Physiologically-based pharmacokinetic modeling approach to identify the drug-drug interaction mechanism of nifedipine and a proton pump inhibitor, omeprazole

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OBJECTIVES

To apply a physiologically-based pharmacokinetic (PBPK) modeling approach investigating the drug-drug interaction (DDI) mechanism between nifedipine and omeprazole.

BACKGROUND

- Nifedipine (NIF) is mainly metabolized by CYP3A4 in human.
- DDI exists between Omeprazole (OMP, 20 mg, enteric-coated tablet) and NIF immediate release (IR) as the increased NIF systemic exposure was observed in healthy subjects after they took OMP for 8 days[1].
- OMP may affect the *in vivo* release of other drugs from their dosage forms by elevating the gastric pH or affecting the elimination of other drugs by interacting with the CYP450 system (e.g. inhibition of CYP2C19).
- The *in vivo* time-dependent inhibition (TDI) of CYP2C19 by OMP has been evaluated using a PBPK model[2].
- The *in vitro* TDI of CYP3A4 by OMP & its metabolites has been investigated[3].

METHODS

- Simcyp v16 → mechanistic PBPK models
- Verified NIF PBPK model was used[4]
- OMP & metabolites PBPK was built as follows:

Published model for OMP solution
- CYP2C19 TDI (no 3A4); solution; no metabolites (data source: Ref. 2)

Developed model for OMP enteric-coated formulation
- *In vitro* dissolution profile (data source: Ref. 5)
- *In vivo* PK for OMP, OH OMP, DM OMP (data source: Ref. 3)

TDI analysis based on solution clinical data
- *In vitro* TDI data for OMP, OH OMP, DM OMP for CYPs 2C19 & 3A4 (data source: Ref. 3)
- Irreversible TDI parameter Ki *in vitro – in vivo* scale up (Ω)

Model verification based on the clinical data for OMP gastro-resistant formulation
- *In vitro* dissolution profile (data source: Ref. 5)
- *In vivo* PK for OMP, OH OMP, DM OMP (data source: Ref. 3)

- Parameter sensitivity analysis (PSA) was conducted to understand the impact of OMP-mediated TDI on NIF PK metrics

Impact of gastric pH on NIF plasma exposure

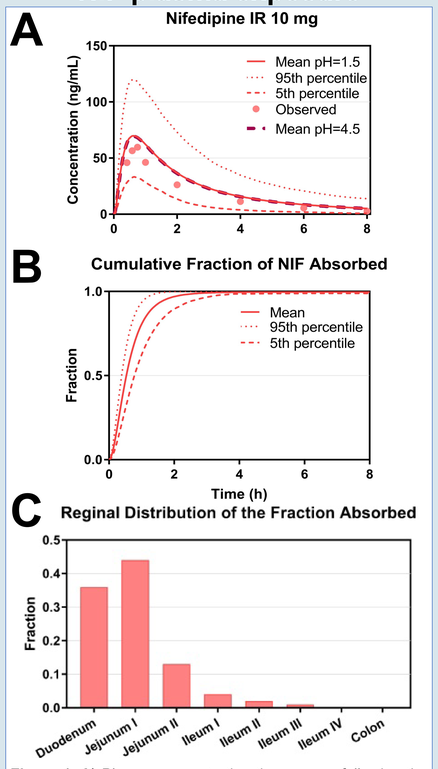


Figure 1. **A)** Plasma concentration time course following the administration of 10 mg of NIF to healthy subjects. Solid lines and dots represent PBPK simulations and observed data[4]. Purple line represents simulated plasma concentration with initial gastric pH of 4.5. **B)** Cumulative fraction of NIF absorbed. **C)** Regional distribution of the fraction absorbed.

OMP & metabolites PBPK model with TDI for CYPs 3A4 & 2C19

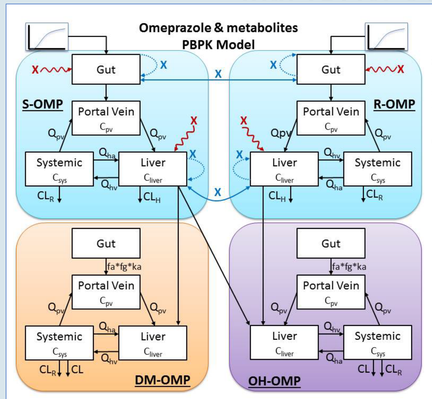


Figure 2: The structure of Simcyp minimal PBPK models used to describe the time course of both OMP enantiomers and two of its main metabolites: DM OMP and OH OMP.
X: auto- or mutual- inhibition in the gut and liver via TDI and/or reversible inhibition of CYP2C19 and CYP3A4.

