Case Studies: Physiologically Based Biopharmaceutics Modeling for Food Effects – Possibilities and Opportunities

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"*Current State and Future Expectations of Translational Modeling Strategies to Support Drug Product Development, Manufacturing Changes and Controls*"

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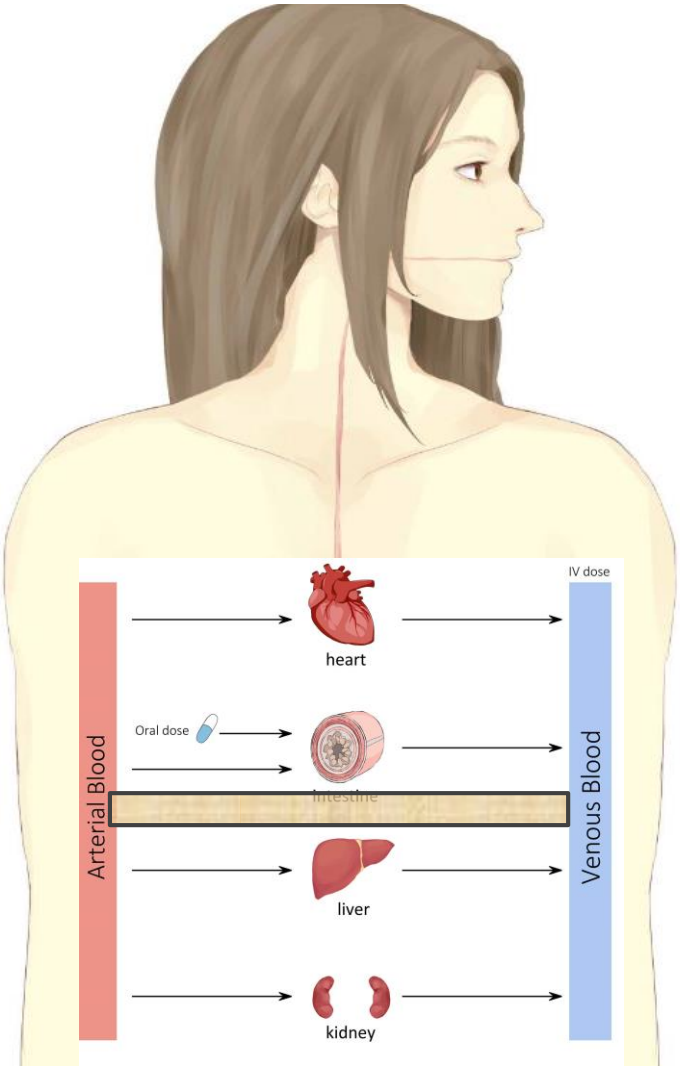
Outline

- **PBPK, PBBM**
  - **Overview**
  - **Food Effect General Workflow**

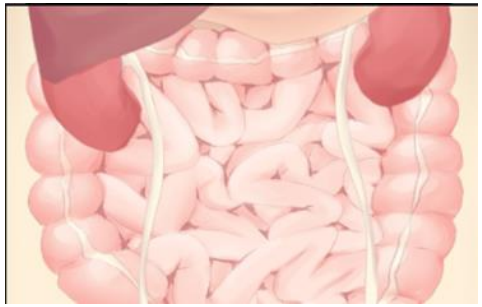
- **PBPK Case example 1 (NVS B)**
  - ❖ **Particle Size Distribution and FE Assessment integrating in vitro and in vivo data**
- **PBPK Case example 2 (NVS345)**
  - ❖ **BA/BE Assessment for New Formulation Variant**

PBPK, PBBM



PBPK, Physiologically Based Pharmacokinetics

PBBM, Physiologically based Biophamaceutics



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Meeting Report

Theme: Dissolution and Translational Modeling Strategies Enabling Patient-Centric Product Development
Guest Editors: Marilyn N. Martinez, Sandra Suarez, and Andreas Abend

Dissolution and Translational Modeling Strategies Toward Establishing an *In Vitro-In Vivo* Link—a Workshop Summary Report

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ABSTRACT. This publication summarizes the proceedings of day 2 of a 3-day workshop on "Dissolution and Translational Modeling Strategies Enabling Patient-Centric Product Development." Patient-centric drug product development from a drug product quality perspective necessitates the establishment of clinically relevant drug product specifications via an *in vitro-in vivo* link. Modeling and simulation offer a path to establish this link; in this regard, physiologically based modeling has been implemented successfully to support regulatory decision-making and drug product labeling. In this manuscript, case studies of physiologically based biopharmaceutics modeling (PBBM) applied to drug product quality are presented and summarized. These case studies exemplify a possible path to achieve an *in vitro-in vivo* link and encompass (a) development of biopredictive dissolution methods to support biowaivers, (b) model-informed formulation selection, (c) predicting clinical formulation performance, and (d) defining a safe space for regulatory flexibility via virtual bioequivalence (BE). Workflows for the development and verification of absorption models/PBBM and for the establishment of a safe space using dissolution as an input are described with examples. Breakout session discussions on topics, such as current challenges and some best practices in model development and verification, are included as part of the Supplementary material.

KEY WORDS: clinically relevant dissolution specifications; IVIVC/IVIVR; physiologically based biopharmaceutics modeling (PBBM); safe space; virtual bioequivalence.

Adobe Acrobat Document

PBBM

PBPK Predictable Food Effects for BCS II Drugs with Fasted Clinical Data

Criteria Supporting the Reliability of Biopharmaceutics PBPK Simulation of Food Effect (FE)

- BCS/BDDCS – Class I and II
- Major mechanism for food effect is related to bile solubilization/supersaturation or delay in gastric emptying[1]
- Linear pharmacokinetics with no significant gut transporter involvement[2]
- Clinical data in one prandial state available for model verification

Build First Human PBPK Model

Develop & Validate PBPK Model

1. Physicochemical properties (i.e. bio-relevant solubility and dissolution data)
2. Clinical PK after oral IR (& i.v. administration if available[3])
3. Simulate with default physiological absorption model (fasted or fed) & verify vs. observed data
4. Optimize model[4]

Predict & Verify FE for Early Stage

Predict and Verify Food Effect Model

1. Apply validated human model using default fasted & fed physiologies
2. Simulate PK for non-tested prandial state
3. Predict food effect & verify vs. clinical food effect data
4. Optimize model[4]

