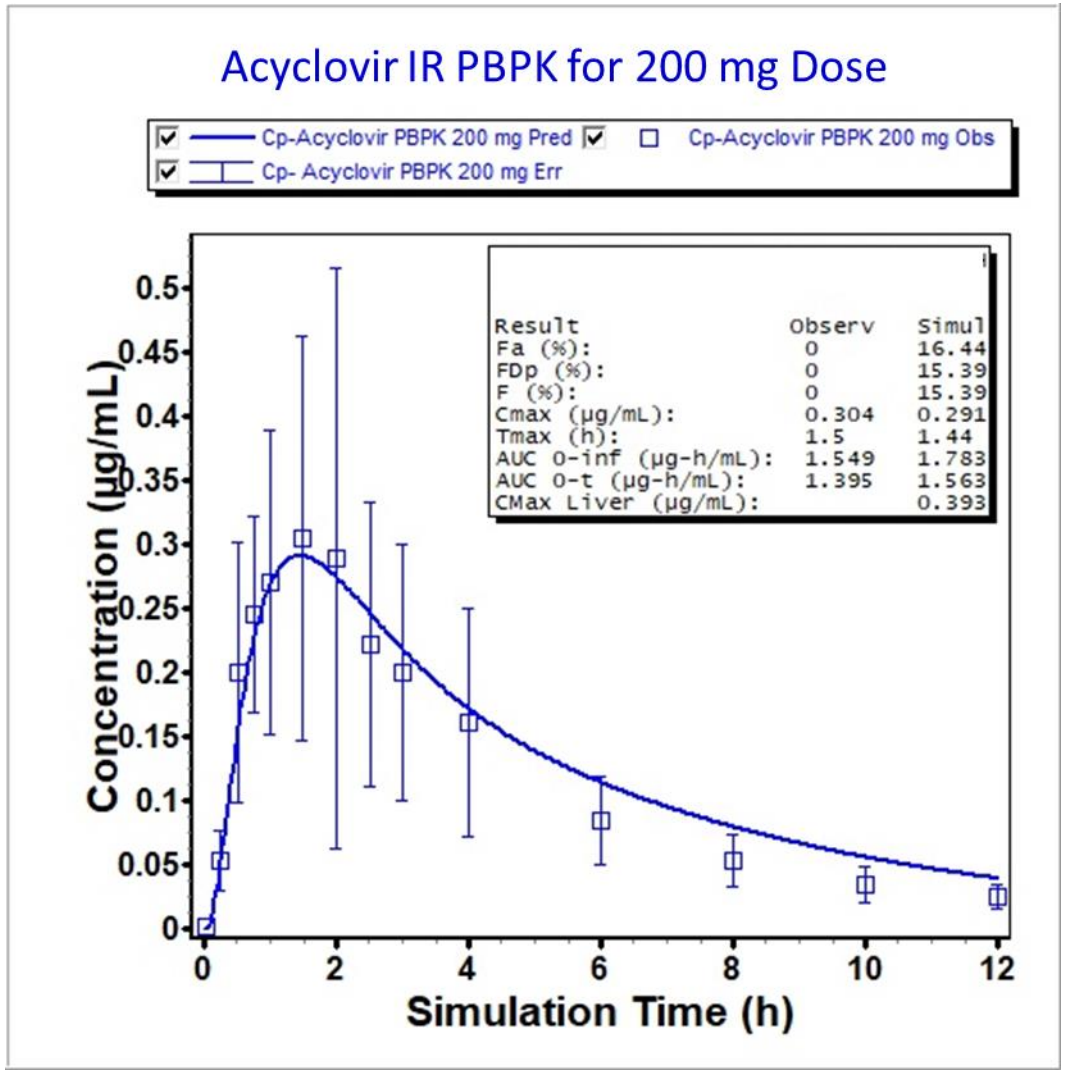


Parameter	PE%
C max	3.7
AUC (0-inf)	3.4
AUC (0-t)	4.5

Laskin RL, Antimicrobial Agents and Chemotherapy-1982

Development of Acyclovir PBPK for **Oral IR Tablet**

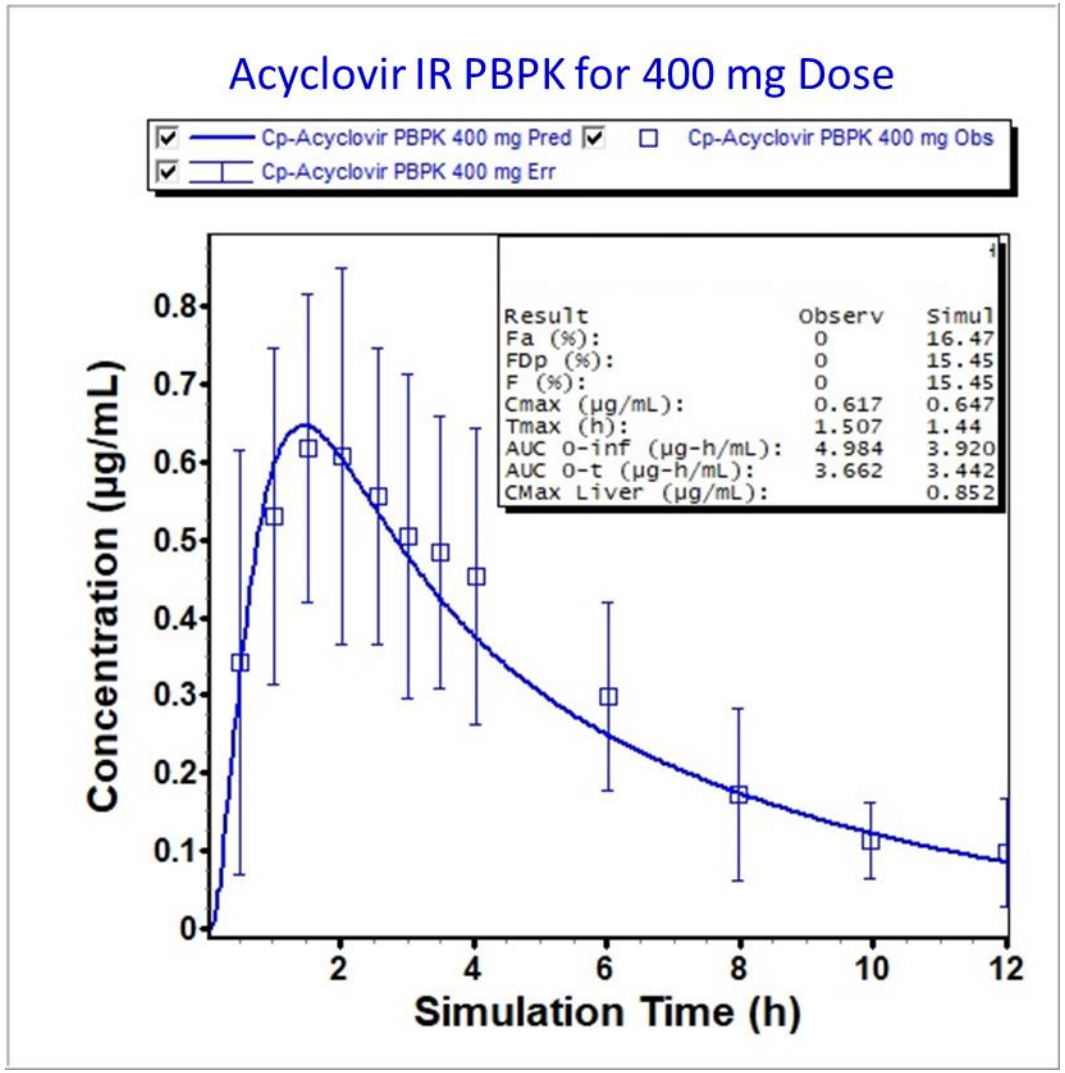
Acyclovir PBPK for IR Tablet-200 mg



Parameter	PE%
C max	-4.2