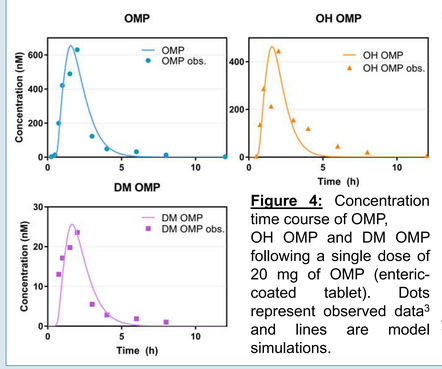
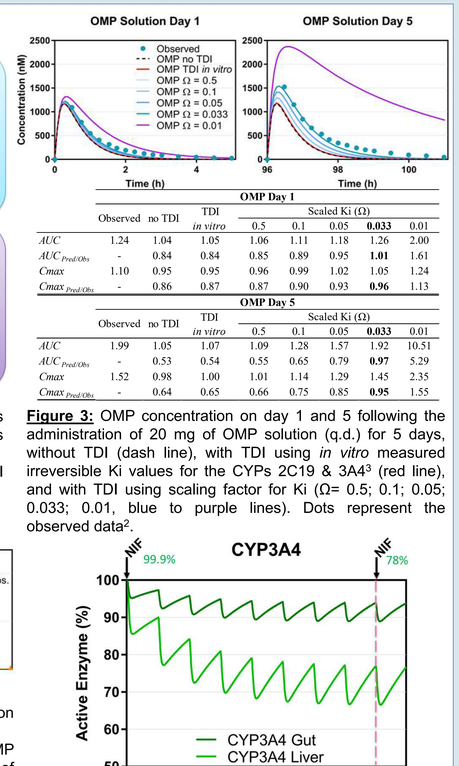


Figure 4: Concentration time course of OMP, OH OMP and DM OMP following a single dose of 20 mg of OMP (enteric-coated tablet). Dots represent observed data[3] and lines are model simulations.



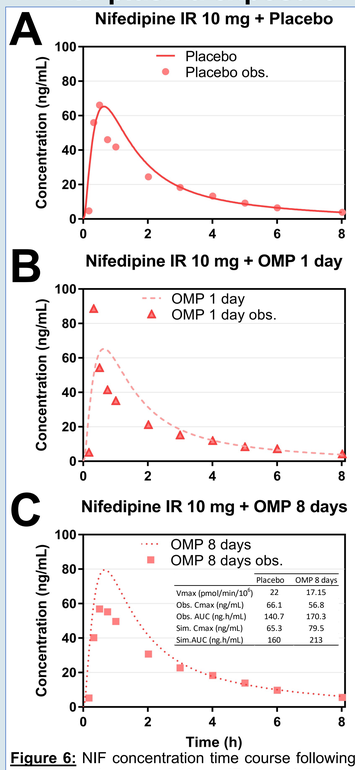
OMP Day 1	Observed	no TDI	TDI *in vitro*	Scaled Ki (Ω) 0.5	0.1	0.05	**0.033**	0.01
AUC	1.24	1.04	1.05	1.06	1.11	1.18	1.26	2.00
$AUC_{Pred/Obs}$	-	0.84	0.84	0.85	0.89	0.95	**1.01**	1.61
Cmax	1.10	0.95	0.95	0.96	0.99	1.02	1.05	1.24
$Cmax_{Pred/Obs}$	-	0.86	0.87	0.87	0.90	0.93	**0.96**	1.13

OMP Day 5	Observed	no TDI	TDI *in vitro*	Scaled Ki (Ω) 0.5	0.1	0.05	**0.033**	0.01
AUC	1.99	1.05	1.07	1.09	1.28	1.57	1.92	10.51
$AUC_{Pred/Obs}$	-	0.53	0.54	0.55	0.65	0.79	**0.97**	5.29
Cmax	1.52	0.98	1.00	1.01	1.14	1.29	1.45	2.35
$Cmax_{Pred/Obs}$	-	0.64	0.65	0.66	0.75	0.85	**0.95**	1.55

Figure 3: OMP concentration on day 1 and 5 following the administration of 20 mg of OMP solution (q.d.) for 5 days, without TDI (dash line), with TDI using *in vitro* measured irreversible Ki values for the CYPs 2C19 & 3A4[3] (red line), and with TDI using scaling factor for Ki (Ω= 0.5; 0.1; 0.05; 0.033; 0.01, blue to purple lines). Dots represent the observed data[2].

Figure 5: Simulated TDI for gut and liver CYP3A4 following the daily administration of OMP (enteric-coated tablet, 20 mg). Black arrows represents time of NIF intakes (10 mg, IR).

Impact of CYP3A4 TDI on NIF plasma exposure



	Placebo	OMP 8 days
Vmax (pmol/min/10^6)	22	17.15
Obs. Cmax (ng/mL)	66.1	56.8
Obs. AUC (ng.h/mL)	140.7	170.3
Sim. Cmax (ng/mL)	65.3	79.5
Sim.AUC (ng.h/mL)	160	213

Figure 6: NIF concentration time course following the single administration of 10 mg IR with **A)** Placebo **B)** OMP, 30 min prior NIF intake **C)** daily OMP treatment for 8 days prior to NIF administration.
CYP3A4 Vmax was set to 99.9 & 78% of the initial published value to account for the CYP3A4 OMP driven TDI for the B and C conditions.

CONCLUSIONS

- The newly developed PBPK absorption model provides a mechanistic understanding of the observed DDI between nifedipine and omeprazole by taking into account both gastric pH change and metabolic inhibition.
- Based on the PBPK model, gastric pH modification after a short-term (one week) dosing of OMP does not alter NIF Cmax and AUC for IR formulation.
- CYP3A4-medidated TDI by OMP seems to be the major cause of the observed systemic exposure increase for IR NIF.

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