Apply FE Model for Late Stage

Apply Food Effect Model

1. Incorporate formulation related changes in model
2. Simulate & verify model with PK data for late stage formulations[5]
3. When confidence is high, predict food effect for market formulations or re-verify vs clinical PK
4. Leverage PBPK Model to inform label

Refine Model, Build Confidence and Robustness

- Parameter sensitivity analyses
- Scenario-based simulations
- Virtual simulations

Notes:

[1] e.g. solubility identified as critical based on sensitivity analysis and biorelevant solubilities support difference in fasted/fed states.
[2] e.g. single ascending doses across a relevant range can be simulated with PBPK model
[3] e.g. in some cases may be obtained with a labelled intravenous micro-dose
[4] e.g. adjust model parameters within a reasonable range based on in vitro inputs and biological plausibility
[5] e.g. challenge model with data from relative bioavailability studies

Tistaert C, Heimbach T, Xia B, Parrott N, Samant TS, Kesisoglou F. Food Effect Projections via Physiologically Based Pharmacokinetic Modeling: Predictive Case Studies. J Pharm Sci. 2018 Jun 12. pii: S0022-3549(18)30332-0.

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Particle Size Distribution Impact on Oral Absorption using PBBM

BCS Class IV – type compound

PBPK Case example 1 (NVS B)

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HA Question received

NVS B is an active substance of BCS class 4, which is hardly soluble in the physiological range (pH 3 to pH 6.8). Therefore, the influence of the particle size of the active substance on its in vivo release, especially with regard to the recommended intake with a meal, must be thoroughly discussed and, if necessary, supported by investigation data.

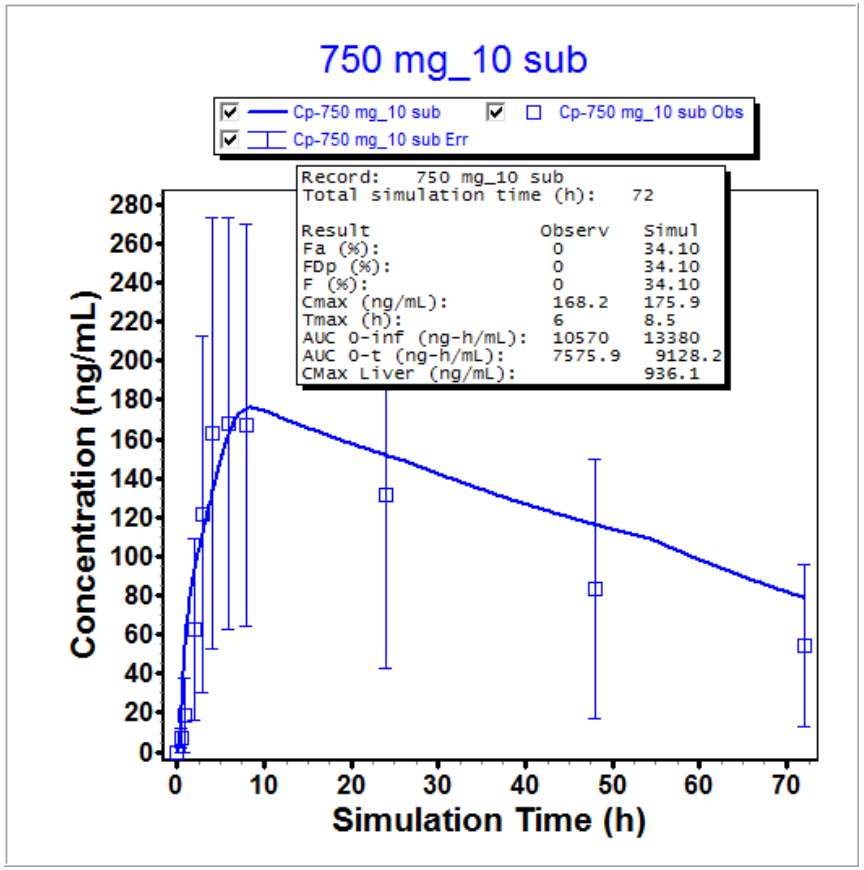
The suitability of the particle size distribution (X90 250 µm, X50 40 µm) determined for the active substance must be justified.

PBBM Model

- Purpose: DS particle size could potentially affects drug absorption (Fa). The impact of particle size on across prandial states Fa was assessed using PSA
- Several studies used for Model: 750 mg, 500 mg, 450 mg
- Absorption: estimated based on pKa, log P, measured pH-solubility profile, particle-size distribution, and measured Caco-2 permeability
- Distribution: 1- compartment model; derived from Pop PK estimated V/F and estimated Fa via ACAT modeling
- Elimination: derived from Pop PK model estimated CL/F and estimated Fa via ACAT modeling

PBPK model can describe 750 mg PK under **fasted** condition

Single Dose PK study in patients



Observed PK data

Small particle size

Radius [um]	Fraction [%]
1.75	10.0
17.5	50.0
33.5	10.0

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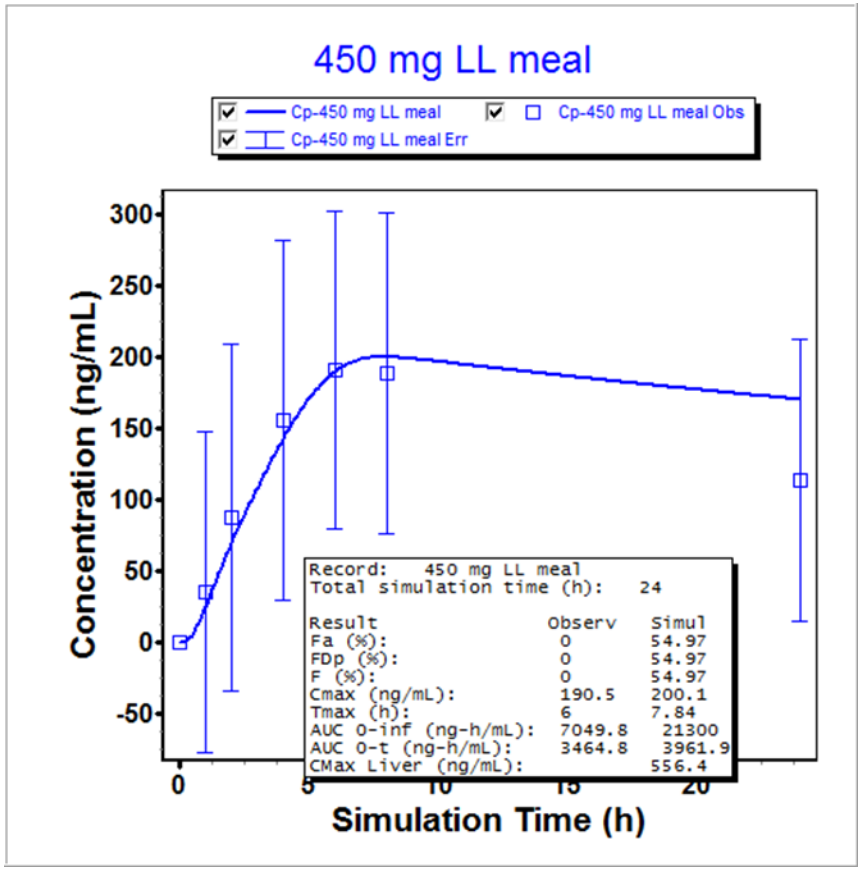
PBPK model can describe the 450 mg PK with low-fat meal