AUC (0-inf)	15
AUC (0-t)	12

Kubbinga M,Pharm Res-2015

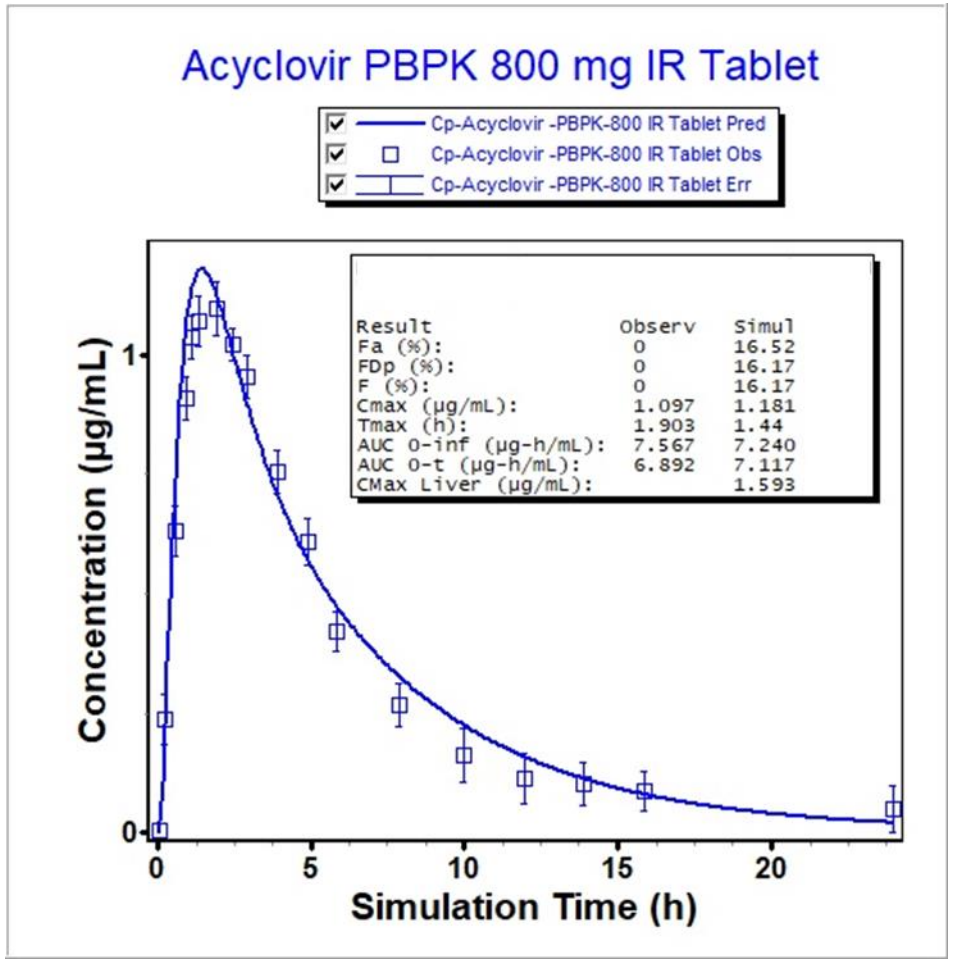
Acyclovir PBPK for IR Tablet-400 mg



Parameter	PE%
C max	3.7
AUC (0-inf)	-21
AUC (0-t)	-6

Amini H, Clin Drug Invest-2008

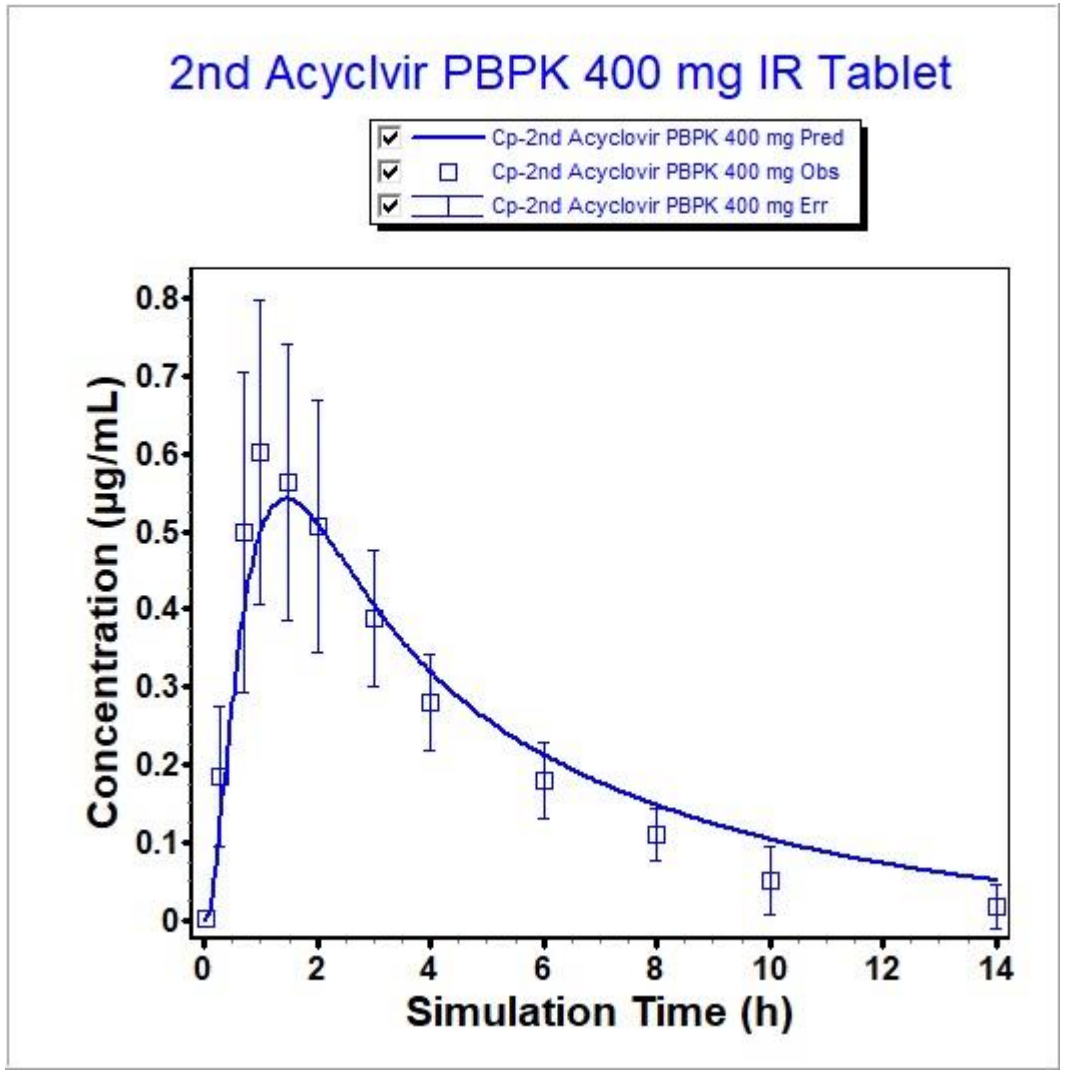
Acyclovir PBPK for 800 mg IR Tablet Under Fasted Condition