Observed data

Medium particle size

Radius [um]	Fraction [%]
7.5	10.0
35.5	50.0
84.0	10.0

Low fat meal ACAT model built based on Sutton S, et. al. AAPS J., 2017

- 100 – 500 calories
- Can be viewed as low calories low fat meal

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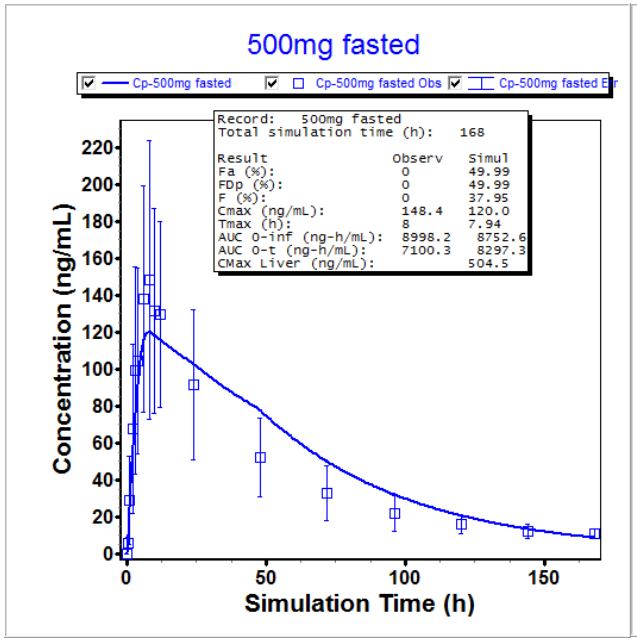
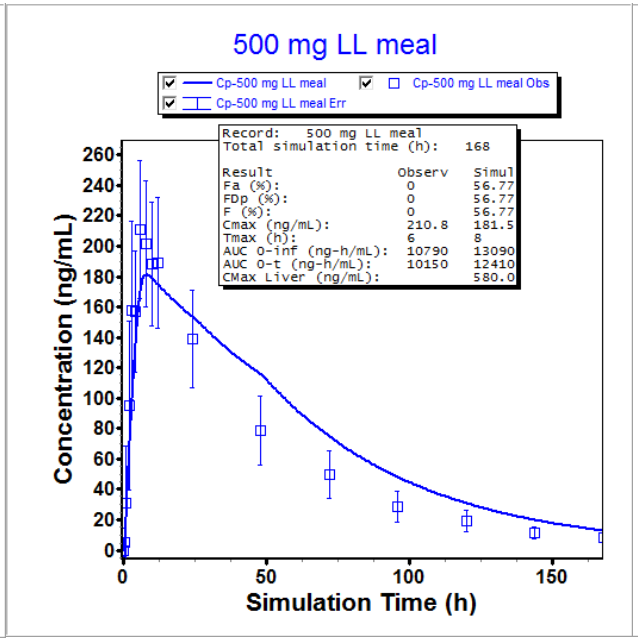
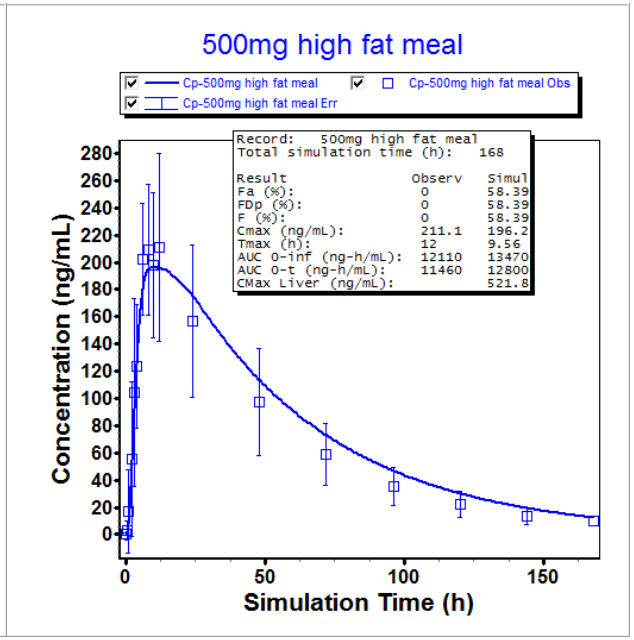
PBPK model can describe 500 mg dose PK under fasted, light meal, or standard meal conditions in HV







- The observed food effect was ~1.4 fold, overall similar to the predicted food effect, ~ 1.5 fold

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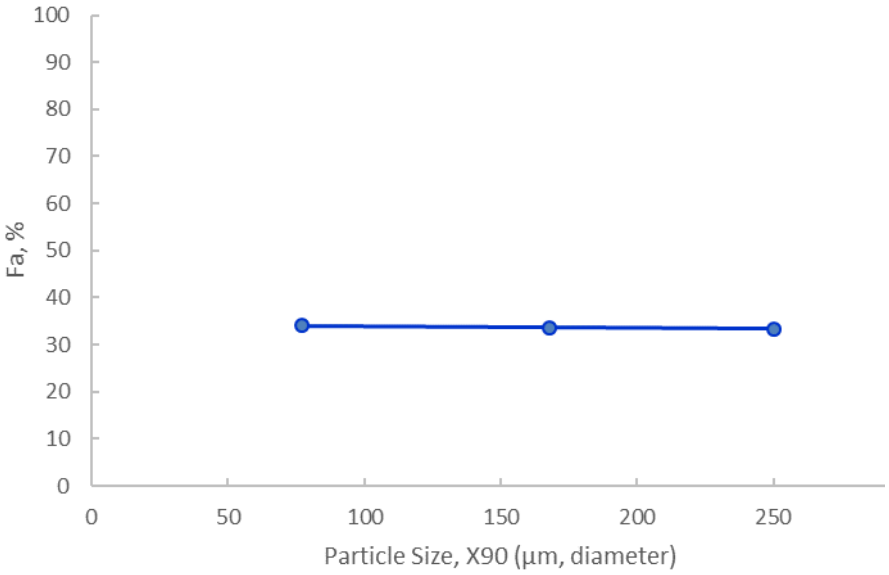
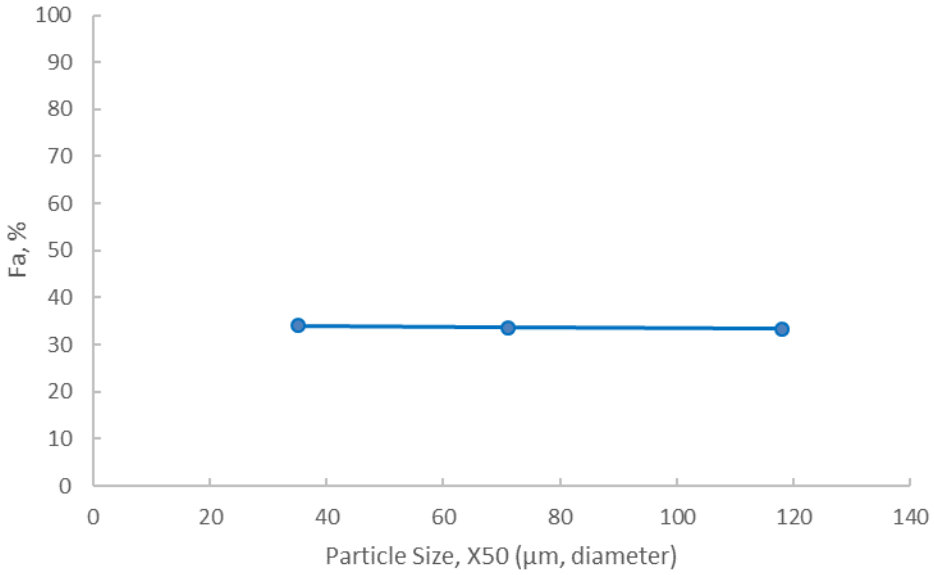
Parameter sensitivity analysis: Absorption under fasted condition is not altered with X90 and X50 values





- Within the DS specification of particle size X90 < 250 µm, the model predicted very minimal impact of X90 values on Fa; Model predicted very minimal change on Fa with increasing X50 values
- Solubility is high in stomach at pH 1.3 under fasted condition. Hence the DS particle size doesn't play a role in drug dissolution in stomach

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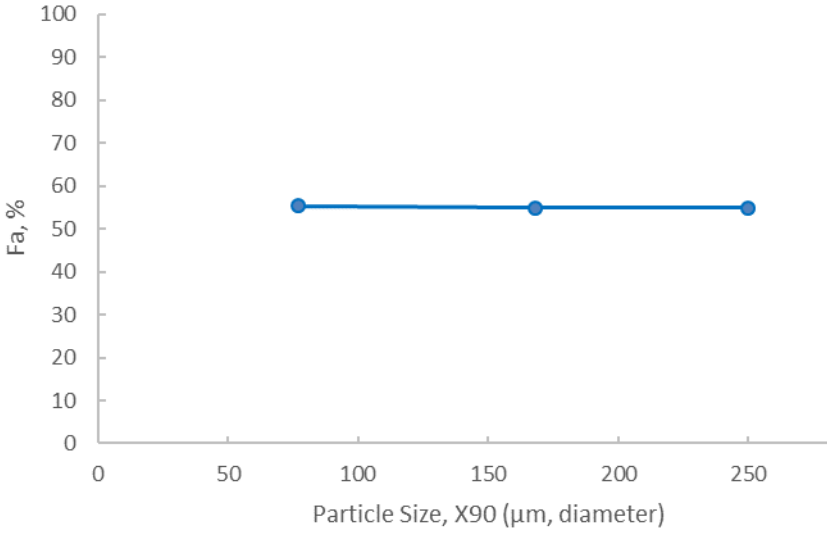
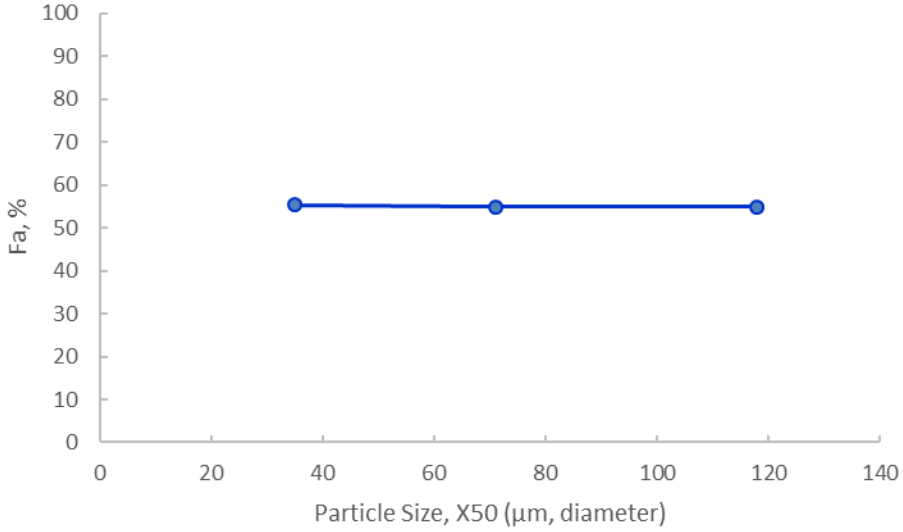
Parameter sensitivity analysis: Absorption is not altered X90 and X50 values after a 450 mg dose with low fat meal





- Within the DS specification of particle size X90 (< 250 µm), the model predicted very minimal impact of X90 values on Fa after a 450 mg dose with low fat meal
- Model predicted very minimal change on Fa with increasing X50 values