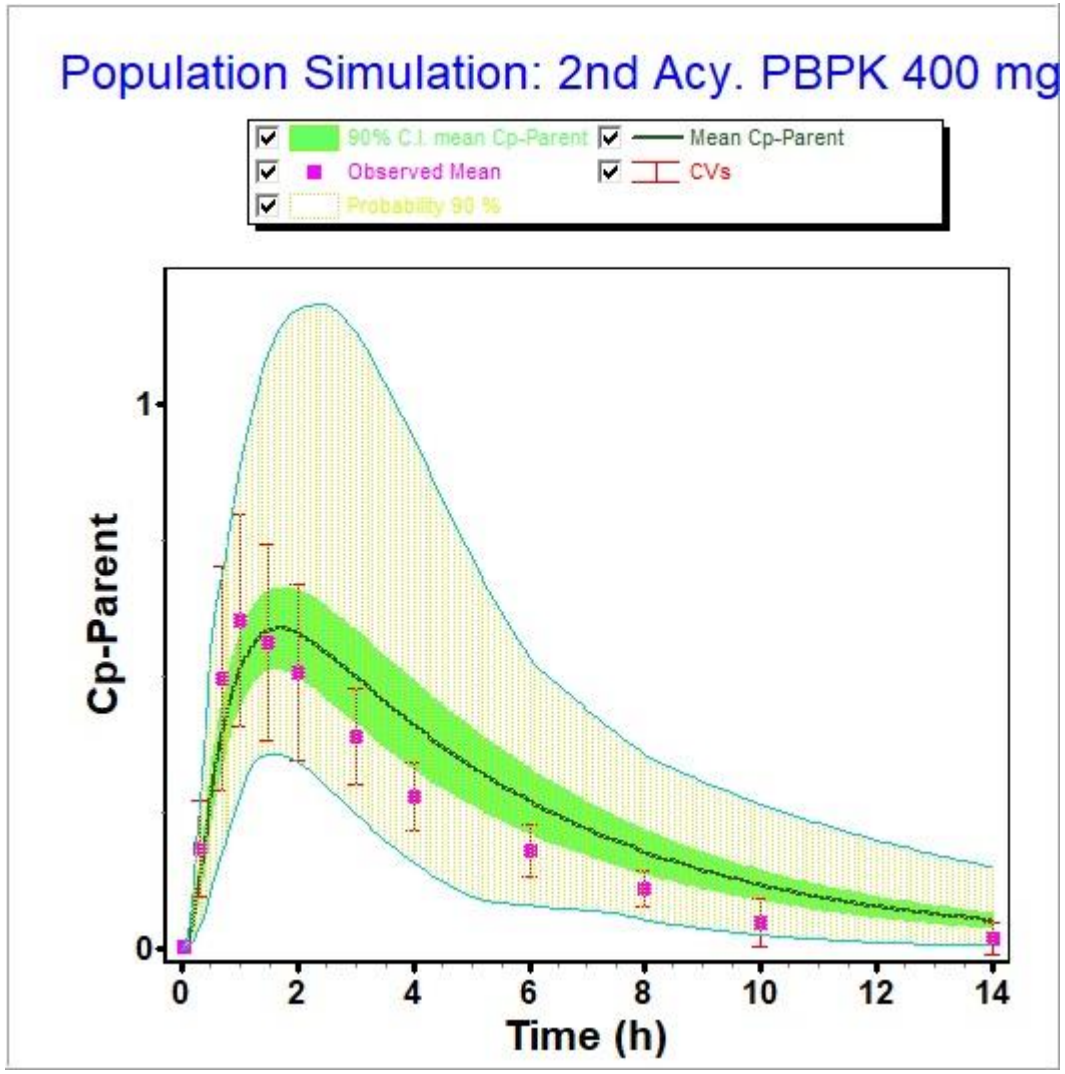


Parameter	PE%
C max	7.6
AUC (0-inf)	-4.3
AUC (0-t)	3.2

Susantakumar P, J Bioequiv Availab-2011

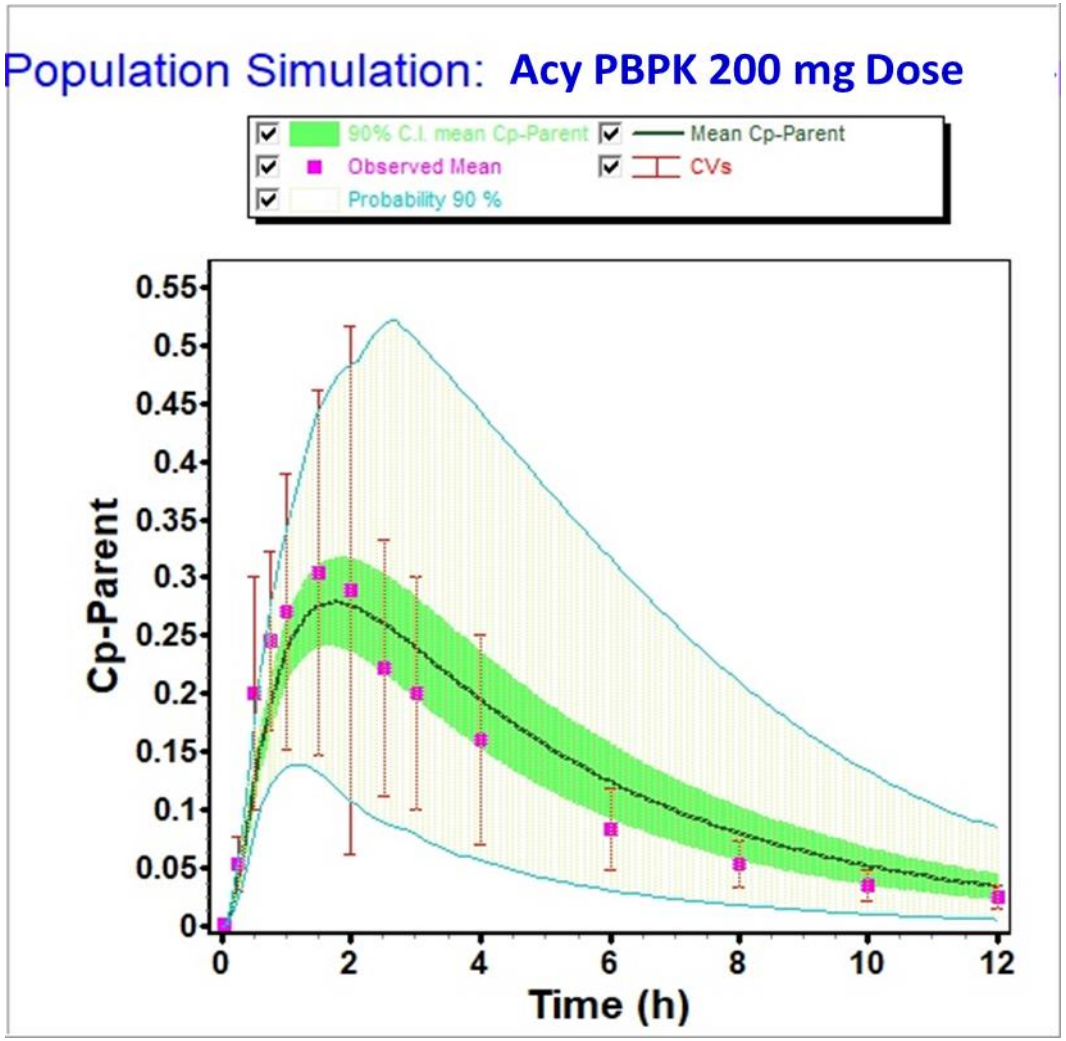
Validation of Oral PBPK of IR Tablet

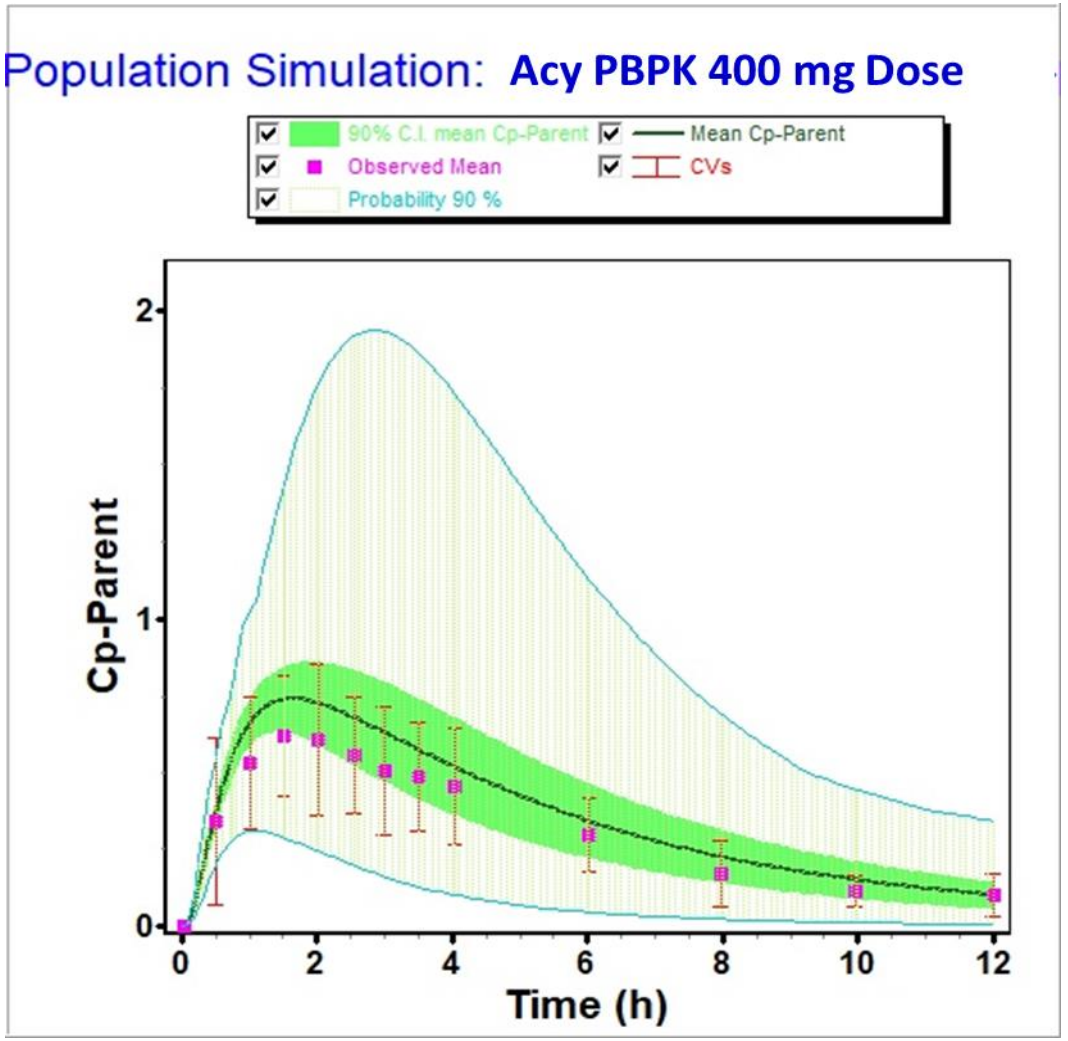




Yuen KH, Drug Development and Industrial Phamacy-1998

Population Simulation for 200 & 400 mg IR Tablet