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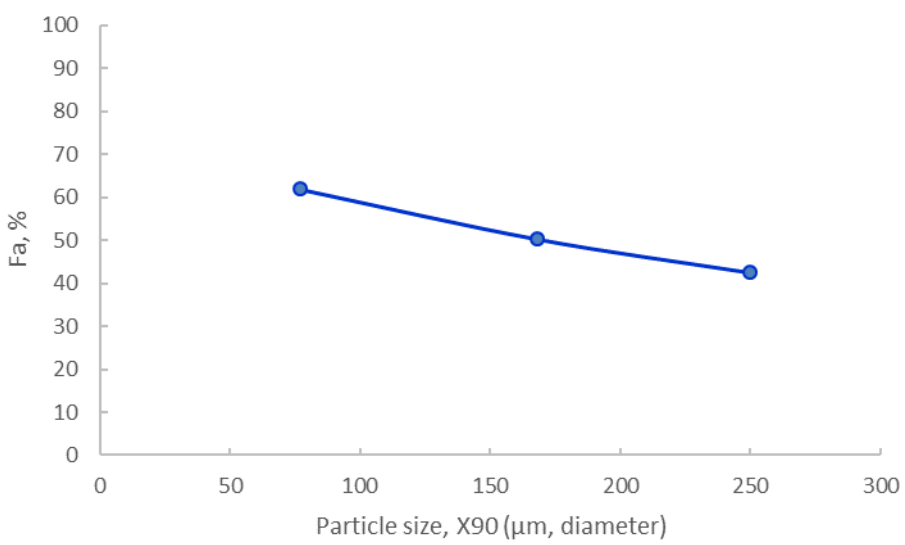
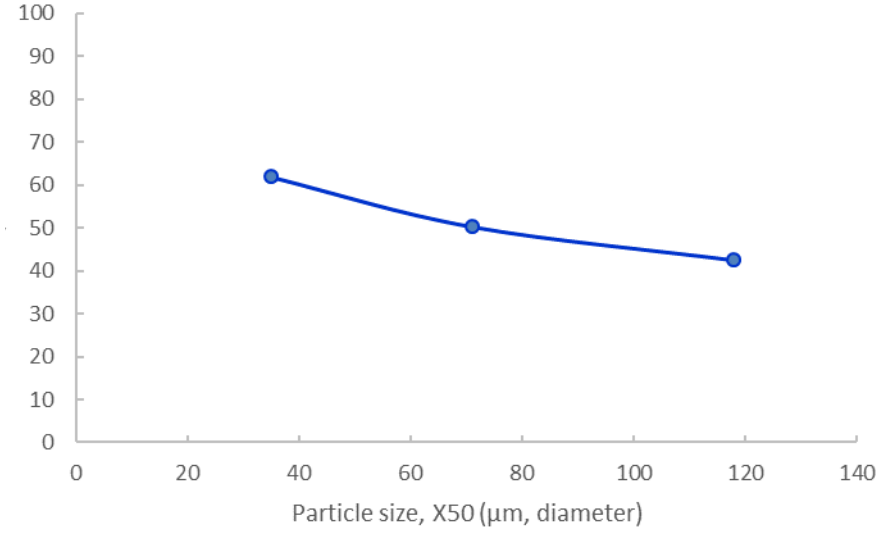
Parameter sensitivity analysis: Absorption decreased with larger X90 and X50 values after a 450 mg dose with high fat meal





- Within the DS specification of particle size X90 (< 250 µm), the model predicted Fa decreased from ~60% to ~40% after a 450 mg dose with high fat meal

- Stomach pH was defined as 4.9 under high fat meal condition.

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Summary

- PBBM parameter sensitivity analysis (PSA) showed that varying particle size diameter (77-250 µm of X90, or 35 -118 µm of X50) did not alter NVS B absorption under fasted and fed conditions.
- When a 450 mg dose is taken with a high-fat meal, parameter sensitivity analyses showed that varying particle size might lead to a slight F_a reduction (from ~60% to ~40%), which would represent the worst-case scenario.

‘Predicting the Predictable’ Food Effect Case Study

BCS Class II – type compound

PBPK Case example 2 (NVS345)

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NVS345 – Compound Overview

Physicochemical Properties	
BCS Class	BCS class 2
pKa(s) / LogD$_{6.8}$	3.3 and 9.4 (weak base) / logD 2.8
Solubility in buffers	pH-dependent solubility; Soluble at pH 1.0 (3.64 mg/mL), pH 2.0 (0.37 mg/mL), low solubility pH ≥ 3.0 (~0.03 mg/mL)
Solubility in bio-relevant media	~10-fold increase in solubility in FeSSIF (pH 5.0; 0.32 mg/mL)
Permeability	High passive permeability in absence of efflux (LE-MDCK); moderate permeability in Caco-2
PK Characteristics	
Dose / Formulation	300 mg oral once daily; **tablet**
Pharmacokinetics	**Linear PK across wide dose range**; available population PK model (estimates of CL/F and Vd/F) and preclinical IV data in mouse, rat and dog
Metabolism and Excretion	Negligible first-pass metabolism and preclinical species and human No known interaction of food with intestinal enzymes and/or disposition transporters
Clinical Pharmacology – Available biopharmaceutic studies	
Food Effect (300 mg)	**Positive Food Effect** (AUC ↑70-80%) independent of type of meal (LFLC and HFHC)
Acid reducing agent DDI	Reduction in exposure in presence of food (LFLC) not clinically significant with ranitidine (H2RA); in the fasted state decrease more pronounced
Absolute / rel. bioavailability study	No absolute BA conducted (no iv data); relative BA not required
Bioequivalence	Originally not thought to be required; requested by HA during pre-submission meeting

NVS345 PBBM

- Can we – in the absence of IV data - adequately simulate the oral absorption under different treatment conditions?
  - Type of food (low fat low calorie vs. high-fat high calorie)
  - Co-administration of acid reducing agents (i.e. ranitidine) under different prandial conditions
  - Different formulations
- Can we identify absorption-rate limiting parameters?
- Can we predict the predict in vivo performance of a modified commercial formulation in the absence of bioequivalence data?