Kubbinga M,Pharm Res-2015
Amini H, Clin Drug Invest-2008

Prediction Error of Acyclovir PBPK for IR Tablets

IR Tablet Dose	Parameter	PE%
200 mg	C max	-4.2
	AUC (0-inf)	15
	AUC (0-t)	12
400 mg	C max	3.7
	AUC (0-inf)	-21
	AUC (0-t)	-6
800 mg	C max	7.6
	AUC (0-inf)	-4.3
	AUC (0-t)	3.2

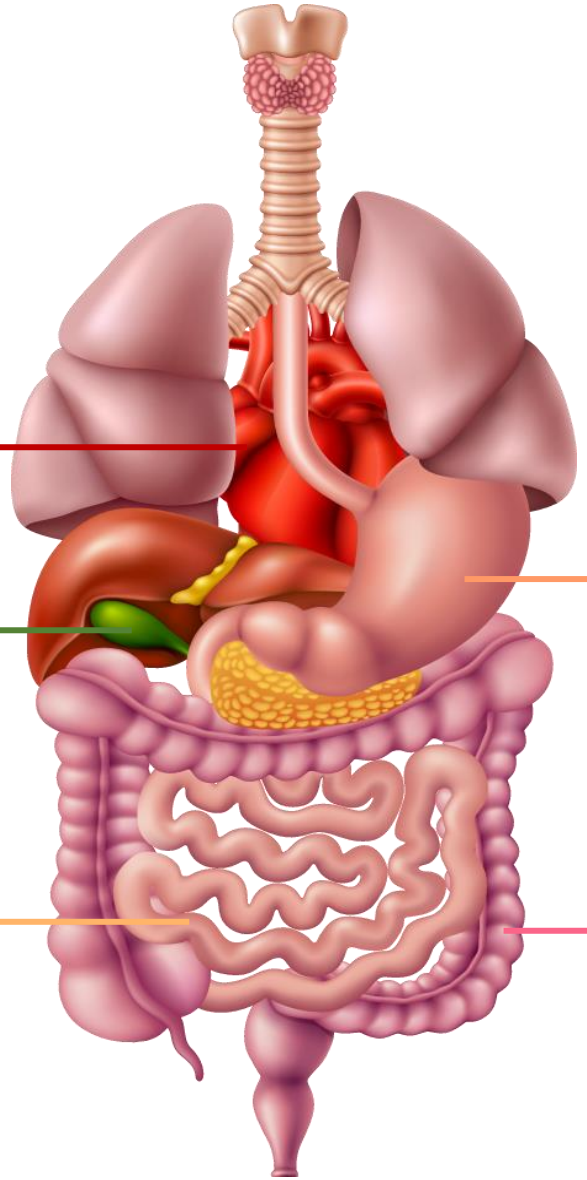
Acyclovir PBPK for Oral IR Tablet under **Fed Condition**