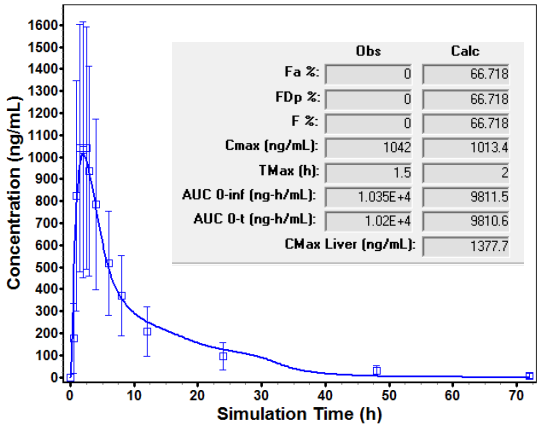
Noteworthy adapations

- Reliable solubility and dissolution data, also in bio-relevant media such as FeSSIF and FaSSIF were available
- ACAT in-built physiological parameters such as pH, transit times, volume and bile salt concentration across the intestinal tract were used to simulate fasted and high- calorie, high-fat (HFHC) meal conditions.
- To simulate food effect for low–calorie/low-fat (LFLC) and low-calorie/ high-fat (HFLC) meal, several adjustments in the ACAT model were made according to Sutton et al AAPS J, 2017.
  - There is only small difference in simulated regional absorption between LFLC and HFLC physiologies.
- For co-administration with ranitidine, pH in stomach was set to 6.50 (when fasted and fed) based on Kakuda and Falcon (2006).

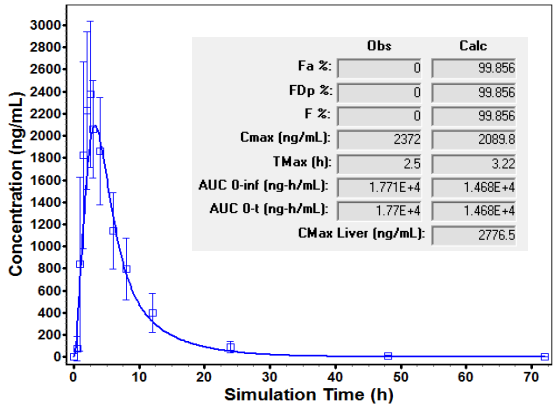
GastroPlus model for healthy subjects simulated well – Food Effect and PPI DDI HV Study

Formulation 1

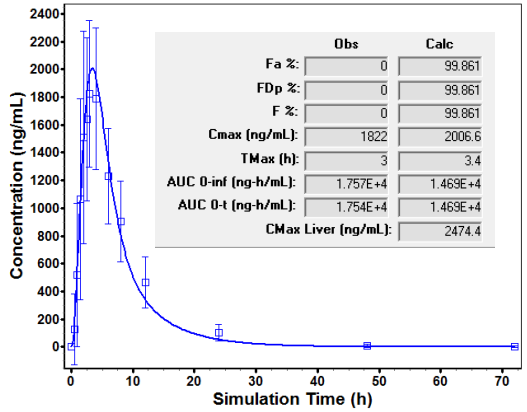
Fasted



Low Fat

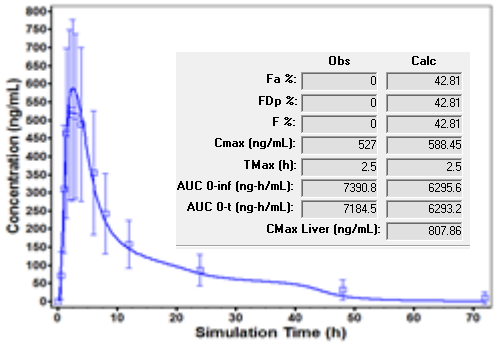


High Fat



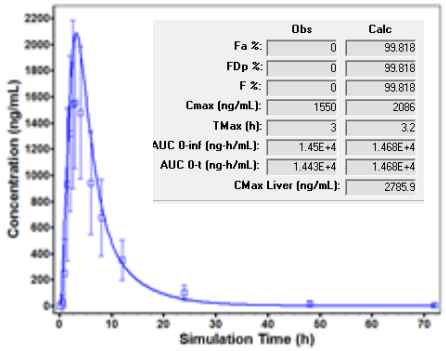
1.7-1.8 Fold Food effect

Fasted + ranitidine



PPI effect

Low Fat + ranitidine



No PPI effect

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Meal Physiologies – Sutton

The impact of gastric pH, volume, and emptying on the food effect of ziprasidone oral absorption.
Sutton SC, Nause R, Gandelman K.
AAPS J. 2017 Jul;19(4):1084-1090. doi: 10.1208/s12248-017-0065-9. Epub 2017 Mar 20.

Meal reference:	Fasted				High Calorie/High Fat				High Calorie/Low Fat			
Compartment	pH	Transit Time (h)	Volume (mL)*	Bile Salt (mM)	pH	Transit Time (h)	Volume (mL)*	Bile Salt (mM)	pH	Transit Time (h)	Volume (mL)*	Bile Salt (mM)
Stomach	1.3	0.25	48.38	0.00	4.9	1.74	788**	0.00	4.65	2.21	1200**	0.00
Duodenum	6.0	0.26	10.94	2.8	5.4	0.26	10.94	14.44	5.4	0.26	10.94	2.8
Jejunum 1	6.2	0.93	40.83	2.33	5.4	0.93	40.83	12.02	5.4	0.93	40.83	2.33
Jejunum 2	6.4	0.74	32.17	2.03	6.0	0.74	32.17	10.46	6.0	0.74	32.17	2.03
Ileum 1	6.6	0.58	24.98	1.41	6.6	0.58	24.98	7.28	6.6	0.58	24.98	1.41
Ileum 2	6.9	0.42	18.52	1.16	6.9	0.42	18.52	5.99	6.9	0.42	18.52	1.16
Ileum 3	7.4	0.29	13.15	0.14	7.4	0.29	13.15	0.73	7.4	0.29	13.15	0.14
Caecum	6.4	4.32	14.91	0.00	6.4	4.32	14.91	0.00	6.4	4.32	14.91	0.00
Asc Colon	6.8	12.95	15.81	0.00	6.8	12.95	15.81	0.00	6.8	12.95	15.81	0.00
*values reflect 10% SI fluid volume in fasted state; 3% LI fluid volume in fasted state												
**calculated from actual volumes of liquids and displacement volumes of solids in meal.												

ACAT Fasted

Compartment Data

Compartment	Peff	ASF	pH	Transit Time (h)	Volume (mL)	Length (cm)	Radius (cm)	SEF	Bile Salt (mM)
Stomach	0	0.0	1.30	0.25	46.56	28.29	9.67	1.000	0.0
Duodenum	0	2.805	6.00	0.26	41.56	14.13	1.53	4.235	2.800
Jejunum 1	0	2.758	6.20	0.93	154.2	58.40	1.45	3.949	2.330
Jejunum 2	0	2.732	6.40	0.74	122.3	58.40	1.29	3.489	2.030
Ileum 1	0	2.695	6.60	0.58	94.29	58.40	1.13	3.029	1.410
Ileum 2	0	2.633	6.90	0.42	70.53	58.40	0.98	2.569	1.160
Ileum 3	0	2.554	7.40	0.29	49.83	58.40	0.82	2.109	0.140
Caecum	0	1.119	6.40	4.19	47.49	13.19	3.39	1.790	0.0
Asc Colon	0	1.816	6.80	12.57	50.33	27.65	2.41	2.480	0.0

ACAT Fed

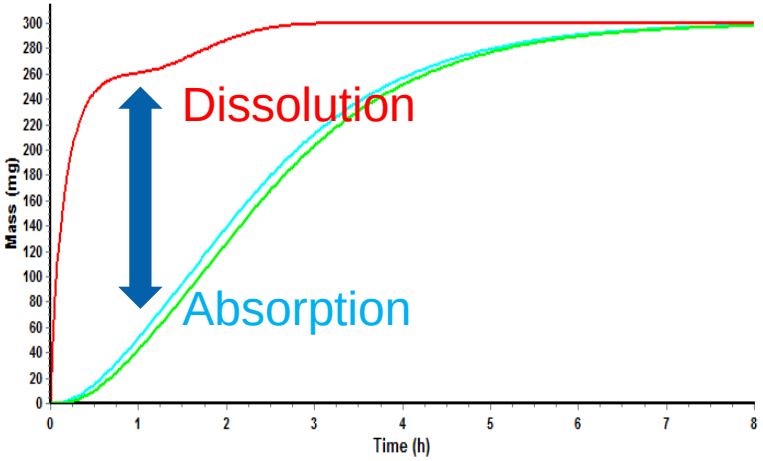
Compartment Data

Compartment	Peff	ASF	pH	Transit Time (h)	Volume (mL)	Length (cm)	Radius (cm)	SEF	Bile Salt (mM)
Stomach	0	0.0	4.90	1.00	931.2	28.29	9.67	1.000	0.0
Duodenum	0	2.810	5.40	0.26	41.56	14.13	1.53	4.235	14.44
Jejunum 1	0	2.766	5.40	0.93	154.2	58.40	1.45	3.949	12.02
Jejunum 2	0	2.740	6.00	0.74	122.3	58.40	1.29	3.489	10.46
Ileum 1	0	2.695	6.60	0.58	94.29	58.40	1.13	3.029	7.280
Ileum 2	0	2.633	6.90	0.42	70.53	58.40	0.98	2.569	5.990
Ileum 3	0	2.554	7.40	0.29	49.83	58.40	0.82	2.109	0.730
Caecum	0	1.119	6.40	4.19	47.49	13.19	3.39	1.790	0.0
Asc Colon	0	1.816	6.80	12.57	50.33	27.65	2.41	2.480	0.0

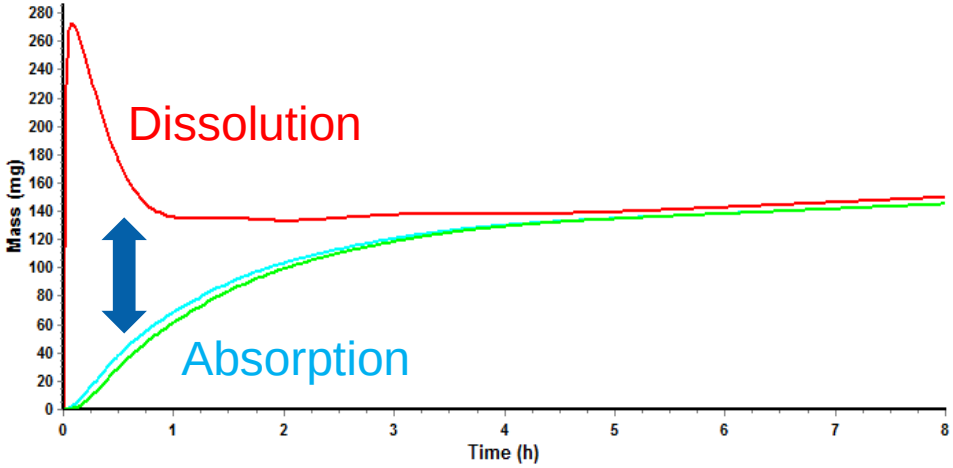
Absorption is limited by solubility / dissolution in the fasted state

- Due to the low first pass effect of NVS345, fraction absorbed is a good estimate of bioavailability
  - Fa in human ADME study (recovery of metabolites) at least 53.5% vs. predicted fraction absorbed of 60.7% after 400 mg SD fasted.
- In the fasted state absorption is limited by dissolution
- In the fed state absorption is **governed** by intestinal permeability

Fed (300 mg)