Effect of Food on Gastrointestinal Physiology

Blood Flow
- Increased Liver and Portal Blood Flow

Gall Bladder
- Release of Bile Salt

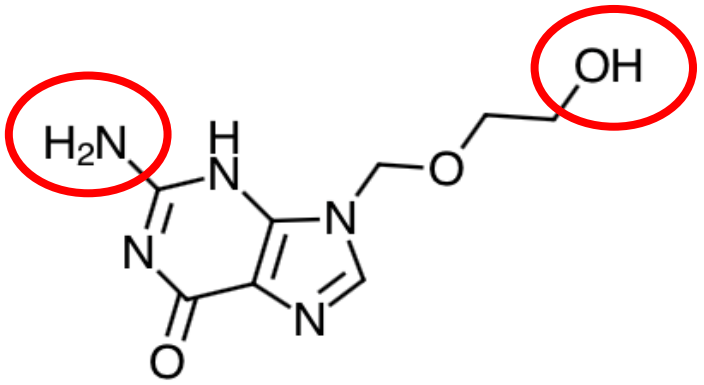
Small Intestine
- Increased Bile Salt Conc.
- Increased Mortality
- Increased Viscosity
- Increased Volume
- Decreased pH
- Change in Enzyme and Transporter's Activity



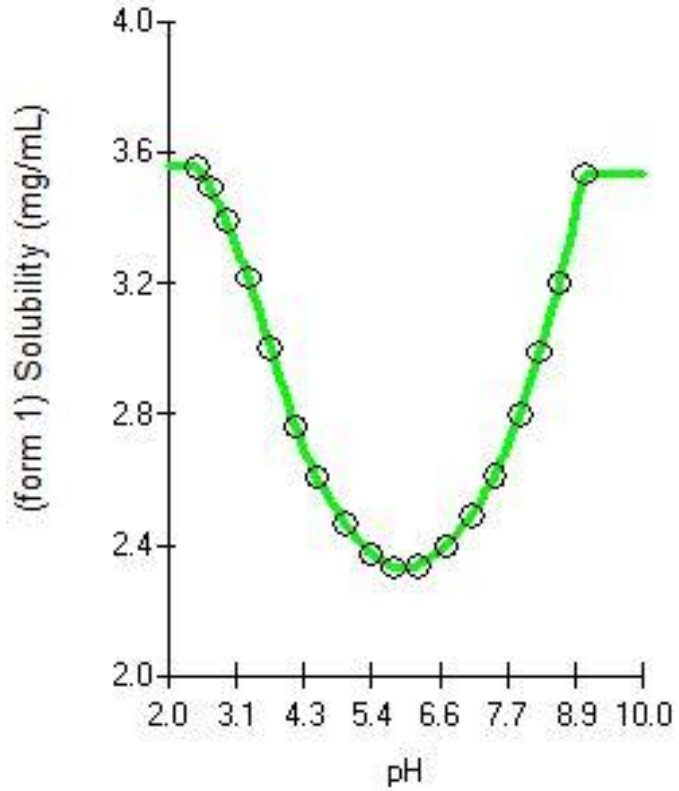
Stomach
- Increased pH
- Increased Mortality
- Increased Acid Secretion
- Increased Volume
- Delayed Gastric Emptying

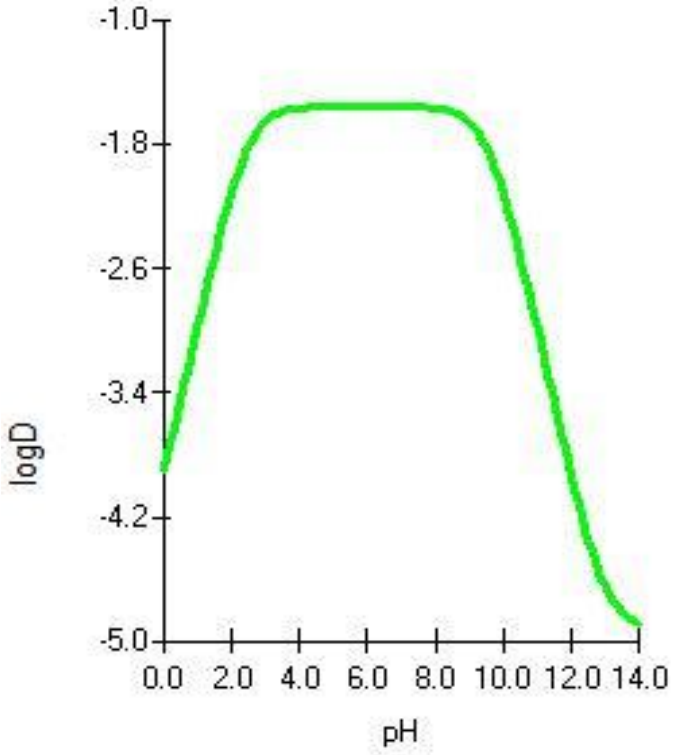
Colon
- Increased Buffer Capacity
- Increased Osmolarity
- Decreased pH