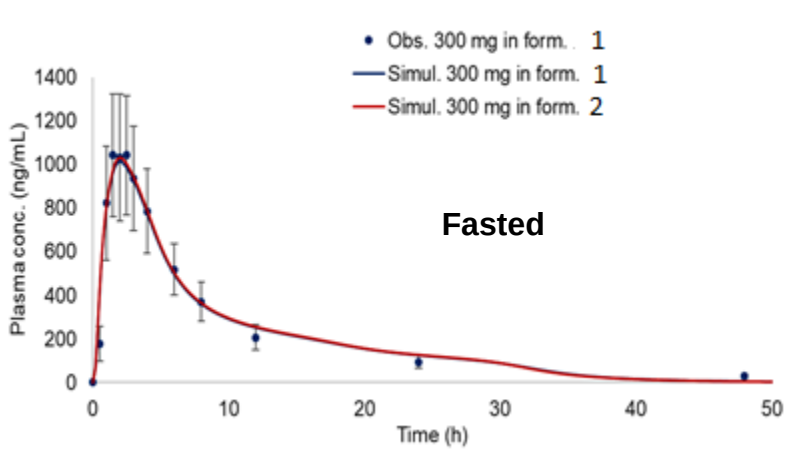


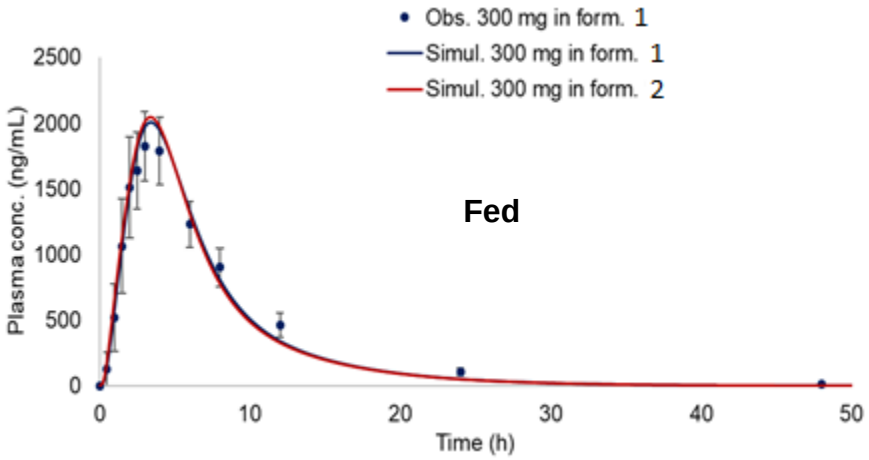
Fasted (300 mg)



BE simulation show that new formulation Form 2 is bioequivalent

- Post-pivotal changes to the FCT formulation of NVS345 were required for product commercialization (Form. 2)
- A constant Z factor (Takano) was fitted with respect to in vitro dissolution data of NVS345 in biorelevant media (FaSSIF and FeSSIF) for both formulations
- Simulations were conducted to simulate clinical (Form 1) and optimized formulation (Form 2) and compare with observed data for Form 1 from food effect study at 300 mg SD.

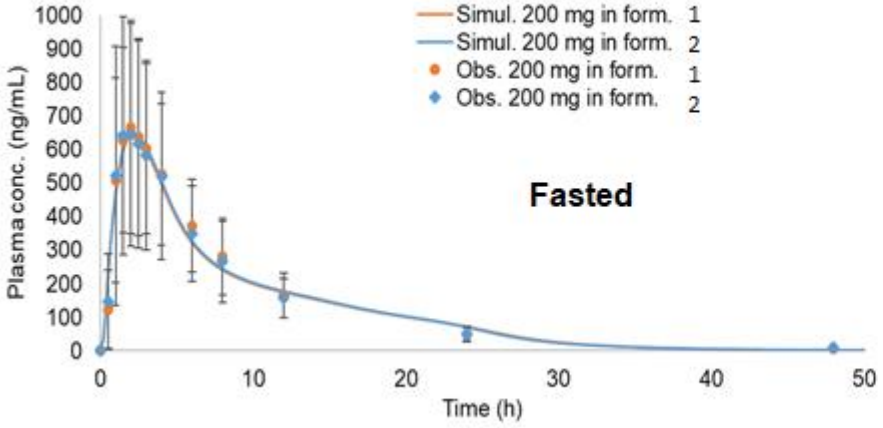


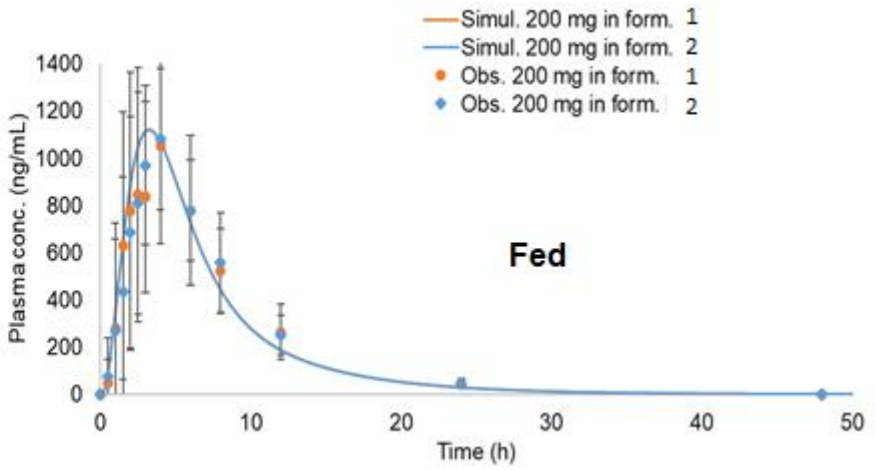


Bioequivalence Validation

A bioequivalence study was requested by HA. The BE study was conducted in the fasted and the fed (HFHC) state with the highest dose strength (200 mg) to satisfy both the guidance (greatest differentiation of formulations in the fasted state) and clinical administration (product administered after food)

- Bioequivalence was shown both in the fasted and fed state for Cmax and AUClast/AUCinf
  - **Fed:** AUCinf 0.987 (0.9386 – 1.0375), AUClast 0.993 (0.9436 – 1.0453), Cmax 0.939 (0.8563 – 1.0298)
  - **Fasted:** AUCinf 0.961 (0.9098 – 1.0160), AUClast 0.957 (0.9034 – 1.0140), Cmax 0.932 (0.8293 – 1.0475)





BE Results, observed vs. predicted

200 mg Group		Fa (%)	Cmax (ng/mL)	Cmax PE (%)	AUC0-inf (ng.h/mL)	AUC PE (%)
Cohort 1 (fed)						
FMI, Formulation 1 (fed, HFHC)	Observed (n =24)	-	1370		9310	
	range		864-2140		6110-14100	
	Simulated	99.9	1120.9	18.2	8175.4	12.2
Opt Formulation 2 (fed, HFHC)	Observed (n =24)		1280		9290	
	range		787-1610		5410-13400	
	Simulated	99.9	1120.3	12.5	8175.6	12.0
Cohort 2 (fasted)						
FMI, Formulation 1 (fasted)	Observed (n =70)	-	789		6570	
	range		248-1840		3340-13600	
	Simulated	78.4	640.5	18.8	5998.5	8.7
Opt. Formulation 2 (fasted)	Observed (n =69)	-	774		6440	
	range		176-2080		2840-13900	
	Simulated	79.4	652.6	15.7	6069.6	5.8

Conclusions

- PBBM **enabled good characterization of the oral absorption of NVS345** under different treatment conditions (formulation, food effect, co-administration of ranitidine) that was used as a surrogate for bioavailability estimation.
- Modeling **identified intestinal permeability as the likely rate-limiting parameter in the fed state**.
- Bioequivalence simulation predicted the outcome of the in **fasted and fed BE** study with new formulation in healthy subjects