pH Dependent Solubility of Acyclovir



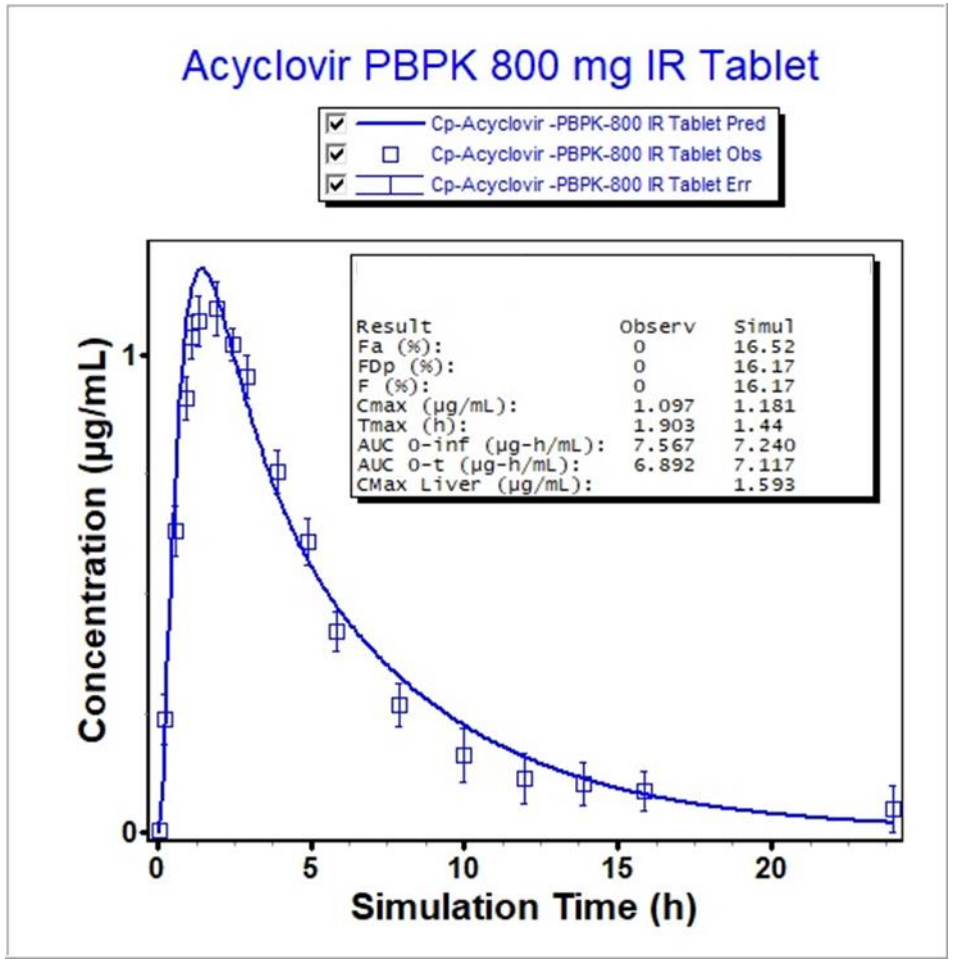
Acyclovir





Arnal J., et. at. Journal of Pharm Sci-2008

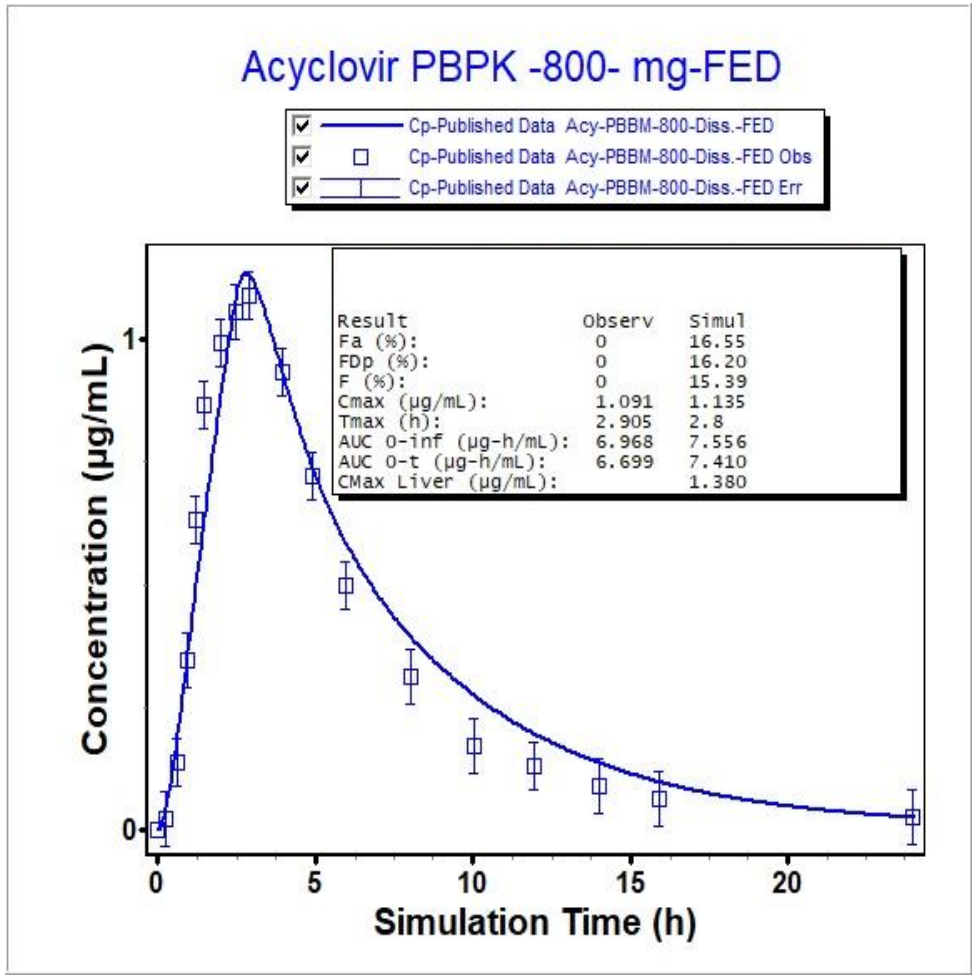
Acyclovir PBPK for 800 mg IR Tablet Under Fasting Condition



Parameter	PE%
C max	7.6
AUC (0-inf)	-4.3
AUC (0-t)	3.2

Susantakumar P, J Bioequiv Availab-2011

Acyclovir PBPK for 800 mg IR Tablet Under FED Condition

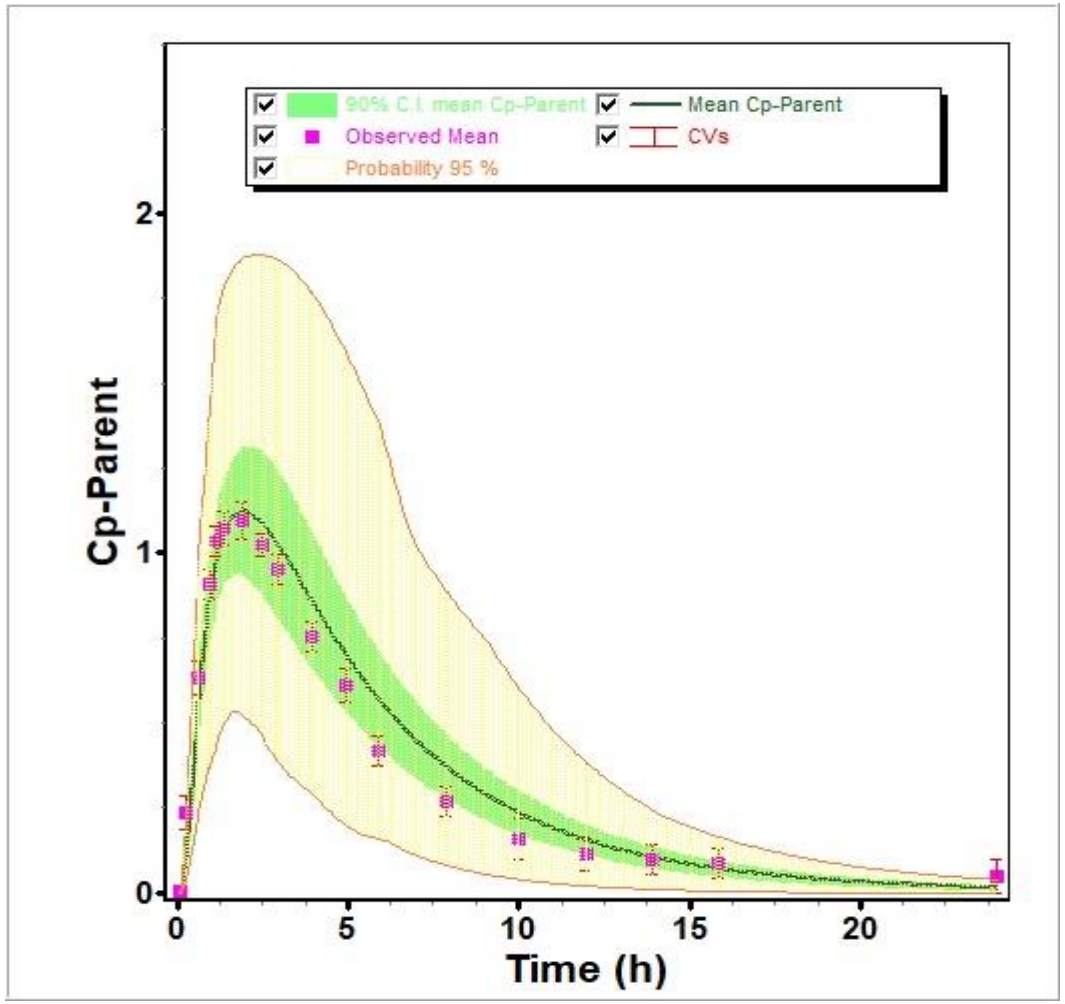


Parameter	PE%
C max	4.03
AUC (0-inf)	8.4
AUC (0-t)	10.6

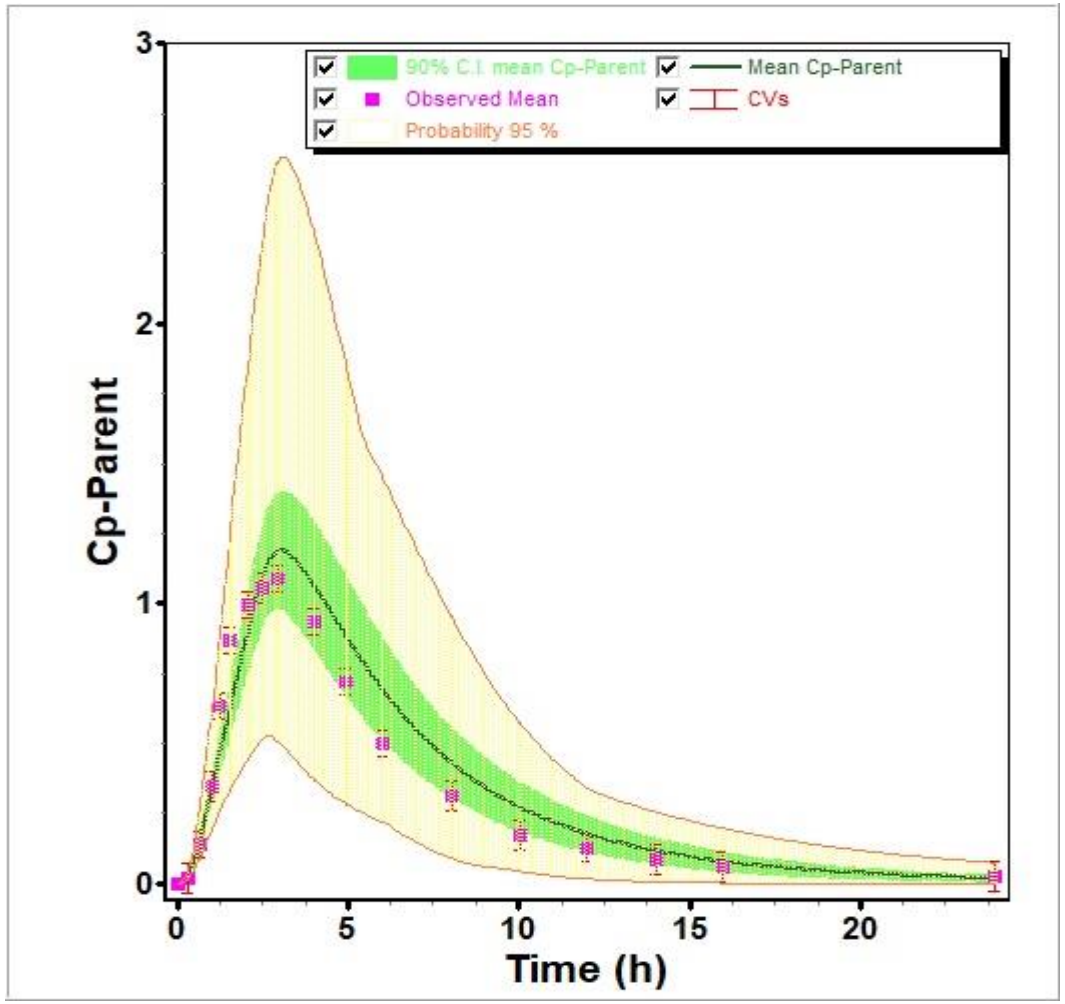
Susantakumar P, J Bioequiv Availab-2011

Population Simulation of Acyclovir IR Tablet-800 mg

Fasting



Fed

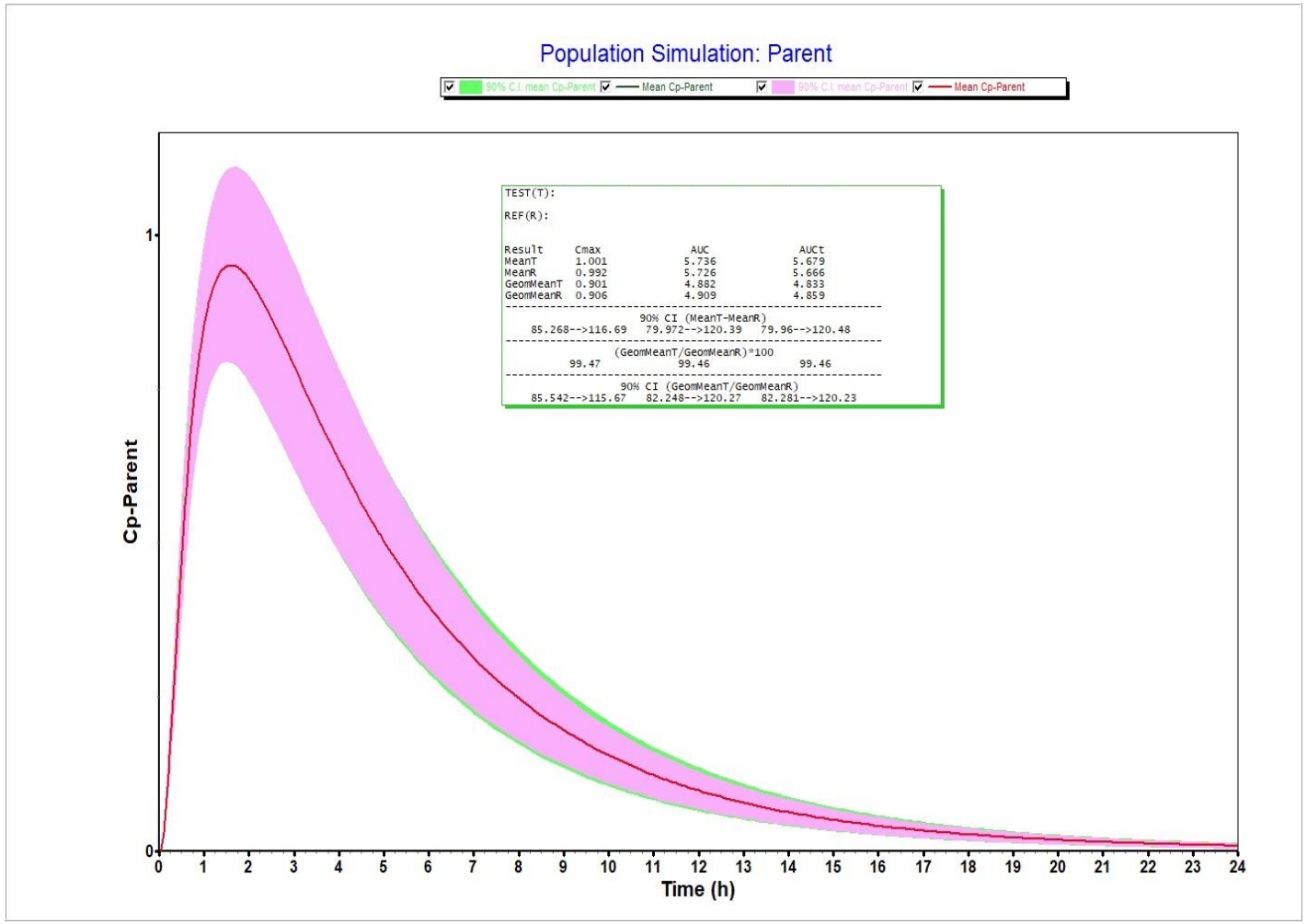


Susantakumar P, J Bioequiv Availab-2011

Virtual Bioequivalence (VBE) Study
of Acyclovir IR Tablet-800 mg

VBE of Acyclovir IR Tablet-800 mg

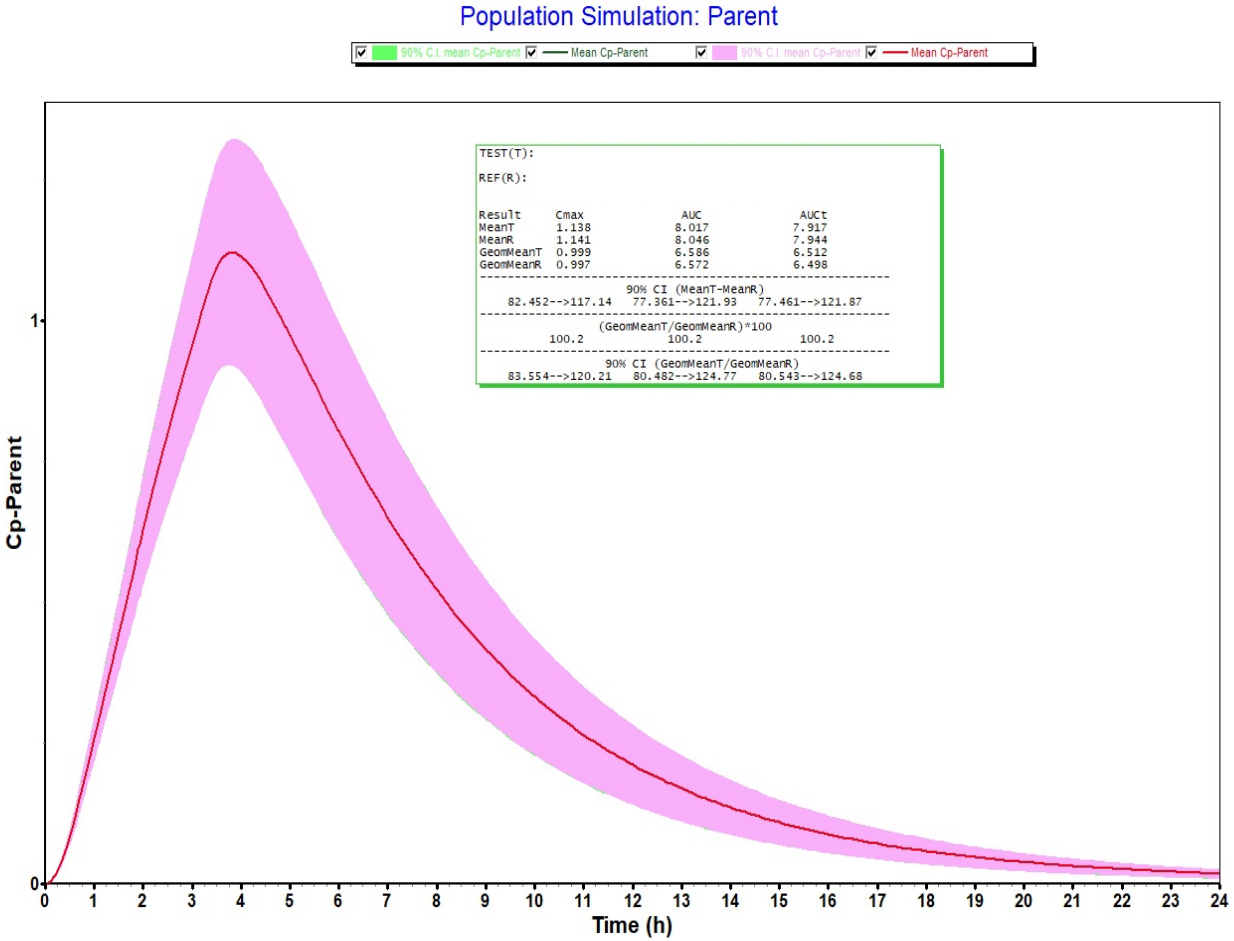
Fasting-Condition



Parameters	C_{max}	$AUC_{(0\text{-}inf)}$	$AUC_{(0\text{-}t)}$
Geom. Mean (T/R)	99.47	99.46	99.46
90% CI	85.54-115.67	82.24-120.27	82.21-120.23
BE Status	Pass	Pass	Pass

VBE of Acyclovir IR Tablet-800 mg

Fed-Condition



Parameters	C_{max}	$AUC_{(0\text{-}inf)}$	$AUC_{(0\text{-}t)}$
Geom Mean (T/R)	100.2	100.2	100.2
90% CI	83.554-120.21	80.482-124.77	80.543-124.68
BE Status	Pass	Pass	Pass

Summary

- Successfully developed an oral PBPK model for acyclovir immediate release (IR) tablet.
- Developed acyclovir PBPK model was validated with PK data from literatures and approved ANDAs.
- Acyclovir oral PBPK model successfully simulated the impact of food for 800 mg IR tablet.
- Virtual bioequivalence (VBE) was conducted for acyclovir IR tablet under fasted and fed condition, indicating food appears not to impact the bioequivalence results for this case.

Acknowledgement

Oral PBPK Team:

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Dr. Yi-Hsien Cheng

DQMM Division:

Dr. Liang Zhao

Dr. Lanyan (Lucy) Fang

Thank You!